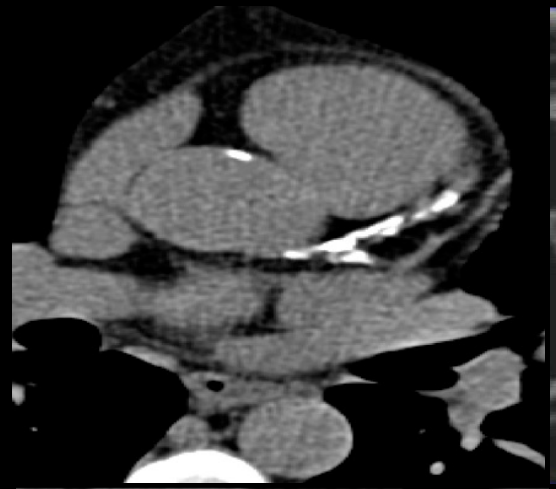
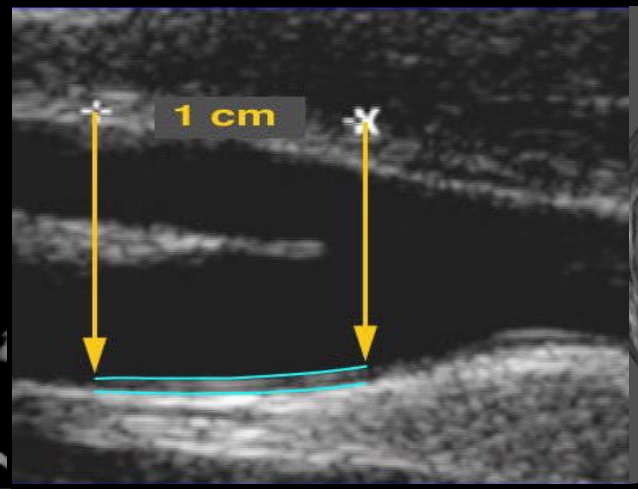
CURRENT GUIDELINES AND FUTURE DIRECTIONS IN LIPID MANAGEMENT

