Tackling risk reduction in ASCVD: A clinical case

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Tackling risk reduction in ASCVD: Clinical Case

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Disclosures

- Relationships with commercial interests:
  - Grants/Research Support, Speakers Bureau, and/or Honoraria:
    - AstraZeneca, Amarin, Amgen, Esperion, HLS, Kowa, Merck, Novartis, Pfizer, Sanofi, The Medicines Company

Clinical History

Ex- Smoker
BMI 28.8kg/m^2
BP 138/98 mmHg
Hypertension X 15 years
STEMI 2 years ago
PCI with LAD stenting

Laboratory Values

TC 151 mg/dL (3.9 mmol/L)
LDL-C 77 mg/dL (2.0 mmol/L)
HDL-C 35 mg/dL (0.9 mmol/L)
TG 195 mg/dL (2.2 mmol/L)
Non-HDL-C 116 mg/dL (3.0 mmol/L)
eGFR 67 mL/min/1.73 m^2
HbA1C 6.0 %

Medical History

Atorvastatin 40 mg OD
ASA 81 mg OD
Valsartan 160 mg OD

Supplements

Fish oil capsules
(1x 300 mg TID)

Maria

68 Years Old
Retiree

High-risk individual with established CVD

VISIT #1

Clinical History

Ex- Smoker
BMI 28.8kg/m^2
BP 138/98 mmHg
Hypertension X 15 years
STEMI 2 years ago
PCI with LAD stenting

Laboratory Values

TC 151 mg/dL (3.9 mmol/L)
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eGFR 67 mL/min/1.73 m^2
HbA1C 6.0 %

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Is Maria at increased risk for future CV events?

- ◯ **Yes**
- ◯ **No**
- ◯ **Unsure**

Maria

68 Years Old
Retired Accountant

High-risk individual with established CVD

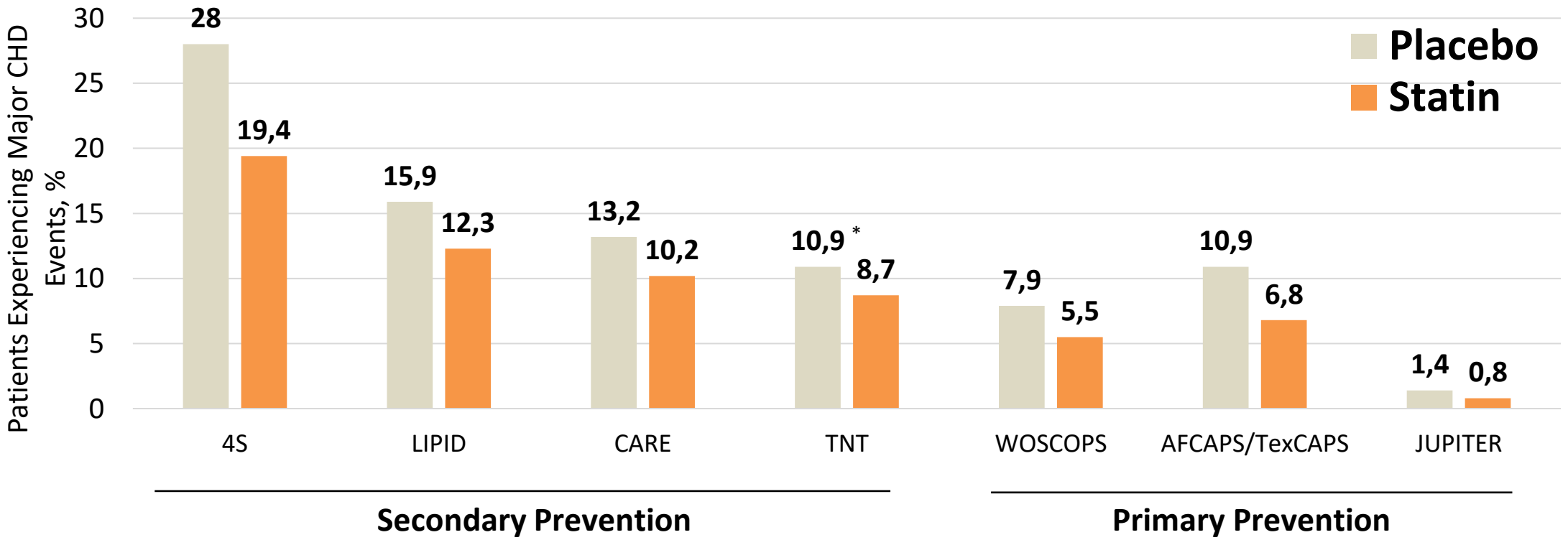
Maria has persistent CV risk despite LDL-C lowering with statin therapy

?

