MHIF FEATURED STUDY:

ATTR CM

OPEN and ENROLLING:

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Transthyretin-Mediated Amyloid Cardiomyopathy	Mosi Bennett, MD	**Sarah Schwager** Sarah.Schwager@allina.com | 612-863-6257 **Jane Fox** Jane.Fox@allina.com | 612-863-6289	Ionis Pharmaceuticals

DESCRIPTION: A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion

- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

Exclusion

- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker

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Food As Medicine

Courtney Jordan Baechler, MD, MS
Medical Director
Emerging Science Centers

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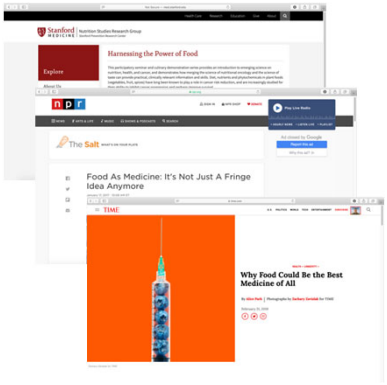
Disclosures…

2

Food as medicine (FAM) is old news

Ask any doctor how to avoid or mitigate the effects of the leading killers of Americans and you'll hear that eating healthier plays a big role.



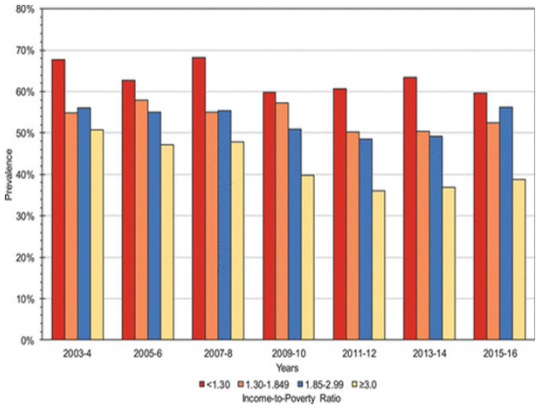
3

Creating a World without Heart and Vascular Disease…

- According to NHANES (National Health and Nutrition Examination Survey; 2015–2016), <10% adults met the guidelines for whole grains (≥3 servings per day), whole fruits (≥2 cups per day), and nonstarchy vegetables (≥2.5 cups per day).
- According to the AHA primary diet score, 47.8% of US adults had poor diet quality in 2015 to 2016. On the basis of the secondary score, 36.4% of US adults had poor diet quality in 2015 to 2016.
- In a large primary prevention trial among patients with CVD risk factors, patients randomized to unrestricted-calorie Mediterranean-style diets supplemented with extra-virgin olive oil or mixed nuts had a ≈30% reduction in the risk of stroke, myocardial infarction, and death attributable to cardiovascular causes, without changes in body weight.

Heart Disease and Stroke, 2021 Statistics

4



Salim S. Virani. Circulation. Heart Disease and Stroke Statistics—2021 Update, Volume: 143, Issue: 8, Pages: e254-e743, DOI: (10.1161/CIR.0000000000000950)

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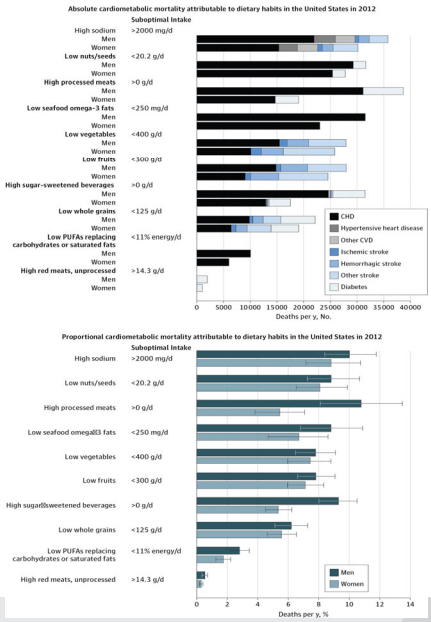

45% of deaths in one year from heart disease, stroke and DMII were linked to poor diet

Micha et al JAMA. 2017;317(9):912-924. doi:10.1001/jama.2017.0947

6

What Foods Are Best?

Benefit

Fruits, Nuts, Fish
Vegetables, Vegetable Oils
Whole Grains, Beans, Yogurt

Cheese
Eggs, Poultry, Milk
Butter
Unprocessed Red Meats

Refined Grains, Starches, Sugars
Processed Meats, High Sodium Foods
Industrial Trans Fat

Harm

Dariush Mozaffarian. Circulation. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity, Volume: 133, Issue: 2, Pages: 187-225, DOI: (10.1161/CIRCULATIONAHA.115.018585) 2016

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	Endpoint	No. of studies	No. of subjects	No. of events	Unit	RR	Reference
Fruits	CHD	16 PCs	817,155	13,786	Each 1 serving/day (100 g)	0.94 (0.91, 0.98)	Gan Y 2015
	Stroke	8 PCs	377,159	9,706	Each 1 serving/day (100 g)	0.82 (0.75, 0.91)	Hu D 2014
	Diabetes	7 PCs	366,232	21,063	Each 1 serving/day (100 g)	0.94 (0.89, 1.00)	Li M 2014
Vegetables	CHD	14 PCs	705,316	13,135	Each 1 serving/day (100 g)	0.95 (0.92, 0.98)	Gan Y 2015
	Stroke	6 PCs	342,118	8,854	Each 1 serving/day (100 g)	0.94 (0.90, 0.98)	Hu D 2014
	Diabetes	5 PCs	173,995	18,758	Each 1 serving/day (100 g)	0.98 (0.89, 1.08)	Li M 2014
Green leafy vegetables	Diabetes	3 PCs	127,148	13,331	Each 1 serving/day (100 g)	0.78 (0.62, 0.94)	Li M 2014
Legumes	Stroke	6 PCs	254,828	6,690	Each 4 servings/wk (400 g)	0.98 (0.84, 1.14)	Afshin A 2014
	CHD	4 PCs	198,904	6,514	Each 4 servings/wk (400 g)	0.86 (0.78, 0.94)	Afshin A 2014
	Diabetes	2 PCs	100,179	2,746	Each 4 servings/wk (400 g)	0.78 (0.50, 1.14)	Afshin A 2014
Whole grains	CHD	8 PCs	--	5,383	high vs low	0.78 (0.71, 0.86)	Tang G 2015
	Stroke	4 PCs	207,984	877	2.5 vs. 0.2 servings/day	0.83 (0.68, 1.14)	Mellen P 2008
	Diabetes	10 PCs	385, 868	19,829	Each 1 serving/day (50 g)	0.81 (0.74, 0.89)	Aune D 2013
Nuts and seeds	CHD death	3 PCs, 1 RCT	206,114	6,749	Each 4 servings/week (4 oz [113 g])	0.76 (0.68, 0.84)	Afshin A 2014
	Nonfatal CHD	3 PCs, 1 RCT	141, 390	4,280	Each 4 servings/week (4 oz [113 g])	0.78 (0.67, 0.92)	Afshin A 2014
	Diabetes	5 PC, 1 RCT	230,216	13,308	Each 4 servings/week (4 oz [113 g])	0.87 (0.81, 0.94)	Afshin A 2014
Fish	CHD Death	12 PCs	282,975	4,195	2-4 servings/week vs. <3 servings/month	0.79 (0.67, 0.92)	Zheng J 2012
	Stroke	8 PCs	394,958	16,890	≥ 5 vs. 1 serving/week	0.88 (0.81, 0.96)	Chowdhury R 2012
	Diabetes	13 PCs	481,489	20,830	Each 1 serving/day (100 g)	1.12 (0.96, 1.34)	Wu J 2012
Unprocessed red meats	CVD death	13 PCs	1,070,215	24,241	high vs low	1.12 (0.95, 1.33)	Abete I 2014
	Stroke	5 PCs	239,251	9,593	Each 1 serving/day (100 g)	1.13 (1.03, 1.23)	Chen G 2013
	Diabetes	9 PCs	447,333	28,206	Each 1 serving/day (100 g)	1.19 (1.04, 1.37)	Pan A 2011
Processed red meats	CVD death	6 PCs	1,186,701	33,537	Each 1 serving/day (50 g)	1.24 (1.09, 1.40)	Abete I 2014
	Stroke	5 PCs	239,251	9,593	Each 1 serving/day (50 g)	1.11 (1.02, 1.20)	Chen G 2013
	Diabetes	8 PCs	372,391	26,234	Each 1 serving/day (50 g)	1.51 (1.25, 1.83)	Pan A 2011
White meat (poultry, rabbit)	CVD death	5 PCs	1,197,835	31,535	Each 1 serving/day (100 g)	1.00 (0.87, 1.15)	Abete I 2014
Total dairy	CHD	10 PCs	253,260	6,792	high vs low	0.94 (0.82, 1.07)	Qin L 2015
	Stroke	16 PCs	764,635	28,138	high vs low	0.88 (0.82, 0.94)	Hu D 2014
	Diabetes	14 PCs	459,790	25,863	Each 1 serving/day	0.98 (0.96, 1.01)	Chen M 2014
Milk	CHD	6 PCs	259,162	4,391	Each 1 serving/day (200 ml)	1.00 (0.96, 1.04)	Soedamah-Muthu S 2011
	Stroke	9 PCs	525,909	22,382	high vs low	0.91 (0.82, 1.01	Hu D 2014
	Diabetes	7 PCs	167,992	15,149	Each 1 serving/day (200 g)	0.87 (0.72, 1.04)	Aune D 2013
Cheese	CHD	7 PCs	--	--	high vs low	0.84 (0.71, 1.00)	Qin L 2015
	Stroke	5 PCs	282,439	9,919	high vs low	0.94 (0.85, 0.986)	Hu D 2014
	Diabetes	8 PCs	242,990	17,820	Each 1 serving/day (50 g)	0.92 (0.86, 0.98)	Aune D 2013
Butter	CHD	5 PCs	--	--	high vs low	1.02 (0.88, 1.20)	Qin L 2015
	Stroke	3 PCs	173,853	5,299	high vs low	0.95 (0.85, 1.07)	Hu D 2014
Yogurt	CHD	5 PCs	--	--	high vs low	1.06 (0.90, 1.34)	Qin L 2015
	Diabetes	9 PCs	438,096	32,995	Each 1 serving/day (½ cup)	0.82 (0.70, 0.96)	Chen M 2014
Eggs	CHD	7 PCs	263,938	5,847	Each 1 serving/day (1 egg)	0.99 (0.85, 1.15)	Rong Y 2013
	Stroke	6 PCs	210,434	7,579	Each 1 serving/day (1 egg)	0.91 (0.81, 1.02)	Rong Y 2013
	Diabetes	5 PCs	69,297	4,889	>1 egg/day vs. never or <1 egg/week	1.42 (1.09, 1.86)	Shin J 2013
100% fruit juice	Diabetes	11 PCs	407,288	34,549	Each 1 serving/day (8 oz.)	1.06 (0.98, 1.14)	Imamura F 2015
Sugar-sweetend beverages	Diabetes, non-BMI adjusted	13 PCs	421,973	36,492	Each 1 serving/day (8 oz.)	1.42 (1.19, 1.69)	Imamura F 2015
	Diabetes, BMI adjusted	17 PCs	464,937	38,253	Each 1 serving/day (8 oz.)	1.27 (1.10, 1.46)	Imamura F 2015
	CHD	4 PCs	194,864	7,396	Each 1 serving/day (8 oz.)	1.17 (1.10, 1.24)	Xi B 2015
Coffee—Caffeinated Decaffeinated	CVD	29 PCs	--	--	3 vs. 0 cups/day, nonlinear	0.89 (0.85, 0.93)	Ding M 2014
	Diabetes	11 PCs	--	--	Each 1 serving/day (1 cup)	0.91 (0.85, 0.94)	Ding M 2014
	Diabetes	11 PCs	--	--	Each 1 serving/day (1 cup)	0.94 (0.91, 0.98)	Ding M 2014
Tea	CHD	7 PCs	235,368	8,328	Each 1 serving/day (1 cup)	0.90 (0.81, 0.996)	Zhang C 2015
	Diabetes	14 PCs	303,165	25,574	Each 1 serving/day (1 cup)	0.88 (0.86, 0.905)	Yang W 2014
	Stroke	8 PCs	307,968	11,329	Each 1 serving/day (1 cup)	0.94 (0.90, 0.973)	Zhang C 2015

0.5 1 2
Realtive risk (95% CI)

Dariush Mozaffarian. Circulation. Dietary and Policy Priorities for Cardiovascular Disease, Diabetes, and Obesity, Volume: 133, Issue: 2, Pages: 187-225, DOI: (10.1161/CIRCULATIONAHA.115.018585) 2016

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$50.4 Billion Dollars Annually

Food Category	Ideal Daily Consumption	Annual Cardiometabolic Costs* (95% CI)
Fruits	300 g/day	9.552 (8.904–10.248)
Vegetables	400 g/day	10.055 (9.408–10.92)
Nuts/seeds	20 g/day	13.574 (12.432–14.448)
Whole grains	125 g/day	7.541 (7.056–8.064)
Red meat	14.3 g/day	0.503 (0.4704–0.588)
Sugar-sweetened beverages	0 oz/day	10.223 (8.904–11.088)
Processed meat	0 g/day	9.72 (9.072–10.248)
Polyunsaturated fatty acids	11% Energy/day	3.352 (3.192–3.696)
Seafood omega-3	250 mg/day	12.736 (11.76–13.944)
Sodium	2000 mg/day	3.854 (3.696–4.2)

*Values given in 2018 US billions of dollars. Total cost does not reflect sum of individual components based on the assumption that the benefits of the 10 food groups are not independent.

https://doi.org/10.1371/journal.pmed.1002981.t004

Jardim TV, Mozaffarian D, Abrahams-Gessel S, Sy S, Lee Y, et al. (2019) Cardiometabolic disease costs associated with suboptimal diet in the United States: A cost analysis based on a microsimulation model. PLOS Medicine 16(12): e1002981. https://doi.org/10.1371/journal.pmed.1002981
https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002981

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Medically Tailored Meals (MTM)

What is the Medi-Cal MTM Program?

The Medi-Cal MTM Pilot Program is a medical nutrition intervention for high utilizing Medi-Cal beneficiaries with a diagnosis of congestive heart failure (CHF). The intervention is 12 weeks in duration.

- **Who:** Discharged Medi-Cal patients who were admitted due to CHF and have a history of being a high utilizer of health care services and/or likely at risk for readmission within 30 days.
- **Intervention Goal:** Reduce hospital and emergency department 30-day and 90-day readmissions.
- **Cost:** No cost to patient. Must be on Medi-Cal.

CALIFORNIA FOOD IS MEDICINE COALITION

for CA RMC internal use only

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What is the Intervention?

MTM Intervention		
Medically Tailored Meals	Medical Nutrition Therapy	Information & Referral Services

Goal: Reduce hospital readmissions and ED visits!

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Ant-Inflammatory Food Pyramid

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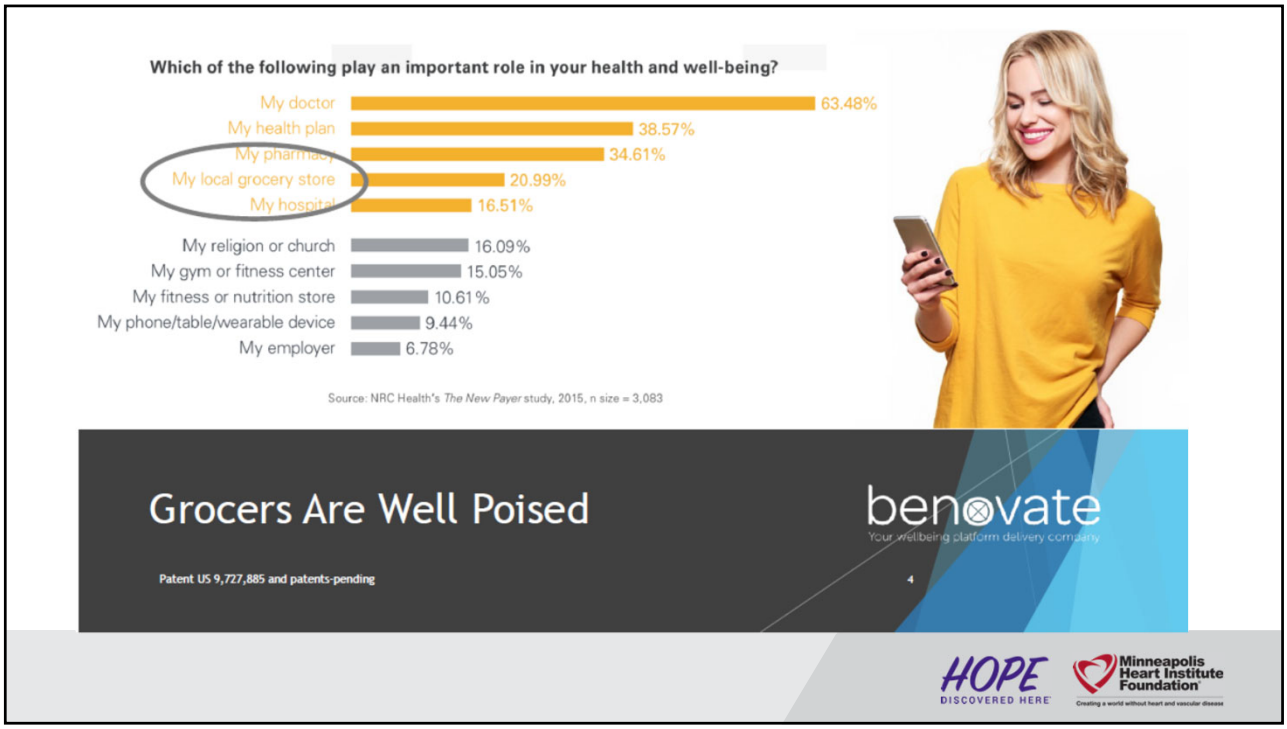
Functionalizing FAM…

13

MHIF Research Project with NUMC & Hy-Vee & Benovate

14


Which of the following play an important role in your health and well-being?
My doctor 63.48%
My health plan 38.57%
My pharmacy 34.61%
My local grocery store 20.99%
My hospital 16.51%
My religion or church 16.09%
My gym or fitness center 15.05%
My fitness or nutrition store 10.61%
My phone/table/wearable device 9.44%
My employer 6.78%
Source: NRC Health's The New Payer study, 2015, n size = 3,083
Grocers Are Well Poised
benovate
Your wellbeing platform delivery company
Patent US 9,727,885 and patents-pending
4
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The WHAT
benovate
Health Snapshot
Steps
Weight
Sleep
3.8 hours
CONNECT
Your Profile
Better-people in your pocket
benovate
Your wellbeing platform delivery company
Patent US 9,727,885 and patents-pending
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Patient Criteria

- Using measurements documented within 6 months of study start date:
  - Adults diagnosed with hypertension (≥140/90 mm HG)
  - Adults diagnosed with pre-diabetes (A1c between 5.7 to 6.4)
  - Adults diagnosed with diabetes (A1c 6.5 and above)

17

Success Measures

Clinical
- Improvement in blood pressure
- Improvement in hemoglobin A1c
- Improvement in fasting blood sugar

App Adoption
- Engagement (percentage of population using the app)
- Stickiness (frequency of use)
- Activation (behavior change)

Retail
- Units (volume of category of items sold)
- Margins (corresponding profit impact of unit change)

18

Fish Oil for Cardiovascular Prevention

Michael D Miedema, MD MPH
Director of Cardiovascular Prevention
Minneapolis Heart Institute

April 5, 2021

1

Low incidence of CHD in Greenland Inuit

human calcitonin; Dr. Len Deftos for the parathyroid-hormone immunoassays; and Mr. J. Martin for the preparation of the histological sections. This work was supported in part by the M.R.C. (N. J. Y. W.), the Swiss Academy of Sciences (M. R.), the American Heart Association (D. N. K. and G. V. F.), I.N.S.E.R.M. (Ph. B.), and the Wellcome Trust.

