Baptist Health
HEART INSTITUTE

Cardiac Pharmacology
Session 2

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Disclosures: None

PCSK9 Inhibitors –Updates & Trials -

A. GLAGOV TRIAL
B. EBINGHAUSER TRIAL
C. EVOPACS TRIAL

Colchicine in patients with AMI -COLCOT Trial – NEJM 2019

ARB/Neprilysin inhibition in HFpEF- PARAGON –HF Trial (NEJM 2019; 381: 1609)

Dapagliflozin in Patients With Heart Failure and Reduced Ejection Fraction - DAPA-HF trial (*Engl J Med* 2019;381:1995.)

Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58 - DECLARE–TIMI 58 Trial (*N Engl J Med* 2019;380:347-57.)

Icosapent Ethyl for Hypertriglyceridemia- REDUCE-IT Trial (NEJM 2019; 380: 11)

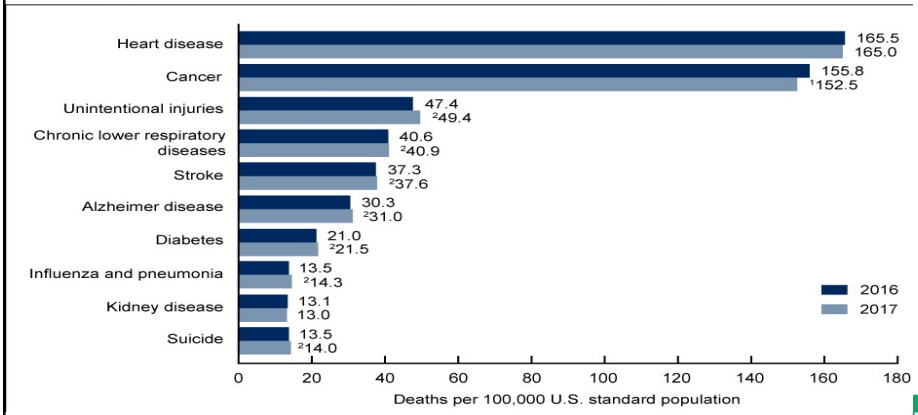
PCSK9 INHIBITORS

- Background:
  - Cardiovascular Mortality
  - Holy Grail of Cardiology – 'Plaque Regression'-GLAGOV TRIAL
  - Financial Aspects
  - EBINGHAUSER TRIAL
  - EVOPACS TRIAL

PCSK9 INHIBITORS

- Despite the present advances in pharmacotherapy, atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of mortality worldwide.

Figure 4. Age-adjusted death rates for the 10 leading causes of death: United States, 2016 and 2017

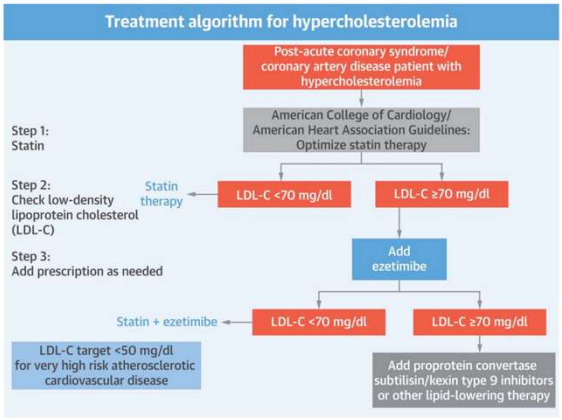


PCSK9 INHIBITORS

- Low density lipoprotein-cholesterol (LDL-C) lowering is the primary target for ASCVD risk reduction, showing demonstrable benefits in mortality.
- However, 70% of events occur even in the presence of statins.
- This residual risk may be approached with additional LDL-C reduction.
- Statin intolerance is a common clinical concern affecting adherence and the benefit with statins.
- Significant Interindividual variation of individual lipid-lowering.
- Following rapid development, proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is now a great new tool in our armanterium for the goal of CVD risk reduction.
- Monoclonal antibodies have demonstrated LDL-C lowering of up to 57% as monotherapy and up to 73% when added to

