Integrating icosapent ethyl in preventive strategies: Practical guidance

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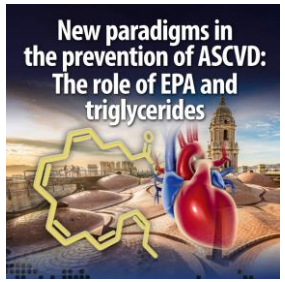
New paradigms in the prevention of ASCVD: The role of EPA and triglycerides

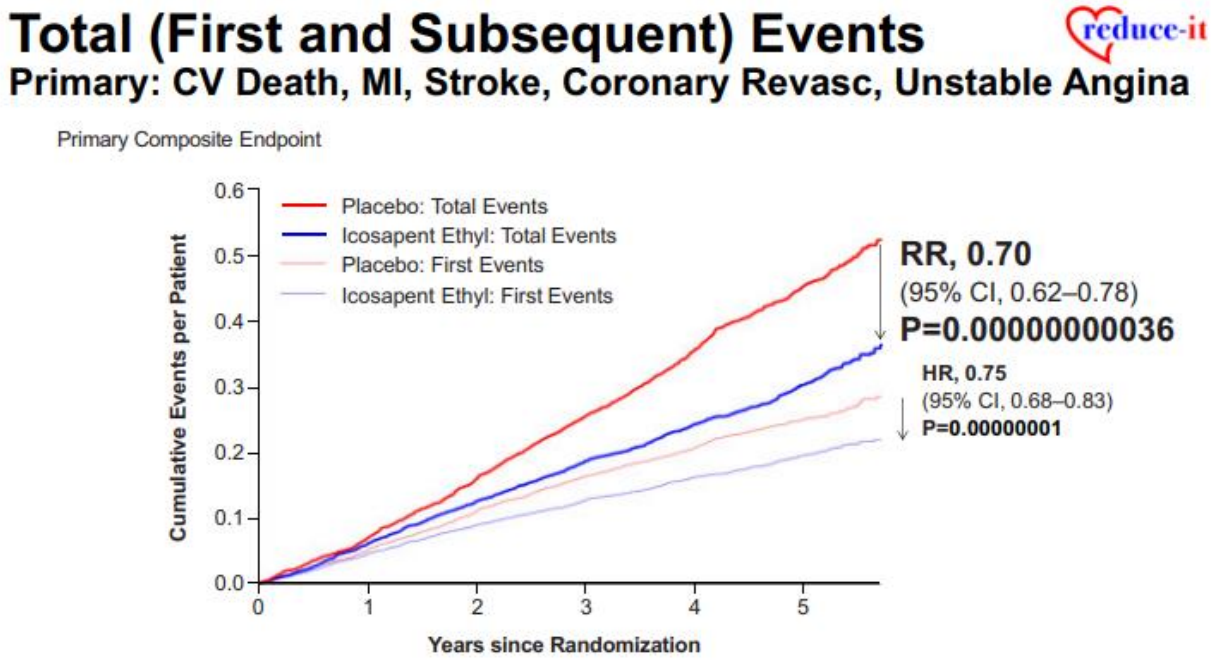


PHYSICIANS' ACADEMY FOR
PACE-CME
CARDIOVASCULAR EDUCATION

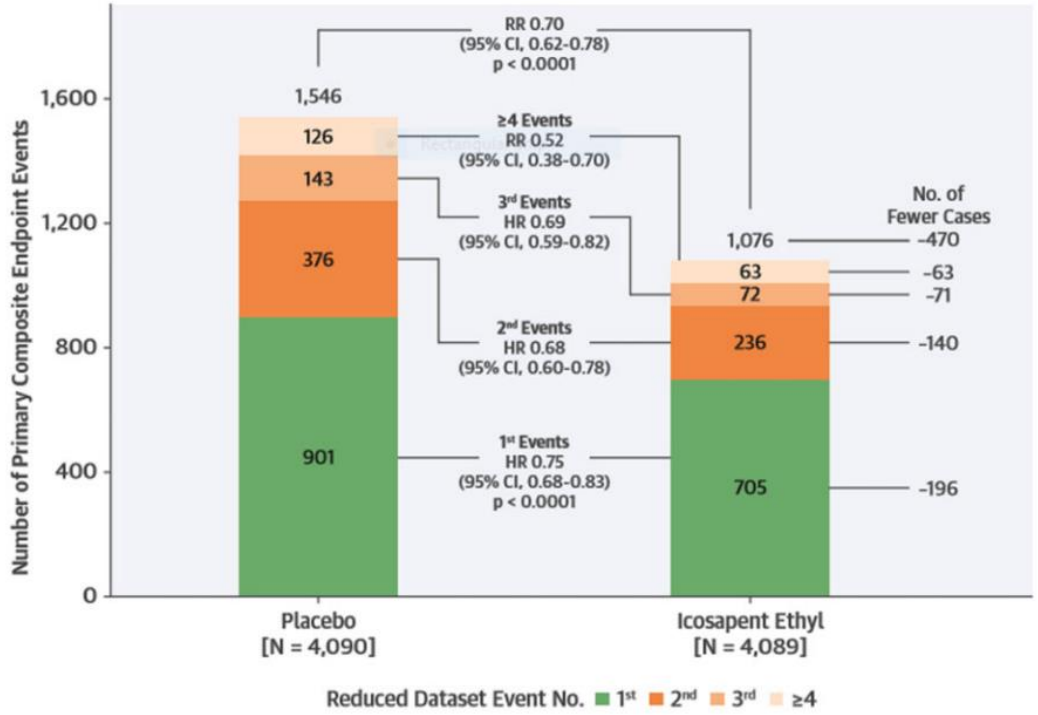
Introduction

- The **REDUCE-IT** demonstrated the efficacy of *icosapent ethyl* to reduce CV events in patients with elevated triglycerides in two major situations:
    - In primary care in patients with diabetes + one other CV risk factor
    - In secondary prevention

Bhatt et al, JACC 2019



Bhatt DL, Steg PG, Miller M, et al. *J Am Coll Cardiol*. 2019;73:2791-2802.



e 5 Distribution of first and subsequent primary composite endpoint events in the reduced dataset for patients randomized 1:1 to icosapent ethyl s placebo. Hazard rations and 95% confidence intervals for between treatment group comparisons were generated using Li-Lagakos modified Wei- Weissfeld method for the first, second, and third event categories. Rage ratio and 95% confidence interval for between group comparisons used a neg- binomial model for additional events beyond first, second, and third occurrences, i.e. fourth event or more and overall treatment comparison. ses are based on reduced dataset accounting for statistical handling of multiple endpoints occurring in a single calendar day by counting as a single t. See Central Illustration, ref.[64] with permission. CI, confidence interval; HR, hazard ration; RR, rage ratio.