REFERENCES

1. Jowsey, J. *Am. J. Med.* 1966, **40**, 485.
2. Collins, D. H. *in* Pathology of Bone; p. 228. London, 1966.
3. Kay, H. D. *Br. J. exp. Path.* 1929, **10**, 253.
4. Sullivan, T. J., Gutman, E. B., Gutman, A. B. *J. Urol.* 1942, **48**, 426.
5. Dull, T. A., Henneman, P. H. *New Engl. J. Med.* 1963, **268**, 132.
6. Nagant de Deuxchaines, C., Krane, S. M. *Medicine, Baltimore*, 1964, **43**, 233.
7. Reiner, M., Woodhouse, N. J. Y., Kalu, D. N., Foster, G. V., Galante, L., Joplin, G. F., MacIntyre, I. *Helv. med. Acta* (in the press).
8. Bijvoet, O. L. M., van der Sluys Veer, J., Jansen, A. P. *Lancet*, 1968, i, 876.
9. Woodhouse, N. J. Y., Reiner, M., Kalu, D. N., Galante, L., Leese, B., Foster, G. V., Joplin, G. F., MacIntyre, I. *in* Proceedings of the Calcitonin 1969 Symposium (edited by S. Taylor); p. 504. London, 1970.
10. Haddad, J. G. Jr., Birge, S. J., Avioli, L. V. *New Engl. J. Med.* 1970, **283**, 549.
11. Bell, N. H., Avery, S., Johnston, C. C. Jr. *J. clin. Endocr.* 1970, **31**, 283.
12. Singer, F., Neer, R. M., Parsons, J. A., Krane, S. M., Potts, J. T. Jr. *J. clin. Invest.* 1970, **49**, 89a.
13. Neher, R., Riniker, B., Maier, R., Byfield, P. G. H., Gudmundsson, T. V., MacIntyre, I. *Nature*, 1968, **220**, 5171.
14. Sieber, P., Riniker, B., Brugger, M., Kamber, B., Rittel, W.

PLASMA LIPID AND LIPOPROTEIN PATTERN IN GREENLANDIC WEST-COAST ESKIMOS

H. O. BANG J. DYERBERG
AASE BRØNDUM NIELSEN
Department of Clinical Chemistry, Aalborg Hospital North, Denmark

Summary The plasma-lipid pattern, including quantitative lipoprotein electrophoresis, was examined in 130 Eskimos (69 females, 61 males) — hunters and/or fishermen, and their wives — in the northern part of the west coast of Greenland, and consuming a predominantly meat diet rich in polyunsaturated fatty acids. Most types of lipid were decreased, compared with Danish controls and Eskimos living in Denmark. The most remarkable finding was a much lower level of pre-β-lipoprotein and consequently of plasma-triglycerides in Greenlandic Eskimos than in Danish controls. These findings may explain the very low incidence of ischæmic heart-disease and the complete absence of diabetes mellitus in Greenlandic Eskimos.

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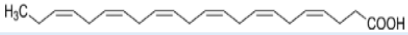
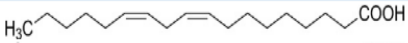
TABLE 1 Biochemical Data for Common Omega-3 and Omega-6 PUFAs

Name	Number of Carbon Atoms	Number of Double Bonds	Position of Double Bond From Methyl Terminal of Fatty Acid	Chemical Structure
Omega-3 PUFAs				
Alpha-linolenic acid	18	3	n-3	
Eicosapentaenoic acid	20	5	n-3	
Docosahexaenoic acid	22	6	n-3	
Omega-6 PUFAs				
Linoleic acid	18	2	n-6	
Arachidonic acid	20	4	n-6	

PUFA = polyunsaturated fatty acid.

Weinberg et al. JACC 2021

3

"Oily Fish"

- Salmon
- Herring
- Trout
- Anchovy
- Sardines
- Mackerel
- Tuna

❖A serving of salmon ~ 1,000mg of Omega-3 Fatty Acids

4

OTC vs Prescription Fish Oil

Over the Counter Options

- Numerous
- Variable dosing
  - Variable ratios

Prescription Fish Oil

- Epanova
- Lovaza
- Omtryg
  - All combinations of EPA/DHA
    - ↓ Triglycerides
      - ↑ LDL-C
- Icosapent Ethyl (Vascepa)
  - Purified EPA

5

Physician's Health Study

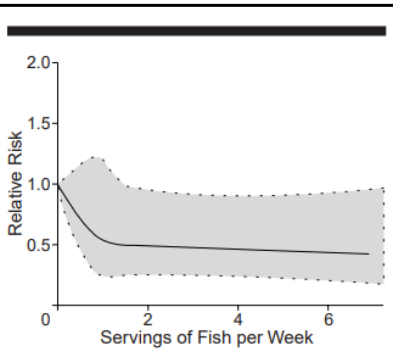


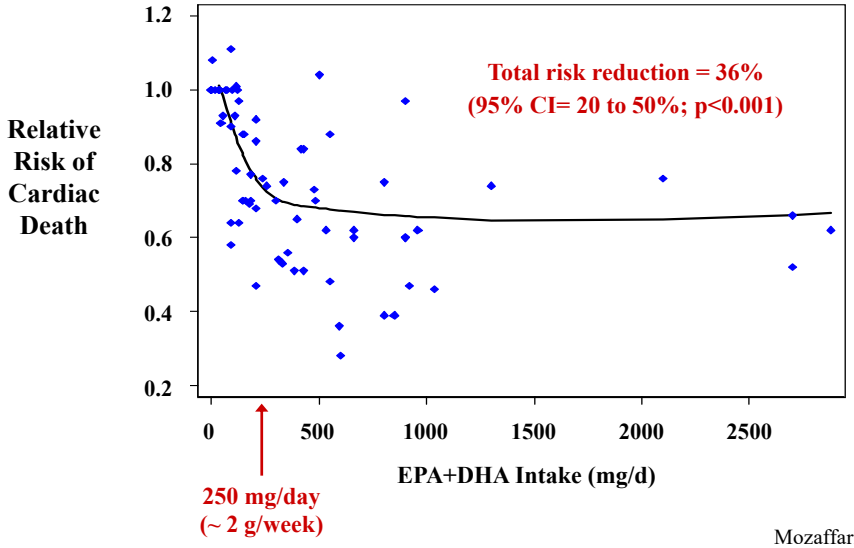
Figure 1.—Multivariate adjusted relative hazard of sudden death across increasing levels of fish intake expressed as servings of fish per week. The solid line represents the maximum partial likelihood estimate of the smooth relative hazard function, using a restricted cubic spline model with 4 knots. The dotted lines represent pointwise 95% confidence intervals for the relative hazard function.

Albert CM at el. PHS, JAMA, 1998

6

Pooled Analysis of Studies of Cardiac Death

Meta-analysis of 16 prospective cohort studies (total n=326,572) and 4 randomized controlled trials (total n=35,115) from the U.S., Europe, and Asia.



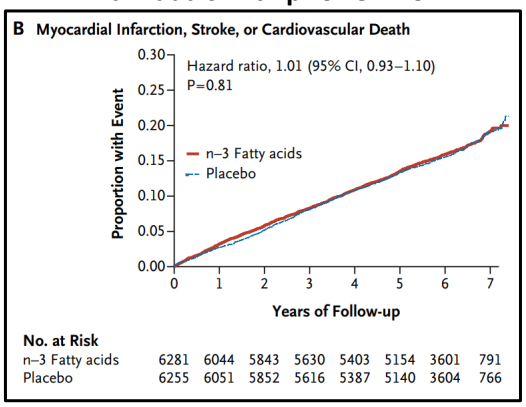
Mozaffarian & Rimm. JAMA 2006

7

Fish Oil for Cardiovascular Prevention

ORIGIN Trial

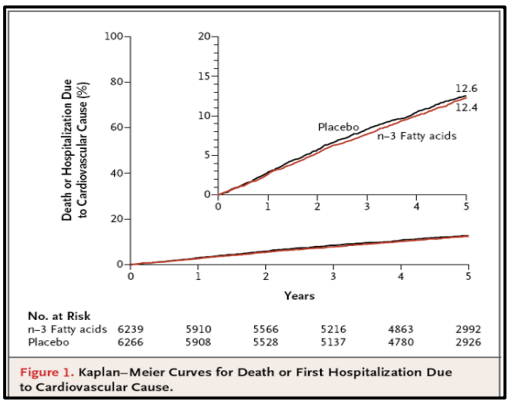
>12k individuals with prior CVD or DM



ORIGIN Trial, NEJM, 2012

R&P Study Group

>12k individuals with CVD risk factors or ASCVD



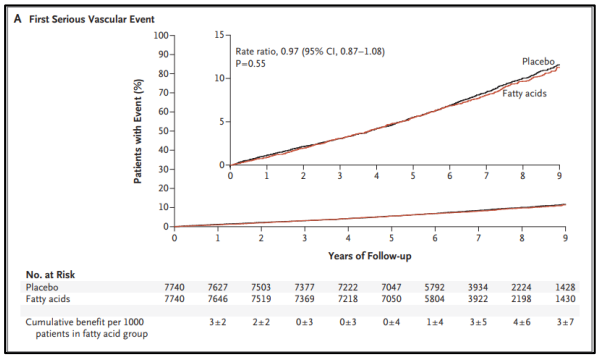
N-3 Fatty Acids, R&P Study Group, NEJM, 2013

8

Fish Oil for Cardiovascular Prevention

ASCEND Trial

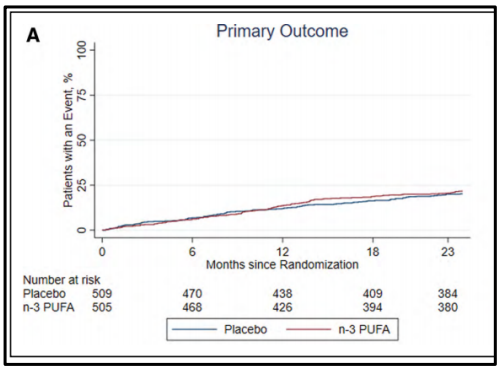
>15k individuals with T2DM



ASCEND Trial, NEJM, 2018

OMEMI

>1k elderly individuals with recent MI



OMEMI, Circulation, 2021

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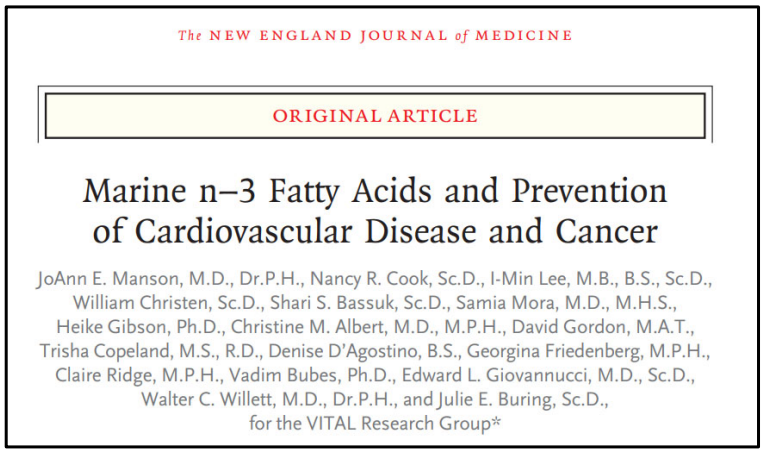


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

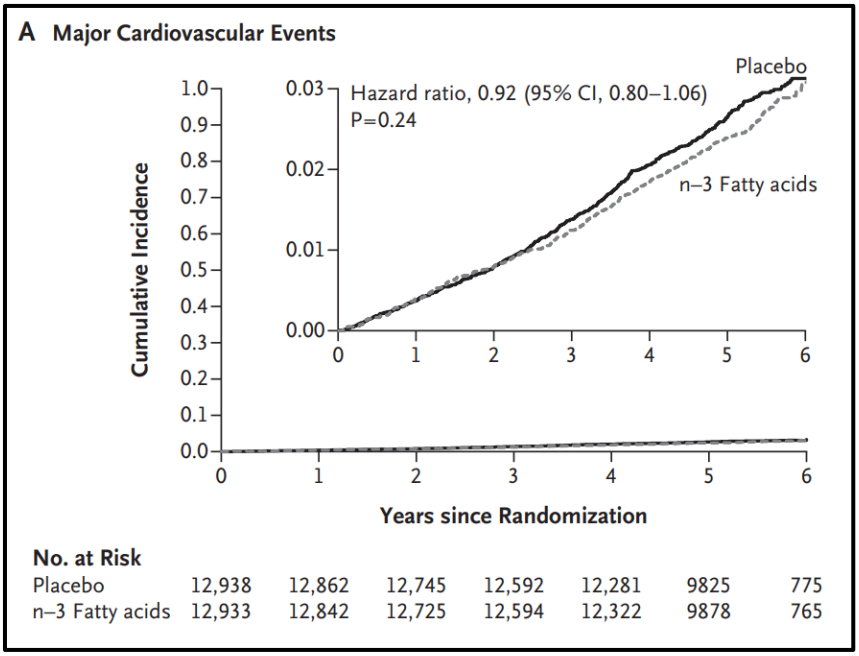
Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., Christine M. Albert, M.D., M.P.H., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

- 25,871 Individuals (men ≥ 50 years or women ≥ 55 years without CVD)
  - Including 5,105 black participants
- 1 Gram of Fish Oil (840mg of EPA/DHA)
- Followed up for 5.3 years
- Primary Outcome of MI, Stroke, or CVD death

Manson et al, VITAL, NEJM, 2018

10



Manson et al, VITAL, NEJM, 2018

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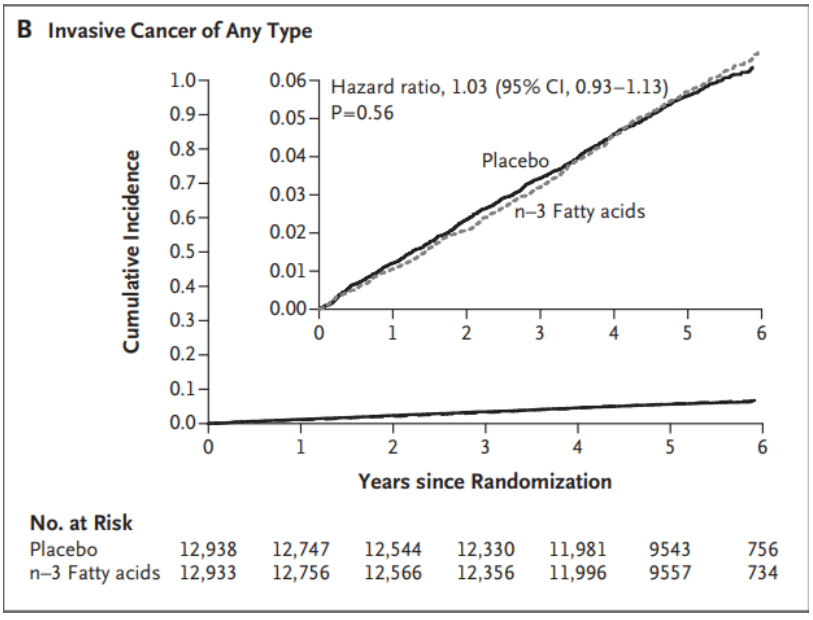

Manson et al, VITAL, NEJM, 2018

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Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to n–3 Fatty Acids or Placebo, in Intention-to-Treat Analyses.*

End Point	n–3 Group (N=12,933)	Placebo Group (N=12,938)	Hazard Ratio (95% CI)
	no. of participants with event		
Cardiovascular disease			
Primary end point: major cardiovascular event†	386	419	0.92 (0.80–1.06)
Cardiovascular event in expanded composite end point‡	527	567	0.93 (0.82–1.04)
Total myocardial infarction	145	200	0.72 (0.59–0.90)
Total stroke	148	142	1.04 (0.83–1.31)
Death from cardiovascular causes	142	148	0.96 (0.76–1.21)

