Presenter Disclosures

Dr. Ronald Goldenberg

Controversies in Dyslipidemia Management

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Inspired Care. Inspiring Science.

Learning Objectives

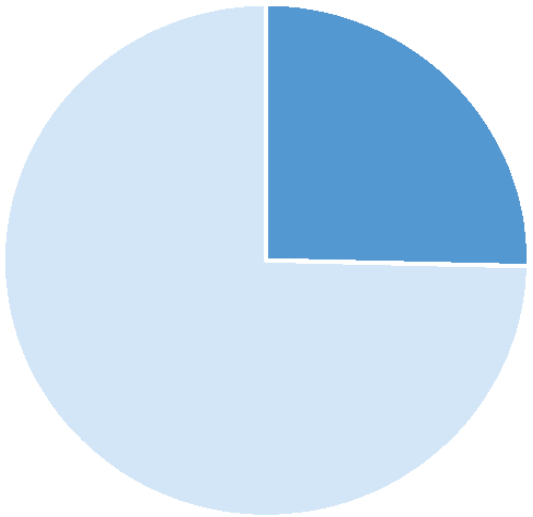
At the conclusion of this activity, participants will be able to:

- Understand the link between hypertriglyceridemia and CVD
- Interpret the evidence from the REDUCE-IT clinical trial
- Incorporate icosapent ethyl into a vascular protection strategy in people with CVD or diabetes with ≥ 1 risk factor
- Know the statin indicated conditions other than clinical atherosclerosis, including Familial Hypercholesterolemia (FH)
- Recognize and manage heterozygous FH as per practice guidelines

Controversies in Dyslipidemia Management: **The Patient with Elevated Triglycerides**

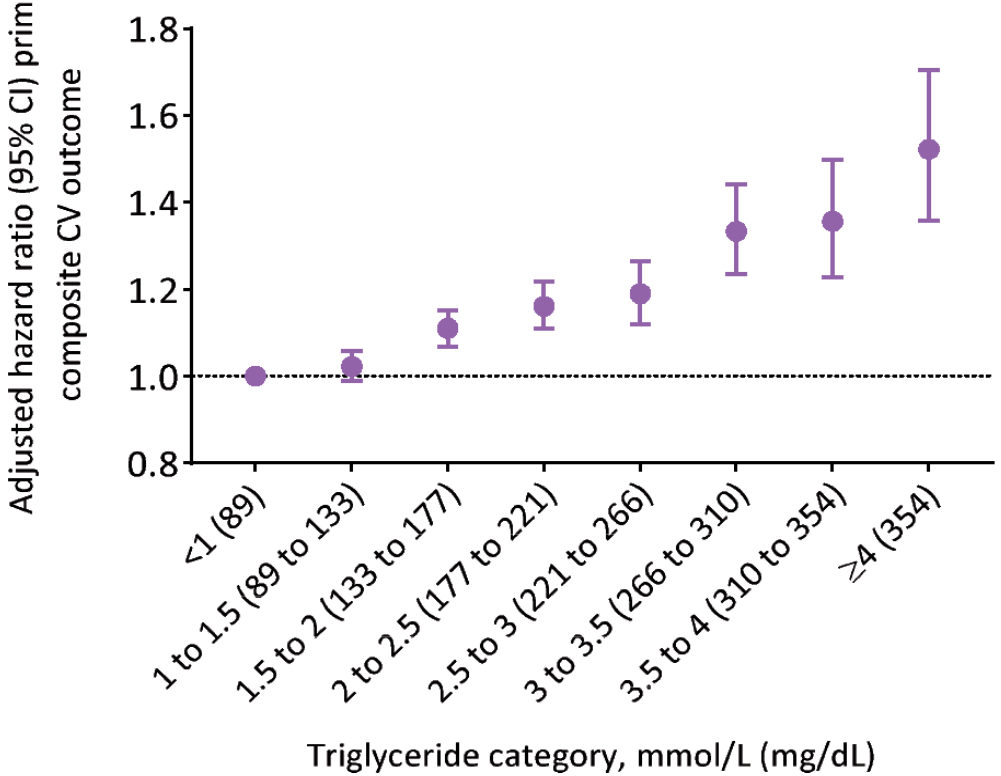
CANHEART ASCVD Cohort: Prevalence of Hypertriglyceridemia with Controlled LDL-C and Risk of CV Events with Rising Triglycerides

Approximately 1 in 4 patients with ASCVD in the general population may have hypertriglyceridemia and controlled LDLc*



*defined as triglyceride 1.52-5.63 mmol/L (135-499 mg/dL) and LDLc 1.06-2.59 mmol/L (41-100 mg/dL)

Risk of ASCVD events associated with triglyceride level among 196,717 patients with prevalent ASCVD in the population