A/PROF. K.KOSTNER
MATER HOSPITAL, UQ, CHOLESTEROLCARE AUSTRALIA

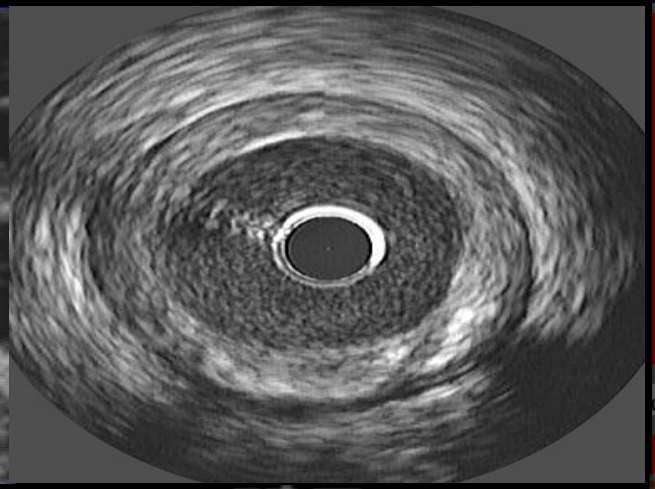
Coronary Calcium



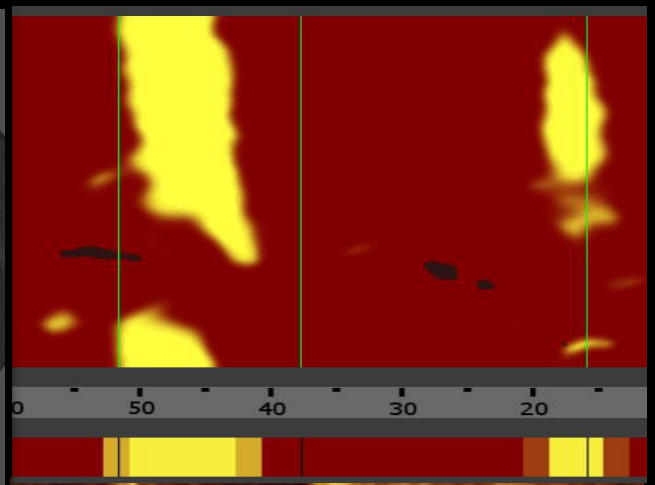
Carotid IMT

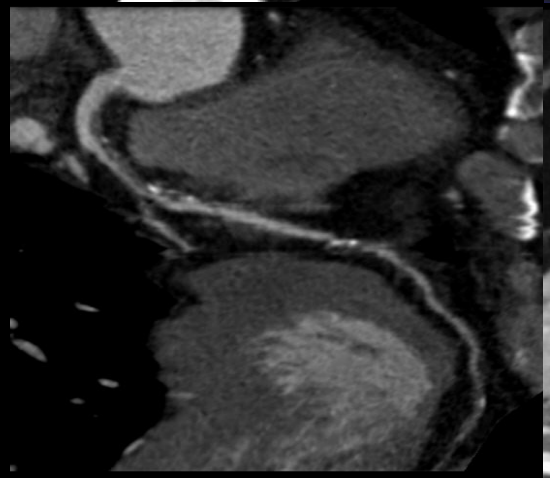


IVUS

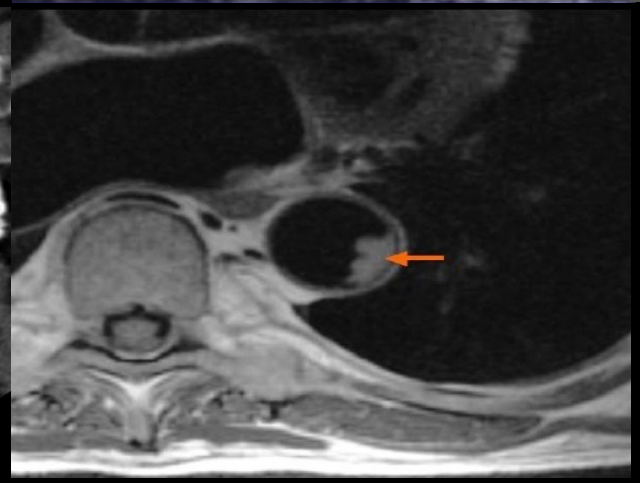


NIR Spectroscopy

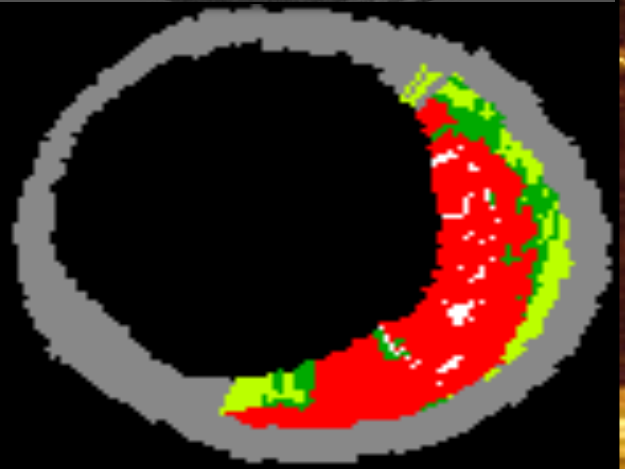




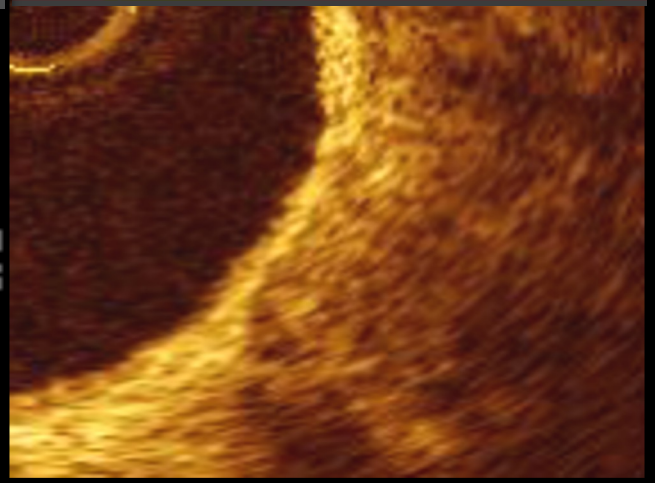
Coronary CT



MR Angiography

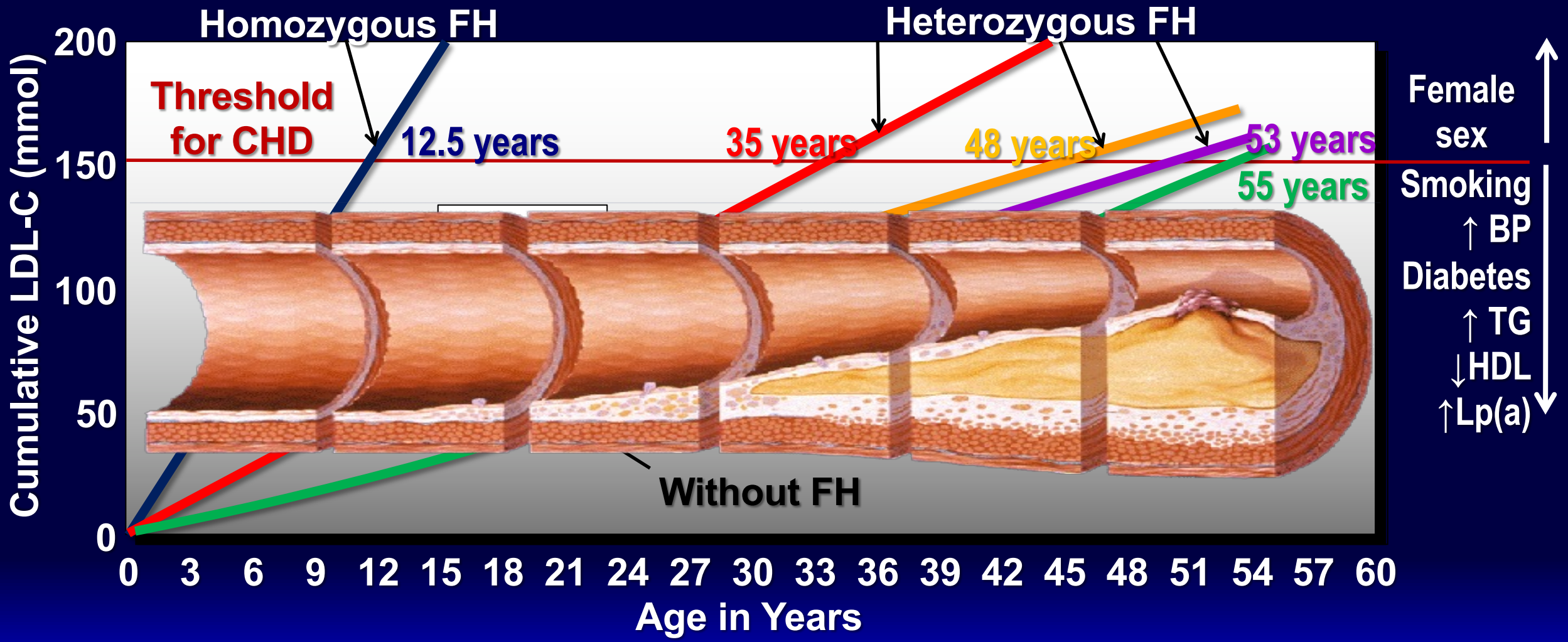


IVUS-VH



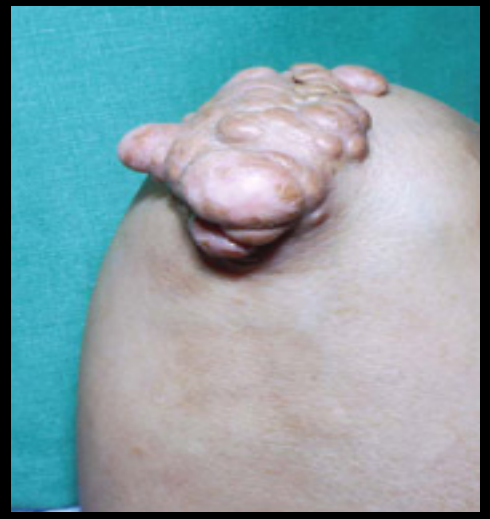