Manson et al, VITAL, NEJM, 2018

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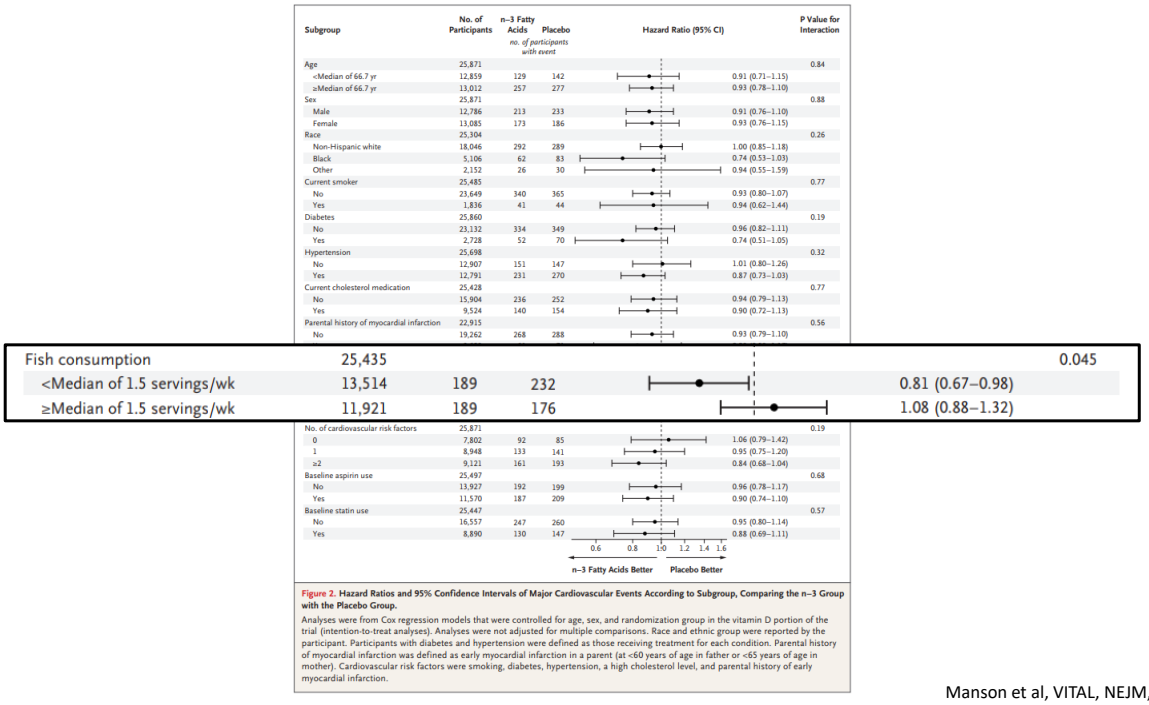

Figure 2. Hazard Ratios and 95% Confidence Intervals of Major Cardiovascular Events According to Subgroup, Comparing the n–3 Group with the Placebo Group.

Analyses were from Cox regression models that were controlled for age, sex, and randomization group in the vitamin D portion of the trial (intention-to-treat analyses). Analyses were not adjusted for multiple comparisons. Race and ethnic group were reported by the participant. Participants with diabetes and hypertension were defined as those receiving treatment for each condition. Parental history of myocardial infarction was defined as early myocardial infarction in a parent (at <60 years of age in father or <65 years of age in mother). Cardiovascular risk factors were smoking, diabetes, hypertension, a high cholesterol level, and parental history of early myocardial infarction.

Manson et al, VITAL, NEJM, 2018

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Research

JAMA | Original Investigation

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

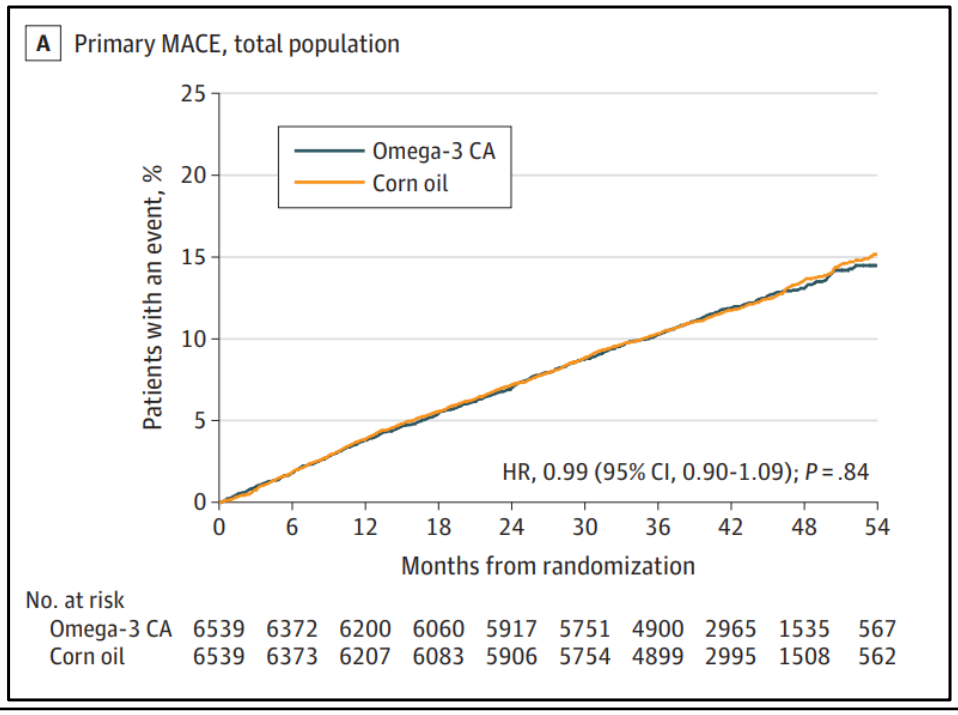
Stephen J. Nicholls, MBBS, PhD; A. Michael Lincoff, MD; Michelle Garcia, RN, BSN, CCRC; Dianna Bash, BSN; Christie M. Ballantyne, MD; Philip J. Barter, MBBS, PhD; Michael H. Davidson, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Darren K. McGuire, MD, MHSc; Dariush Mozaffarian, MD, DrPH; Paul M Ridker, MD; Kausik K. Ray, MBChB, MD, MPhil; Brian G. Katona, PharmD; Anders Himmelmann, MD, PhD; Larrye E. Loss, PharmD, MBA; Martin Rensfeldt; Torbjörn Lundström, MD, PhD; Rahul Agrawal, MD; Venu Menon, MD; Kathy Wolski, MPH; Steven E. Nissen, MD

- 13,078 individuals with elevated CVD risk, high trig's, and low HDL-C
- 4 grams/day of Fish Oil vs Placebo (corn oil)
- Primary outcome of MI, stroke, USA, PCI/CABG, or CVD death

Nicholls et al, STRENGTH, JAMA, 2020

15

- Study stopped early at ~3.5 years for futility



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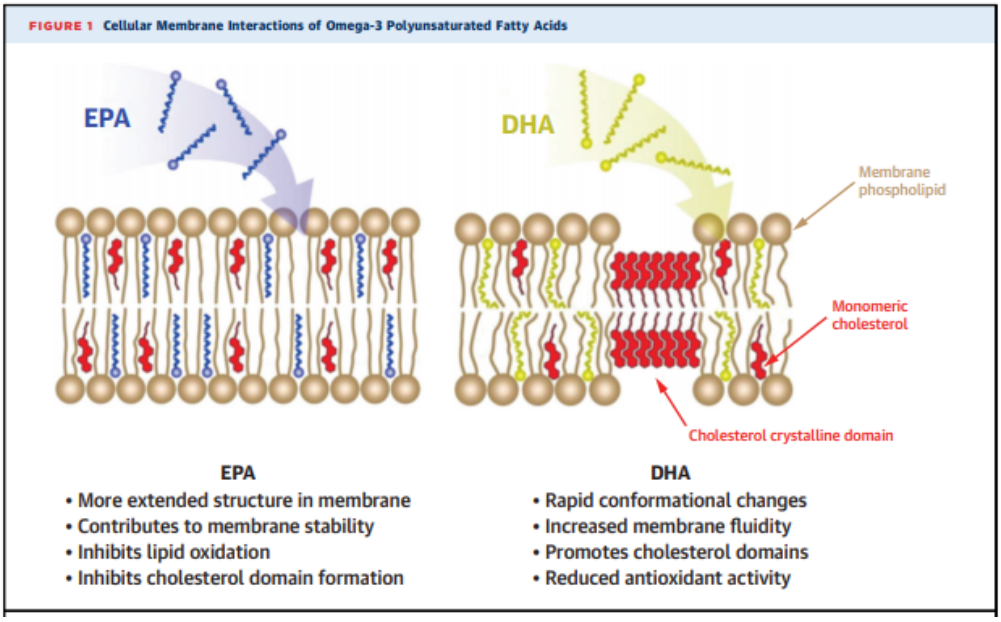

Weinberg et al. JACC 2021

17

Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis

MitsuhiroYokoyama, Hideki Origasa, Masunori Matsuzaki, Yuji Matsuzawa, Yasushi Saito, Yuichi Ishikawa, Shinichi Oikawa, Jun Sasaki, Hitoshi Hishida, Hiroshige Itakura, Toru Kita, Akira Kitabatake, Noriaki Nakaya, Toshiie Sakata, Kazuyuki Shimada, Kunio Shirato, for the Japan EPA lipid intervention study (JELIS) Investigators

- 18,645 individuals (~70% women) aged 45-75 with hyperlipidemia
  - Primary and Secondary Prevention
  - In Japan (high background fish intake)
- Statin + 1,800mg of EPA vs Statin only
- Mean follow-up of 4.6 years
- Primary outcome – major coronary event

Yokoyama et al, JELIS, Lancet, 2007

18

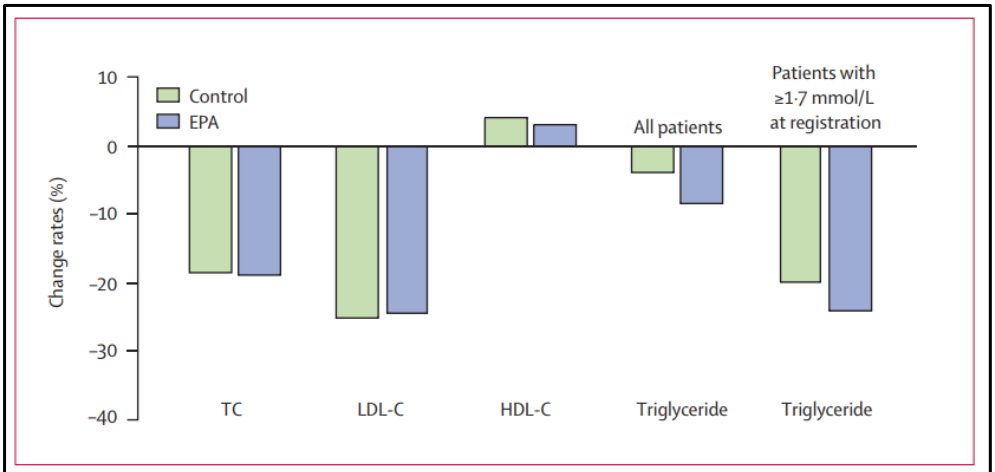

Figure 4: **Percentage changes from baseline in serum lipid profile**
TC=total cholesterol. LDL C=low-density lipoprotein cholesterol. HDL C=high-density lipoprotein cholesterol.

Yokoyama et al, JELIS, Lancet, 2007

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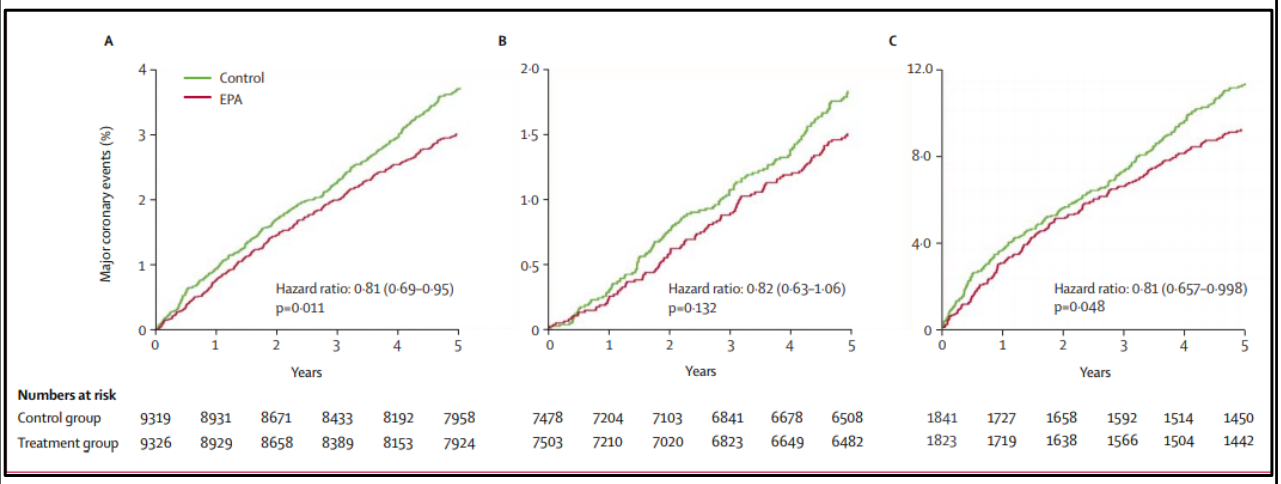

Yokoyama et al, JELIS, Lancet, 2007

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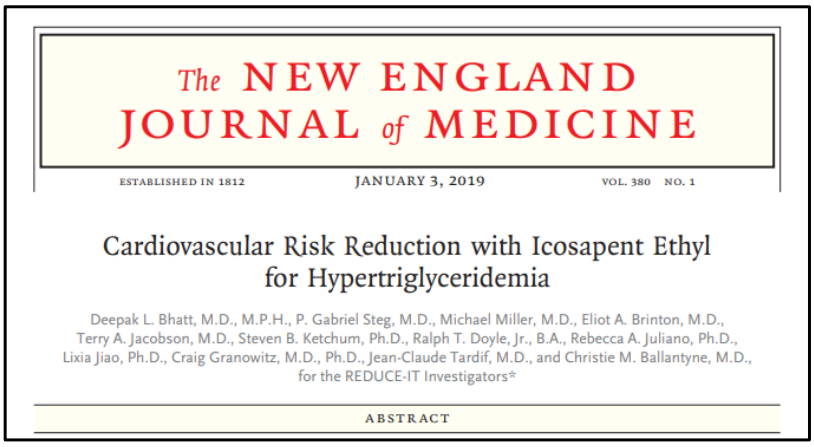

The NEW ENGLAND JOURNAL of MEDICINE

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

- 8,179 patients with either established CVD or diabetes + 2 CVD risk factors
  - Triglycerides 135-499mg/dl and LDL 41-100mg/dl
- Randomized to 2 grams of EPA bid vs placebo (mineral oil)
- Follow-up for median 4.9 years
- Primary end-point of MI, CVA, CVD death, or USA

Bhatt et al, REDUCE-IT, NEJM, 2019

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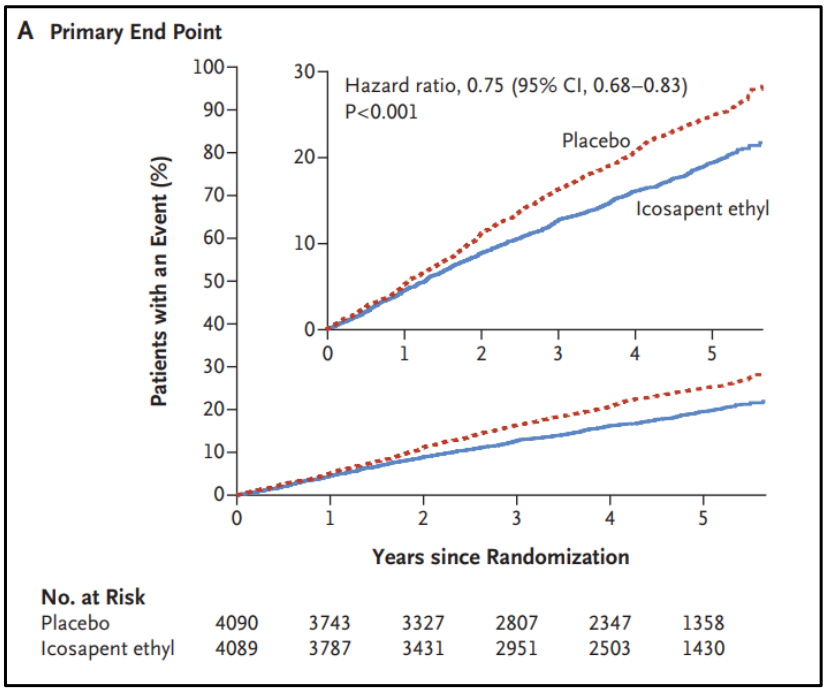

Bhatt et al, REDUCE-IT, NEJM, 2019

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REDUCE-IT

- Slight increase in LDL in the placebo group
  - Unlikely to impact trial results
- Slight increase in atrial fibrillation/flutter
  - 5.3% vs 3.9%, p-value 0.004
- Comparison with STRENGTH
  - >250% increase in EPA levels in both studies
    - Inverse relation with CVD events in REDUCE-it but not STRENGHT
  - 20% reduction in Trig's vs 20% reduction in Trig's

Bhatt et al, REDUCE-IT, NEJM, 2019

23

ESC European Society of Cardiology
European Heart Journal (2020) 41, 3925–3932
doi:10.1093/eurheartj/ehaa652
FASTTRACK CONGRESS
Dyslipidaemias

Effect of icosapent ethyl on progression of coronary atherosclerosis in patients with elevated triglycerides on statin therapy: final results of the EVAPORATE trial