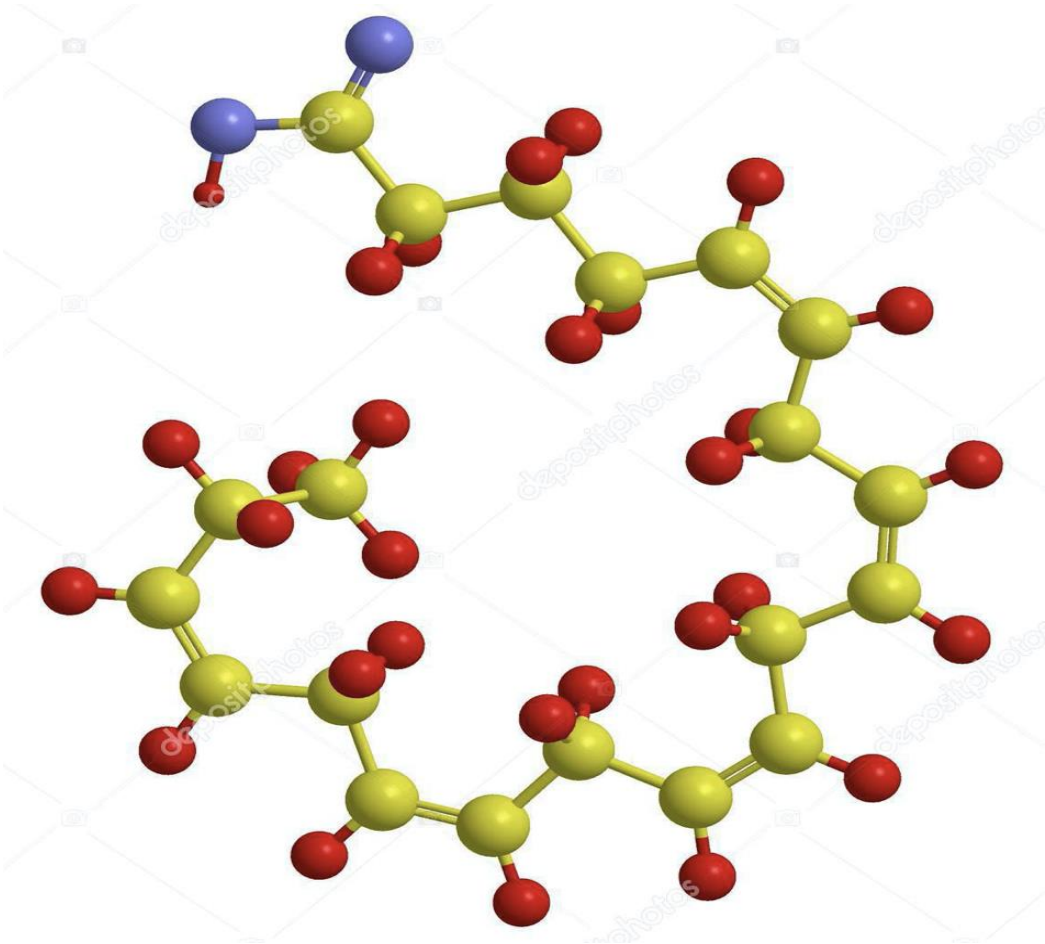


European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 86–94, https://doi.org/10.1093/eurheartj/ehz767

Can we reduce residual risk in high-risk patients with hypertriglyceridemia and controlled LDL-C

Can this risk be attenuated with icosopent ethyl (IPE)?

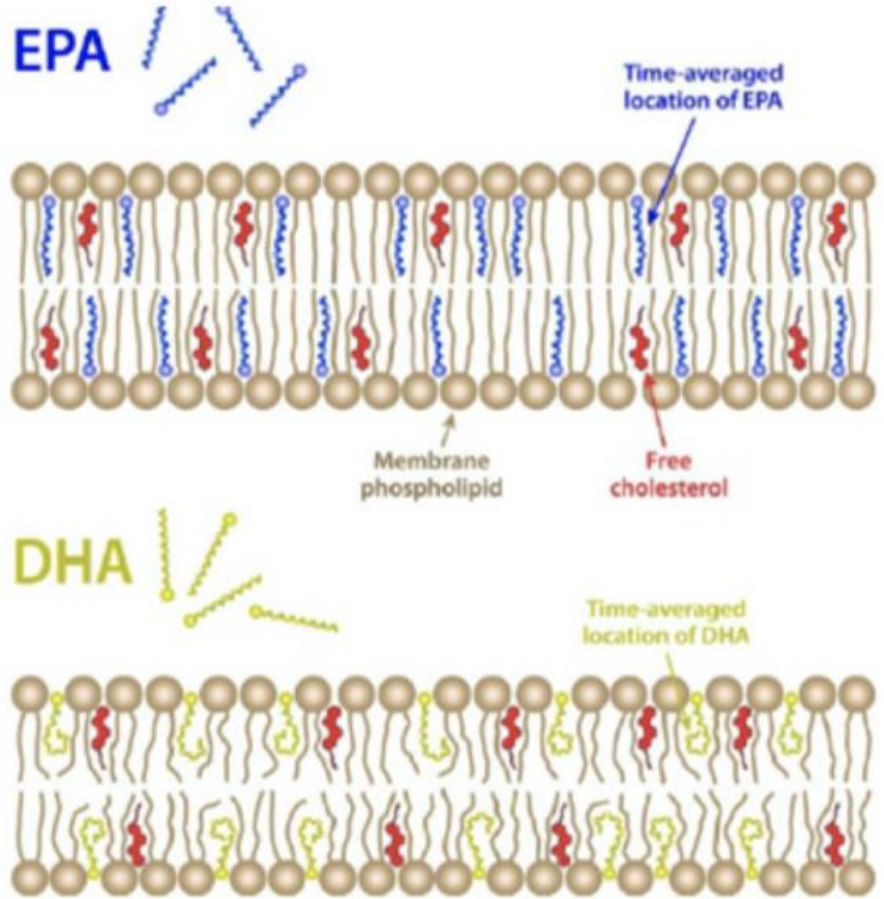
Icosapent Ethyl



Icosapent ethyl is a highly purified and stable ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA) and requires a prescription