Which factor(s) are contributing to Maria's persistent CV risk?

- ◯ Established CVD
- ◯ Hypertension
- ◯ Diabetes/Pre-diabetes
- ◯ Obesity
- ◯ eGFR
- ◯ Smoking
- ◯ Unhealthy lifestyle habits
- ◯ LDL-C
- ◯ Low HDL-C
- ◯ Elevated non-HDL-C
- ◯ Elevated TG
- ◯ Other

CV Events Remains High Despite Use of LDL-Lowering Therapies



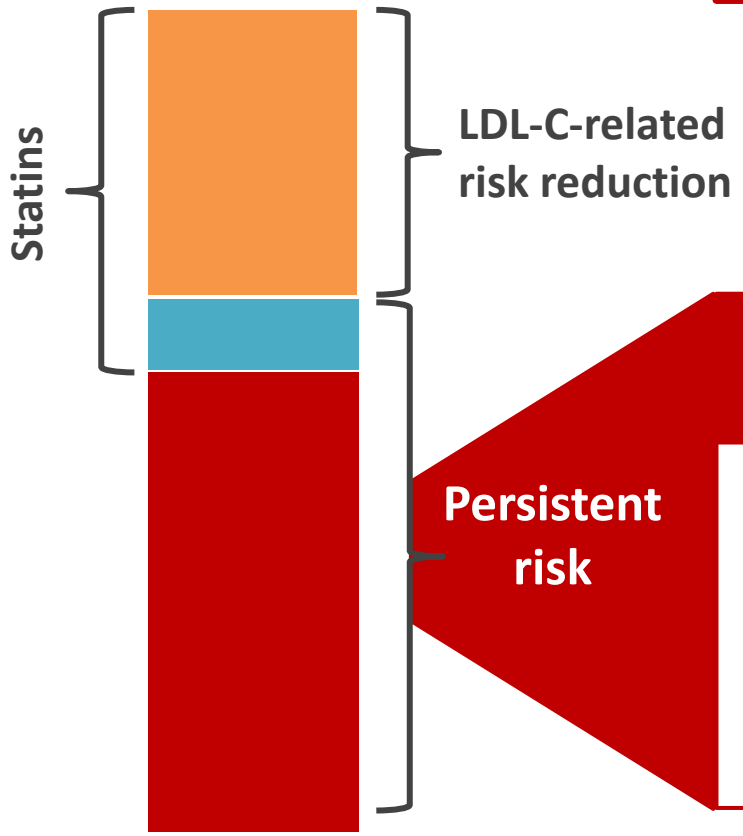
On treatment LDL-C							
(mg/dL)	117	112	97	93	140	115	55
(mmol/L)	3.02	2.90	2.51	2.40	3.62	2.97	1.42

*, 10 mg atorvastatin was compared to 80 mg atorvastatin in the TNT trial.

1. 4S Group. Lancet. 1994;344:1383-9. 2. LIPID Study Group. N Engl J Med. 1998;339:1349-57. 3. Sacks FM et al. N Engl J Med. 1996;335:1001-9. 4. Sabatine MS. N Engl J Med 2017; 376:1713-1722. 5. Shepherd J et al. N Engl J Med. 1995;333:1301-7. 6. Downs JR et al. JAMA. 1998;279:1615-22. 7. Ridker PM et al. N Engl J Med. 2008;359:2195-207.