Matthew J. Budoff[1]*, Deepak L. Bhatt[2], April Kinninger[1], Suvasini Lakshmanan[1], Joseph B. Muhlestein[3], Viet T. Le[3,4], Heidi T. May[3], Kashif Shaikh[1], Chandana Shekar[1], Sion K. Roy[1], John Tayek[1], and John R. Nelson[5]

[1]Department of Medicine, Lundquist Institute at Harbor-UCLA Medical Center, 1124 W Carson Street, Torrance, CA 90502, USA; [2]Department of Medicine, Brigham and Women's Hospital Heart & Vascular Center and Harvard Medical School, Boston, MA, USA; [3]Intermountain Heart Institute, Intermountain Medical Center, Salt Lake City, UT, USA; [4]Department of Medicine, Rocky Mountain University of Health Profession, Provo, UT, USA; and [5]California Cardiovascular Institute, Fresno, CA, USA

Received 1 July 2020; revised 10 July 2020; editorial decision 26 July 2020; accepted 29 July 2020; online publish-ahead-of-print 29 August 2020

See page 3933 for the editorial comment on this article (doi: 10.1093/eurheartj/ehaa750)

- 80 patients with non-obstructive coronary atherosclerosis, on statin therapy, with elevated triglycerides
- Treated with 4 gram of IPE vs placebo
- CT coronary angiography performed after 18 months of therapy to determine the impact of IPE on plaque progression

Budoff et al, EVAPORATE, EHJ, 2020

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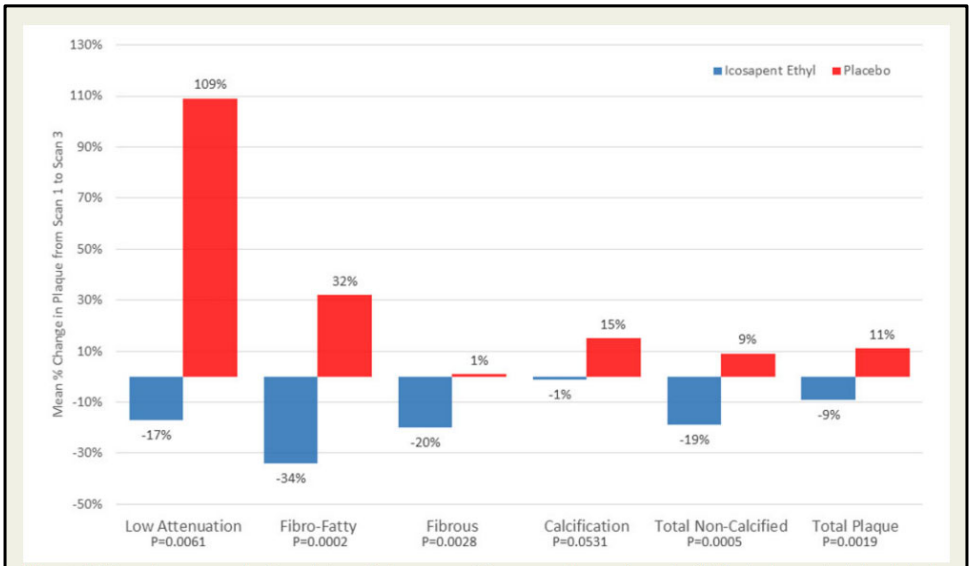

Figure 1 Mean plaque progression for each type of plaque composition measured on cardiovascular CT for the icosapent ethyl and placebo groups (icosapent ethyl group, $n = 31$ and placebo group, $n = 37$) after multivariable adjustment. Univariable analysis and multiple linear regression were used to examine the change in plaque levels between the cohorts. Multivariable models were adjusted by age, sex, diabetes status, hypertension, and baseline triglyceride levels. All statistical analyses report two-sided *P*-values for the outcomes. A *P*-value <0.048 was considered significant for the outcomes.

Budoff et al, EVAPORATE, EHJ, 2020

25

Final Conclusions

- Seafood, especially fish high in omega-3 fatty acids, is an important part of a heart-healthy diet
- Routine fish oil supplementation is not supported by large randomized trials
  - Eat the real thing!!
  - An opportunity to reduce medication burden
  - Individuals with low fish intake may be an exception
- Consider icosapent ethyl (Vascepa) for patients at very high CVD risk
  - Vascepa is not the same as OTC fish oil
  - $$$

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Thank You

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SGLT2 Inhibitors & Cardiovascular Risk Reduction

Elizabeth Tuohy, MD

Cardiologist, United Heart & Vascular Clinic,
MHI/Allina Health Heart Institute

Medical Director, Heart Disease Prevention Clinic

MHI Grand Rounds 4/2/2021

Allina Health

1

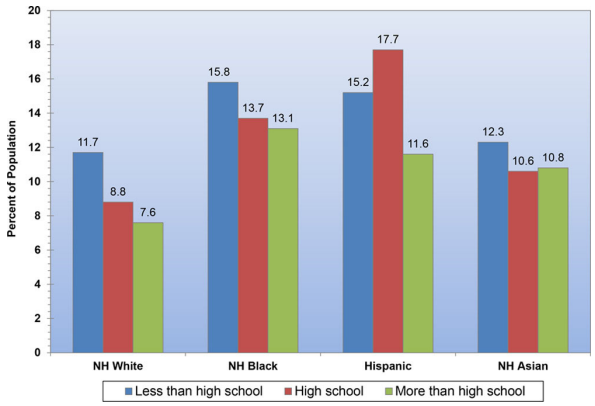
10-minute rapid overview of SGLT2 Inhibitors

- No disclosures
- Objectives:
  1) Understand the mechanism of action of SGLT2 Inhibitors
  2) Appreciate the cardiovascular risk reduction with SGLT2 Inhibitors
  3) Review utilization in clinical practice

2

Why should cardiologists know about a diabetes medication?

- ~12% of Americans have physician diagnosed diabetes (noting heterogeneity across demographics)
- ~2-5% have undiagnosed diabetes
- ~34% have prediabetes



NHANES 2013-2015

3

Why should cardiologists know about a diabetes medication?

- At least 68% of people >65 years of age with diabetes die of some form of heart disease; 16% die of stroke
- Heart disease death rates among adults with diabetes are 2 to 4 times higher than the rates for adults without diabetes

AHA Stats 2019

4

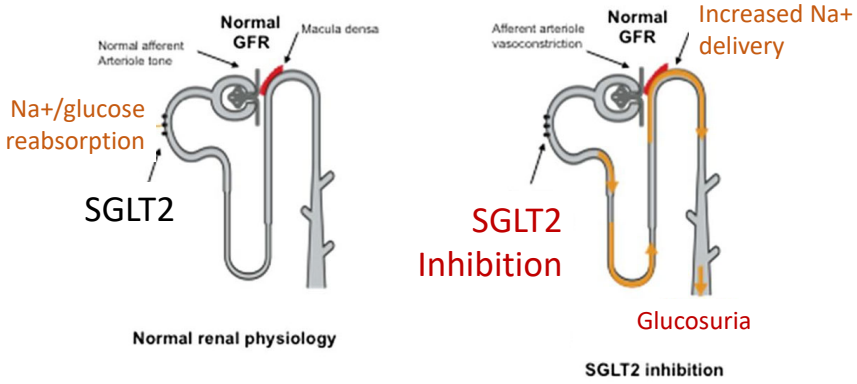
2019 ACC/AHA Guidelines for Primary Prevention of Cardiovascular Disease

- For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial.
- If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor (SGLT2i) or a glucagon-like peptide-1 (GLP-1)receptor agonist.

5

SGLT2-Inhibitor Glucose Effect

- Inhibitors of sodium glucose cotransporter-2 act in the proximal renal tubule to increase urinary excretion of glucose, leading to a reduction in rates of hyperglycemia in patients with type 2 diabetes (A1c reduction of ~0.5-1%)



Paola Fioretto et al. Dia Care 2016;39:S165-S171

6

SGLT2-Inhibitor Glucose Effect

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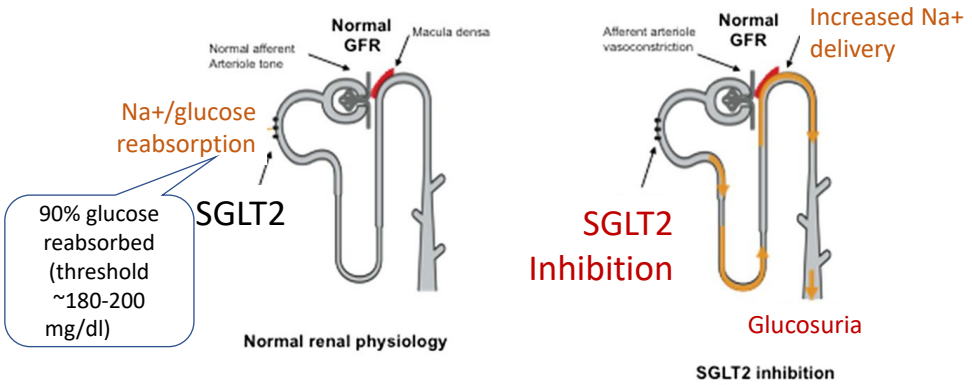

Paola Fioretto et al. Dia Care 2016;39:S165-S171

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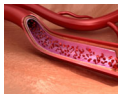
Additional Potential SGLT2-Inhibitor Effects

- **Kidney:** decreased blood glucose (glycosuria), increased natriuresis/diuresis, decreased hyperuricemia, improved energy metabolism

- **Heart**- Improved energy metabolism, decreased inflammation, improved remodeling, decreased ischemia, decreased oxidative stress, decreased epicardial fat



- **Vasculature**: decreased inflammation, decreased BP, increased pro-vascular progenitor cells, improved vascular function

- **Whole body**: weight loss, inhibited sympathetic nervous system, increased erythropoietin

JACC Basic Transl Sci. 2020 Jun; 5 (6): 632-644

8

Available SGLT2 Inhibitors

- empagliflozin (Jardiance)
- canagliflozin (Invokana)
- dapagliflozin (Farxiga)
- ertugliflozin (Steglatro)

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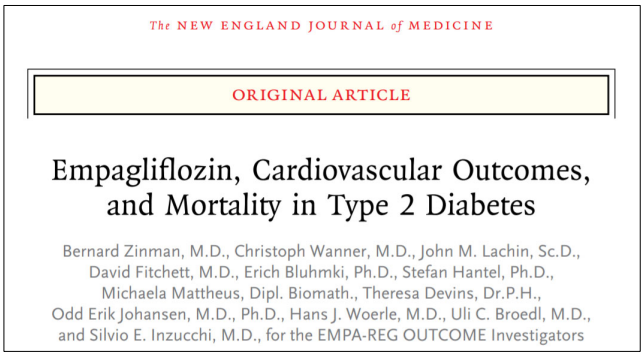


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

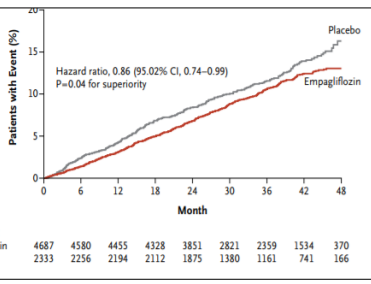
- EMPA-REG OUTCOME trial examined the effects of empagliflozin on cardiovascular morbidity and mortality in patients with DM2 and established ASCVD
- Mean A1c decreased from 8.2% to 7.8%

Zinman, NEJM, 2015. 373: 2117-28

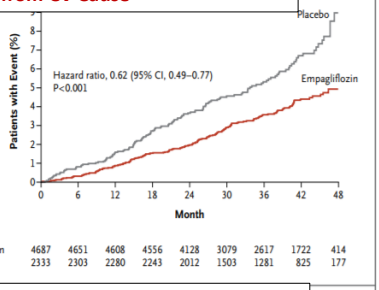
10

10.5% vs 12.1%
HR 0.86
RRR 14%

CV death, nonfatal MI, nonfatal stroke



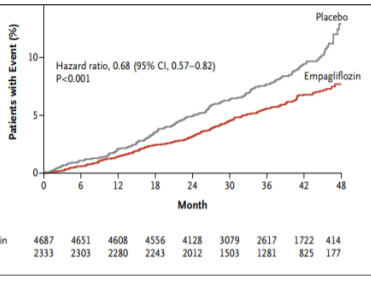
Death from CV Cause



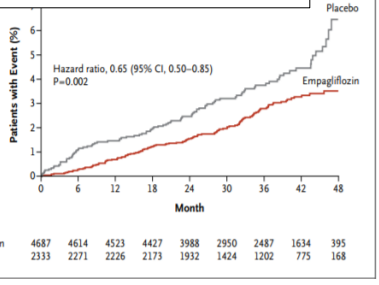
3.7% vs 5.9%
HR 0.62
RRR 38%

5.7% vs 8.3%
HR 0.68
RRR 32%

Death from Any Cause



Hospitalization for Heart Failure



2.7% vs 4.1%
HR 0.65
RRR 35%

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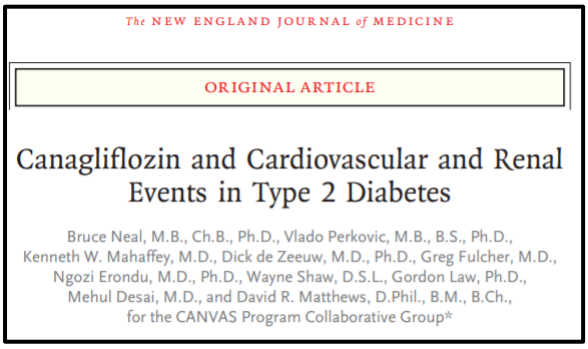
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

- CANVAS Program: 10,142 participants, 4330 in CANVAS and 5812 in CANVAS-R
- ≥ 30 years old with ASCVD
- ≥ 50 years old with 2 risk factors (DM for ≥ 10 years, SBP >140 mmHg while on at least one antihypertensive, current smoking, albuminuria, HDL < 38.7 mg/dl)

Neal B, NEJM 2017. 377: 644-57

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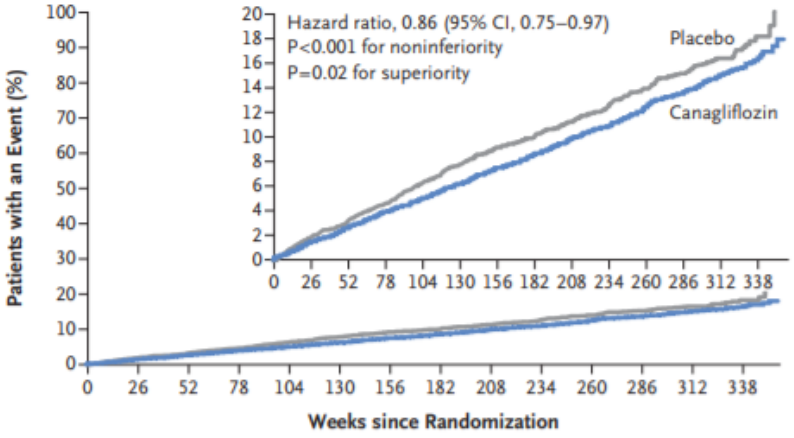
Death from CV cause, Nonfatal MI, or Nonfatal stroke



No. at Risk														
Placebo	4347	4239	4153	4061	2942	1626	1240	1217	1187	1156	1120	1095	789	216
Canagliflozin	5795	5672	5566	5447	4343	2984	2555	2513	2460	2419	2363	2311	1661	448

* Non-significant difference between individual endpoints of death from CV cause, nonfatal MI or nonfatal stroke

Neal B, NEJM 2017. 377: 644-57

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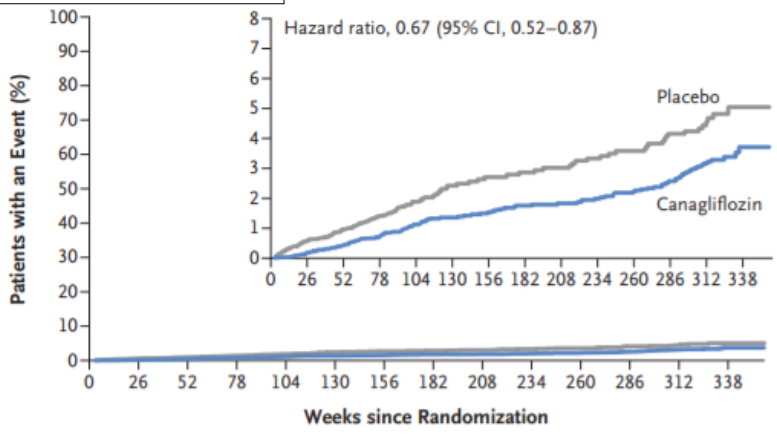
Hospitalization for Heart Failure



No. at Risk														
Placebo	4347	4267	4198	4123	3011	1667	1274	1256	1236	1210	1180	1158	829	233
Canagliflozin	5795	5732	5653	5564	4437	3059	2643	2610	2572	2540	2498	2451	1782	490

Neal B, NEJM 2017. 377: 644-57

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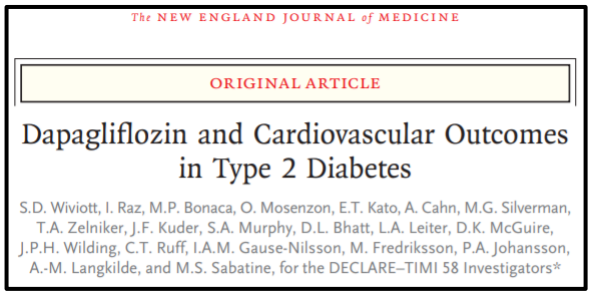
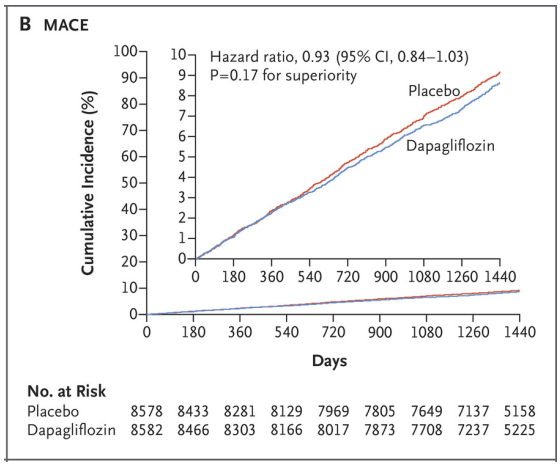