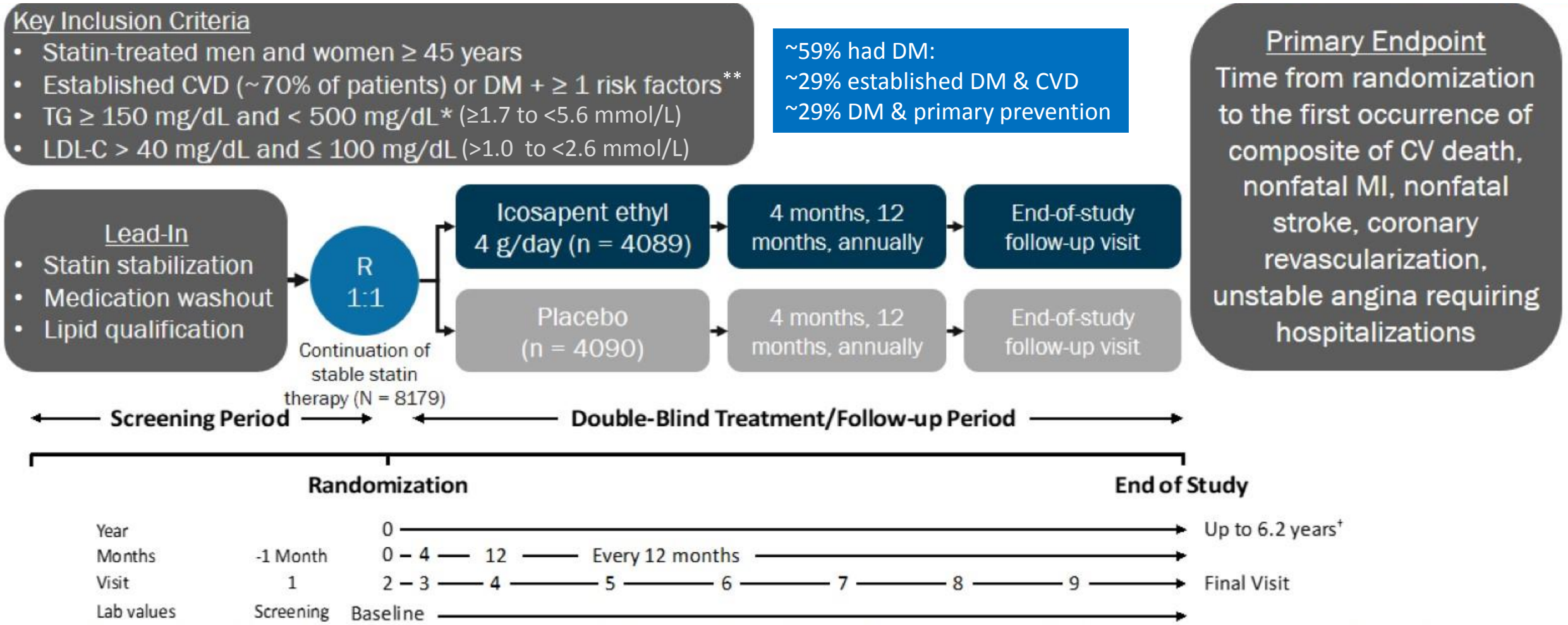
Rationale for the Use of Highly Purified Eicosapentaenoic Acid (EPA)

- **EPA and Docosahexaenoic acid (DHA)** have different properties and **distinct membrane locations**[1]
  - **Purified EPA** has demonstrated potent **antioxidant** and **anti-inflammatory effects**[1]
  - **DHA** associated with **modest LDL-C elevation** while **EPA** is **LDL-C neutral**
- Sources for EPA and DHA include fish/seafood, omega-3 fatty acid supplements and fortified foods
- **Contemporary trials** (ASCEND[2], VITAL[3], STRENGTH[4]) and **meta-analyses[5] of mixed EPA/DHA omega-3 fatty acid** products at doses from **1-4 g daily** have **not shown a CV benefit** in patients receiving statins
- **JELIS** demonstrated a **reduction in major coronary events** with **EPA 1.8 g** plus statin vs statin alone[6]
- **Icosapent ethyl lowers TGs by 22%** in statin treated patients with TG in 2.3 to <5.6 mmol/L range[7]



1. Sherratt SCR et al. Chem Phys Lipids 2018;212:73-79. 2. Bowman L et al. NEJM 2018;379:1540-1550. 3. Manson JE et al. NEJM 2019;380:23-32.
4. https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-phase-iii-strength-trial-for-epanova-in-mixed-dyslipidaemia-13012020.html
5. Aung T et al. JAMA Cardiol 2018;3:225-234. 6. Yokoyama M et al. Lancet 2007;369:1090-1098. 7.Ballantyne CM et al. Am J Cardiol 2012;110:984-992.

REDUCE-IT Design



*Due to the variabliity of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥ 135 mg/dL.(≥1.5 mmol/L) Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance. †Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years)

Bhatt DL, et al. *N Engl J Med*. 2018;380:11-22. **Risk factors: male ≥55, female ≥65; smoking; hypertension; HDL <1.0 male, <1.3 female; hsCRP>3; CrCl 30-60; albuminuria; retinopathy; ABI <0.9

Effects on Biomarkers from Baseline to Year 1

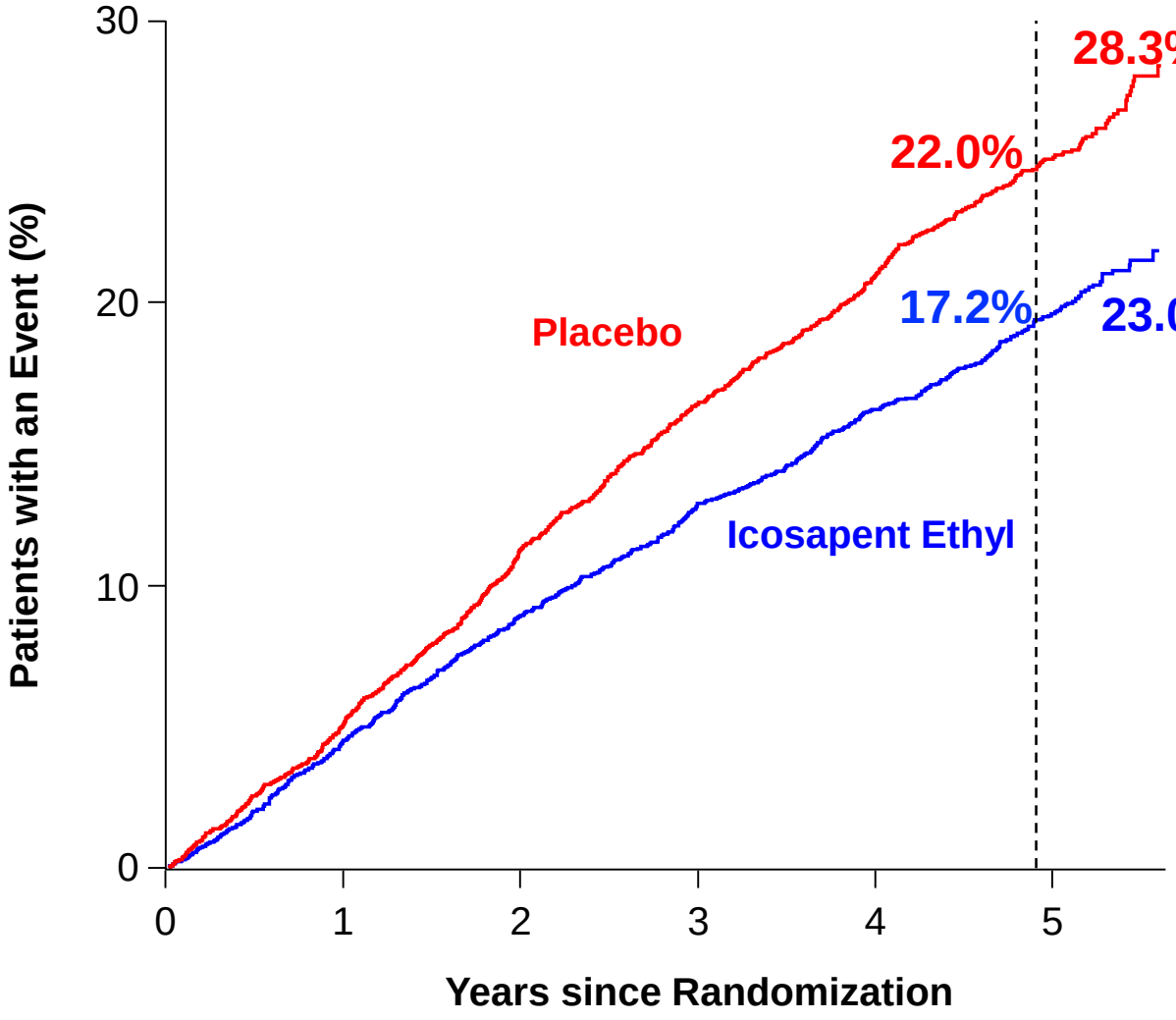
Biomarker*	Baseline Median	Median Between Group Difference at year 1	
		% Change from Baseline	% Change P-value
Triglycerides (mmol/L)	2.4	**-19.7**	**<0.0001**
Non-HDL-C (mmol/L)	3.1	**-13.1**	**<0.0001**
LDL-C (mmol/L)	1.9	**-6.6**	**<0.0001**
HDL-C (mmol/L)	1.0	**-6.3**	**<0.0001**
Apo B (g/L)	0.83	**-9.7**	**<0.0001**
hsCRP (mg/L)	2.2	**-39.9**	**<0.0001**
Log hsCRP (mg/L)	0.8	**-22.5**	**<0.0001**
EPA (µg/ml)	26.1	**+385.8**	**<0.0001**