Introduction

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    - In primary care in patients with diabetes + one other CV risk factor
    - In secondary prevention

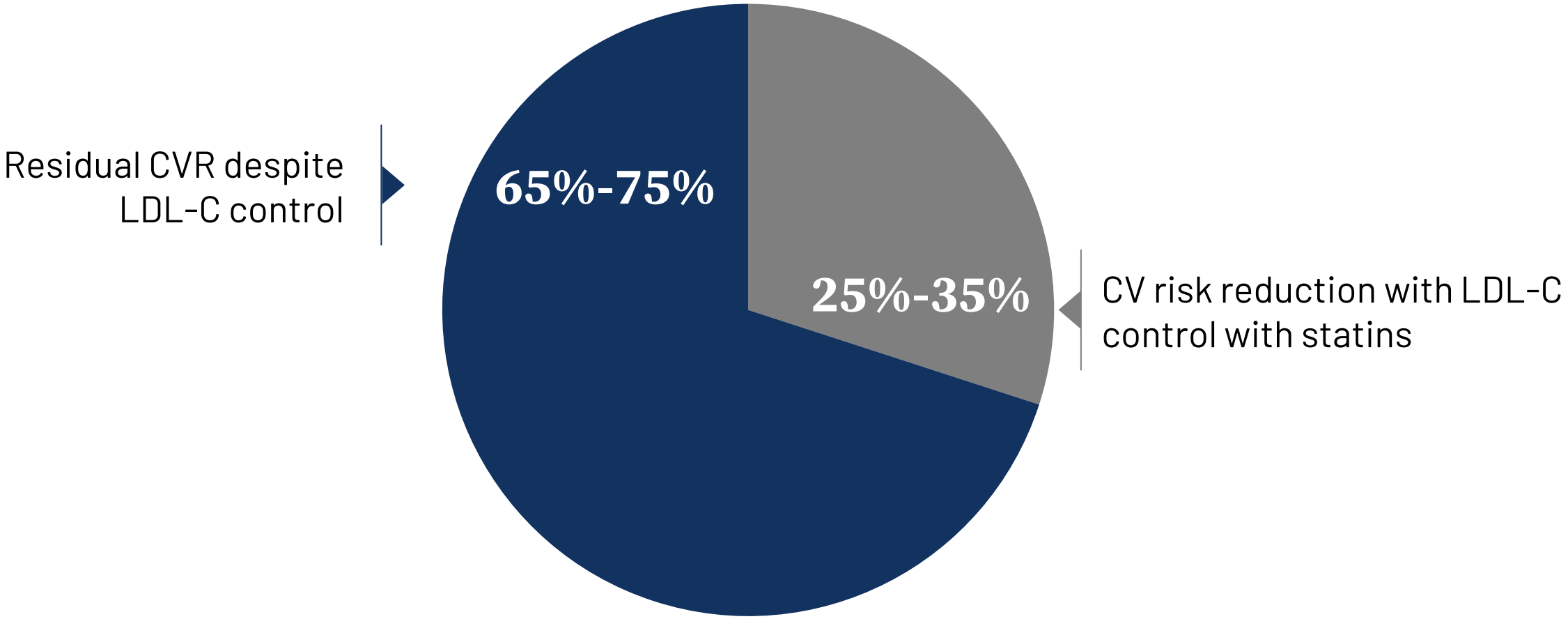
➢ **How to implement these major findings into clinical practice ?**

√ *What is the need?*
√ *What do the Drug Agencies say?*
√ *What do the guidelines say?*
√ *To whom should we propose in the real life setting?*
√ *What is the tolerance of the treatment?*
√ *Are there patients requiring special caution?*
√ *Does the treatment have a favorable cost/benefit ratio?*

What is the need?