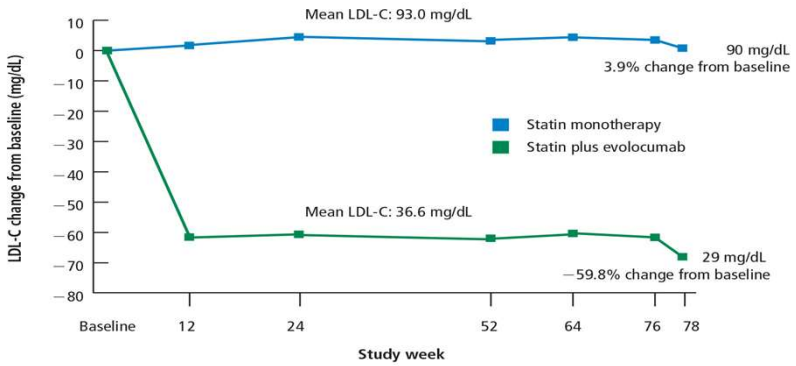
PCSK9 INHIBITORS

CENTRAL ILLUSTRATION: Clinical Algorithm for Managing Low-Density Lipoprotein Cholesterol



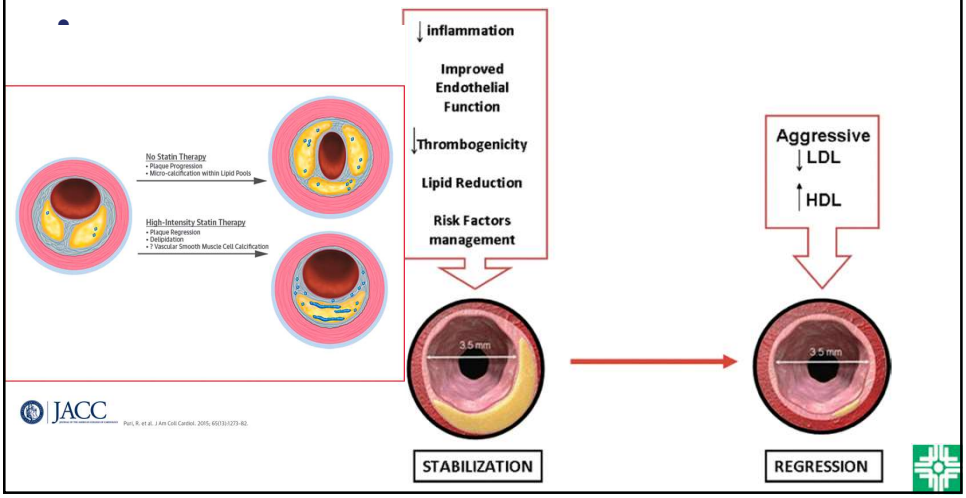
Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314-29.

PCSK9 INHIBITORS

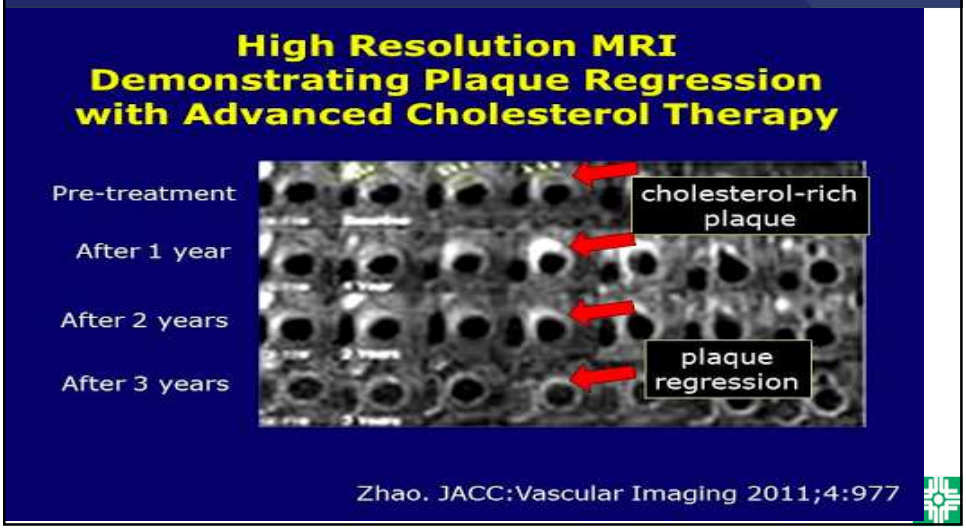


No. of patients							
Statin monotherapy	484	446	441	447	441	425	418
Statin + evolocumab	484	456	452	444	449	426	434