*Apo B and hsCRP were measured at Year 2.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.
Bhatt DL. ACC/WCC 2020, Chicago (virtual).

Primary End Point:

CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)

RRR = 24.8%

ARR = 4.8%

NNT 4.9y = 21 (95% CI, 15–33)

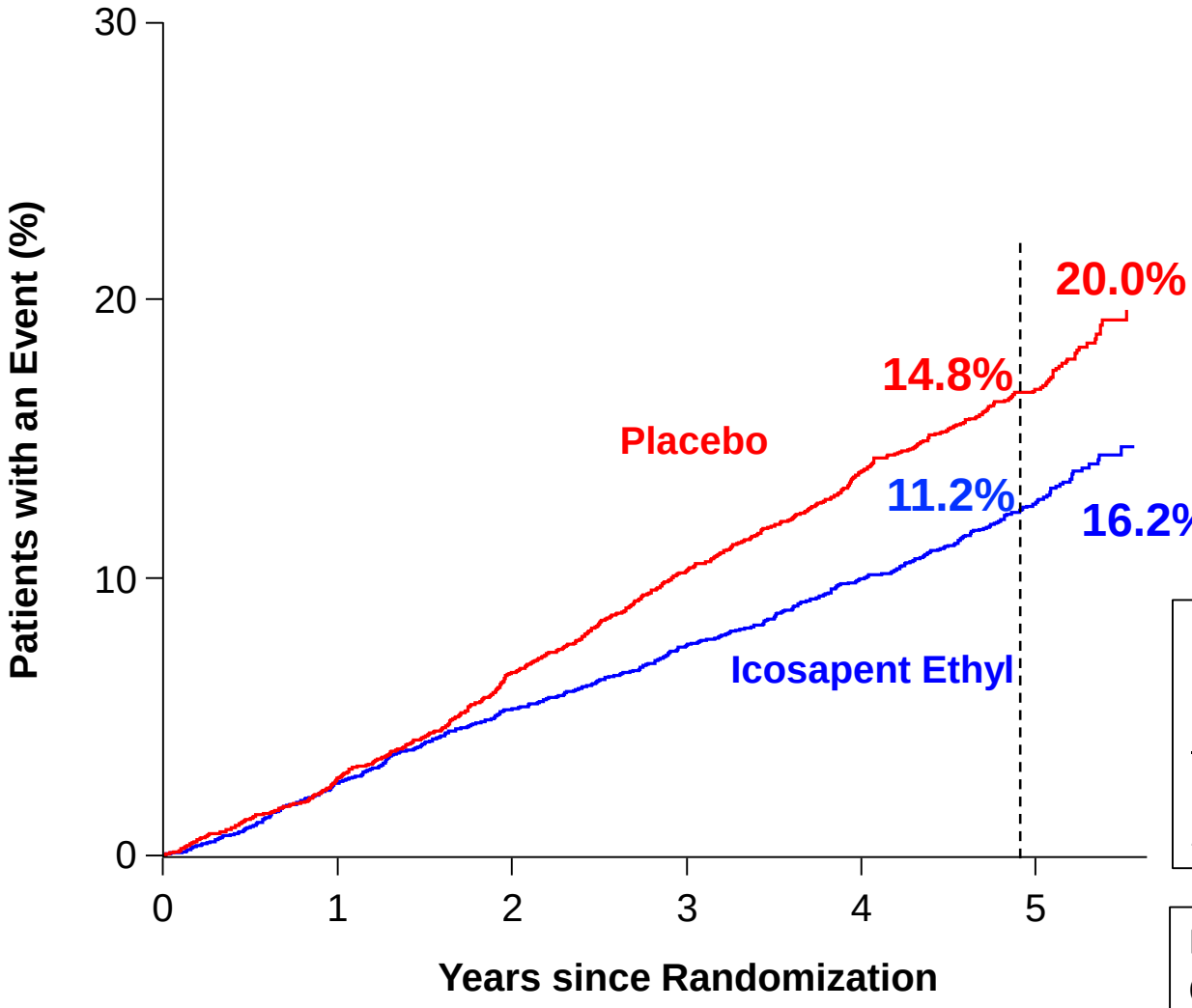
P=0.00000001

Consistent efficacy across multiple subgroups:
Risk category (secondary or primary prevention)
Diabetes (diabetes or no diabetes)
Baseline TG (<1.7 or ≥ 1.7)
Baseline TG by tertiles (0.9-2.1/>2.1-2.8/>2.8-15.8)
Achieved TG (< 1.7 or ≥ 1.7)