CV Risk Persists Beyond LDL-C Treatment

CV risk persists in people who are on stable statin therapy



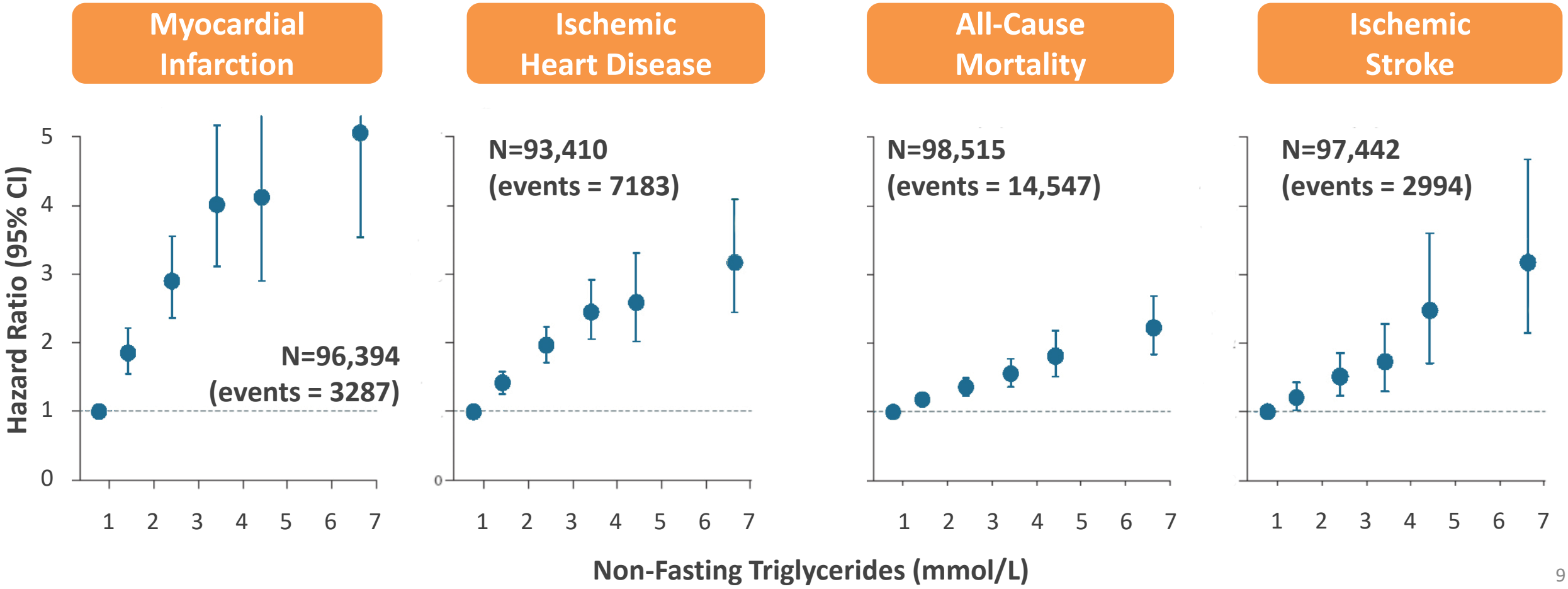
Many factors beyond LDL-C may play a role in the pathogenesis of CVD and contribute to CV risk

- **Triglycerides**
- Oxidation
- Diabetes mellitus
- Hypertension
- Lp(a)
- Thrombosis
- Endothelial dysfunction
- Inflammation
- Membrane instability/cholesterol crystals
- Plaque instability

Ference BA et al. JAMA. 2019;321(4):364-373. Ganda OP et al. J Am Coll Cardiol. 2018;72:330-343. Libby P. Eur Heart J. 2015;36:774-776.