OCT

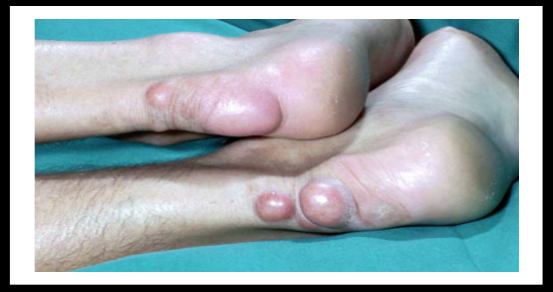
Cumulative Cholesterol Burden

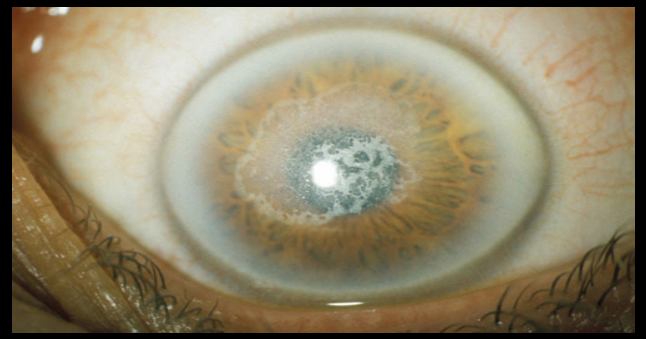


Adapted from Nordestgaard *Eur Heart J* 2013;34:3478-90

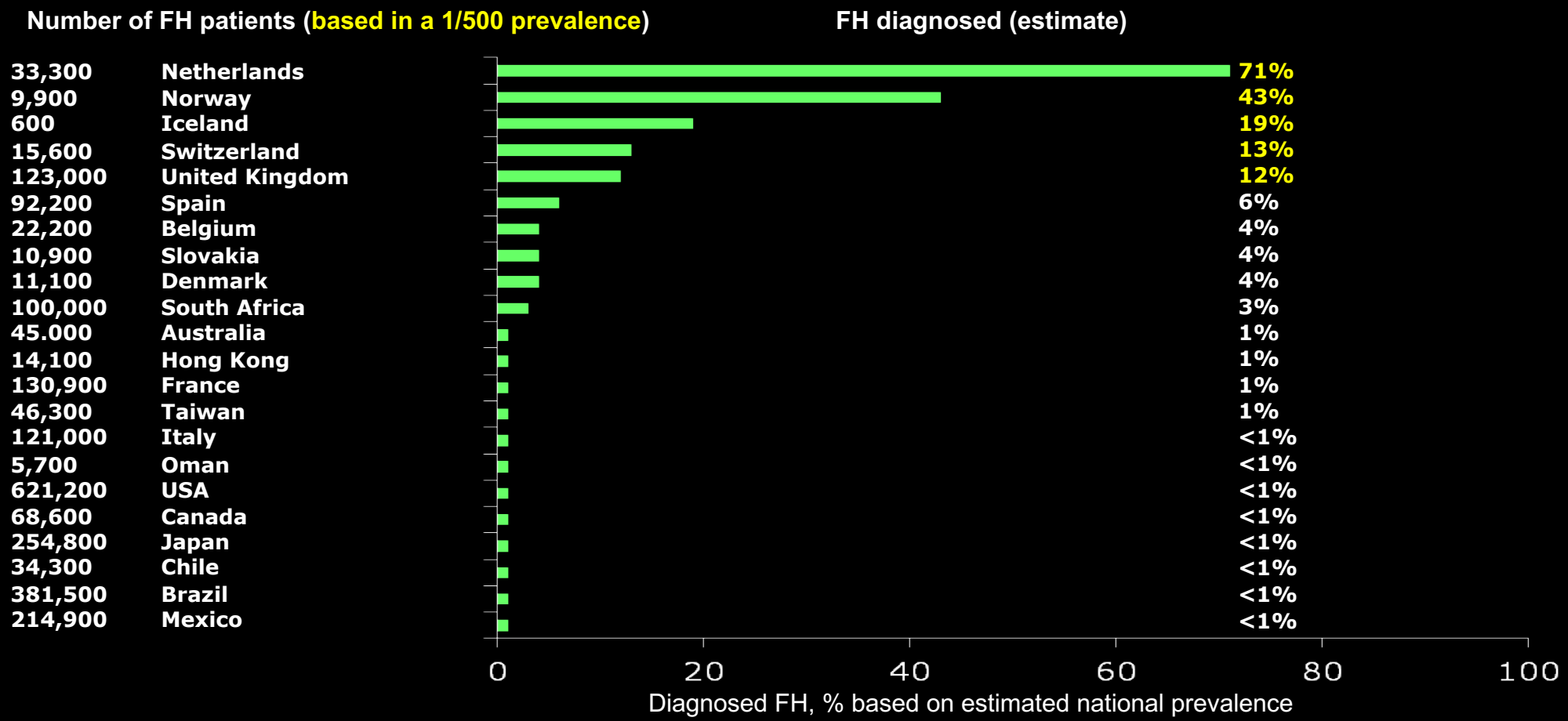
Familial Hypercholesterolemia







Familial Hypercholesterolaemia: Under-diagnosed and Undertreated



Patients diagnosed as FH in different countries expressed as percentage of individuals predicted to have FH based upon a disease prevalence of 1/500 of the general population