Benefit beyond what can be explained by TG lowering
On-treatment EPA levels via icosapent ethyl correlate strongly with the primary endpoint

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago. Bhatt DL et al. JACC 2019;74:1159-1161. Bhatt DL. ACC/WCC 2020.Chicago (virtual)

Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)

RRR = 26.5%

ARR = 3.6%

NNT 4.9y = 28 (95% CI, 20–47)

P=0.0000006

Consistent efficacy across multiple subgroups:
Risk category (secondary or primary prevention)
Diabetes (diabetes or no diabetes)
Baseline TG (<1.7 or ≥ 1.7)
Achieved TG (< 1.7 or ≥ 1.7)

Benefit beyond what can be explained by TG lowering
On-treatment EPA levels via icosapent ethyl correlate strongly with the secondary endpoint

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019. Bhatt DL. AHA 2018, Chicago. Bhatt DL. ACC/WCC 2020, Chicago (virtual)

Treatment-Emergent Adverse Event of Interest: Bleeding

	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Any bleeding event	482 (11.8%)	404 (9.9%)	0.006
Serious bleeding related disorders	111 (2.7%)	85 (2.1%)	0.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	0.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	0.42
Other bleeding	41 (1.0%)	30 (0.7%)	0.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke - no significant difference between treatments (13 (0.3%) icosapent ethyl versus 10 (0.2%) placebo; P=0.55)
- Bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin (approx. 13% icosapent ethyl vs 11% placebo)

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.
Vascepa Canadian Product Monograph; December 30, 2019.FDA Ad Com Nov. 14, 2019. FDA Briefing Document.

Adjudicated Events: Hospitalization for Atrial Fibrillation or Atrial Flutter

Primary System Organ Class Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P-value
Positively Adjudicated Atrial Fibrillation/Flutter[1]	127 (3.1%)	84 (2.1%)	0.004

Note: Percentages are based on the number of subjects randomized to each treatment group in the Safety population (N).
All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[1] Includes positively adjudicated Atrial Fibrillation/Flutter clinical events by the Clinical Endpoint Committee (CEC). P value was based on stratified log-rank test.

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

Update to ESC/EAS Dyslipidemia Guidelines 2019

Recommendations for drug treatment of patients with hypertriglyceridaemia

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

Mach F, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *European Heart Journal* (2019) 00, 1-78. doi:10.1093/eurheartj/ehz455

Icosapent Ethyl Indications and Dosage in Canada

Indications:

Icosapent ethyl is indicated to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides*, who are at high risk of cardiovascular events due to:

- established cardiovascular disease, or
- diabetes, and at least one other cardiovascular risk factor.

Dosage:

4 grams per day, taken as two 1 g capsules twice a day with food

*** Triglycerides ≥ 1.5 mmol/L**

Vascepa Canadian Product Monograph; December 30, 2019.

REDUCE-IT in the Context of Targeting Residual Risk in Patients with CVD

Known Cardiovascular Disease

High intensity statin + ASA + ACEi/ARB

Residual LDL- C Risk	Residual TG Risk	Residual Risk in Diabetes	Residual Thrombotic Risk	Residual Inflammatory Risk
LDL ≥ 2.0 mmol/L	TG ≥ 1.5 mmol/L			hsCRP ≥ 2 mg/L
Ezetemibe PCSK9i	**Icosapent Ethyl (IPE)**	GLP-1RA SGLT2i	Low-dose rivaroxaban Extended DAPT Low-dose ticagrelor	Canakinumab Colchicine

Controversies in Dyslipidemia Management:
The Patient with Familial Hypercholesterolemia

Conditions Other Than Clinical Atherosclerosis For Which Statins Are Indicated

ABDOMINAL AORTIC ANEURYSM

Abdominal aorta > 3.0 cm or
Previous aneurysm surgery

CHRONIC KIDNEY DISEASE

> 3 months duration and
ACR > 3.0 mg/mmol or
eGFR < 60 ml/min/1.73m^2

DIABETES MELLITUS

≥ 40 years of age or
> 15 years duration and age ≥ 30 years or
Microvascular complications