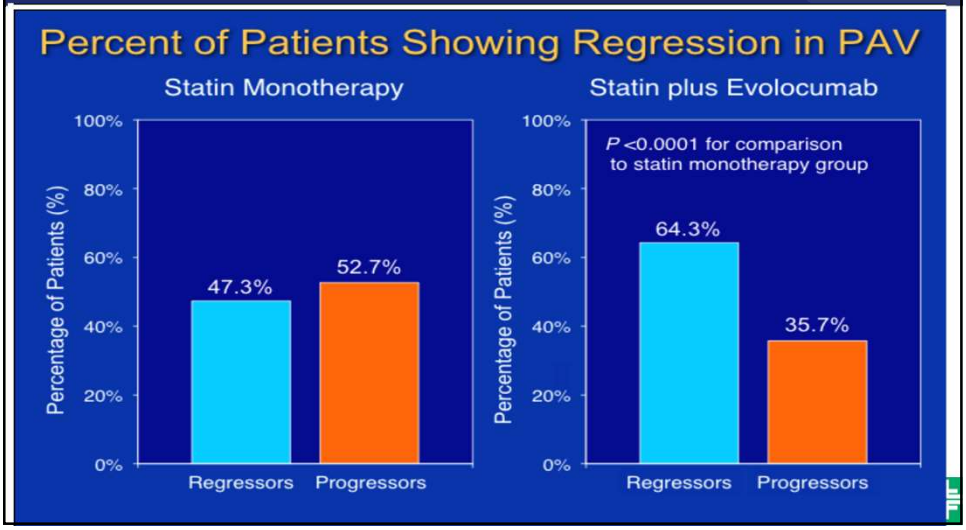
PCSK9 INHIBITORS



PCSK9 INHIBITORS



PCSK9 INHIBITORS – GLAGOV STUDY



PCSK9 INHIBITORS – GLAGOV STUDY

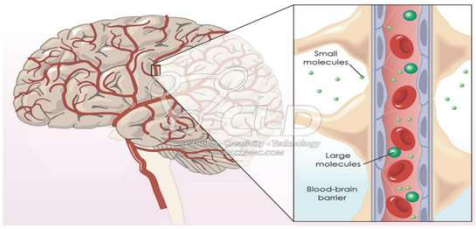
Adverse Clinical Events and Safety Findings

Event	Placebo (N=484)	Evolocumab (N=484)
Death	0.8%	0.6%
Nonfatal MI	2.9%	2.1%
Nonfatal Stroke	0.6%	0.4%
Hosp. for Unstable Angina	0.8%	0.6%
Coronary Revascularization	13.6%	10.3%
First Major Cardiovascular Event	15.3%	12.2%
Injection site reactions	0%	0.4%
Anti-evolocumab binding antibody	NA	0.2%
Neutralizing antibodies	NA	0%
Neurocognitive events	1.2%	1.4%
New onset diabetes	3.7%	3.6%
Myalgia	5.8%	7.0%

PCSK9 INHIBITORS – EBBINGHAUS TRIAL

- In 2012 FDA added risk of adverse cognitive effects to label of all statins

Brain synthesizes cholesterol locally



mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

PCSK9 INHIBITORS – EBBINGHAUS TRIAL

FOURIER Study Population: 27,564 stable patients with CV disease, age 40-85 years; additional CV risk factor(s), LDL ≥ 70 mg/dL (or non-HDL ≥ 100)