The concept of residual risk

The residual risk under standard medical therapy

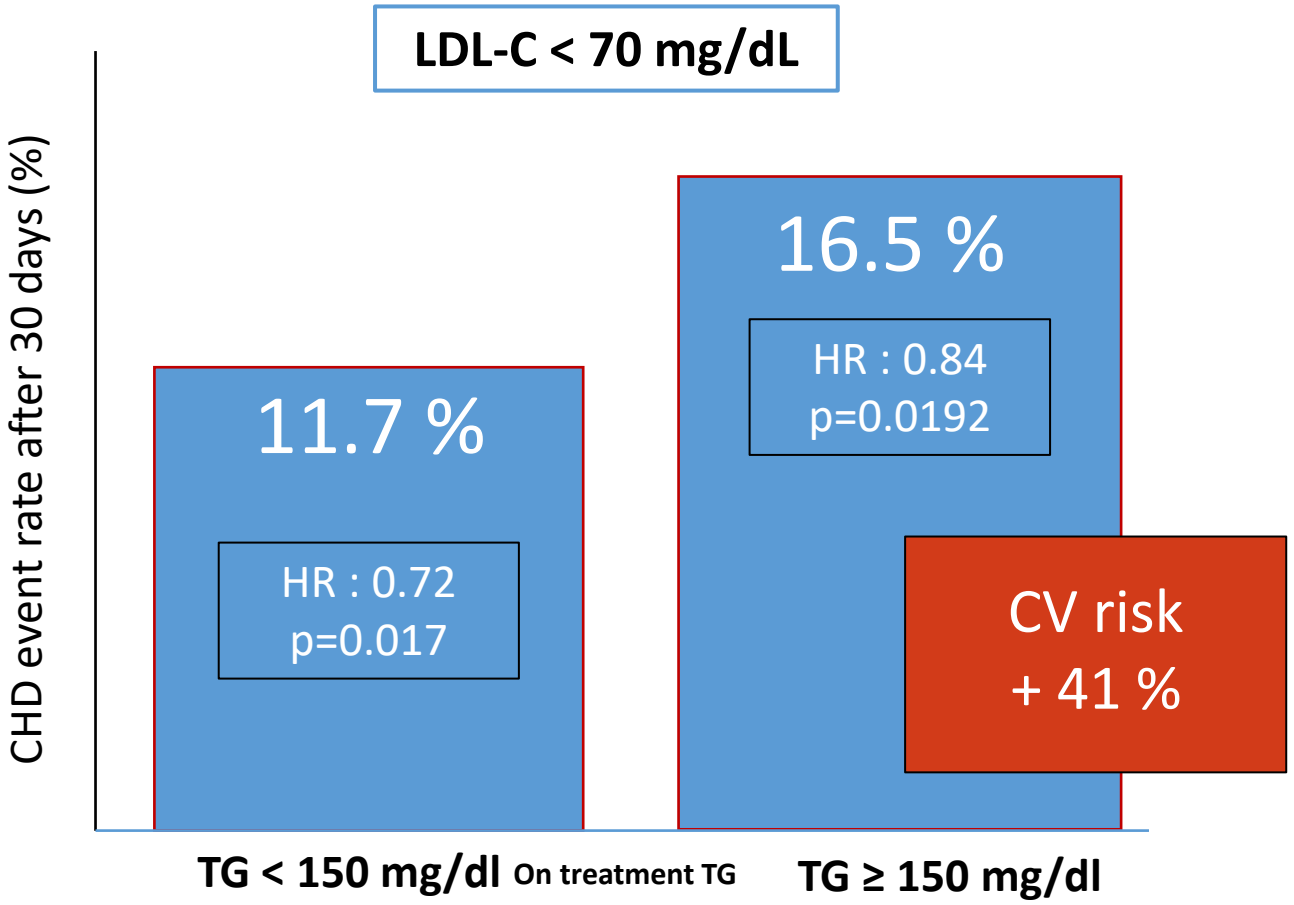


CV: cardiovascular; CVR: cardiovascular risk; LDL-C: low density lipoprotein-cholesterol.

Hong KN, et al. *J Am Coll Cardiol*. 2017;70(17):2171-2185; Collins R, et al. *Lancet*. 2016;388(10059):2532-2561; 3. Boekholdt SM, et al. *J Am Coll Cardiol*. 2014;64(5):485-494; Ganda OP, et al. J Am Coll Cardiol. 2018;72(3):330–343.

The residual risk according to the TG levels

- PROVE-IT TIMI22 : Despite adequate LDL-c control, the risk is increased in HTG



PROVE-IT TIMI 22

For each reduction of 10 mg/dl of TG levels :

The incidence of death and MI is reduced by 1.6% ($p < 0.001$)

A lower risk of CAD is observed when TG < 150 mg/dl and LDL-C < 70 mg/dl

(HR 0.72, 95% CI 0.54 to 0.94; p = 0.017)

PROVE-IT TIMI 22 : 4,162 patients hospitalized for ACS and randomized to atorva 80 mg or prava 40 mg daily.
LDL-C < 0,70 g/L was associated with greater CHD event reduction than LDL-C <1 g/L after ACS.
Impact of on-treatment TG on CHD risk after an ACS ?

Miller M et all. J Am coll Cardiol 2008; 51(7):724-30

The residual risk according to the TG levels

- The residual risk related to TG levels in real life

In a large database in Canada, almost 25% of patients in secondary prevention had high levels of TG (135 to 499 mg/dl) despite controlled LDL-c levels.