LDL-C ≥ 5.0 MMOL/L

LDL-C ≥ 5.0 mmol/L or
Document familial hypercholesterolemia
Excluded 2nd causes

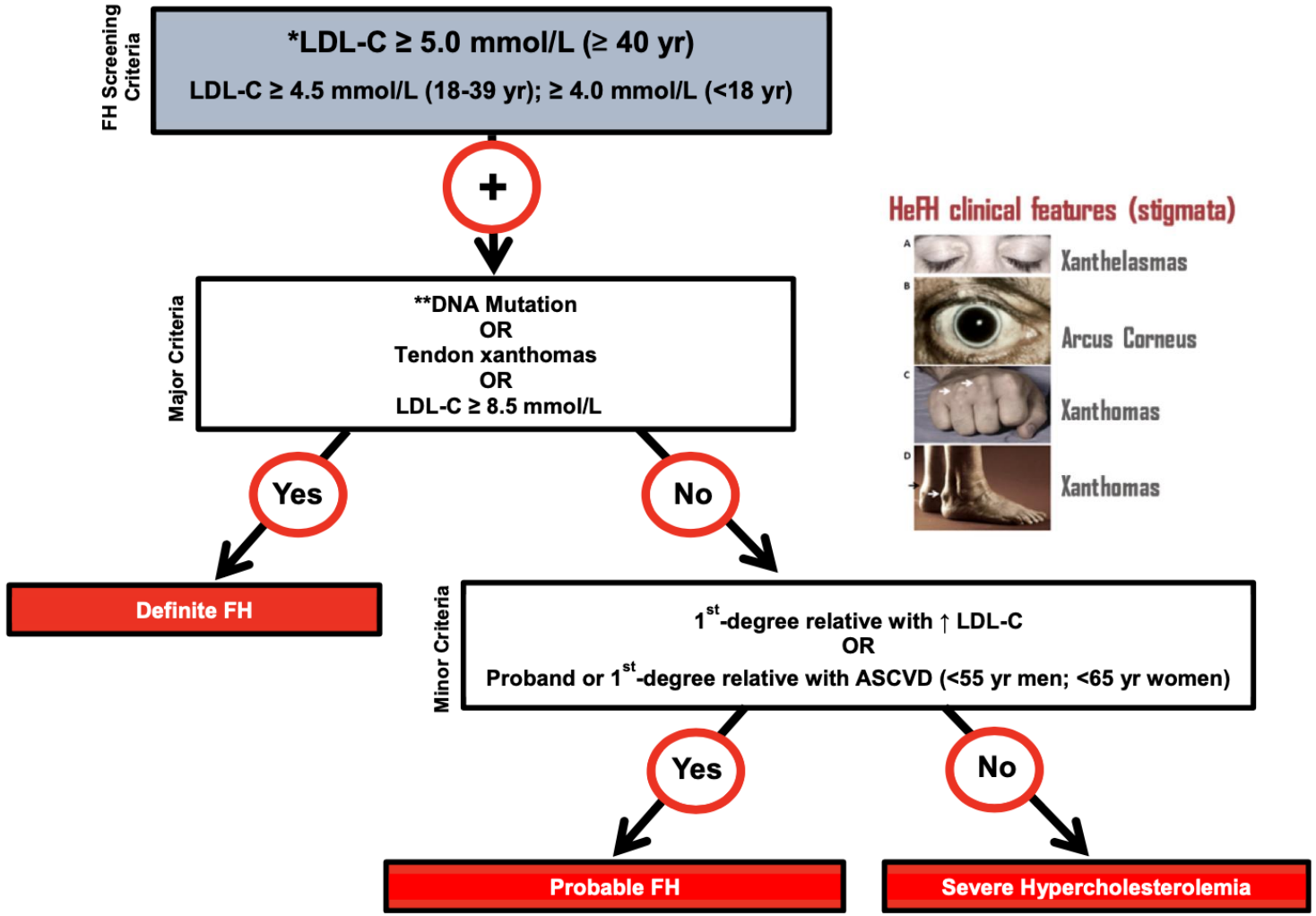
Anderson T et al. Can J Cardiology 2016;32:1263-1282.

Heterozygous Familial Hypercholesterolemia (HeFH)
A Clinically Recognizable Genetic Disorder

- Heritable, **autosomal co-dominant** disorder
- HeFH is not a rare genetic disorder: **prevalence is at least 2x other inherited conditions yet it is frequently undiagnosed**
- Usually due to mutations in LDL receptor gene
  - > 1700 mutations
  - **LDL-R mutation 1/80-270 in Quebec, 1 in 250 – 500 in Rest of Canada**
  - **~ 1 in 220 globally**
  - Other mutations include those in the APOB and PCSK9 genes
- Decreased clearance of LDL-C particles from plasma
- Severe hypercholesterolemia and lifelong accumulation of plasma LDL-C leading to atherosclerosis
- If left untreated, men and women with HeFH typically develop **early CAD** before the age of 55 and 60 years respectively. Risk of CAD is estimated to be **increased a least 10-fold. However, early diagnosis and appropriate treatment can dramatically reduce the risk for CAD.**

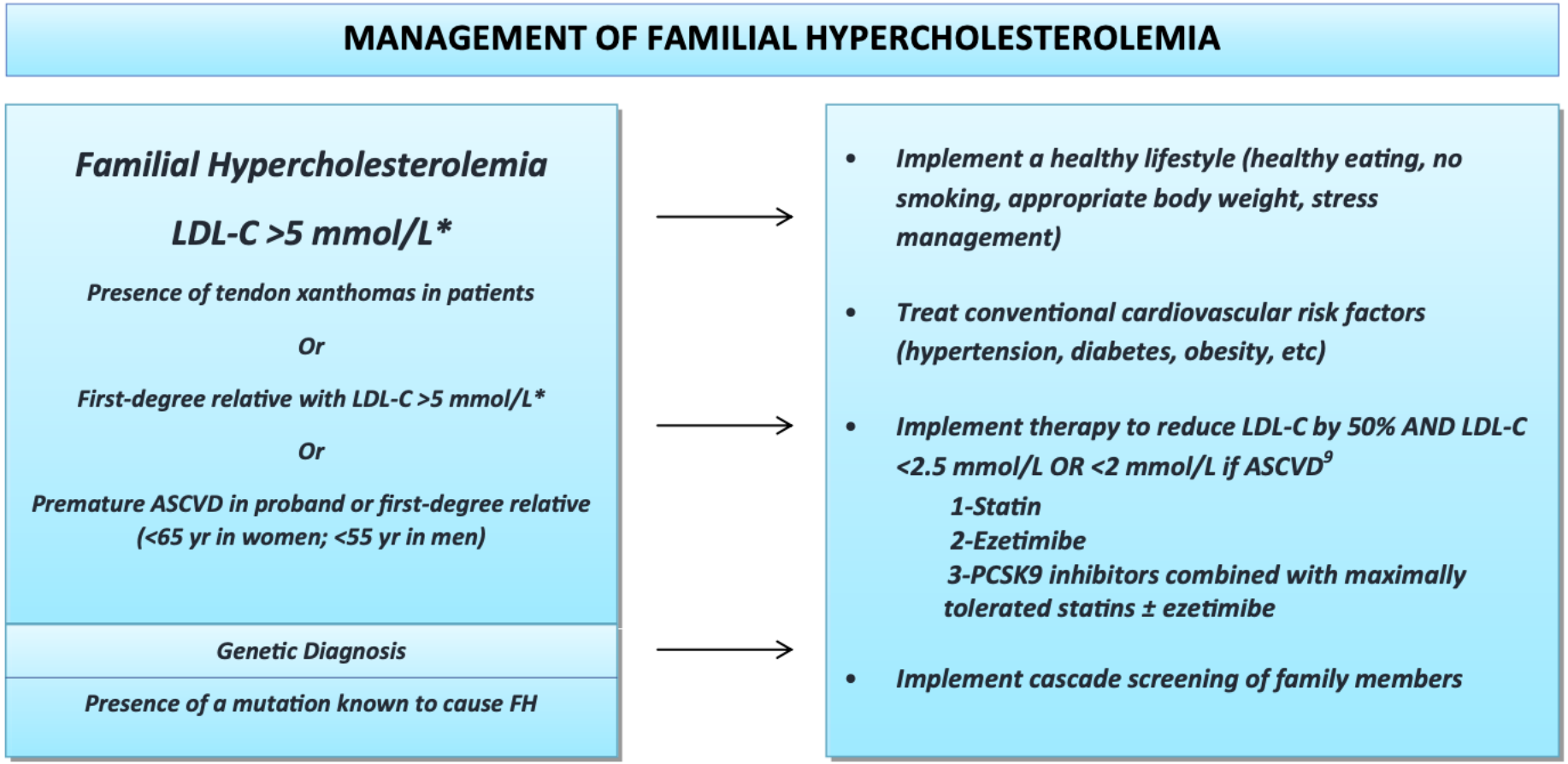
1. Marais AD. Clin Biochem Rev. 2004;25:45-68.
2. Maniey KW, et al. In: Kronenberg: Williams Textbook of Endocrinology. 2008
3. Rader DJ, et al. J Clin Invest. 2003;111:1795-1803.
4. Scandinavian Simvastatin Survival Study Group, 1995, Lancet
5. De Ferranti SD, et al. Circulation. 2016;133:1067-1072.
5. 2019 EASC/EAS Guidelines. European Heart Journal 2019.
6. Sturm AC et al. J Am Coll Cardiol. 2018;72:662-680.