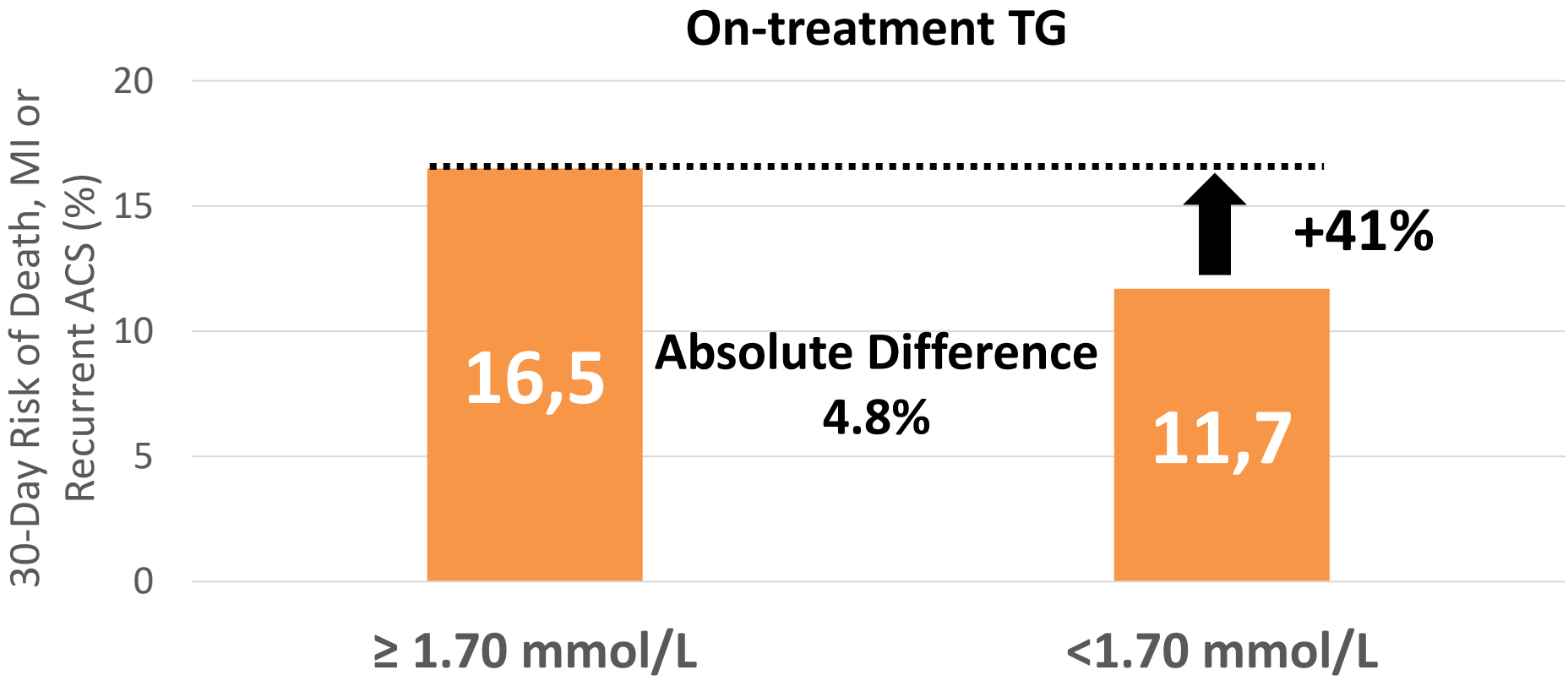
Elevated TGs Are Risk Markers of CV Risk and Mortality

Copenhagen City Heart Study and Copenhagen General Population Study



Nordestgaard BG, Varbo A. Lancet. 2014;384:626-635.

PROVE-IT TIMI-22: TG is an Independent CV Risk Marker and Predicts Coronary Events Risk Despite At LDL-C Goal With Statin Monotherapy



Despite achieving LDL-C <1.70 mmol/L with a high-dose statin, patients with TG ≥1.70 mmol/L have a 41% higher risk of coronary events

Miller M et al. J Am Coll Cardiol. 2008;51:724-30.