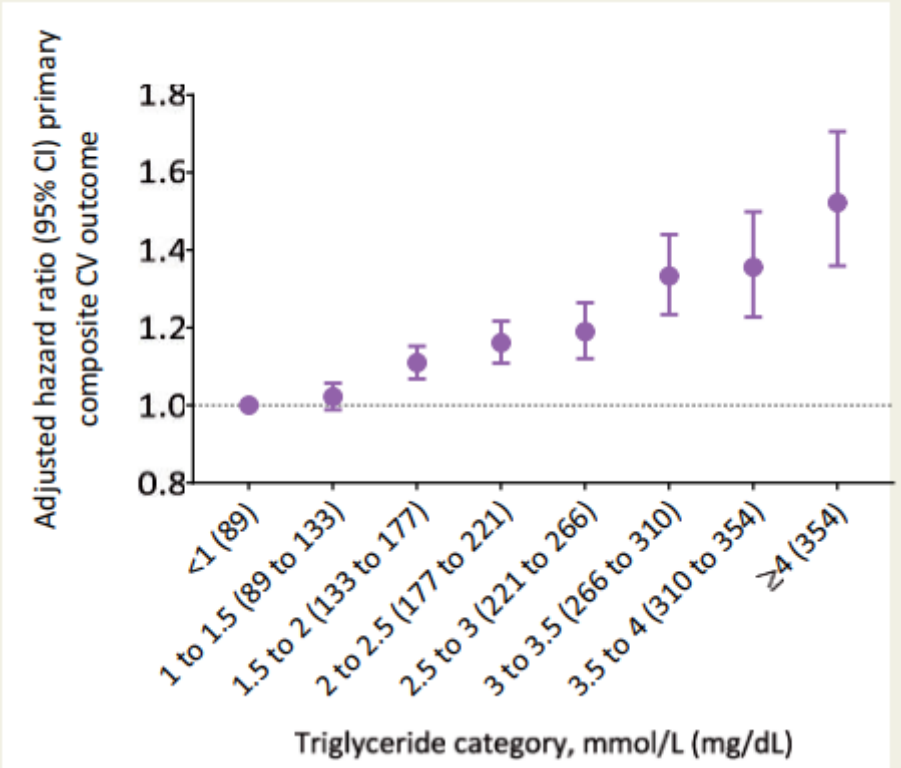


Figure 2 Adjusted hazard ratios (95% confidence intervals) for the composite outcome (cardiovascular death, myocardial infarction, unstable angina, arterial revascularization, or ischaemic stroke) by varying levels of triglyceride among 196 717 individuals with atherosclerotic cardiovascular disease. Models were adjusted for age, sex, income, low-density lipoprotein cholesterol, baseline diabetes, and baseline hypertension. CI, confidence interval; HR, hazard ratio.

Lawler PR, et al. *Eur Heart J* 2020; 41: 86-94.

What do the Drug Agencies say ?

EMA

Indications of icosapent ethyl

Reduction of CV events in adult patients with :

- High CV risk (established CV disease, or diabetes + 1 additional risk factor)
- Treated under statins
- And TG ≥ 150 mg/dL

What do the Guidelines say ?

ESC & EAS

Drug therapy to reduce the residual risk under statins

ESC/EAS 2019 Recommendations for drug treatment of patients with hypertriglyceridemia

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

- High risk
- On statin
- TG 1,35-4,99 g/L

- Prim. Prevention
- High risk
- On statin
- At LDL-C goal
- TG > 2 g/L

ESC 2021 Guidelines on CVD prevention in clinical practice

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice for reducing CVD risk in high-risk individuals with hypertriglyceridaemia [triglycerides >2.3 mmol/L (200 mg/dL)].[533]	I	A
In patients taking statins who are at LDL-C goal with triglycerides >2.3 mmol/L (200 mg/dL), fenofibrate or bezafibrate may be considered.[534–536]	IIb	B
In high-risk (or above) patients with triglycerides >1.5 mmol/L (135 mg/dL) despite statin treatment and lifestyle measures, n-3 PUFAs (icosapent ethyl 2 × 2 g/day) may be considered in combination with a statin.[84]	IIb	B

CVD = cardiovascular disease; LDL-C = low-density lipoprotein cholesterol; PUFA = polyunsaturated fatty acid.
aClass of recommendation.
bLevel of evidence.

"REDUCE-IT is the only study that tested a high icosapent ethyl dose "

Clinical trials with EPA+DHA vs. EPA

Omega-3 Content	Trial Name	Sample Size	Study Population	MACE Endpoint Definition	RRR	NNT	CV Death RRR	All-Cause Death RRR
Purified EPA 4 g/day	REDUCE-IT®[1]	N=8,179	Patients with established ASCVD (aged ≥45) or type 2 DM and ≥1 CV risk factor (aged ≥50)	Primary endpoint: Composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina	25%	21	20%	NS
Purified EPA 1.8 g/day	JELIS[2]	N=18,645	Hypercholesterolaemic patients with or without coronary artery disease	Primary endpoint: Composite of sudden cardiac death, fatal and non-fatal MI, unstable angina, angioplasty, stenting, or coronary artery bypass grafting	19%	143	NS	NS
EPA + DHA	RISK & PREVENTION[3]	N=12,513	Patients with CV risk factors, clinical evidence of ASCVD, or any condition putting them at high CV risk	Primary endpoint: Composite of all-cause death, non-fatal MI, or non-fatal stroke	NS	–	NS	N/A
EPA + DHA	ORIGIN[4]	N=12,611	Patients aged ≥50 with DM and history of MI, stroke or revascularisation	Secondary endpoint: Composite of CV death, non-fatal MI, or non-fatal stroke	NS	–	NS	NS
EPA + DHA	OMEGA[5]	N=3,851	Adults admitted to the hospital for acute MI	Primary endpoint: Sudden cardiac death	NS	–	N/A	NS
EPA + DHA	ASCEND[6]	N=15,480	Patients aged ≥40 with DM and no evidence of ASCVD	Primary endpoint: Composite of non-fatal MI, non-fatal stroke, TIA or CV death	NS	–	18%	NS
EPA + DHA	VITAL[7]	N=25,871	Men aged ≥50 and women aged ≥55	Primary endpoint: Composite of CV death, MI or stroke	NS	–	NS	NS
EPA + DHA	STRENGTH[8]	N=13,078	Adults at high risk for future CV events	Primary endpoint: Composite of CV death, non-fatal MI, non-fatal stroke, coronary revascularisation or unstable angina requiring hospitalisation	NS	–	NS	NS

ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; DHA, docosahexaenoic acid; DM, diabetes mellitus; EPA, eicosapentaenoic acid; MACE, major adverse cardiovascular event; MI, myocardial infarction; N/A, not available; NNT, number needed to treat; NS, not significant; OM3FA, omega-3 fatty acid; RRR, relative risk reduction; rx, prescription; TIA, transient ischaemic attack.

1. Bhatt DL, et al. *N Engl J Med* 2019;380:11-22. 2. Yokoyama M, et al. *Lancet* 2007;369:1090-8. 3. Risk and Prevention Study Collaborative Group. *N Engl J Med* 2013;368:1800-8.
4. ORIGIN Trial Investigators. *N Engl J Med* 2012;367:309-18. 5. OMEGA Study Group. *Circulation* 2010;122:2152-9. 6. ASCEND Study Collaborative Group. *N Engl J Med* 2018;379:1540-50.
7. Manson JE, et al. *N Engl J Med* 2019;380:23-32. 8. Nicholls SJ, et al. *JAMA* 2020;324:2268-80.