Consensus Statement of the EAS, European Heart Journal e-pub August 15, 2013

Dutch Lipid Clinic Network Criteria for diagnosis of heterozygous familial hypercholesterolaemia

	Points
➢ Family history	
- First-degree relative with known premature coronary heart disease (CHD)	1
- First-degree relative with known LDL cholesterol >95th percentile by age and gender	1
- First-degree relative with tendon xanthoma and/or corneal arcus	2
- Children <18 years with LDL cholesterol >95th percentile by age and gender	2
➢ Clinical history	
- **Subject has premature** (<55 years, men; <60 years, women) **CHD**	**2**
- Subject has premature cerebral or peripheral vascular disease	1
➢ Physical examination	
- Tendon xanthoma	6
- Corneal arcus in a person <45 years	4
➢ Biochemical results (LDL cholesterol)	
- >8.5 mmol/L (>325 mg/dL)	8
- 6.5–8.4 mmol/L (251–325 mg/dL)	5
- **5.0–6.4 mmol/L (191–250 mg/dL)**	**3**
- 4.0–4.9 mmol/L (155–190 mg/dL)	1
➢ Molecular genetic testing (DNA analysis)	
- Causative mutation shown in the LDLR, APOB, or PCSK9 genes	8

Score >8: DEFINITE FH; Score 6-8: PROBABLE FH; **Score 3-5 POSSIBLE FH**; Score 0-2 UNLIKELY FH