RANDOMIZED DOUBLE BLIND

Placebo SC Q2W or QM

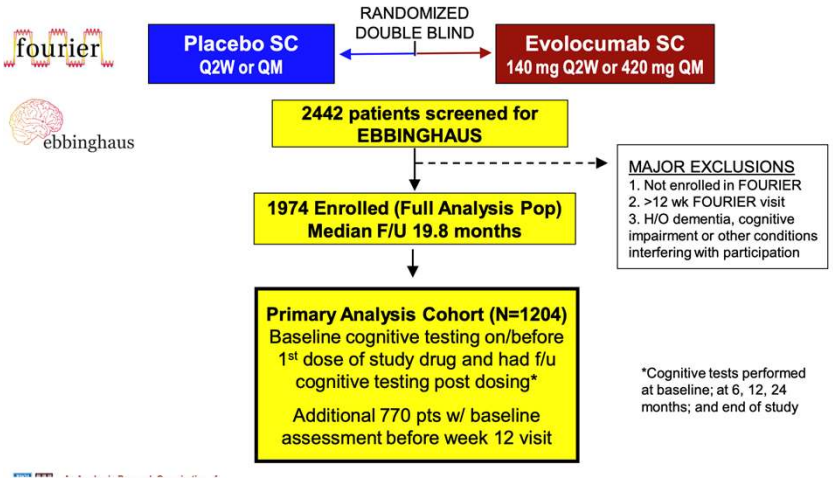
Evolocumab SC 140 mg Q2W or 420 mg QM

26 mos. mean f/u

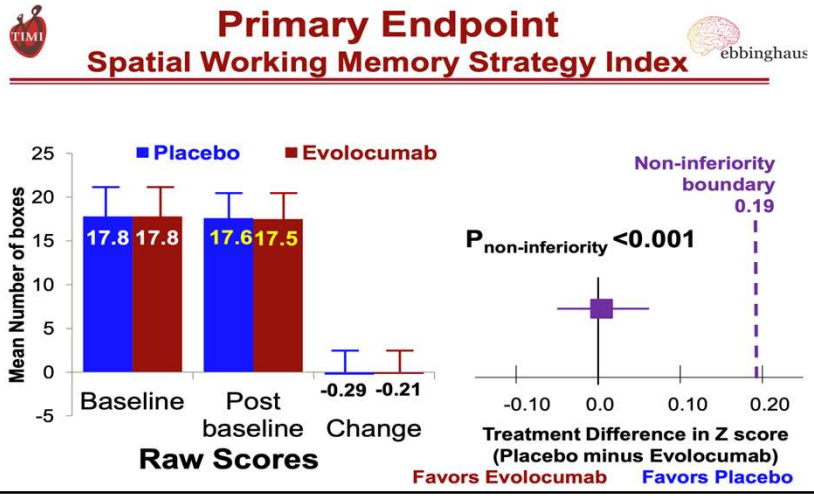
Evolocumab on background of statin c/w placebo:

- **↓ LDL-C by 59%**
- **↓ CV outcomes on background of statin therapy**
- **Safe and well-tolerated**