- DECLARE-TIMI 58 Trial: 17,160 patients
- Established ASCVD or multiple risk factors
- followed for a median of 4.2 years

Wiviott SD, NEJM 2019 380:347-57

15

Major Adverse CV Events – no significant difference

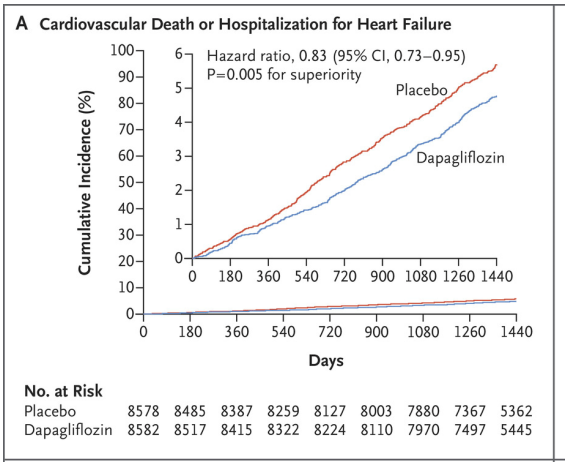


8.8% in the dapagliflozin group and
9.4% in the placebo group;
hazard ratio, 0.93;
95% CI, 0.84 to 1.03;
P=0.17 for superiority

Wiviott SD, NEJM 2019 380:347-57

16

CV Death or Hospitalization for Heart Failure



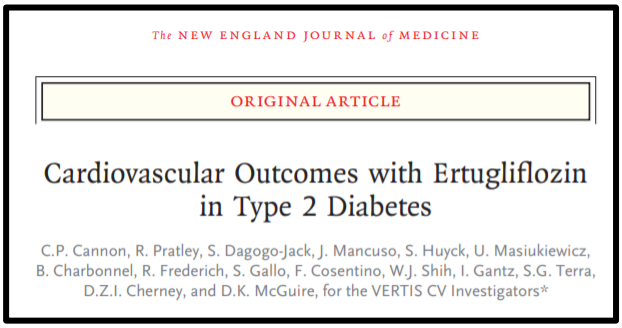
4.9% vs. 5.8%;
hazard ratio, 0.83
95% CI, 0.73 to 0.95; P=0.005

HF hospitalization 6.2% vs 8.5%
HR 0.73; 95% CI, 0.61 to 0.88

No between-group difference in cardiovascular death.
HR 0.98; 95% CI, 0.82 to 1.17

Wiviott SD, NEJM 2019 380:347-57

17


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Outcomes with Ertugliflozin in Type 2 Diabetes

C.P. Cannon, R. Pratley, S. Dagogo-Jack, J. Mancuso, S. Huyck, U. Masiukiewicz, B. Charbonnel, R. Frederich, S. Gallo, F. Cosentino, W.J. Shih, I. Gantz, S.G. Terra, D.Z.I. Cherney, and D.K. McGuire, for the VERTIS CV Investigators*

- VERTIS CV
- 8246 patients with DM2 and ASCVD, followed for a mean of 3.5 years
- Non-significant difference in MACE
- Significant reduction in heart failure hospitalization (2.5% vs 3.6%, HR 0.7, 95% CI 0.54-0.90)

Cannon, NEJM 2020;383:1425-35.

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SGLT2 Inhibitor Adverse Events

- Urinary tract infections, yeast infections
  - Incidence of infections are 15-20% higher vs. placebo
  - Women >>>>> Men
- Urethritis and vaginal irritation
- Hypovolemia / orthostatic hypotension
- Slight increase risk DKA
- Canagliflozin – increase in amputations (6.3% vs 3.4%, P <0.001). Caution in patients with neuropathy, hx foot ulceration, foot deformity

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Contraindications/Precautions

- Type 1 diabetes
- Prior DKA
- Caution in CKD:

Drug	Dosing	CKD
empagliflozin	10mg, 25mg	Discontinue if GFR < 45
dapagliflozin	5mg, 10mg	Discontinue if GFR < 45
canagliflozin	100mg, 300mg	100mg if GFR < 60, Ok to cont until dialysis
ertugliflozin		Discontinue if GFR < 60

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Available SGLT2 Inhibitors and Cost/Month

- empagliflozin (Jardiance) $529
- canagliflozin (Invokana) $570
- dapagliflozin (Farxiga) $504
- ertugliflozin (Steglatro) $316

www.goodrx.com 4/3/2021

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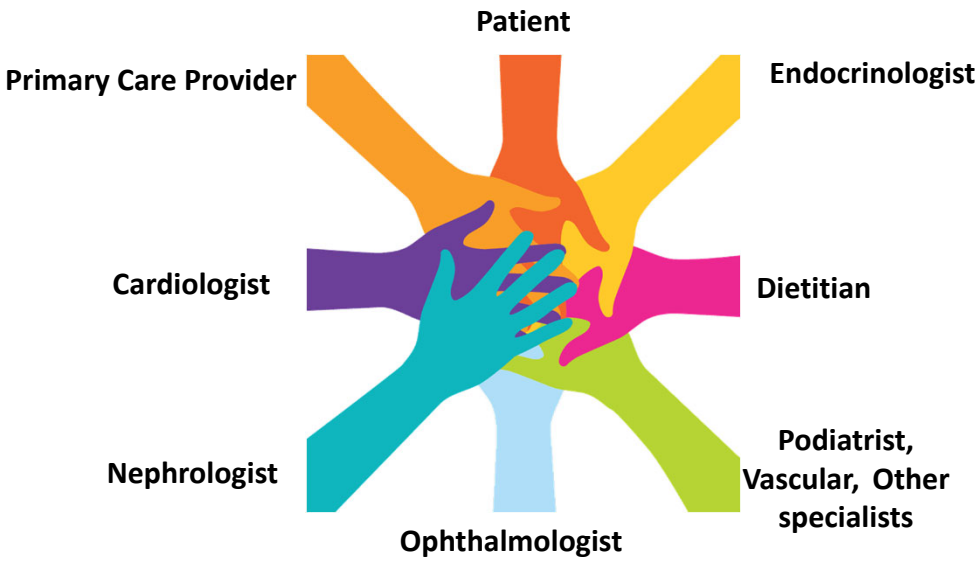
Cardiodiabetes Care Team



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Thank you

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Update in Lipid Management

Thomas Knickelbine, MD

Objectives

Review Updated Cholesterol Treatment Guidelines

Lipid Lowering Therapies Beyond Statins

64 yo male with recent ACS, h/o DM, HTN and CKD. Current therapy rosuvastatin 40 mg with 53% reduction from baseline. Current LDL of 74 mg/dl and normal triglycerides.

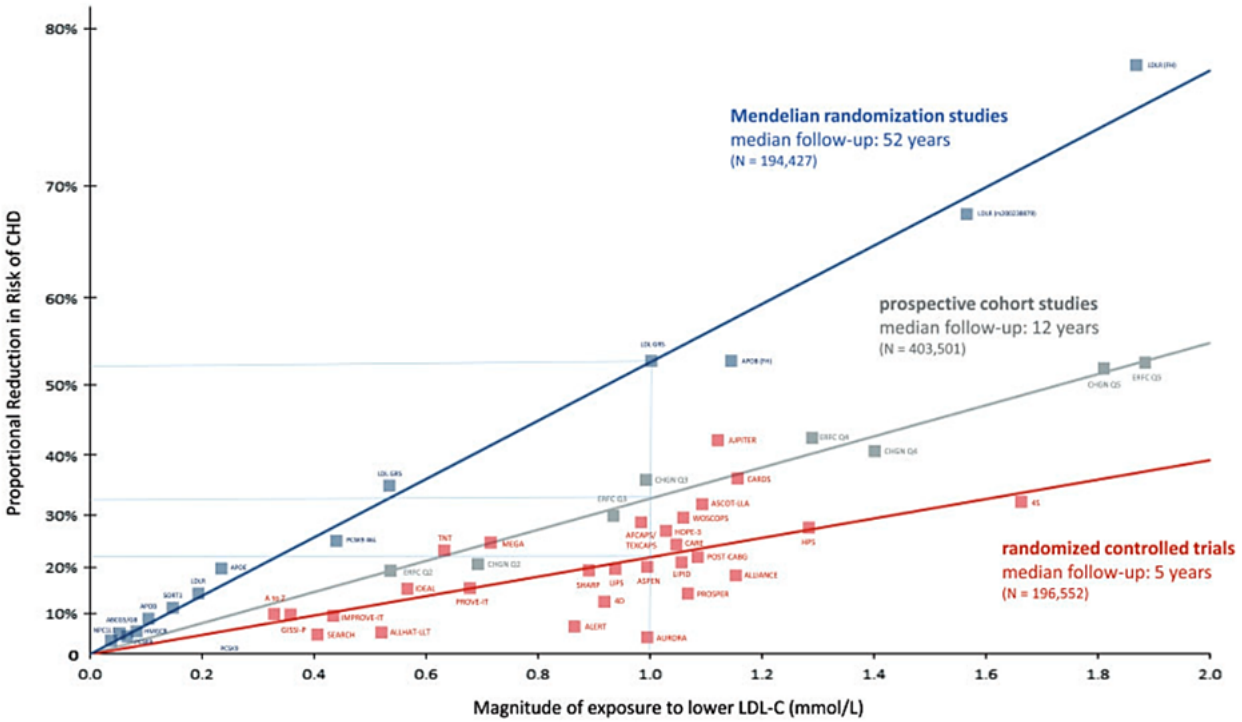
What is the next best option according to the 2018 AHA/ACC multi-society guidelines?

1. Add Icosapent ethyl (Vascepa)
2. No further rx, Pt has achieved goal of > 50% LDL reduction.
3. Add ezetimibe 10 mg
4. Add PCSK9i

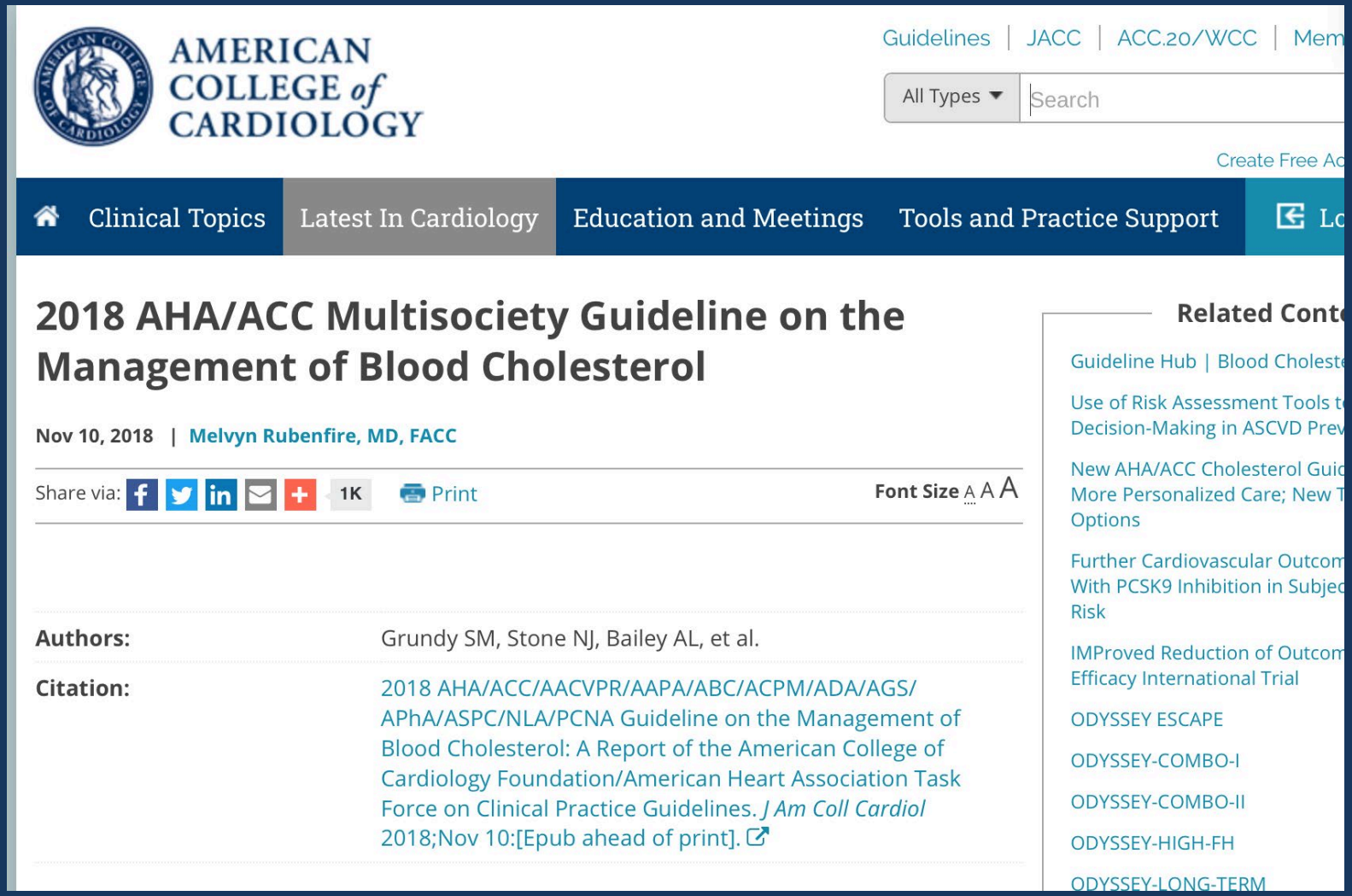
LDL is primary target in lipid RX guidelines

A Direct Correlation
LDL-C and CVD Risk

Slope steepens over time: Causal and cumulative effect of LDL-C on CVD risk



Ference BA, et al. *Eur Heart J*. 2017;38:2459-2472.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2018 AHA/ACC Multisociety Guideline on the Management of Blood Cholesterol
Nov 10, 2018 | Melvyn Rubenfire, MD, FACC
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Authors: Grundy SM, Stone NJ, Bailey AL, et al.
Citation: 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2018;Nov 10:[Epub ahead of print].
Related Cont
Guideline Hub | Blood Choleste
Use of Risk Assessment Tools t Decision-Making in ASCVD Prev
New AHA/ACC Cholesterol Guic More Personalized Care; New T Options
Further Cardiovascular Outcom With PCSK9 Inhibition in Subjec Risk
IMProved Reduction of Outcom Efficacy International Trial
ODYSSEY ESCAPE
ODYSSEY-COMBO-I
ODYSSEY-COMBO-II
ODYSSEY-HIGH-FH
ODYSSEY-LONG-TERM

"Very High Risk" in ASCVD Patients
2018 AHA/ACC Guidelines

Major ASCVD Events

- ACS within 12 months
- Prior MI
- Prior ischemic stroke
- Symptomatic PAD

Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.

"Very High Risk" in ASCVD Patients
2018 AHA/ACC Guidelines (cont)

Major ASCVD Events

- ACS within 12 months
- Prior MI
- Prior ischemic stroke
- Symptomatic PAD

High Risk Conditions

- Age ≥ 65 years
- Heterozygous FH
- Prior CABG or PCI
- Diabetes
- Hypertension
- CKD
- Current smoking
- LDL-C ≥ 100 mg/dL on maximally tolerated statin
- History of heart failure

Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.

"Very High Risk" in ASCVD Patients
2018 AHA/ACC Guidelines (cont)

Major ASCVD Events

- ACS within 12 months
- Prior MI
- Prior ischemic stroke
- Symptomatic PAD

Definition: Very High Risk

- Multiple major ASCVD events or
- 1 major ASCVD event and multiple high risk conditions

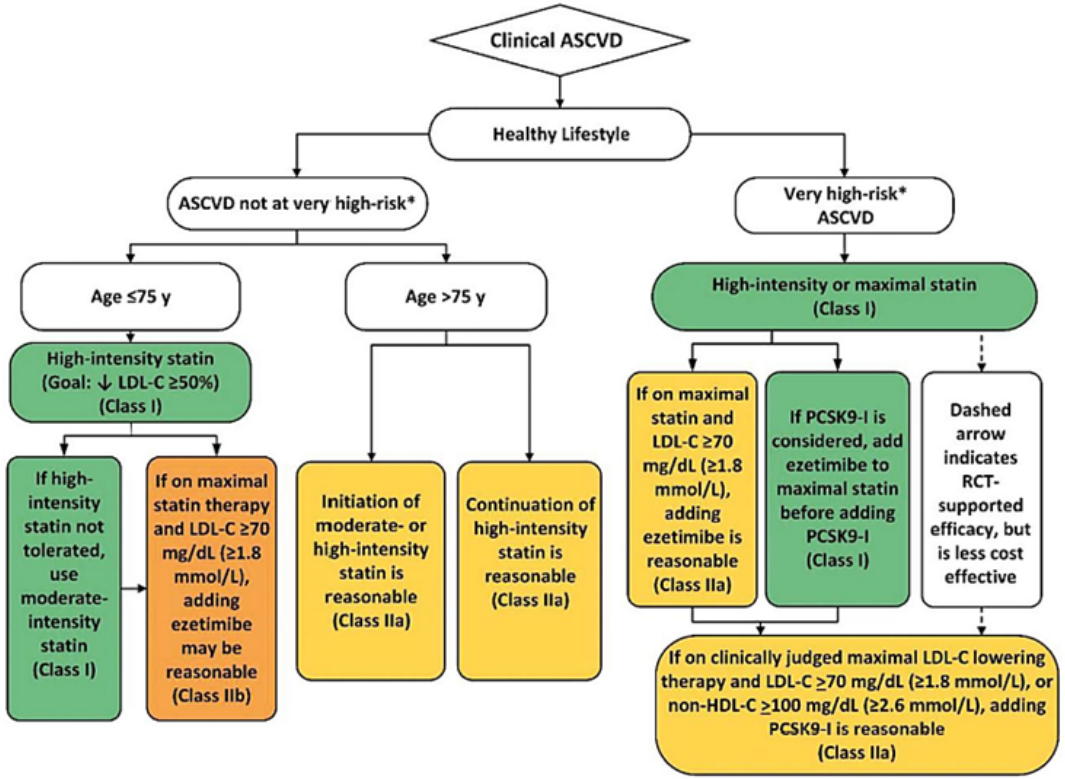
Not a one-time assessment

High Risk Conditions

- Age ≥ 65 years
- Heterozygous FH
- Prior CABG or PCI
- Diabetes
- Hypertension
- CKD
- Current smoking
- LDL-C ≥ 100 mg/dL on maximally tolerated statin
- History of heart failure

Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.