Consensus Statement of the EAS, European Heart Journal e-pub August 15, 2013

ELSEVIER

Atherosclerosis 221–263

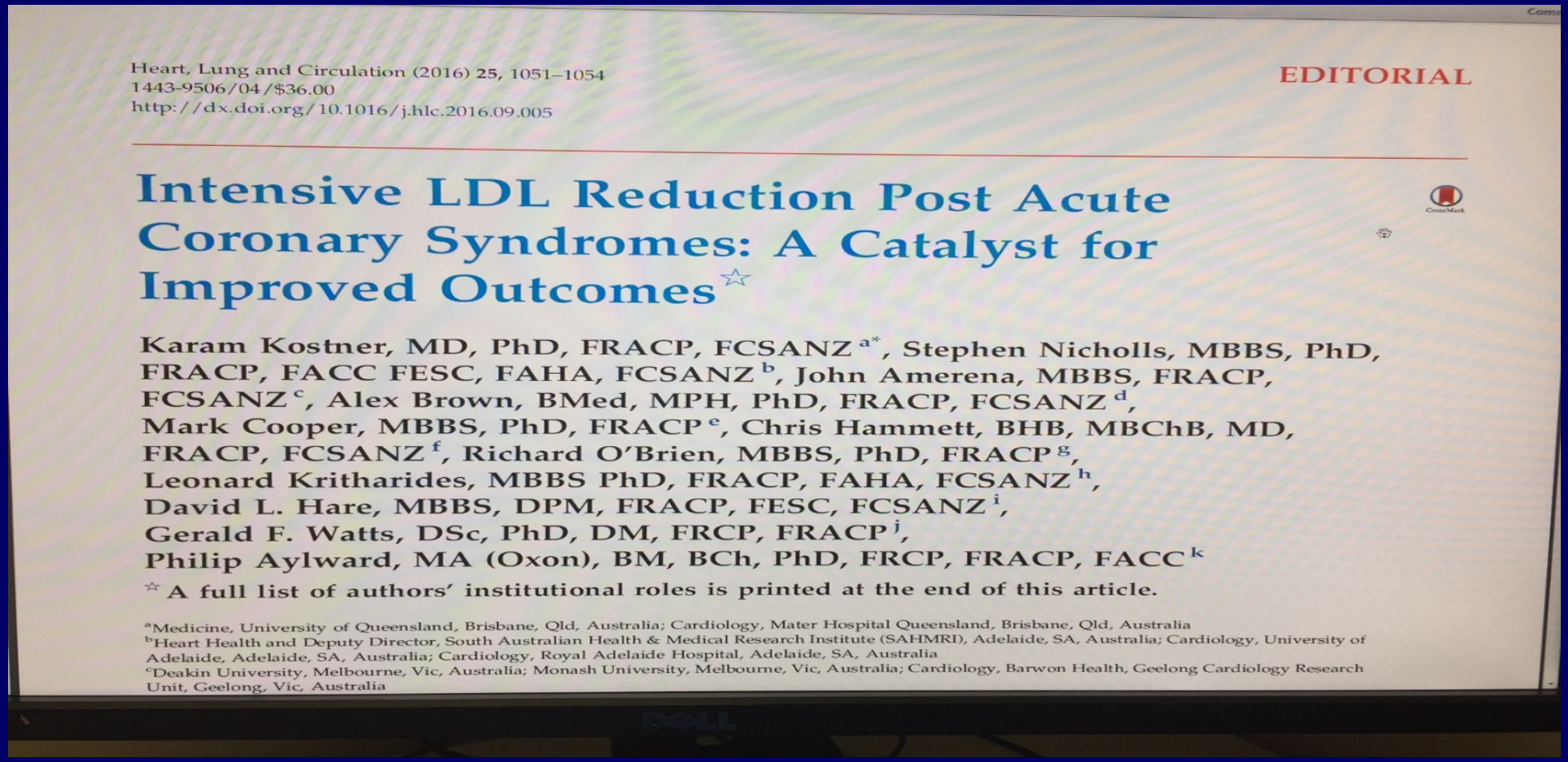
ATHEROSCLEROSIS
SUPPLEMENTS

www.elsevier.com/locate/atherosclerosis

Familial hypercholesterolaemia: A model of care for Australasia

Gerald F. Watts[a,*], David R Sullivan[b], Nicola Poplawski[c], Frank van Bockxmeer[d], Ian Hamilton-Craig[e], Peter M. Clifton[f], Richard O'Brien[g], Warrick Bishop[h], Peter George[i], Phillip J. Barter[j], Timothy Bates[a], John R. Burnett[k], John Coakley[l], Patricia Davidson[m], Jon Emery[n], Andrew Martin[o], Waleed Farid[p], Lucinda Freeman[q], Elizabeth Geelhoed[r], Amanda Juniper[a,s], Alexa Kidd[t], Karam Kostner[u], Ines Krass[v], Michael Livingston[w], Suzy Maxwell[s], Peter O'Leary[s], Amal Owaimrin[x], Trevor G. Redgrave[a], Nicola Reid[y], Lynda Southwell[a], Graeme Suthers[c], Andrew Tonkin[z], Simon Towler[aa], Ronald Trent[q], Familial Hypercholesterolaemia Australasia Network Consensus Group (Australian Atherosclerosis Society)[l]

LDL Goal < 1.4 mmol/L in high risk patients



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1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2016.09.005

EDITORIAL

Intensive LDL Reduction Post Acute Coronary Syndromes: A Catalyst for Improved Outcomes☆

Karam Kostner, MD, PhD, FRACP, FCSANZ[a*], Stephen Nicholls, MBBS, PhD, FRACP, FACC FESC, FAHA, FCSANZ[b], John Amerena, MBBS, FRACP, FCSANZ[c], Alex Brown, BMed, MPH, PhD, FRACP, FCSANZ[d], Mark Cooper, MBBS, PhD, FRACP[e], Chris Hammett, BHB, MBChB, MD, FRACP, FCSANZ[f], Richard O'Brien, MBBS, PhD, FRACP[g], Leonard Kritharides, MBBS PhD, FRACP, FAHA, FCSANZ[h], David L. Hare, MBBS, DPM, FRACP, FESC, FCSANZ[i], Gerald F. Watts, DSc, PhD, DM, FRCP, FRACP[j], Philip Aylward, MA (Oxon), BM, BCh, PhD, FRCP, FRACP, FACC[k]

☆ A full list of authors' institutional roles is printed at the end of this article.

[a]Medicine, University of Queensland, Brisbane, Qld, Australia; Cardiology, Mater Hospital Queensland, Brisbane, Qld, Australia
[b]Heart Health and Deputy Director, South Australian Health & Medical Research Institute (SAHMRI), Adelaide, SA, Australia; Cardiology, University of Adelaide, Adelaide, SA, Australia; Cardiology, Royal Adelaide Hospital, Adelaide, SA, Australia
[c]Deakin University, Melbourne, Vic, Australia; Monash University, Melbourne, Vic, Australia; Cardiology, Barwon Health, Geelong Cardiology Research Unit, Geelong, Vic, Australia

Evidence for efficacy of lipid-lowering therapies < 1.4 mmol/L (< 55 mg/dL)

Source	Reduction in LDL-C Between Treatment Groups (%)	Prespecified Primary CV Outcomes	Risk Estimate for Primary Endpoint (95% CI)
CTT meta-analysis (high-intensity vs standard-intensity statin)[1]	NR	Major coronary event, stroke, coronary revascularisation	0.71 (0.52–0.98) *per mmol/L reduction in LDL-C when LDL-C < 2.0 mmol/L (< 77 mg/dL)*[a]
IMPROVE-IT (ezetimibe plus statin vs statin alone)[2]	24%	CV death, major coronary event, stroke[b]	0.94 (0.89–0.99)[c]
FOURIER (evolocumab plus high-dose statin ± ezetimibe vs high-dose statin ± ezetimibe[3]	59%	CV death, MI, stroke, UA, coronary revascularisation[b]	0.85 (0.79–0.92)[d]
ODYSSEY outcomes (alirocumab plus high-dose statin ± ezetimibe vs high-dose statin ± ezetimibe)[4]	55%	CHD death, MI, stroke, UA[b]	0.85 (0.78–0.93)[d]

[a]Indicates the study reported risk estimate as a rate ratio. [b]Indicates the study used a composite endpoint. [c]Indicates the study reported risk estimate as absolute risk reduction. [d]Indicates the study reported risk estimate as a hazard ratio.

CHD, coronary heart disease; **CI,** confidence interval; **CTT,** Cholesterol Treatment Trialists'; **CV,** cardiovascular; **FOURIER,** Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Patients With Elevated Risk; **IMPROVE-IT**, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; **LDL,** low-density lipoprotein; **LDL-C,** low-density lipoprotein cholesterol; **MI,** myocardial infarction; **NR,** not reported; **ODYSSEY,** Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; **UA,** unstable angina.

1. Cholesterol Treatment Trialists' Collaboration. *Lancet*. 2010;376(9753):1670-1681. **2.** Cannon CP, et al. *N Engl J Med*. 2015;372(25):2387-2397. **3.** Sabatine MS, et al. *N Engl J Med*. 2017:376(18):1713-1722. **4.** Schwartz GG, et al. *N Engl J Med*. 2018;379(22):2097-2107.