Simplified Canadian Definition for Familial Hypercholesterolemia (CCS 2018)



Ruel I et al. Can J Cardiol. 2018;doi:10.1016/j.cjca.2018.05.015.

Summary of Diagnostic and Treatment Flow when FH is Suspected: CCS 2018 Position Statement

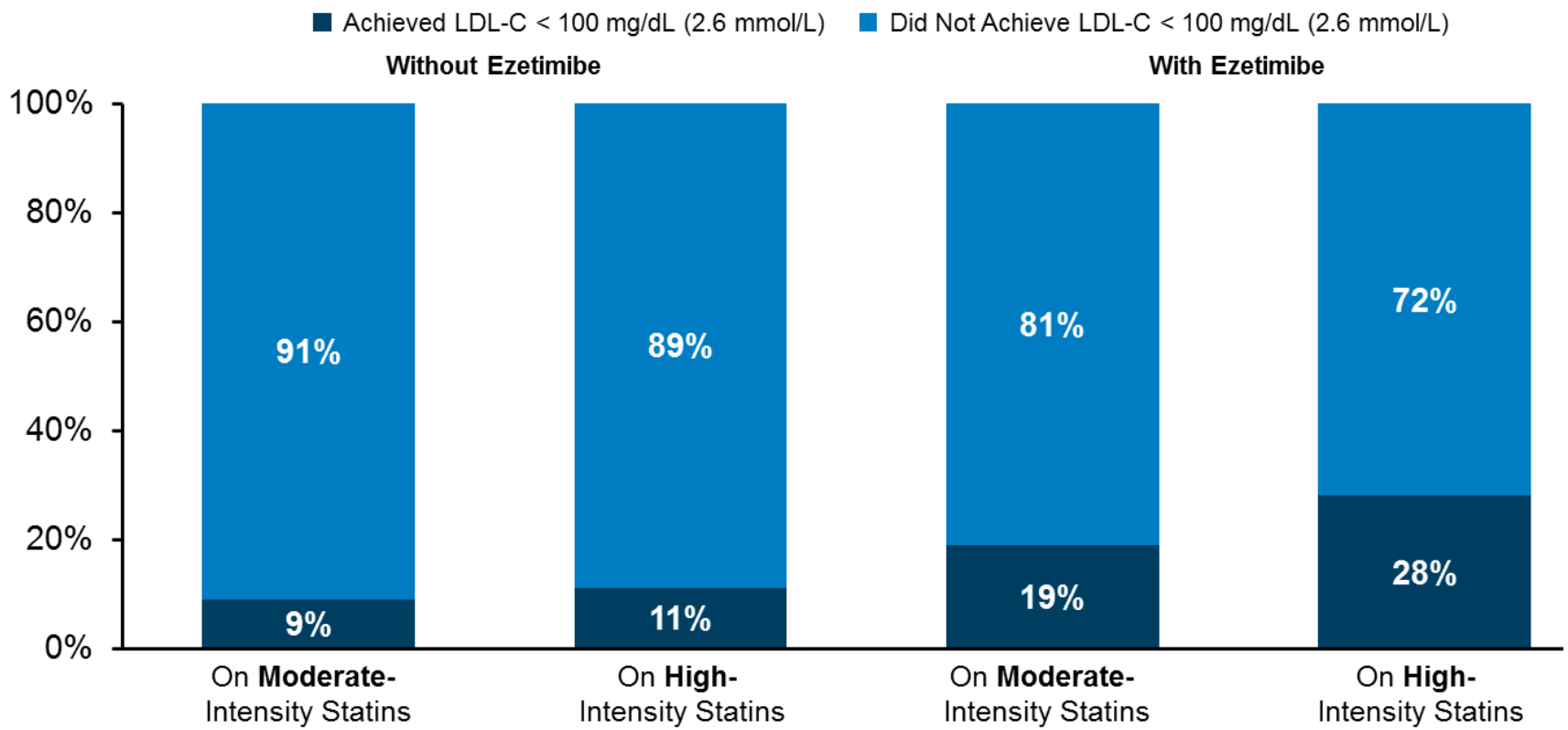


* LDL-C ≥ 4.0 mmol/L for age younger than 18 years; LDL-C ≥ 4.5 mmol/L for age 18 years to 39 years

Brunham L et al. Can J of Cardiology 2018; 34:1553-1563.