Impact of TG-Lowering Therapies on CV Risk in Statin-Treated Individuals

Fibrate

Niacin

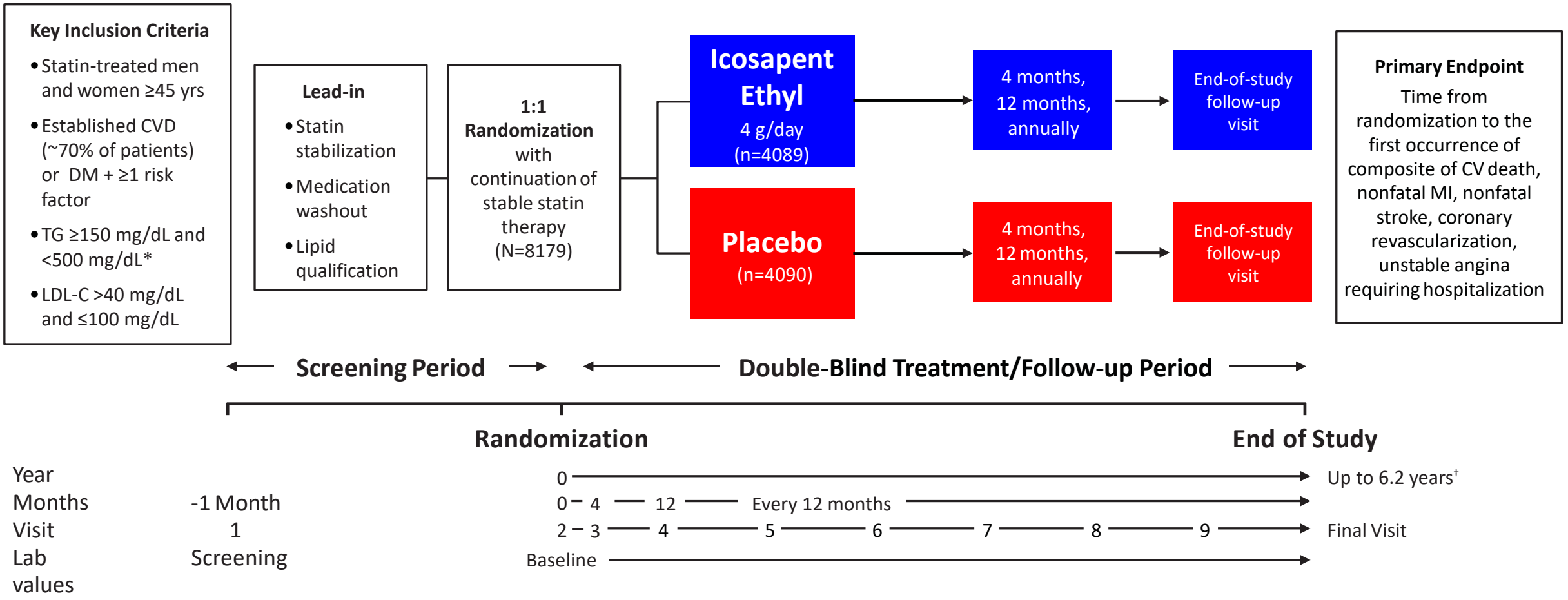
Omega-3 fatty acid mixtures (DHA + EPA)