Current Clinical Guidelines Underscore the Importance of LDL-C Lowering in Patients at Highest Risk of CVD

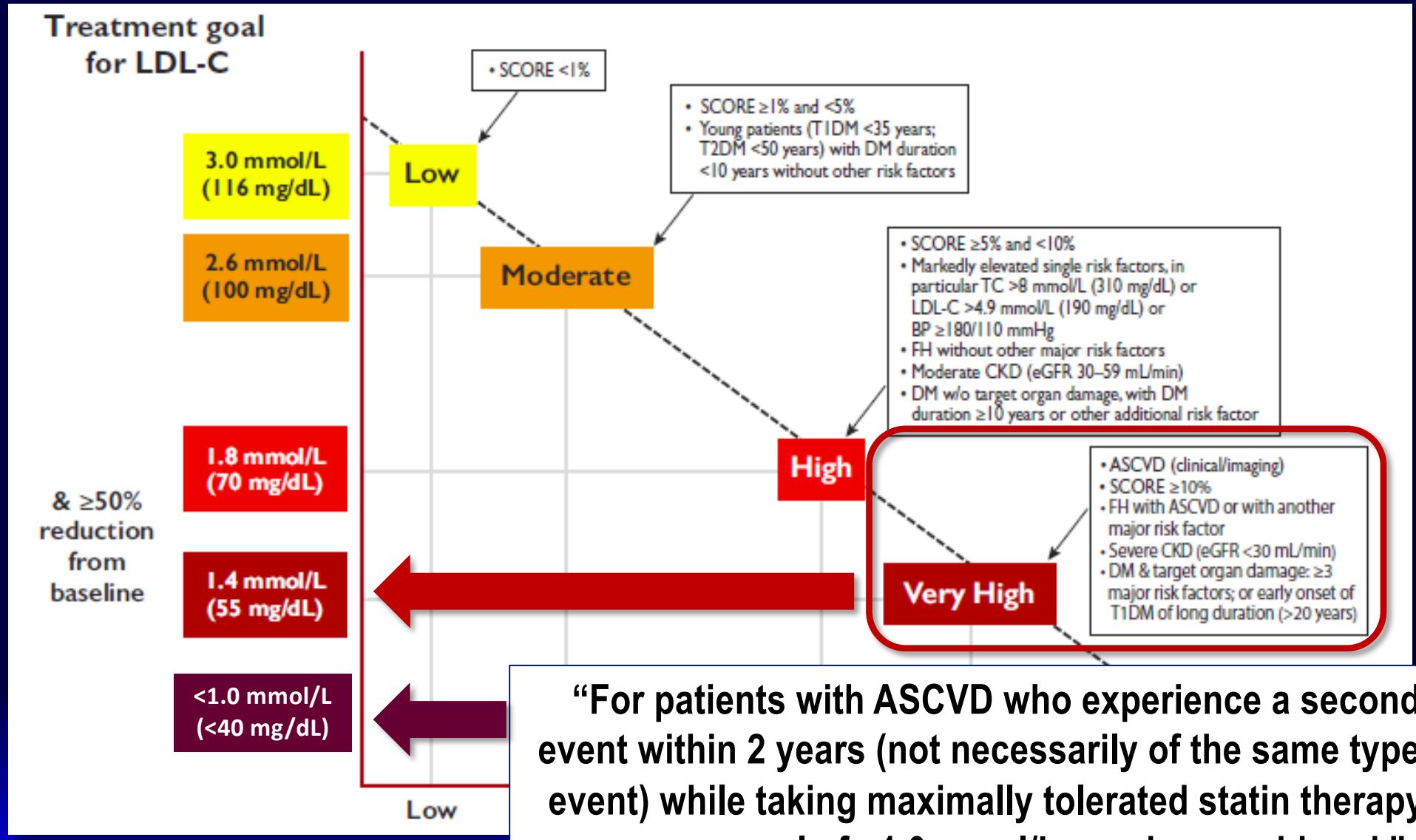
Guideline	Recommendation
2019 ESC/EAS Guidelines for the Management of Dyslipidaemias[1]	**Very High CV Risk** LDL-C level **< 55 mg/dL (1.4 mmol/L)** and **≥ 50% reduction** from baseline
2016 ESC/EAS Guidelines for the Management of Dyslipidaemias[2]	**Very High CV Risk** LDL-C level **< 70 mg/dL (1.8 mmol/L)** or **≥ 50% reduction** if baseline LDL-C is between 70 (1.8) and 135 (3.5) mg/dL (mmol/L)
2018 AHA/ACC Cholesterol Clinical Practice Guidelines[3]	**Very High ASCVD Risk** Addition of a PCSK9 inhibitor is reasonable for patients with **LDL-C ≥ 70 mg/dL (1.8 mmol/L)** on maximally tolerated LDL-C lowering therapy
2017 AACE/ACE Guidelines for Dyslipidemia Management and CVD Prevention[4]	**Extreme* ASCVD Risk** LDL-C goal of **< 55 mg/dL (1.4 mmol/L)**

*Progressive ASCVD, including unstable angina that persists after achieving an LDL-C < 70 mg/dL (1.8 mmol/L), or established clinical ASCVD in individuals with diabetes, CKD stage 3 or 4, and/or HeFH, or in individuals with a history of premature ASCVD (< 55 years of age for males or < 65 years of age for females).