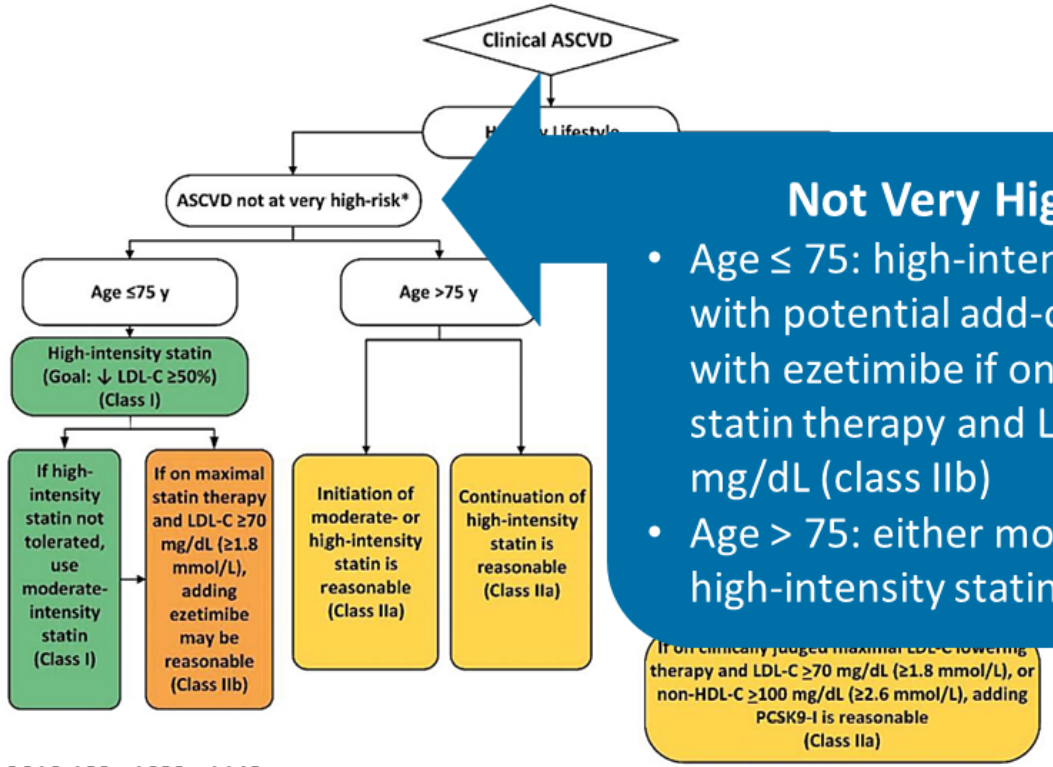
AHA/ACC Clinical ASCVD Algorithm



Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.

Age is not a key consideration in the very high risk group

Clinical ASCVD Algorithm (cont)



Not Very High Risk

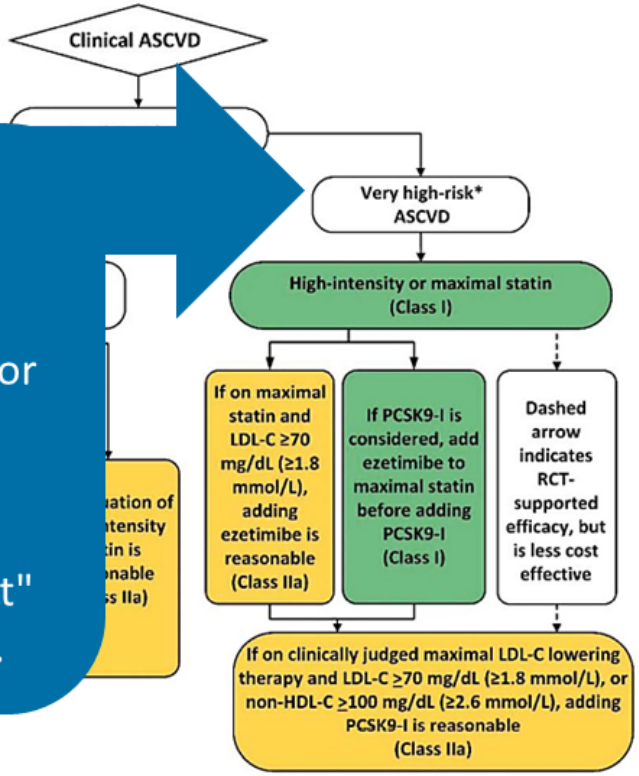
- Age ≤ 75: high-intensity statin first, with potential add-on therapy with ezetimibe if on maximal statin therapy and LDL-C is ≥ 70 mg/dL (class IIb)
- Age > 75: either moderate- or high-intensity statin (class IIa)

Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.

Clinical ASCVD Algorithm

Very High Risk ASCVD

- Step 1: high-intensity or maximally tolerated statin
- Step 2: If inadequate response or LDL-C is ≥ 70 mg/dL, ezetimibe and PCSK9 inhibitor are considered. Guideline recommends an "ezetimibe first" approach due to cost concerns.



Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143.

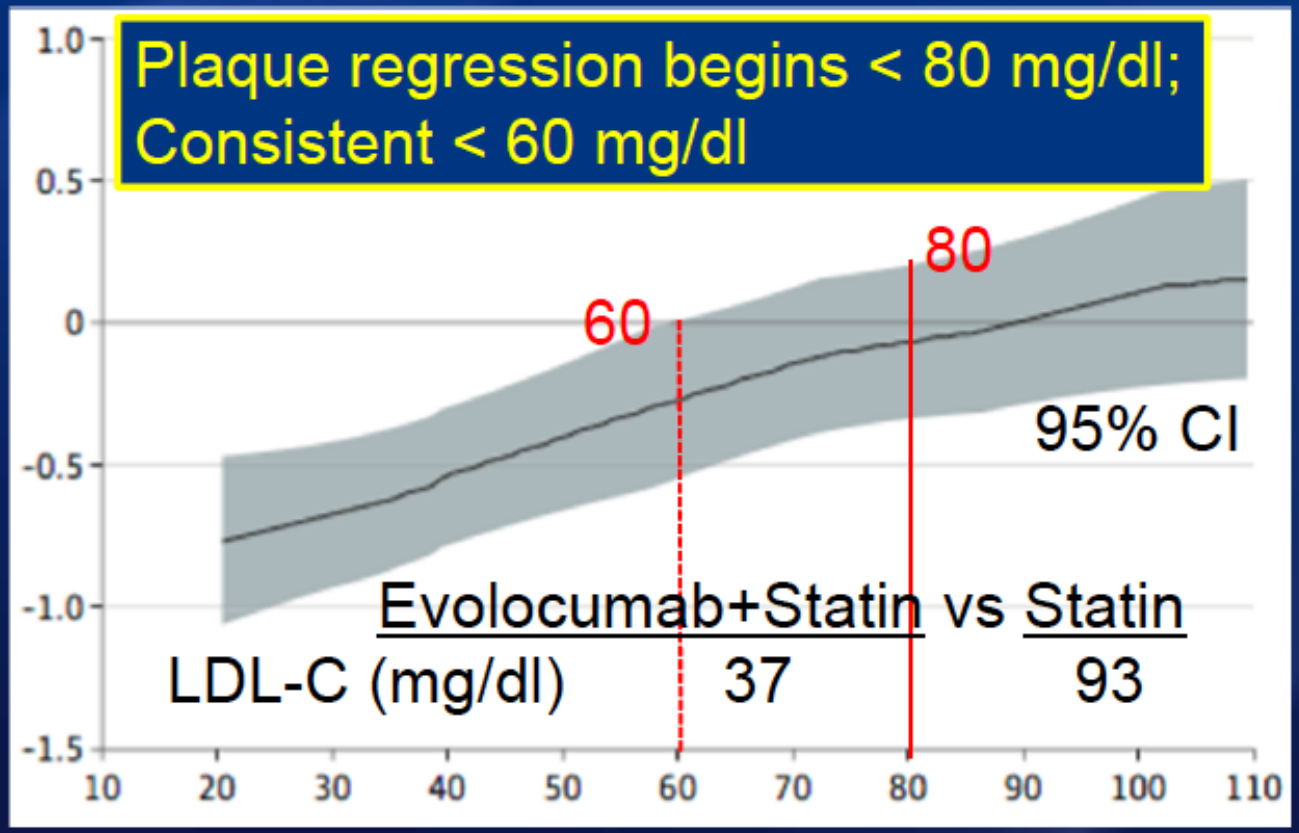
Getting to Goal Is Possible

Expected Benefit of Lipid-Lowering Therapies

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%

Mach F, et al. *Eur Heart J*. 2020;41:111-188.

Relationship Between Achieved LDL-C and Change in Percent Atheroma Volume



MAYO CLINIC

Nicholls et al JAMA Nov 2016

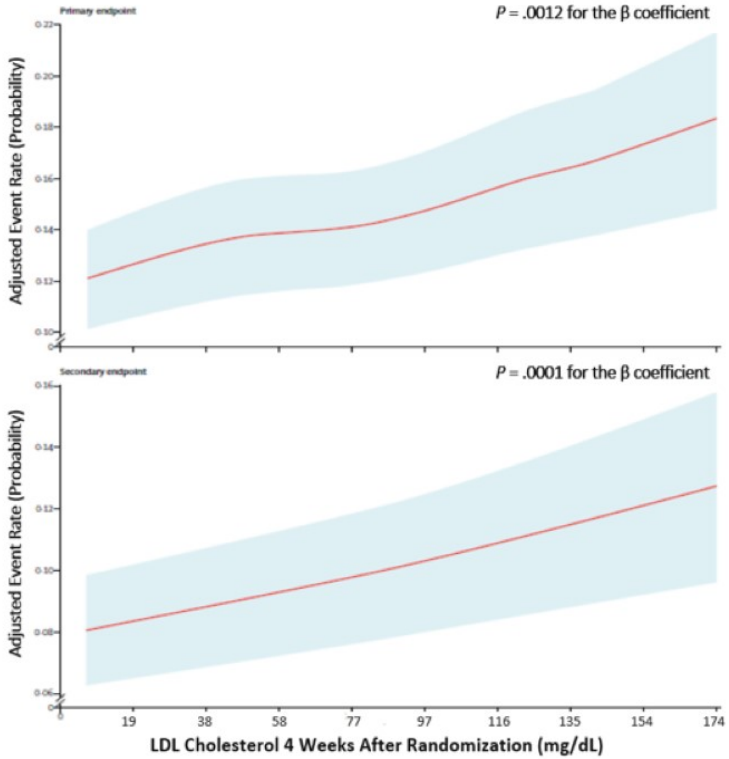
CI=95% Confidence Interval

Lower LDL-C Is Better for CV Outcomes

Data From FOURIER

Primary efficacy endpoint:
composite of CV death, MI, stroke, coronary revascularization, or hospital admission for unstable angina

Key secondary efficacy endpoint:
composite of CV death, MI, or stroke



Lower LDL-C, lower risk for MACE

Giugliano RP, et al. *Lancet*. 2017;390:1962-1971.

"Very High Risk" in ASCVD Patients
2019 ESC/EAS Guidelines

2016 ESC/EAS Guidelines[a]

- **Very high risk:** < 1.8 mmol/L (< 70 mg/dL) *or* ≥ 50% ↓ if LDL-C 1.8 to 3.5 mmol/L (70-135 mg/dL)
- **High risk:** < 2.6 mmol/L (< 100 mg/dL) *or* ≥ 50% ↓ if LDL-C 2.6 to 5.2 mmol/L (100-200 mg/dL)
- **Moderate risk:** < 3 mmol/L (< 115 mg/dL)
- **Low risk:** < 3 mmol/L (< 115 mg/dL)

LOWER

2019 ESC/EAS Guidelines[b]

- **Very high risk: < 1.4 mmol/L** (< 55 mg/dL) *and* ≥ 50% ↓
- **High risk:** < 1.8 mmol/L (< 70 mg/dL) *and* ≥ 50% ↓
- **Moderate risk:** < 2.6 mmol/L (100 mg/dL)
- **Low risk:** *(no change from 2016)* < 3 mmol/L (< 116 mg/dL)

a. Catapano AL, et al. *Eur Heart J*. 2016;37:2999-3058; b. Mach F, et al. *Eur Heart J*. 2020;41:111-188.

64 yo male with recent ACS, h/o DM, HTN and CKD. Current therapy rosuvastatin 40 mg with 53% reduction from baseline. Current LDL of 77 mg/dl and normal triglycerides.

What is the next best option according to the 2018 AHA/ACC multi-society guidelines?

1. Add Icosapent ethyl (Vascepa)
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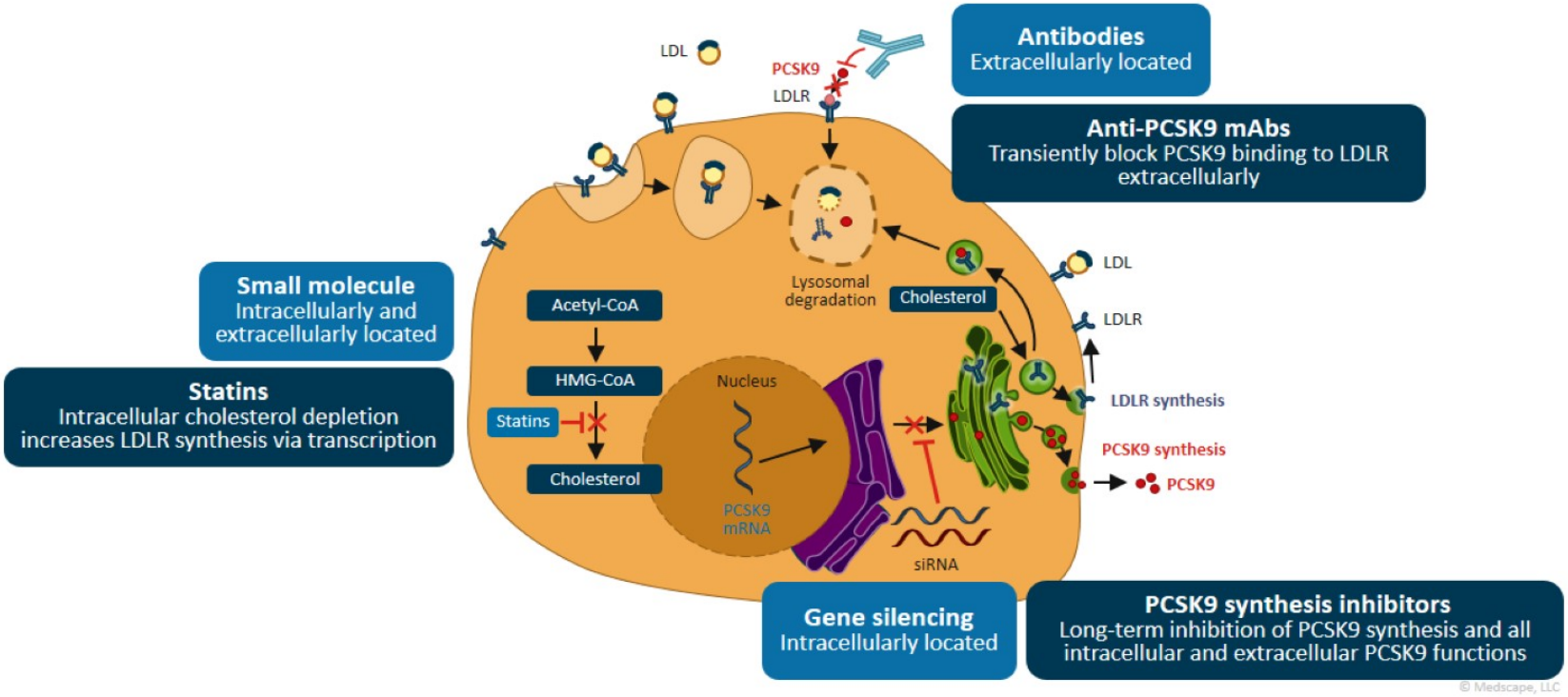
3. Add ezetimibe 10 mg
4. Add PCSK9i

Emerging Therapies

Therapeutic Approaches to Reducing LDL-C

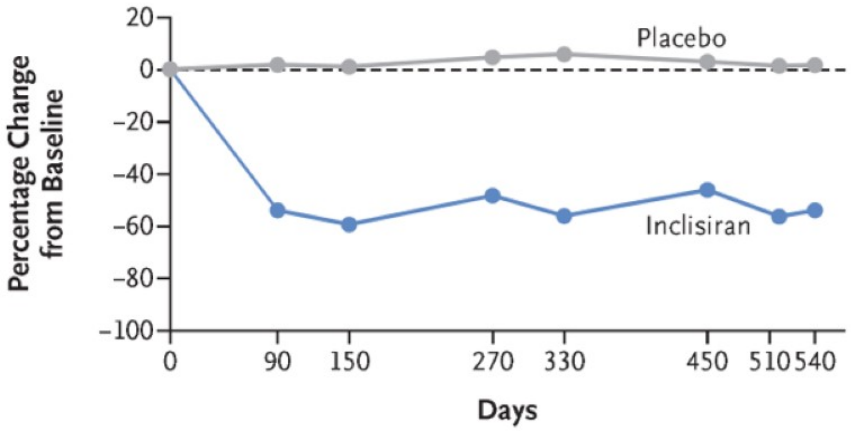


Nordestgaard BG, et al. *Nat Rev Cardiol*. 2018;15:261-272.