Rx/supplement as common fish oil (including carboxylic acids) and krill oil

Primary MACE endpoint was not achieved in key CV outcome trials

1. Ganda OP et al. J Am Coll Cardiol. 2018;72:330-343. 2. Anderson TJ et al. Can J Cardiol. 2016; 32:1263-1282.

REDUCE-IT Design

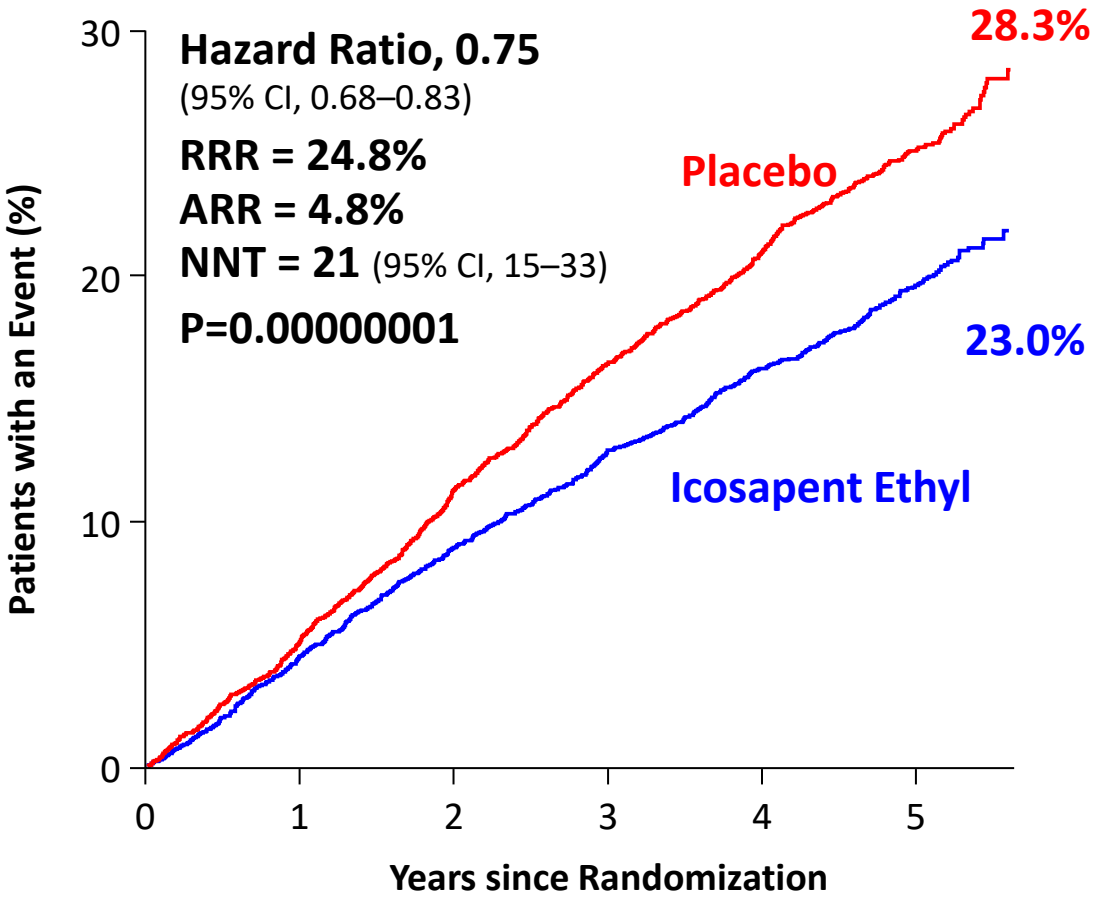


*, Due to the variability of triglycerides, a 10% allowance existed in the initial protocol, which permitted patients to be enrolled with qualifying triglycerides ≥135 mg/dL.
Protocol amendment 1 (May 2013) changed the lower limit of acceptable triglycerides from 150 mg/dL to 200 mg/dL, with no variability allowance.
†, Median trial follow-up duration was 4.9 years (minimum 0.0, maximum 6.2 years).
Bhatt DL et al. Clin Cardiol. 2017;40:138-148.

REDUCE-IT: Primary and Key Secondary Composite Endpoints

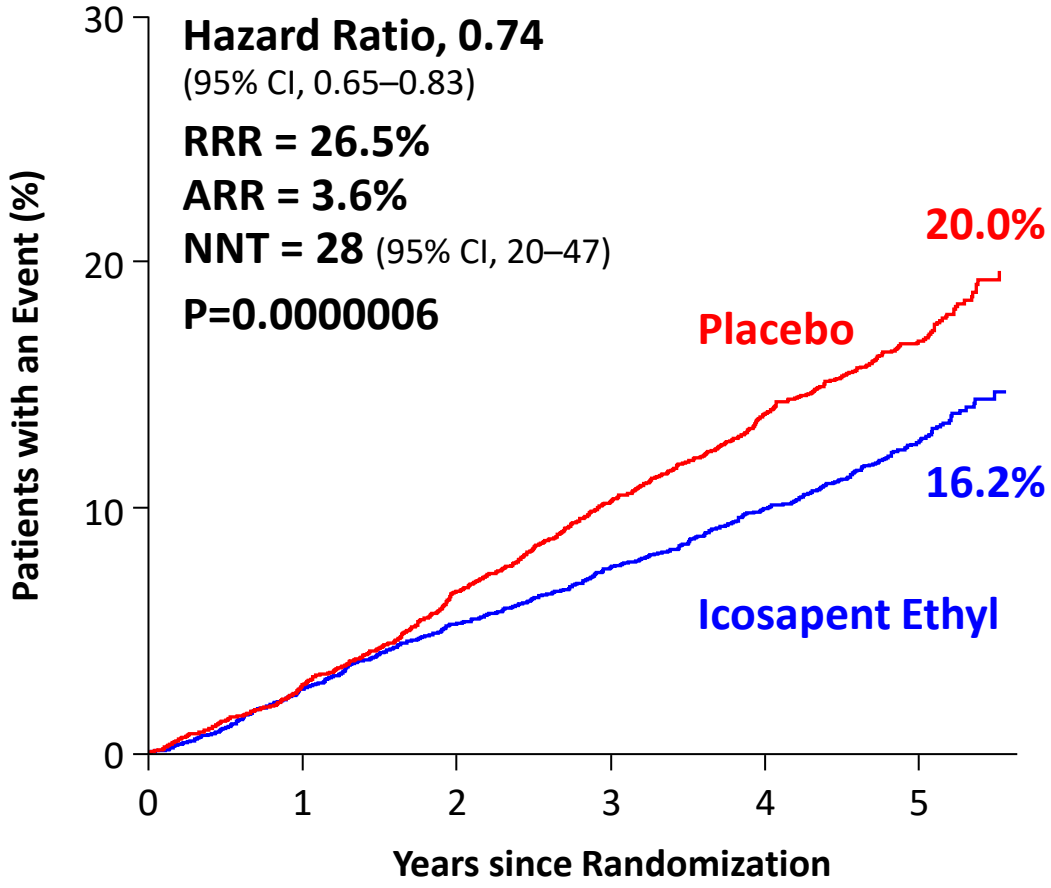
Primary Composite Endpoint:

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



Key Secondary Composite Endpoint:

CV Death, MI, Stroke



Bhatt DL et al. N Engl J Med. 2019; 380:11-22.

Maria’s TG level is 195 mg/dL (2.2 mmol/L)

?

Does Maria’s TG level fall within the TG range that confers CV risk?

- ◯ Yes
- ◯ No
- ◯ Unsure

Clinical History

Ex- Smoker
BMI 28.8kg/m^2
BP 138/98 mmHg
Hypertension X 15 years
STEMI 2 years ago
PCI with LAD stenting

Laboratory Values

TC 151 mg/dL (3.9 mmol/L)
LDL-C 77 mg/dL (2.0 mmol/L)
HDL-C 35 mg/dL (0.9 mmol/L)
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eGFR 67 mL/min/1.73 m^2
HbA1C 6.0 %

Medical History

Atorvastatin 40 mg OD
ASA 81 mg OD
Valsartan 160 mg OD

Supplements

Fish oil capsules
(1x 300 mg TID)

Maria

68 Years Old
Retiree

High-risk individual with established CVD

VISIT #1

Clinical History

Ex- Smoker
Lost 4 kg
BP 134/85 mmHg

Laboratory Values

TC 120 mg/dL (3.1 mmol/L) ↓
LDL-C 50 mg/dL (1.3 mmol/L) ↓
HDL-C 39 mg/dL (1.0 mmol/L) ↑
TG 168 mg/dL (1.9 mmol/L) ↓
Non-HDL-C 81 mg/dL (2.1 mmol/L) ↓
eGFR 67 mL/min/1.73 m^2 ~
HbA1C 5.8 % ↓

Medical History

Atorvastatin 80 mg OD
Ezetimibe 10 mg
ASA 81 mg OD
Valsartan 160 mg OD
Amlodipine 5 mg

Supplements

Fish oil capsules D/C'ed

Maria

68 Years Old
Retiree

High-risk individual with established CVD

VISIT #2

Maria’s current TG level is 168 mg/dL (1.9 mmol/L)

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Would you add IPE 2 g BID?

- ◯ Yes
- ◯ No
- ◯ Unsure

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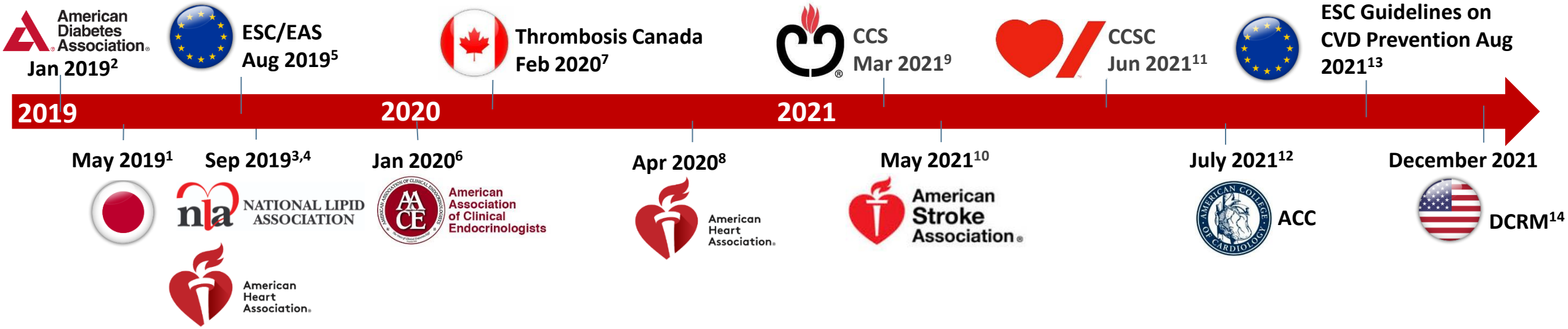
Expert Review of Cardiovascular Therapy