Up to 90% of FH patients Do Not Achieve LDL-C Target Despite Moderate- or High-intensity Statin Therapy, and Up to 80% Do Not Achieve Target Despite the Addition of Ezetimibe

% of Patients Achieving LDL-C Target* Level < 100 mg/dL (< 2.6 mmol/L) on Moderate- or High-Intensity Statins With or Without Ezetimibe

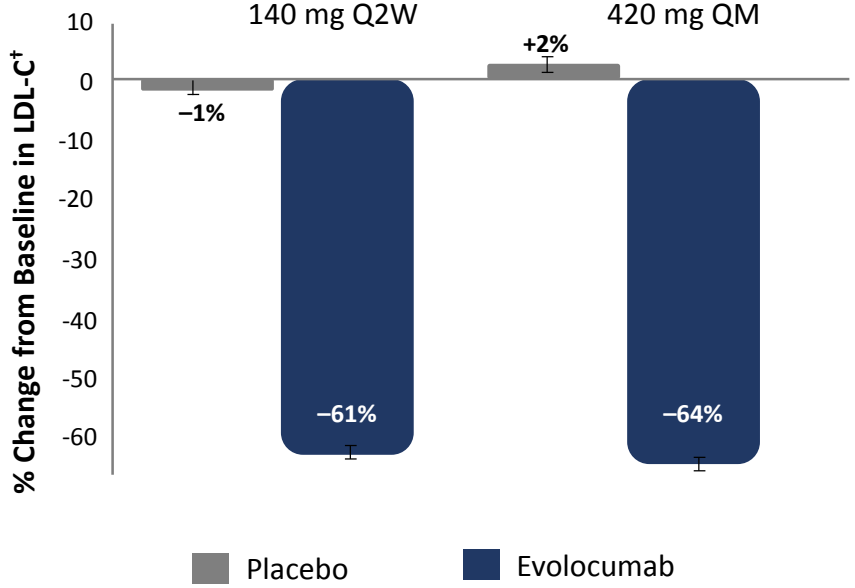


*Target LDL-C levels refer to those in the ESC/EAS guidelines; however, they should be adapted to local/regional guidelines in submissions.
The study included both primary prevention and secondary prevention patients with FH – for secondary prevention FH patients ESC guidelines state that LDL-C target should be < 70 mg/dL (< 1.8 mmol/L).
EAS = European Atherosclerosis Society; ESC = European Society of Cardiology; FH = familial hypercholesterolemia; LDL-C = low-density lipoprotein cholesterol.
Hartgers ML, et al. 2016. Poster presented at the 84th EAS Congress, May 29-June 1 2016, Innsbruck, Austria.

PCSK-9 Inhibitors in Heterozygous FH: Significant LDL-C Lowering as Add-on to Statins

Evolocumab

RUTHERFORD-2

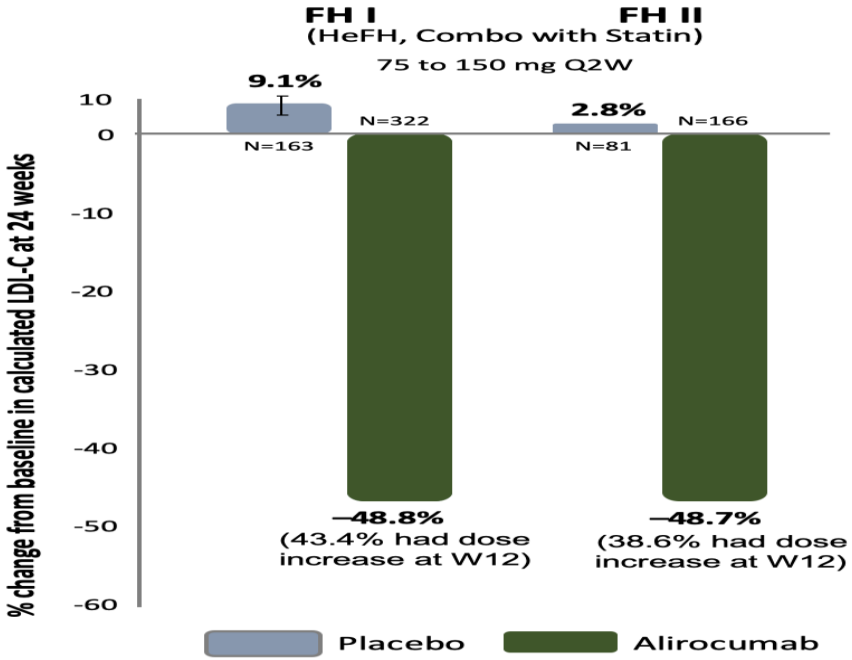


HeFH Study (N = 331)

- HeFH patients unable to achieve an LDL-C < 2.6 mmol/L despite statin therapy with or without ezetimibe

- ~ 60% LDL-C lowering in this difficult patient group

Alirocumab



ODYSSEY FH (n = 732)

- HeFH patients with LDDL-C ≥ 1.8 mmol/L with a history of documented CVD or HeFH patients with LDL-C ≥ 2.6 mmol/L with no CVD history
- Combination with statin: Atorva, Rosuva or Simva stable dose

- ~ 50% LDL-C lowering in this difficult patient group

† Reflexive LDL-C measurements; Co-primary Endpoints: Mean % change from baseline in LDL-C at week 10/12

HeFH: Heterozygous Familial Hypercholesterolemia; FH: Familial Hypercholesterolemia

Adapted from Raal F, et al. Lancet. 2015;385(9965):331-40 (RUTHERFORD-2). Kastelein JJP et al. *Eur Heart J.* 2015; **36**: 2996-3003 (ODYSSEY FHI and FHII)

Key recommendations for the treatment of patients with heterozygous FH: 2019 ESC/EAS Guidelines

- Treat FH patients with **ASCVD as very-high-risk**, and treat to achieve at least a **50% reduction** from baseline and an **LDL-C < 1.4 mmol/L** is recommended
- In **primary prevention**, treat those who have **another major risk factor** as **very-high-risk**, and an LDL-C reduction of at least **50% from baseline** and an **LDL-C goal of <1.4 mmol/L** should be considered
- In **primary prevention without another major risk factor**, treat as **high-risk**, and LDL-C goals are a **≥ 50% reduction** from baseline and an **LDL-C < 1.8 mmol/L**
- Treatment with a **PCSK-9 inhibitor** is recommended in **very-high-risk** FH patients if the treatment goal is not achieved on **maximal tolerated statin plus ezetimibe**

2019 EASC/EAS Guidelines. European Heart Journal 2019.


THANK
YOU