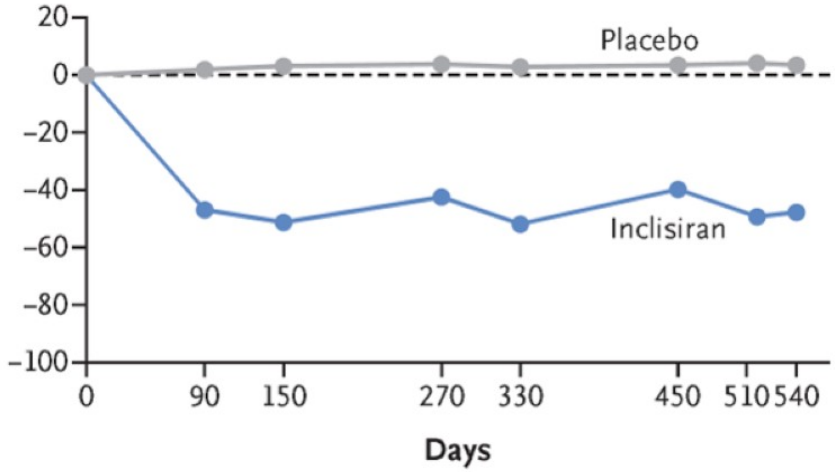
siRNA to PCSK9

ORION-10 and ORION-11: Efficacy of Inclisiran

Percentage Change in LDL-C, ORION-10 Trial

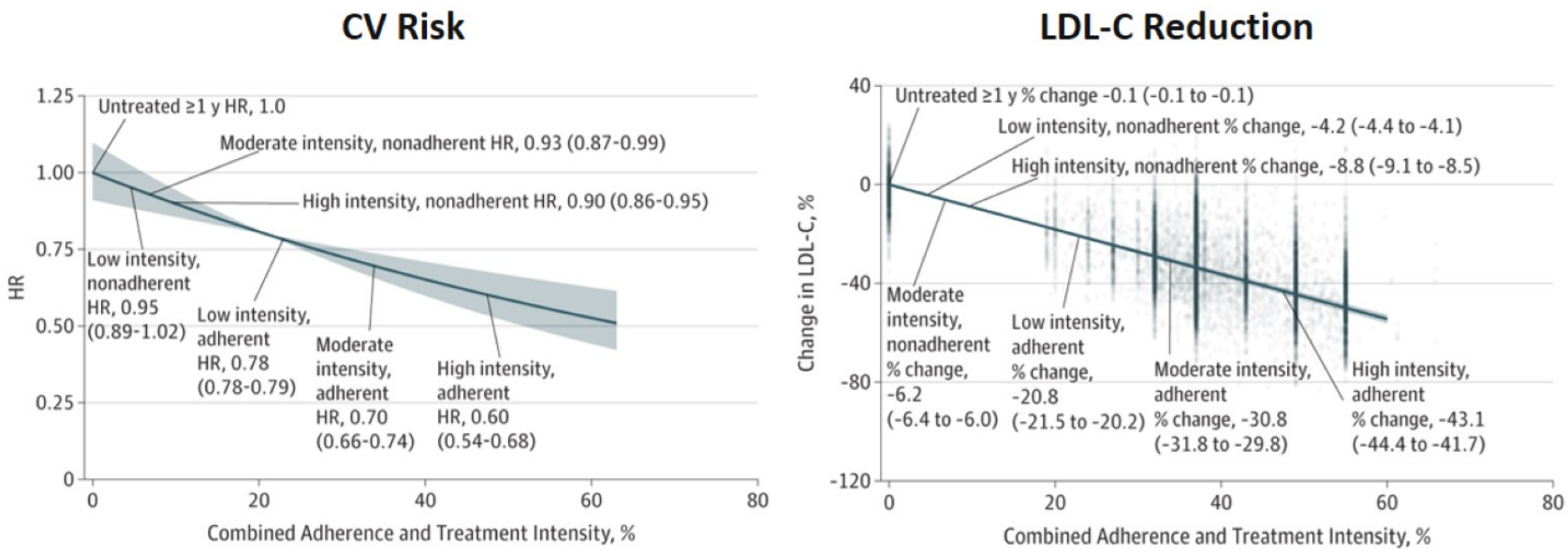


Percentage Change in LDL-C, ORION-11 Trial



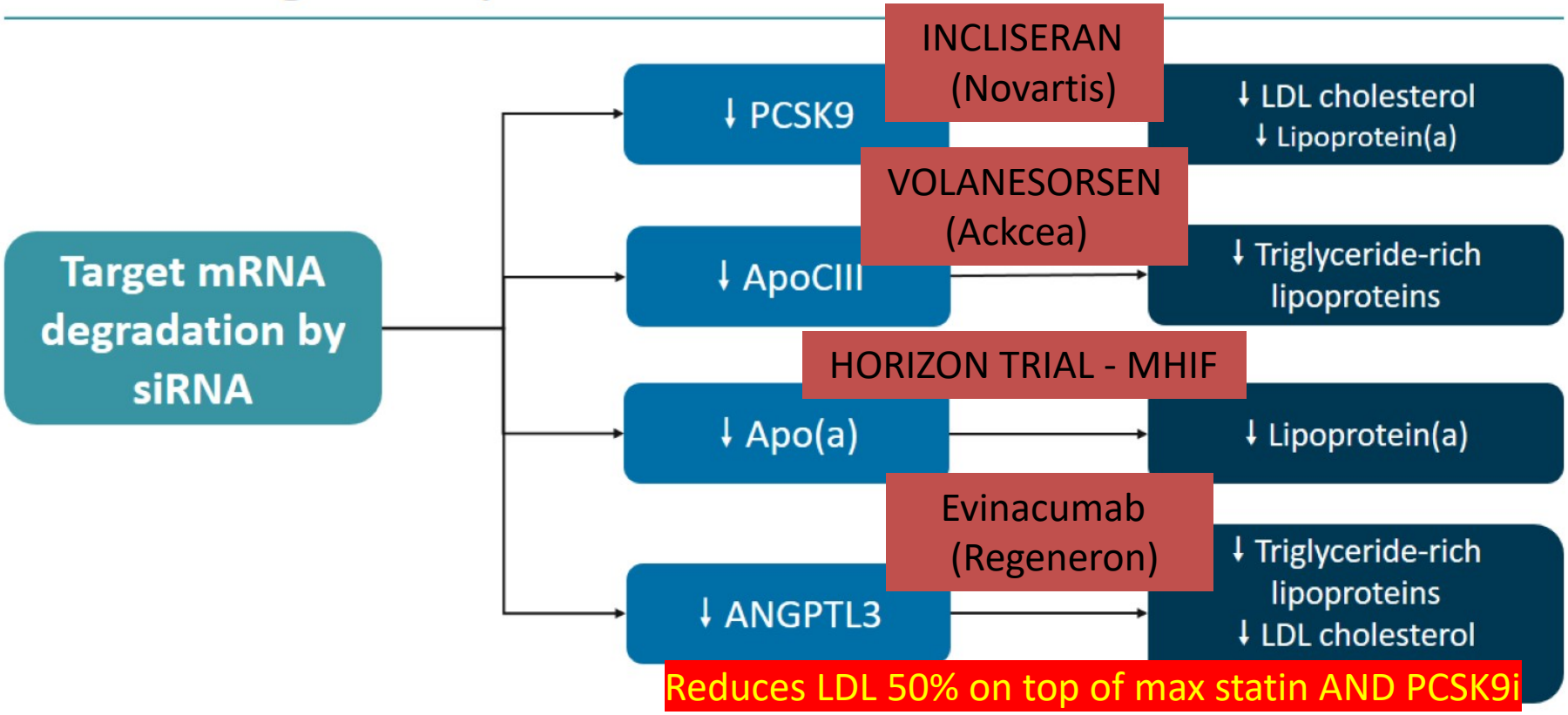
Ray KK, et al. *N Engl J Med.* 2020;382:1507-1519.

CV Risk Reduction and LDL-C Reduction Based on Adherence and Treatment Intensity



Khunti K, et al. *JAMA Netw Open*. 2018;1:e185554.

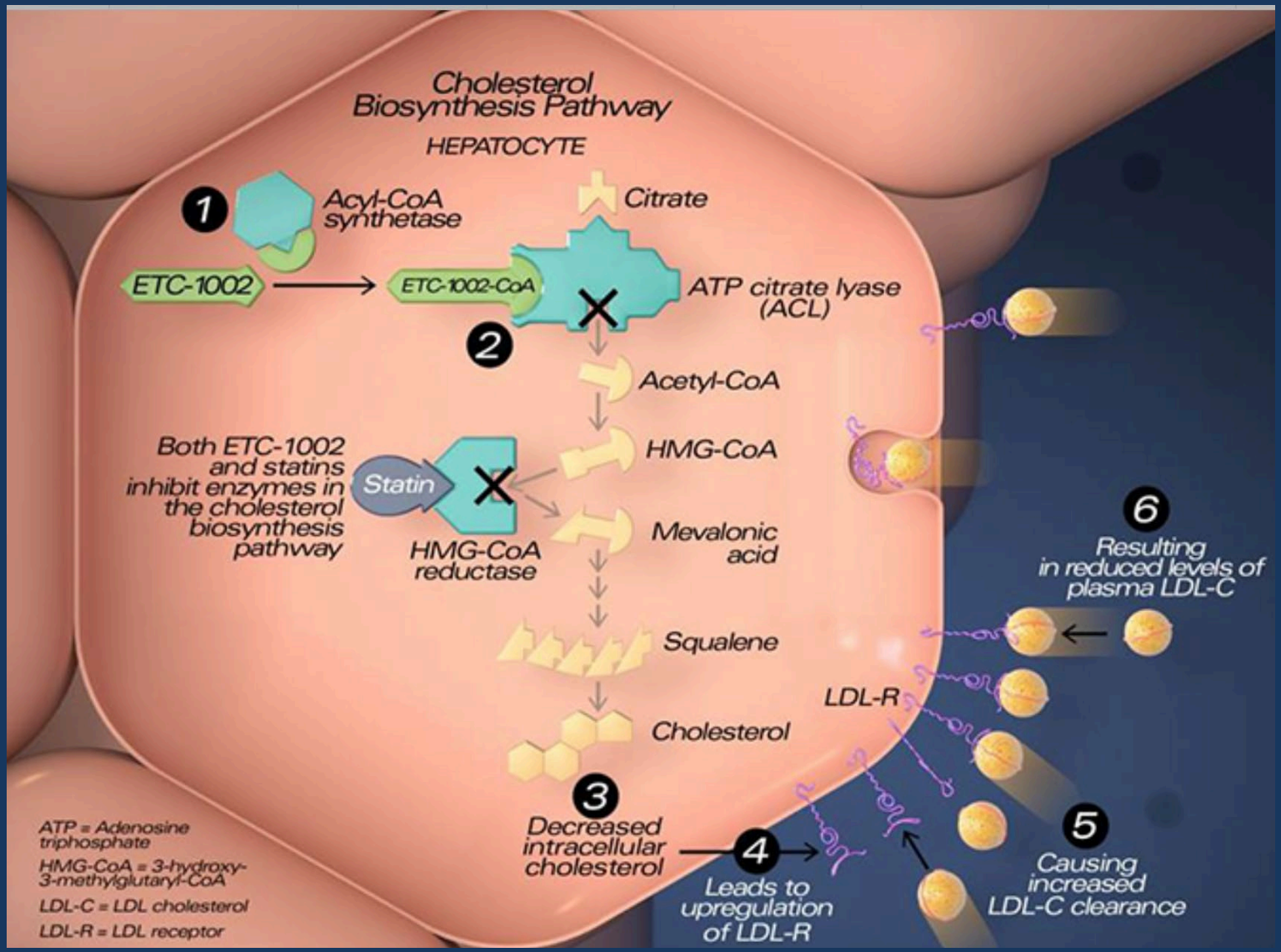
siRNA Targets Beyond PCSK9 and LDL-C



Katzmann JL, et al. *J Am Coll Cardiol*. 2020;76:563-579.


The End

Bempedoic Acid: Esperion Pharmaceuticals
Bemedoic acid 180 mg+/-exetibibe 10 mg

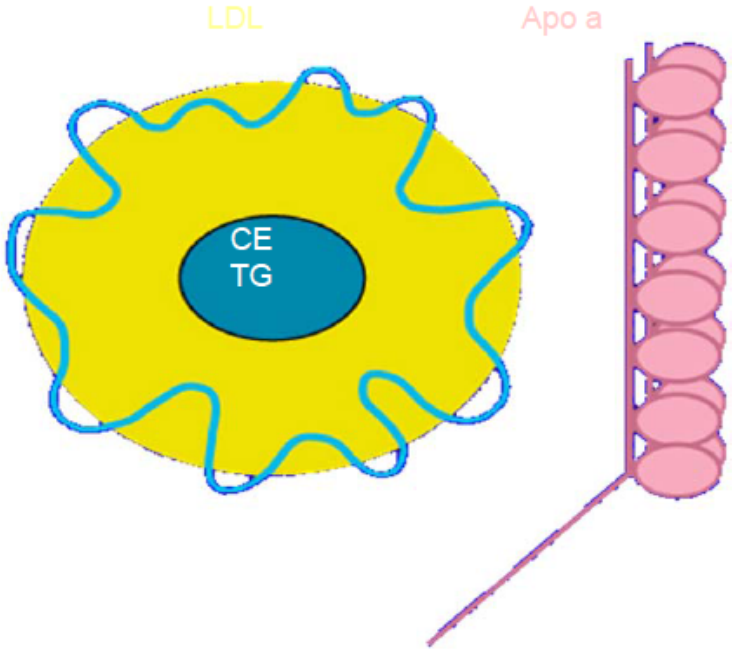


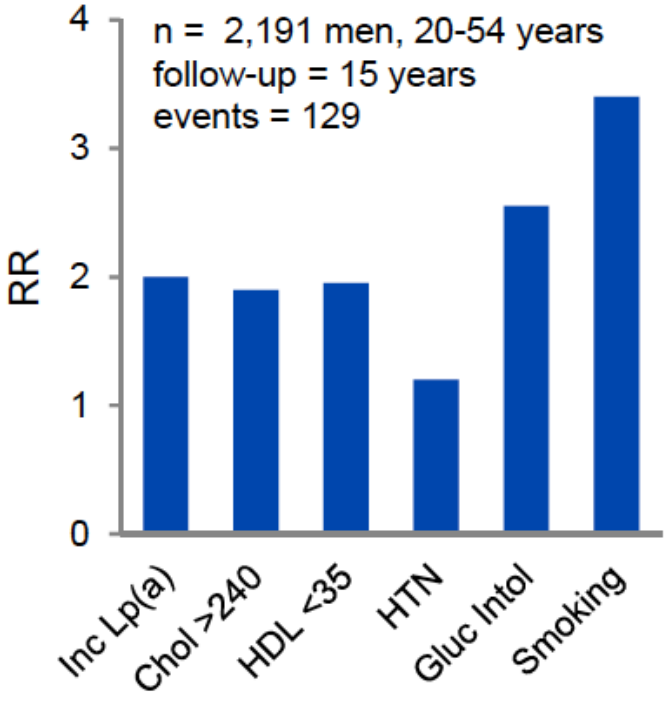
	CLEAR Harmony (1002-040) (N=2,230) (BA: n=1,488) (placebo: n=742)	CLEAR Wisdom (1002-047) (N=779) (BA: n=522) (placebo: n=257)	CLEAR Serenity (1002-046) (N=345) (BA: n=234) (placebo: n=111)	CLEAR Tranquility (1002-048) (N=269) (BA: n=181) (placebo: n=88)	Bempedoic Acid/Ezetimibe Combination Tablet (1002FDC-053) (N=382) (BA/EZE: n=108) (BA: n=110) (EZE: n=109) (placebo: n=55)
LDL-C Reduction (% reduction from baseline, placebo corrected)	-18.1% (*P*<0.001) **BA:** -16.5% **Placebo:** +1.6%	-17.4% (*P*<0.001) **BA:** -15.1% **Placebo:** +2.4%	-21.4% (*P*<0.001) **BA:** -22.6% **Placebo:** -1.2%	-28.5% (*P*<0.001) **BA:** -23.5% **Placebo:** +5.0%	-29.0% (*P*<0.001) **BA/EZE:** -31.5% **BA:** -17.7% **Ezetimibe:** -21.0%

- Long term nature of new therapies
- Improved adherence
- Simple dosing with lasting effects
- Can target various protein modulators

Lp (a)

Lp(a)