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ierk20

Icosapent ethyl for reduction of persistent cardiovascular risk: a critical review of major medical society guidelines and statements

Michael Miller, Lale Tokgozoglu, Klaus G. Parhofer, Yehuda Handelsman, Lawrence A. Leiter, Ulf Landmesser, Eliot A. Brinton & Alberico L. Catapano

Leading Global Medical Societies Recognize IPE as An Important CV Treatment Option



32 Global Medical Societies recognize IPE as an important treatment for ASCVD

4 Years of continuous and progressive recognition from multiple societies with supports from endocrinologists, cardiologists, and stroke neurologists.

1. American Diabetes Association. Diabetes Care. 2020;43(Suppl 1): S111-S134; 2. Kimura K, et al. Circ J. 2019;83(5):1085-1196; 3. Orringer CE, et al. J Clin Lipidol. 2019;13(6):860-872; 4. Skulas-Ray AC, et al. Circulation. 2019;140(12):e673-e691; 5. Mach F, et al. Eur Heart J. 2020;41(1):111-188; 6. Garber AJ, et al. Endocr Pract. 2020;26(1):107-139; 7. Thrombosis Canada. 2020; https://thrombosiscanada.ca/wp-content/uploads/2020/02/Stroke-Secondary-Prevention_26Feb2020.pdf; 8. Arnold SV, et al. Circulation. 2020;141:e000–e000. 9. Pearson GJ, et al. Can J Cardiol. 2021;37(8):1129-1150; 10. Kleindorfer DO, et al. Stroke. 2021;52(7):e364-e467; 11. Gladstone DJ, et al. Can J Neurol Sci. 2021:1-69; 12. Virani SS, et al. J Am Coll Cardiol. 2021;78(9):960-993; 13. Visseren FLJ, et al. Eur Heart J. 2021;42(34):3227-3337; 14. Handelsman y, et al. J Diabetes Complications. 2021; https://doi.org/

Clinical History

Ex- Smoker
BP 134/82 mmHg

Laboratory Values

TC 116 mg/dL (3.0 mmol/L) ↓
LDL-C 50 mg/dL (1.3 mmol/L) ~
HDL-C 43 mg/dL (1.1 mmol/L) ↑
TG 133 mg/dL (1.5 mmol/L) ↓
Non-HDL-C 73 mg/dL (1.9 mmol/L) ↓
eGFR 67 mL/min/1.73 m^2 ~
HbA1C 5.8 % ~

Medical History

Atorvastatin 80 mg OD
Ezetimibe 10 mg
ASA 81 mg OD
Valsartan 160 mg OD
Amlodipine 5 mg
IPE 2 g BID

Maria

68 Years Old
Retiree

High-risk individual with established CVD

VISIT #3

Shared Decision Making for CV Reduction

Risk Perception and Priorities

Understand patient's perception of risk and explore their preferences and priorities

Determine Recommendations

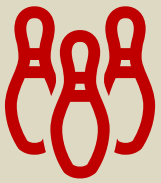
Consider patient's unique needs, situation and CV risk alongside trial data and guidelines

Shared Decision

Monitor adherence and response

Re-address approach and goals as necessary

Communicate Risks vs Benefits



Discuss available options, alternatives and avoid information overload

Adapted from Navar AM et al. Curr Opin Cardiol. 2016;31:537-544.

Summary

- Many individuals with even significantly reduced LDL-C levels are still at elevated CV risk
- Icosapent ethyl 4 g/day lowered CV events in statin-treated patients and offers a novel add-on lipid-lowering option in the appropriate population
- The REDUCE-IT results cannot be generalized to other fish oil preparations
- We must effectively share decision making with our patients in order to enhance uptake and persistence with evidence-based therapies