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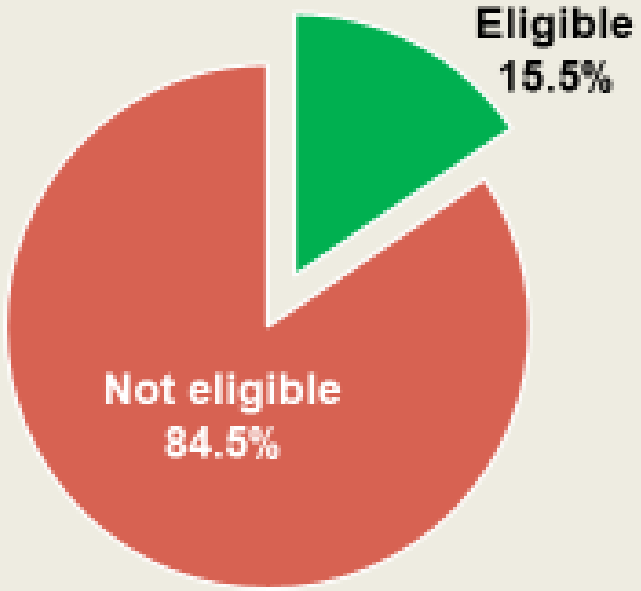
To whom should we propose in the real life setting ?

Clarify & FAST-MI

Generalizability of REDUCE-IT in broad populations

Stable CAD

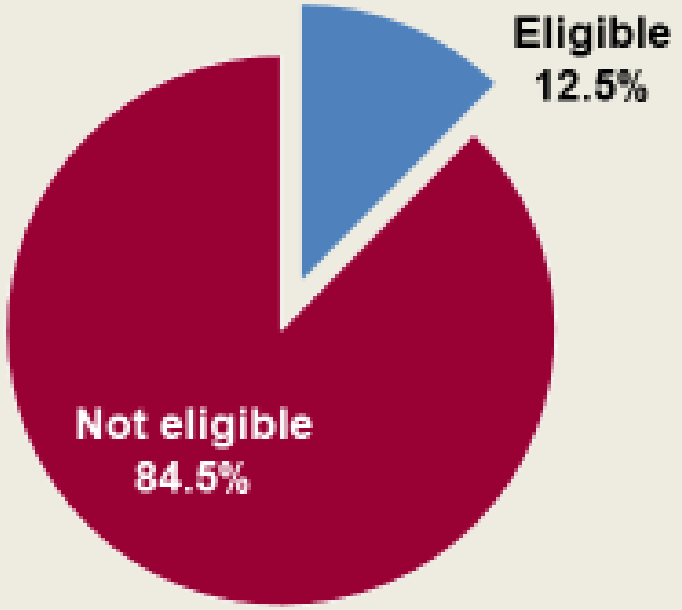
An analysis of 24,146 patients from the CLARIFY registry



Picard et al. *JACC* 2019

Post MI

An analysis of 3,789 patients from the FAST MI registry



Ferrières J et al; for the FAST-MI investigators. *Clin Cardiol.* 2020;43(11):1260–1265.

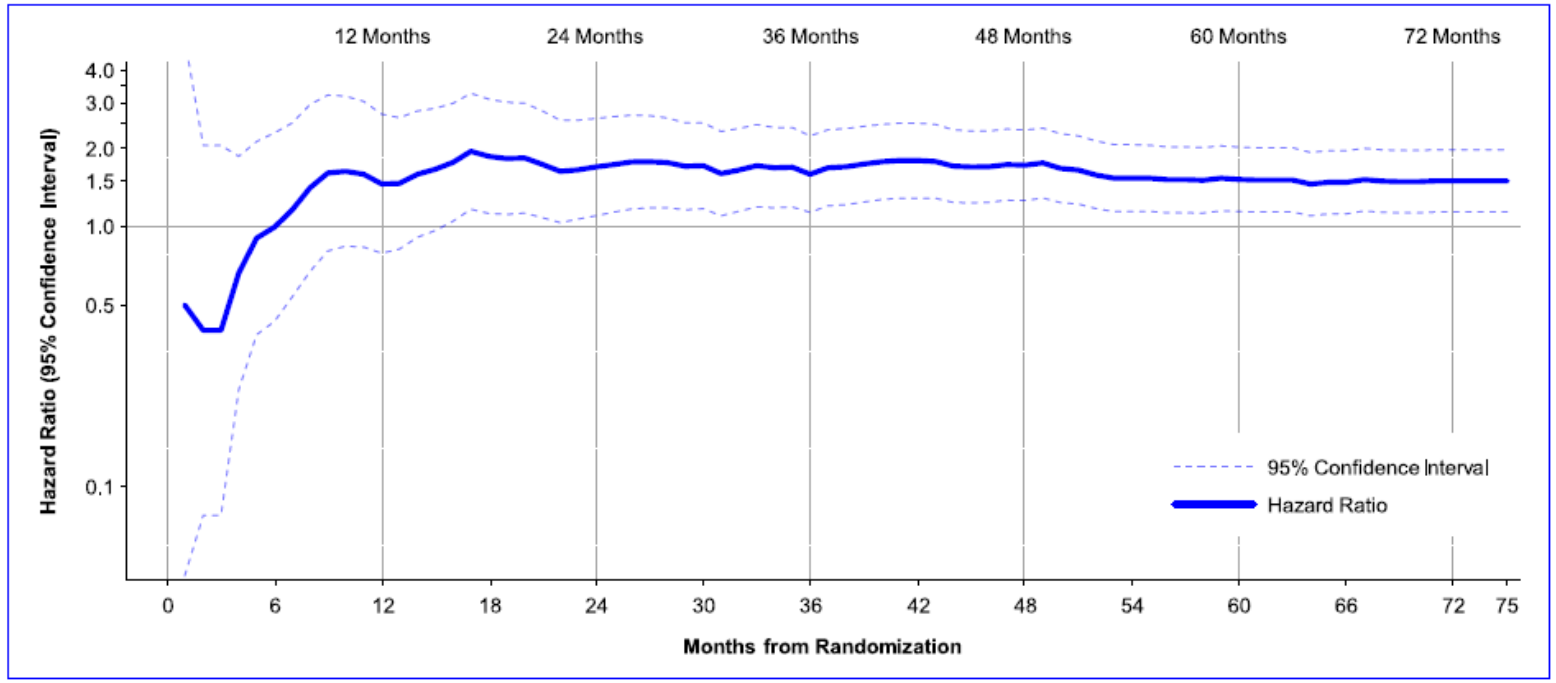
Is the treatment well tolerated ?