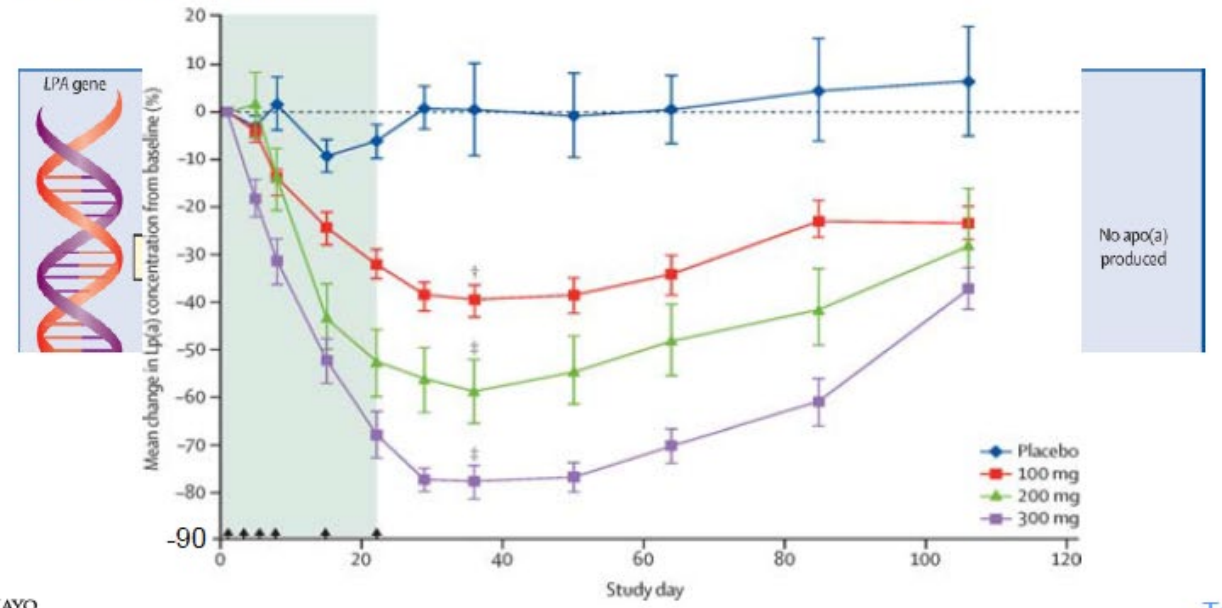


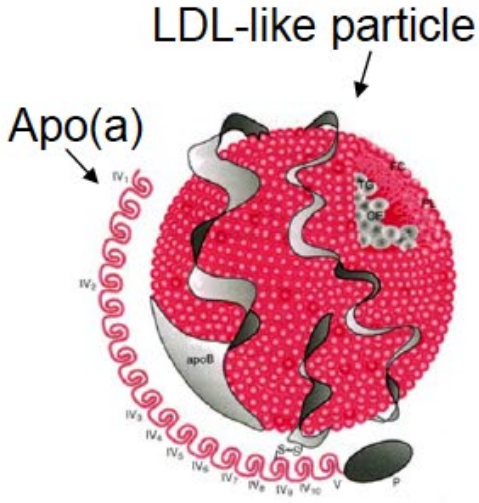
Bostom: JAMA 276:544, 1996

Apo(a) antisense technology

RCT, double-blind, placebo-controlled, phase 1, UK

ISIS-APO(a)Rx





Tsimikas etal Lancet 386:1472–1483, 2015

HORIZON TRIAL

RESEARCH CONTACT:
Steph Ebnet
Stephanie.ebnet@allina.com | 612-863-6286

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	7680 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Randomized Double-blind, Placebo-controlled, Multicenter Trial Assessing the Impact of Lipoprotein (a) Lowering With TQJ230 on Major Cardiovascular Events in Patients With Established Cardiovascular Disease
Actual Study Start Date :	December 12, 2019
Estimated Primary Completion Date :	March 1, 2024
Estimated Study Completion Date :	March 1, 2024

AKCEA-APO(a)-LRx, from Akcea Therapeutics, an affiliate of Ionis Pharmaceuticals, for targeted cardiovascular therap

TQJ230 80 mg injected monthly administered subcutaneously

Key Inclusion Criteria

- Lp(a) ≥ 70 mg/dL at the screening visit, measured at the Central laboratory
- Myocardial infarction: ≥ 3 months from screening and randomization to ≤ 10 years prior to the screening visit
- Ischemic stroke: ≥ 3 months from screening and randomization to ≤ 10 years prior to the screening visit
- Clinically significant symptomatic peripheral artery disease

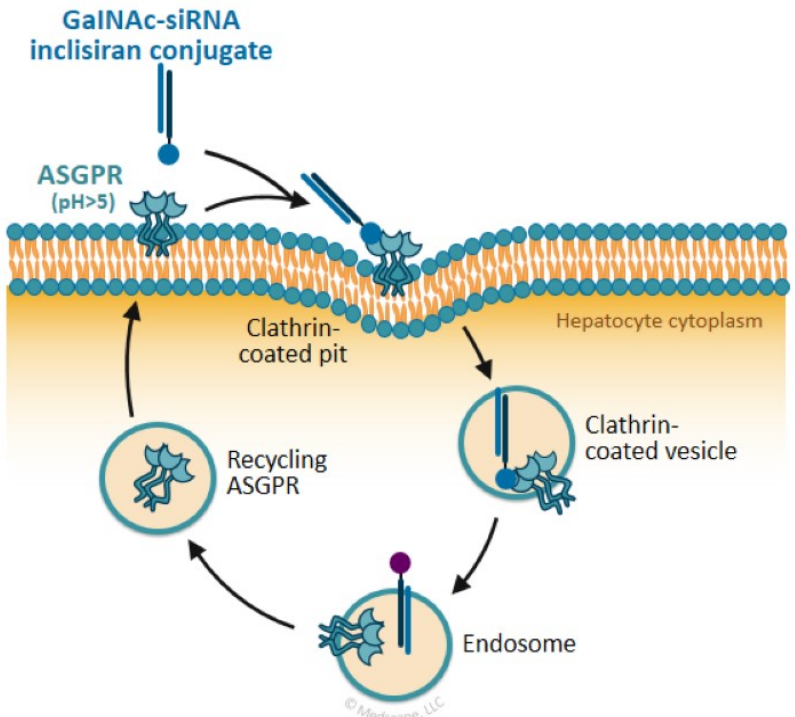
GalNAc-siRNA Conjugate Facilitates Hepatic Uptake

Asialoglycoprotein receptor (ASGPR)

- Highly expressed in hepatocytes only
- High rate of uptake

Inclisiran*

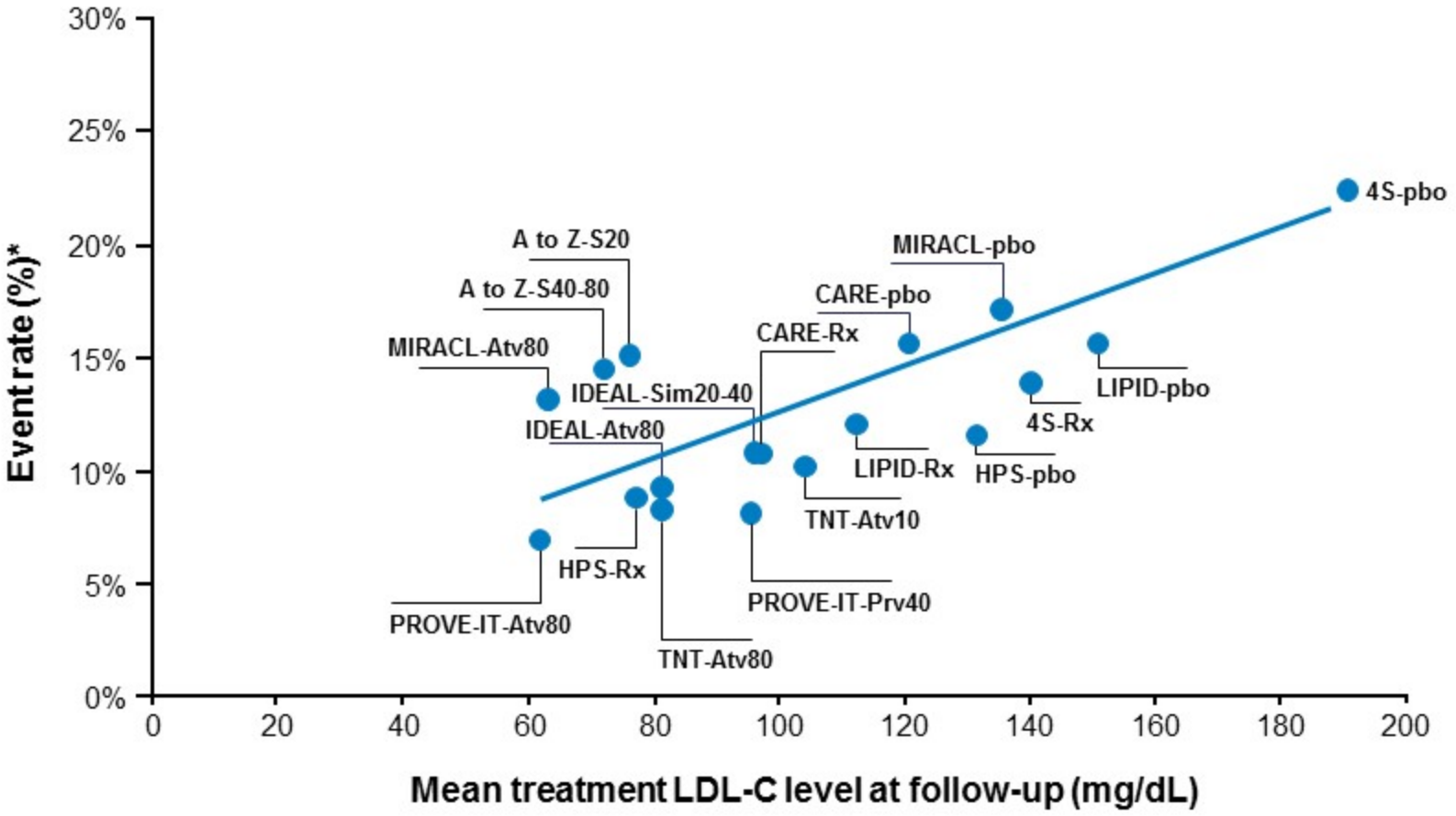
- siRNA conjugated to N-acetylgalactosamine (GalNAc)
- Subcutaneous administration
- Targeted delivery to hepatocytes



*Inclisiran is pending FDA and EMA approval for adults with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia who have elevated LDL-C while on statin therapy (as of October 6, 2020)

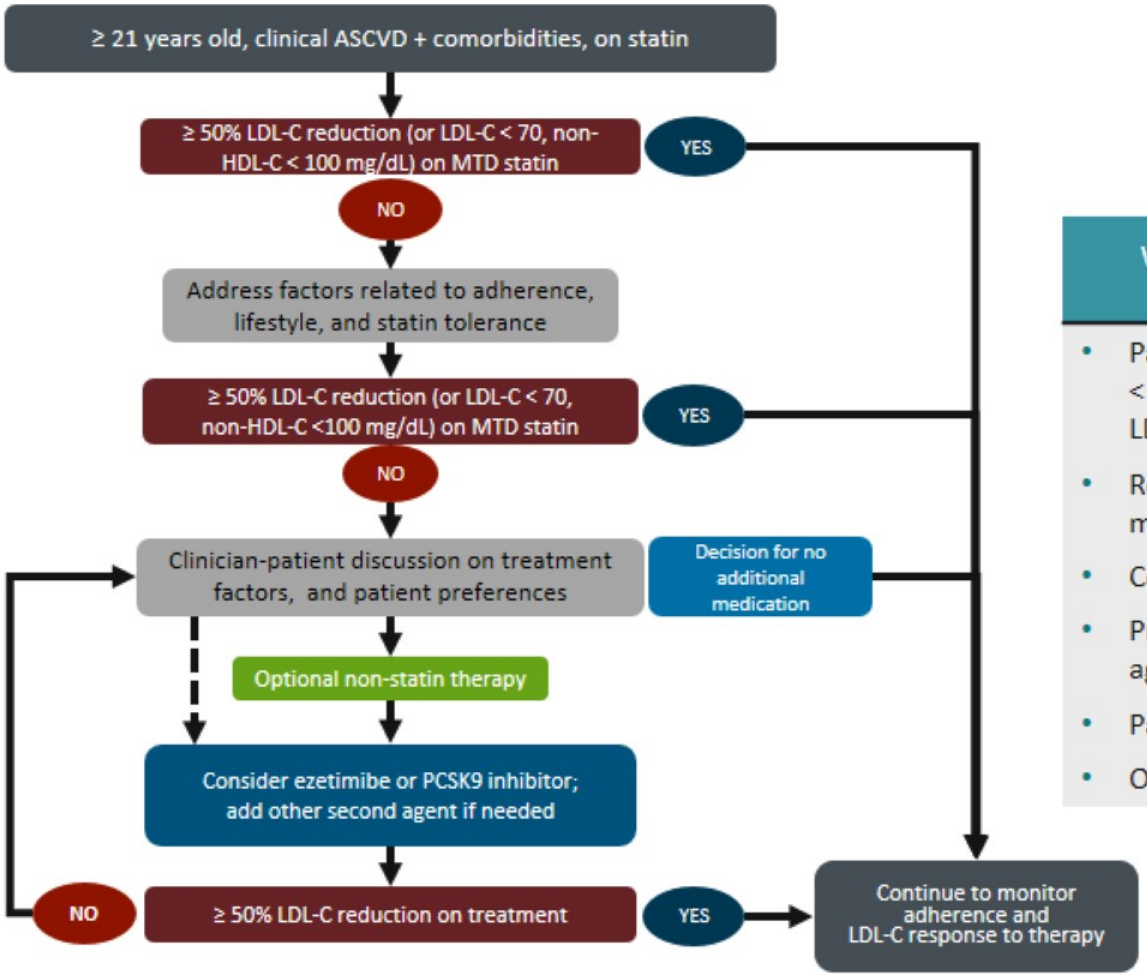
Springer AD, et al. *Nucleic Acid Ther.* 2018;28:109-118.

There Is a Linear Correlation Between LDL-C Lowering and Risk of CV Events



*Secondary prevention trials.
Adapted from Raymond C, et al. *Clev Clin J Med.* 2014; 81:11-19.

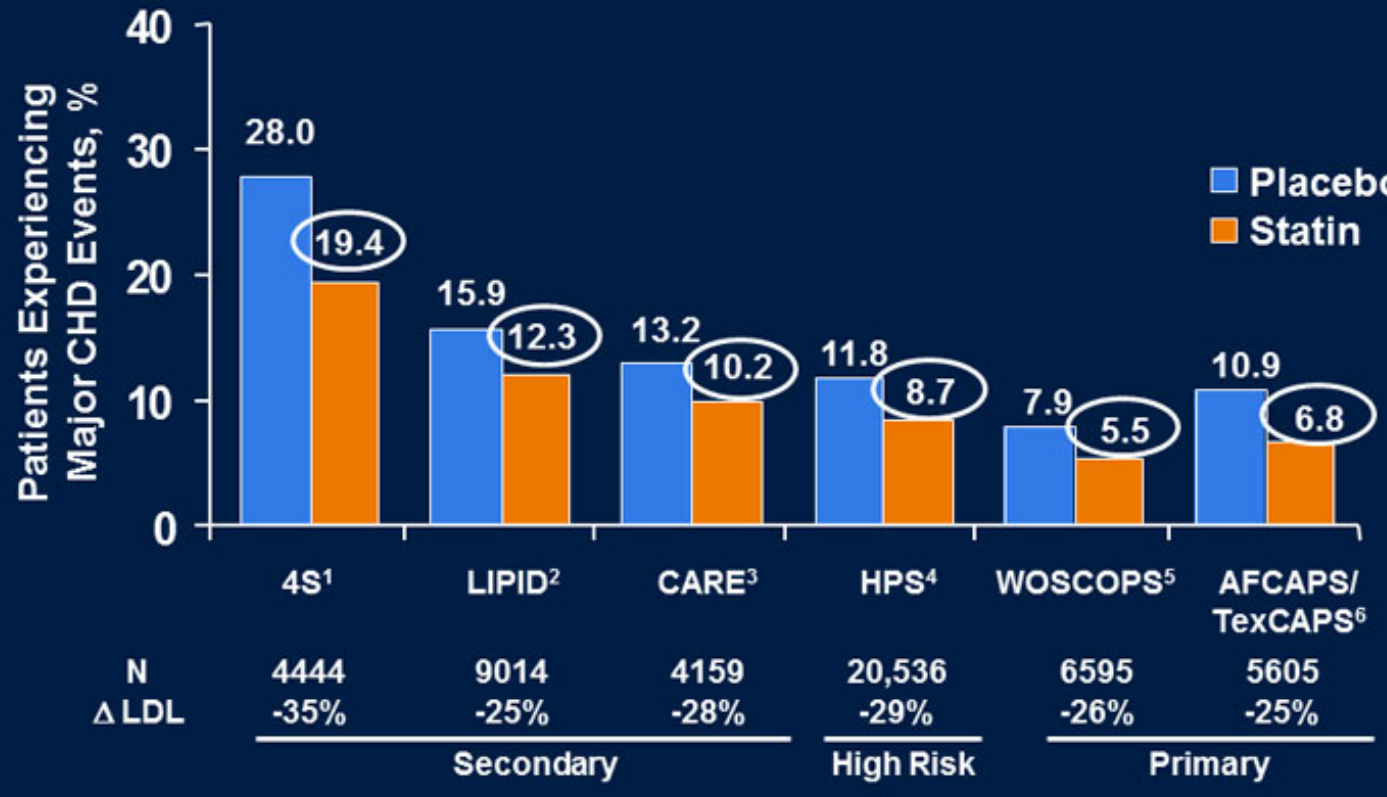
2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway: Nonstatin Therapies for ASCVD



When to Choose Ezetimibe?	When to Choose PCSK9 Inhibitor?
• Patients requiring < 25% additional LDL-C lowering	• Patients requiring > 25% additional LDL-C lowering
• Recent ACS < 3 months	• Cost-benefit considerations should be discussed
• Cost considerations	• Administration, dosing schedule, and storage should be discussed
• Preference of oral agent	
• Patient preference	
• Other risk factors	

Reprinted from *J Am Coll Cardiol*, 70, Lloyd-Jones DM, et al., 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways, 1785-1822., Copyright 2017, with permission from Elsevier.

Residual Cardiovascular Risk in Placebo-Controlled Statin Trials



[1]4S Group. *Lancet.* 1994;344(8934):1383-1389. [2]LIPID Study Group. *N Engl J Med.* 1998;339(19):1349-1357.
[3]Sacks FM, et al. *N Engl J Med.* 1996;335(14):1001-1009. [4]HPS Collaborative Group. *Lancet.* 2002;360(9326):7-22.
[5]Shepherd J, et al. *N Engl J Med.* 1995;333(20):1301-1307. [6]Downs JR, et al. *JAMA.* 1998;279(20):1615-1622.