AACE, American Association of Clinical Endocrinologists; ACC, American College of Cardiology; ACE, American College of Endocrinology; AHA, American Heart Association; ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; HeFH, heterozygous familial hypercholesterolemia; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

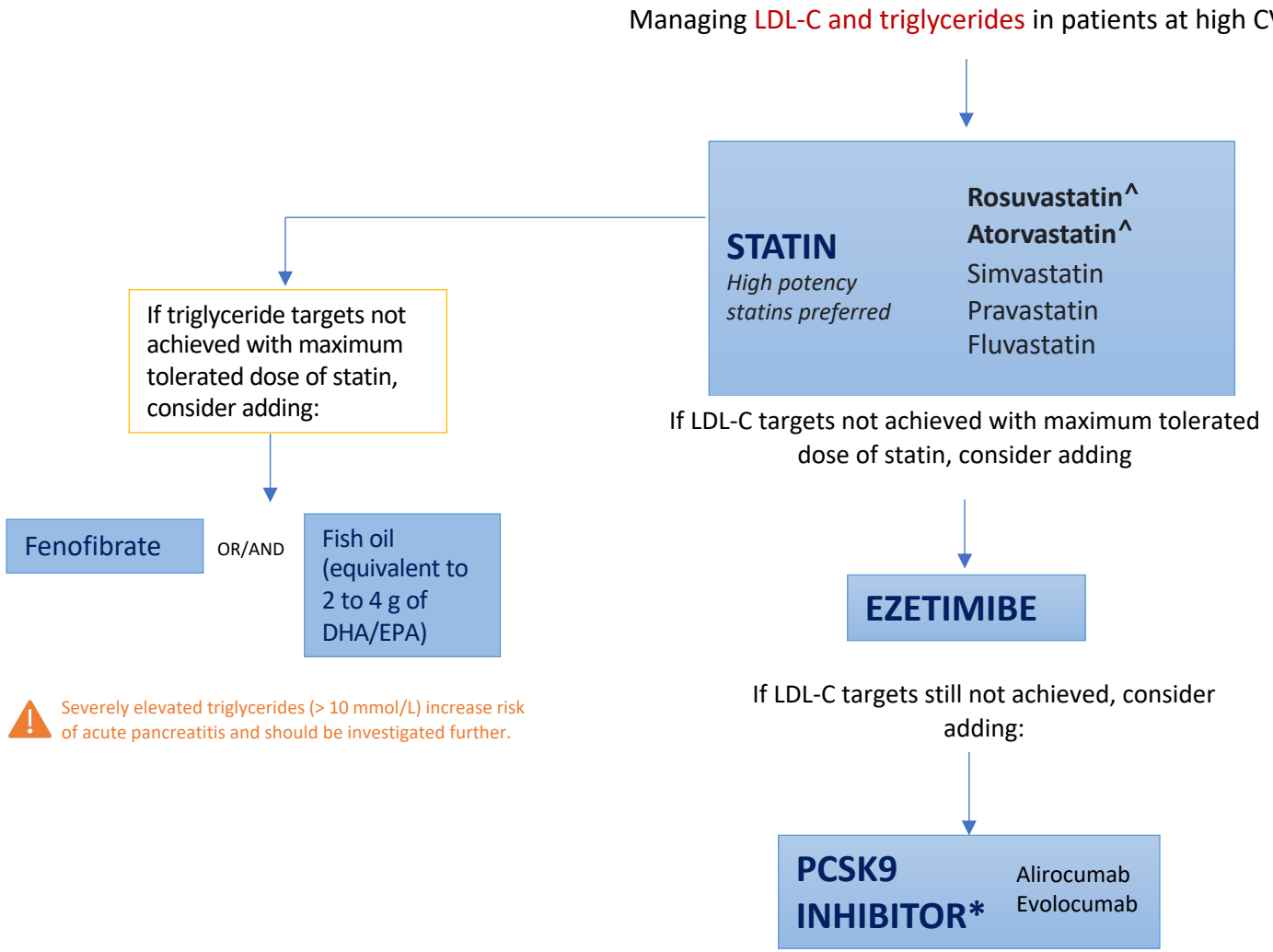
1. Mach F, et al. *Eur Heart J*. 2019 Aug 31. pii: ehz455. **2.** Catapano AL, et al. *Eur Heart J*. 2016;37(39):2999-3058. **3.** Grundy SM, et al. *Circulation*. 2019;18;139(25):e1082-e1143. **4.** Jellinger PS, et al. *Endocr Pract*. 2017 Apr 2;23(4):479-497.

ESC/EAS Dyslipidemia Guidelines



"For patients with ASCVD who experience a second vascular event within 2 years (not necessarily of the same type as the first event) while taking maximally tolerated statin therapy, an LDL-C goal of <1.0 mmol/L may be considered."

Practical Guide to Pharmacological Lipid Management



+ Defined as patients with established CVD, high absolute CVD risk score > 15% or who are at clinically determined high risk
^ High potency statins
* Visit Product Information and PBS website for details on PCSK9 inhibitor clinical indications and PBS subsidies
DHA = docosahexaenoic acid EPA = eicosapentaenoic acid

Practice considerations

- Strongly recommend healthy lifestyle changes (diet, physical activity, smoking cessation and weight management) to all patients, regardless of medicine initiation.[2,3] Visit the Heart Foundation's nutrition position statements.
- Encourage adherence to medicines by explaining the benefits on overall CVD risk. Explain serious side effects are rare.[2]
- Initiate the highest tolerated dose of statin therapy for patients following hospitalisation for acute coronary syndrome.[4] Allow at least four weeks between statin dose increases to optimise effects from current dose.[5]
- For patients unable to tolerate a prescribed statin, consider a lower dose or switching to an alternative statin. Statin intolerance is often overestimated (true prevalence 8-10%).[6]
- If LDL-C targets are still not met with a combination of statin, ezetimibe and PCSK9 inhibitor, bile acid binding resins may be added. Side effects often limit their use.[7]
- Bile acid binding resins, fibrates and nicotinic acid have been shown to improve lipid levels but evidence to support their addition to statin therapy to improve cardiovascular outcomes is limited.[1]
- Note: Pharmacological management of familial hypercholesterolaemia (FH) may differ from this algorithm, see 2020 FH Guidelines.[8]

Figure 1. Practical guide to pharmacological lipid management – flowchart.[1]

Many patients require statins plus additional lipid-lowering therapy to achieve their LDL-C goal