Reduce-IT

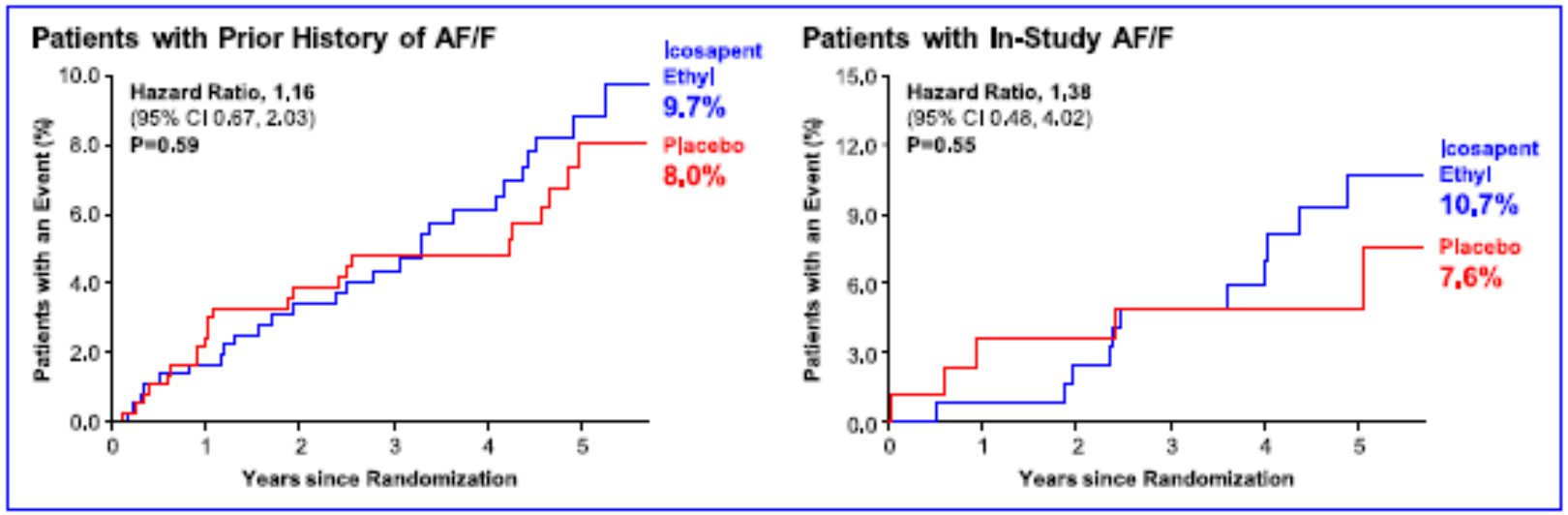
- Side effects >5% :

Preferred Term	Icosapent Ethyl (N=4089)	Placebo (N=4090)	P value [1]
Diarrhea	367 (9.0%)	453 (11.1%)	0.002
Back pain	335 (8.2%)	309 (7.6%)	0.29
Hypertension	320 (7.8%)	344 (8.4%)	0.35
Nasopharyngitis	314 (7.7%)	300 (7.3%)	0.56
Arthralgia	313 (7.7%)	310 (7.6%)	0.90
Upper respiratory tract infection	312 (7.6%)	320 (7.8%)	0.77
Bronchitis	306 (7.5%)	300 (7.3%)	0.80
Chest pain	273 (6.7%)	290 (7.1%)	0.48
Peripheral edema	267 (6.5%)	203 (5.0%)	0.002
Pneumonia	263 (6.4%)	277 (6.8%)	0.56
Influenza	263 (6.4%)	271 (6.6%)	0.75
Dyspnea	254 (6.2%)	240 (5.9%)	0.52
Urinary tract infection	253 (6.2%)	261 (6.4%)	0.75
Cough	241 (5.9%)	241 (5.9%)	1.00
Osteoarthritis	241 (5.9%)	218 (5.3%)	0.27
Dizziness	235 (5.7%)	246 (6.0%)	0.64
Pain in extremity	235 (5.7%)	241 (5.9%)	0.81
Cataract	233 (5.7%)	208 (5.1%)	0.22
Fatigue	228 (5.6%)	196 (4.8%)	0.11
Constipation	221 (5.4%)	149 (3.6%)	<0.001
Atrial fibrillation	215 (5.3%)	159 (3.9%)	0.003
Angina pectoris	200 (4.9%)	205 (5.0%)	0.84
Anemia	191 (4.7%)	236 (5.8%)	0.03

Landmark Analysis of In-Study AF/F Endpoint: *Significance reached by 16 months*



Serious Bleeding by Prior AF/F History or In-Study AF/F: *No significant difference*



Bleeding

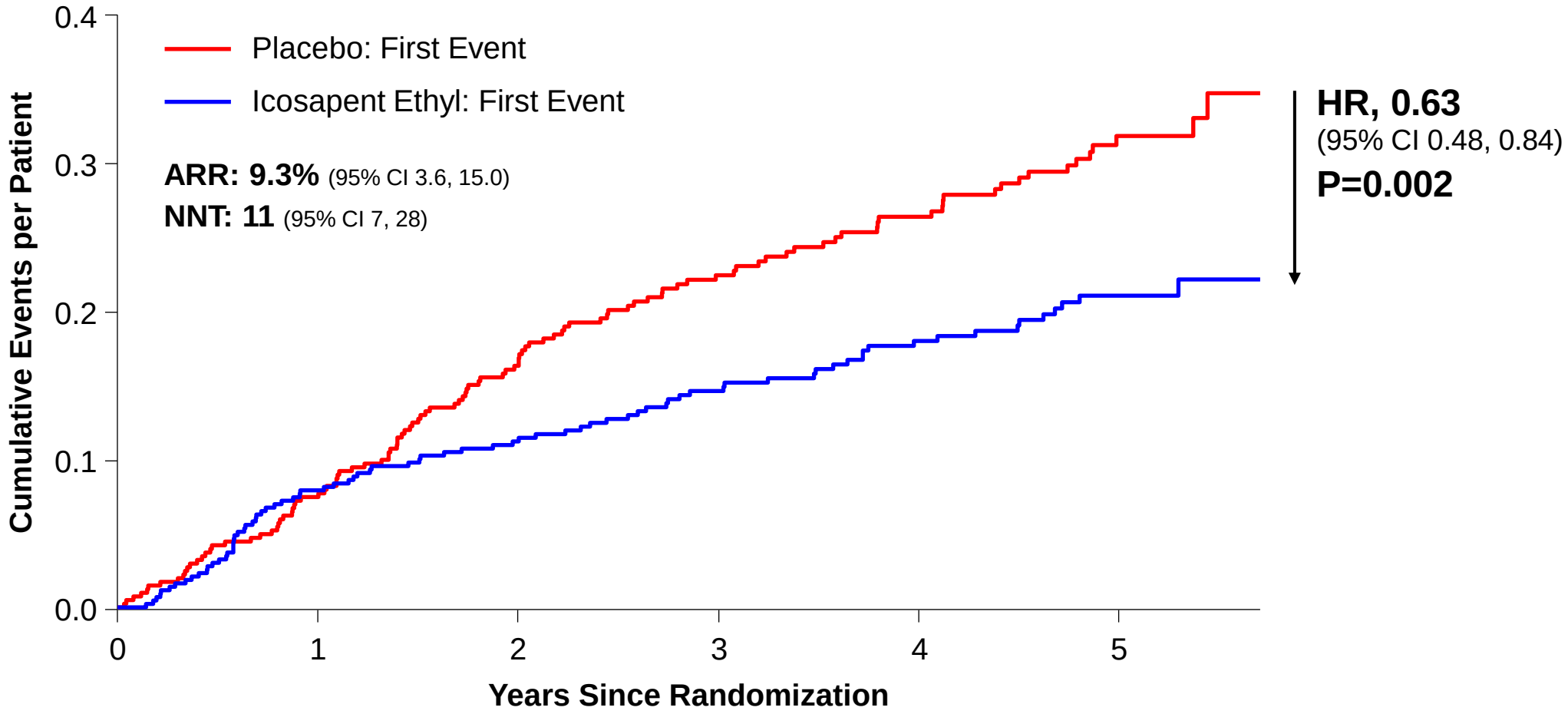
	Icosapent Ethyl (n = 4089)	Placebo (n = 4090)	*P* value
Bleeding related disorders	111 (2.7%)	85 (2.1%)	.06
Gastrointestinal bleeding	62 (1.5%)	47 (1.1%)	.15
Central nervous system bleeding	14 (0.3%)	10 (0.2%)	.42
Other bleeding	41 (1.0%)	30 (0.7%)	.19

- No fatal bleeding events in either group
- Adjudicated hemorrhagic stroke – no significant difference between treatments (13 icosapent ethyl vs 10 placebo; *P* = .55)

What about patients under DAPT ?


reduce-it
RECENT ACS

Time to First Event, Primary Composite Endpoint in Patients with Recent ACS <12 Months



No. at Risk:

Placebo	407	395	373	311	253	150
Icosapent Ethyl	433	425	402	338	284	142

Steg PG, Bhatt DL, Miller M, et al. ACC 2023.

Treatment Emergent Bleeding Adverse Events or Hemorrhagic Stroke Endpoints in Patients with Recent ACS <12 Months on Dual Anti-platelet Therapy at Baseline

	Icosapent Ethyl (N=287)	Placebo (N=297)	Overall (N=584)	Fisher's Exact P-value
	n (%)	*n (%)*	*n (%)*	
Subjects with Any Bleeding TEAE or Hemorrhagic Stroke				
All Bleeding TEAEs	22 (7.7)	28 (9.4)	50 (8.6)	0.46
Bleeding SAEs	5 (1.7)	11 (3.7)	16 (2.7)	0.20
Gastrointestinal Bleeding	2 (0.7)	7 (2.4)	9 (1.5)	0.18
Central Nervous System Bleeding	0 (0.0)	1 (0.3)	1 (0.2)	1.00
Other Bleeding	3 (1.0)	3 (1.0)	6 (1.0)	1.00
Hemorrhagic Stroke	0 (0.0)	0 (0.0)	0 (0.0)	

Note: Dual anti-platelet therapy is two or more anti-platelet therapies.

Note: A treatment emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. For each subject, multiple TEAEs of the same grouped term are counted only once within each grouped term. Events that were positively adjudicated as clinical endpoints are not included.

Bleeding-related TEAEs are identified by the standardized MedDRA queries of 'Gastrointestinal haemorrhage', 'Central Nervous System haemorrhages and cerebrovascular conditions' and 'Haemorrhage terms (excl laboratory terms)'.