- Patients requiring additional treatment are typically **high-risk patients or those with very high LDL-C levels**
- In patients who are very high risk and remain at high risk despite maximally tolerated statin treatment, combination with ezetimibe is recommended (Class I*)
- If the LDL-C goal is still not achieved, the **addition of a PCSK9 inhibitor is recommended,** either to a statin alone or a statin plus ezetimibe

Guideline-provided estimates of the LDL-C–lowering benefit of recommended lipid-lowering regimens

Treatment	Average LDL-C reduction
Moderate-intensity statin	~ 30%
High-intensity statin	~ 50%
High-intensity statin + ezetimibe	~ 65%
PCSK9 inhibitor	~ 60%
PCSK9 inhibitor + high-intensity statin	~ 75%
PCSK9 inhibitor + high-intensity statin + ezetimibe	~ 85%

*Class I recommendations, the highest level recommendations in the guidelines, are based on evidence and/or general agreement that a given treatment is beneficial, useful, and effective.

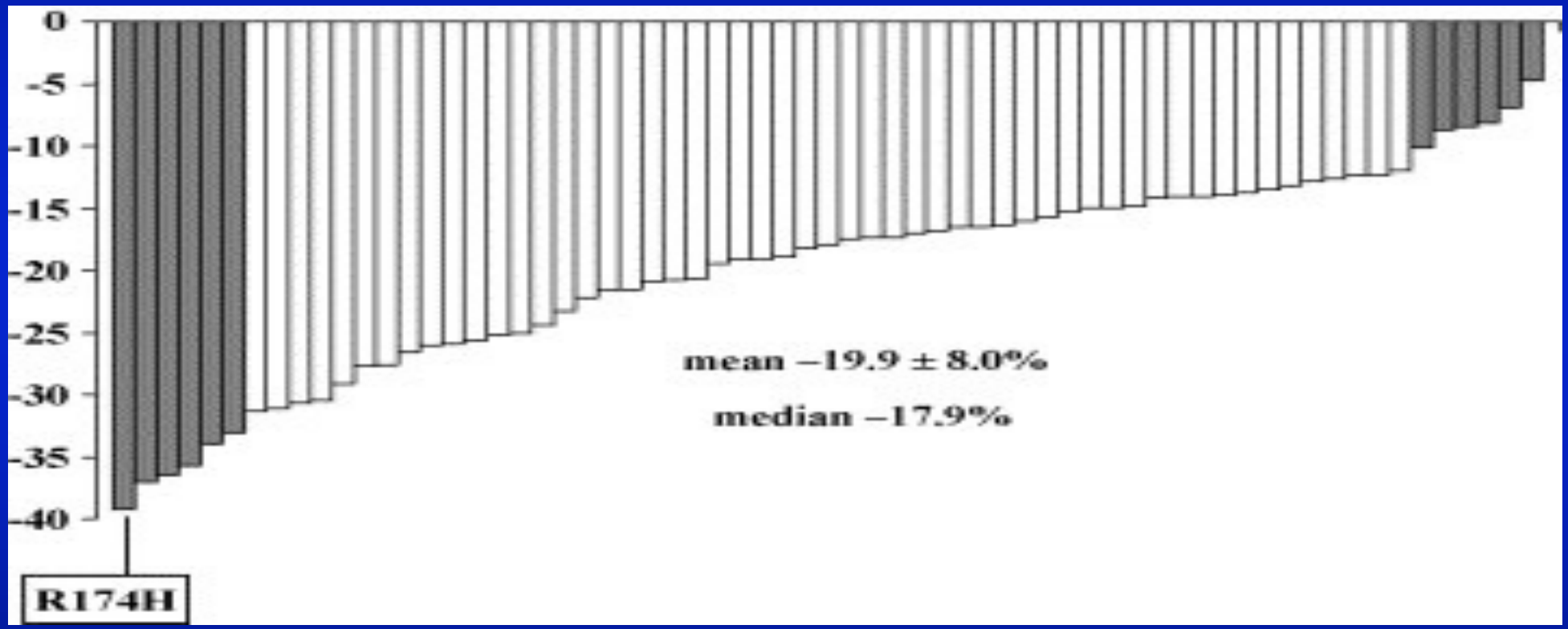
LDL-C, low-density lipoprotein cholesterol; **PCSK9,** proprotein convertase subtilisin/kexin type 9.

1. Mach F, et al. *Eur Heart J.* 2019. doi:10.1093/eurheartj/ehz455. [Epub ahead of print.].

LL-Therapy	LDL-C Lowering	HDL-C Raising	TG Lowering
Statins	++++	++	++
Niacins	++	++++	+++
Resins	++	+	0/-
Fibrates	+/-	+++	++++
Ezetimibe	++	+	+
n-3 Ethyl Esters	0/-	+	++++

+ = positive effect - = negative effect 0 = no effect

Effect of ezetimibe coadministered with statins in heterozygous FH patients



Piciotta L et al. Atherosclerosis 2006

Management of Patient with Intolerable Muscle Symptoms on Statin Therapy

- Low dose statin (5 mg/day)
- Alternate day statin dosing (i.e., rosuvastatin 5-10 mg)
- Hydrophilic statins (rosuva, prava, fluva)
- Non-statin therapy (ezetimibe, BAS)
- Red rice yeast (has been associated with myopathy)
- Plant sterols - 5-10% LDL reduction
- Soluble Fiber/Portfolio Diet (5-25% LDL reduction)
- Vitamin D supplementation – anecdotal – need RCT
- Coenzyme Q10 – unproven
- Magnesium Oretate
- Clinical Trials with new LL meds

Conclusions

- Hypercholesterolemia is very common (FH) and an important CV risk factor
- LDL target depends on CV risk category, as low as possible in very high risk patients
- This is often achievable with statin/ezetimibe combinations
- In high risk patients who do not achieve targets, PCSK9 Inhibitors are reimbursed in Australia and are safe and effective