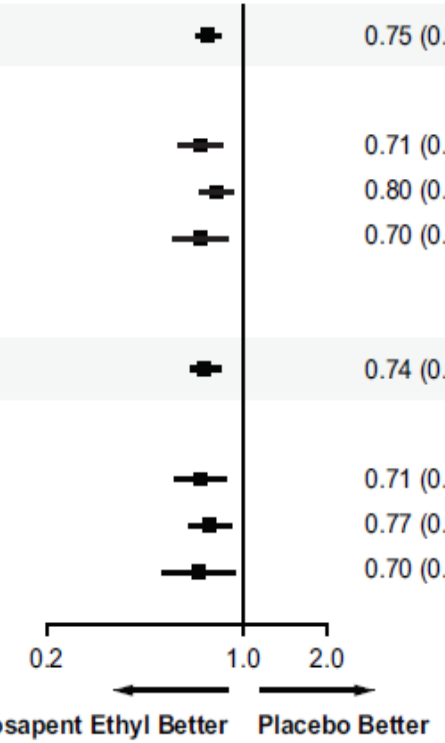
Note: Hemorrhagic stroke is an adjudicated endpoint.

Steg PG, Bhatt DL, Miller M, et al. ACC 2023.

Any subgroup requiring precautions ?

- **No adjustment proposed in :**
  - Elderly
  - Renal failure
  - Hepatic failure

End point/Subgroup	Icosapent Ethyl	Placebo	Icosapent Ethyl vs.Placebo	Interaction P-value
	n/N (%)	*n/N (%)*	*HR (95%CI)*	
Primary Composite End point				
Overall Population	705/4089 (17.2)	901/4090 (22.0)	0.75 (0.68, 0.83)	
Prespecified Baseline eGFR Group				0.41
<60 mL·min^{-1}·1.73 m^{-2}	197/905 (21.8)	263/911 (28.9)	0.71 (0.59, 0.85)	
60 to <90 mL·min^{-1}·1.73 m^{-2}	380/2217 (17.1)	468/2238 (20.9)	0.80 (0.70, 0.92)	
≥90 mL·min^{-1}·1.73 m^{-2}	128/963 (13.3)	170/939 (18.1)	0.70 (0.56, 0.89)	
Key Secondary Composite End point				
Overall Population	459/4089 (11.2)	606/4090 (14.8)	0.74 (0.65, 0.83)	
Prespecified Baseline eGFR Group				0.77
<60 mL·min^{-1}·1.73 m^{-2}	152/905 (16.8)	205/911 (22.5)	0.71 (0.57, 0.88)	
60 to <90 mL·min^{-1}·1.73 m^{-2}	229/2217 (10.3)	296/2238 (13.2)	0.77 (0.64, 0.91)	
≥90 mL·min^{-1}·1.73 m^{-2}	78/963 (8.1)	105/939 (11.2)	0.70 (0.52, 0.94)	



Majithia et al, *Circulation* 2021

Cost-effectiveness ?

Chapman et al,
Pharmacology & Therapeutics 2022

Cost-Effectiveness of IPE.

Study	Country	Type of Analysis	Time Horizon	IPE Price	Results
The Cost-Effectiveness of Icosapent Ethyl in Combination With Statin Therapy Compared With Statin Alone for Cardiovascular Risk Reduction (Ademi et al., 2021)		CUA and CEA (cost per QALY and cost per YoLS)	20 years	AU$ 1637 (AU$ 4.49/day)	ICER: AU $45,036 per QALY and AU $38,480 per YoLS; Primary prevention: AU$ 96,136 per QALY, AU $113,916 per YoLS; Secondary prevention: AU$ 35,935 per QALY, AU $29,250 per YoLS
Cost-Effectiveness of Icosapent Ethyl in REDUCE-IT (Weintraub et al., 2020)		CUA (cost per QALY)	Lifetime	US$ 4.16/day (WAC tested in sensitivity analysis)	The mean costs for IPE and placebo in trial were US$ 23,926 and US$ 24,563 and lifetime US$ 87,077 and US$ 88,912, respectively
Icosapent Ethyl for Primary Versus Secondary Prevention of Major Adverse Cardiovascular Events in Hypertriglyceridemia – Value for Money Analysis (Arbel et al., 2021)		NNT/CNT-based analysis corresponding to ICER's annual budget impact threshold to estimate number of preventable MACE	4.9	Cost of IPE estimated as 75% of the published US National Average Drug Acquisition Cost (US$ 2915 baseline annual cost)	US$ 819 million worth of IPE can avoid 20,069 MACE for secondary prevention and 4762 MACE for primary prevention
Scenario Analyses of Lifetime Cost-Effectiveness of Icosapent Ethyl in REDUCE-IT (Zhang et al., 2020)		CUA (cost per QALY)	Lifetime	US$ 4.16/day (WAC and Optum costs tested in sensitivity analysis)	IPE cost less than the standard of care both in-trial ($23,926 vs $24,563) and over the lifetime ($87,077 vs $88,912) and yielded more QALYs than the standard of care (3.34 vs 3.27 in-trial and 11.61 vs 11.35 lifetime)
The Effectiveness and Value of Rivaroxaban and Icosapent Ethyl as Additive Therapies for Cardiovascular Disease (Synnott et al., 2020)		CUA and CEA (cost per QALY, cost per LYG and evLYG) for IPE and rivaroxaban	Lifetime	Estimated annual net price: US$ 1625	ICER: US$ 18,000 per QALY for IPE vs medical management alone; US$ 17,000 per LYG and US$ 17,000 per evLYG
Cost-Effectiveness of Icosapent Ethyl (IPE) for the Reduction of the Risk of Ischemic Cardiovascular Events in Canada (Lachaine et al., 2020)		CUA (cost per QALY)	20 years	Unknown	ICER: CA$ 42,797 per QALY gained (SD: CA$ 15,884)

Icosapent ethyl in practice

- ✓ *The residual risk under statins remains substantial especially in those with high TG.*
- ✓ *Around 15% of patients in secondary prevention (estimation of 188,000 persons in France)*
- ✓ *Greenlight from the European Medicines Agency*
- ✓ *Recommended (IIa) by the ESC/EAC*
- ✓ *Well tolerated*
  - ➢ *Caution is patients at risk of AF*
  - ➢ *No increased risk of bleeding in elderly / renal or hepatic failure / post-ACS*
- ✓ *Cost-beneficial*