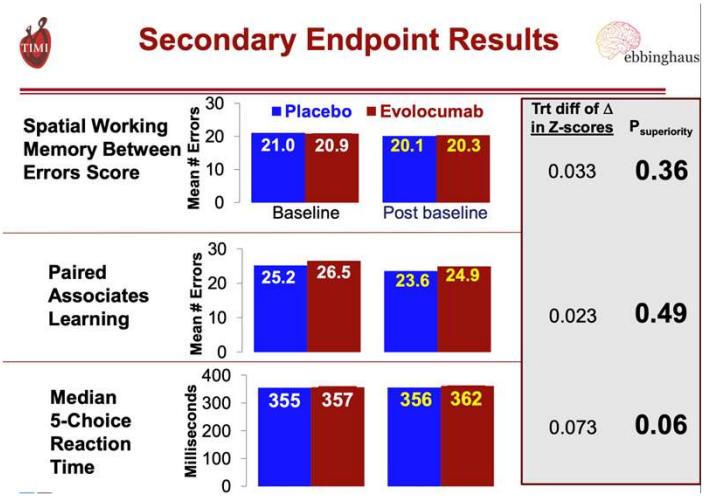
PCSK9 INHIBITORS – EBBINGHAUS TRIAL



PCSK9 INHIBITORS – EBBINGHAUS TRIAL



PCSK9 INHIBITORS – EBBINGHAUS TRIAL



PCSK9 INHIBITORS – EBBINGHAUS TRIAL

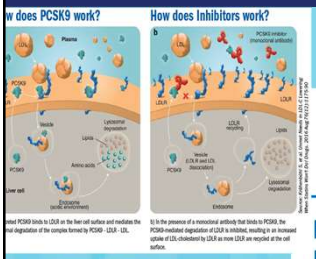
- In patients with known cardiovascular disease on background statin followed for 20 months
- - No differences btw evolocumab vs placebo
- A. A battery of cognitive tests
- B. Patient-reported everyday cognition
- C. Adverse cognitive events reported by MD

- - No evidence of differences in cognitive tests by achieved nadir LDL-C, even

PCSK9 INHIBITORS- EVOPACS TRIAL

- **Role of PCSK9 inhibition in the management of ACS (November 2019)**
- Early initiation of high-intensity statin therapy to reduce serum levels of low-density lipoprotein cholesterol (LDL-C) is recommended for all patients with an acute coronary syndrome (ACS).
- The addition of a PCSK9 inhibitor to statin therapy during initial hospitalization was evaluated in the EVOPACS trial
- The primary end point of a decrease in mean percentage change from baseline LDL-C was significantly lower with PCSK9 treatment at eight weeks compared with placebo. Additional studies, which evaluate clinical outcomes such as cardiac death or myocardial infarction, are needed prior to our using this class of drug during hospitalization for ACS.

PCSK9 INHIBITORS- EVOPACS TRIAL



Evolocumab for Early Reduction of LDL-Cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS)

Konstantinos C. Koskinas[1], Stephan Windecker[1], Giovanni Pedrazzini[2], Christian Mueller[3], Stéphane Cook[4], Christian M. Matter[5], Olivier Muller[6], Jonas Häner[1], Baris Gencer[7], Carmela Crijenica[2], Poorya Amini[8], Olga Deckarm[1], Juan F. Iglesias[7], Lorenz Räber[1], Dik Heg[8], François Mach[7]

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Koskinas KC, et al. *J Am Coll Cardiol*. 2019. [epub ahead of print]. doi.org/10.1016/j.jacc.2019.08.010.

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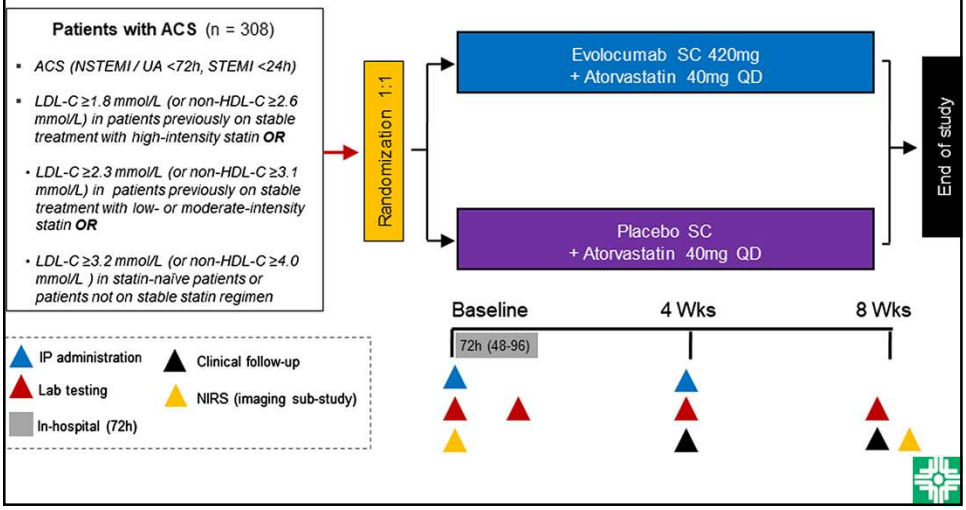
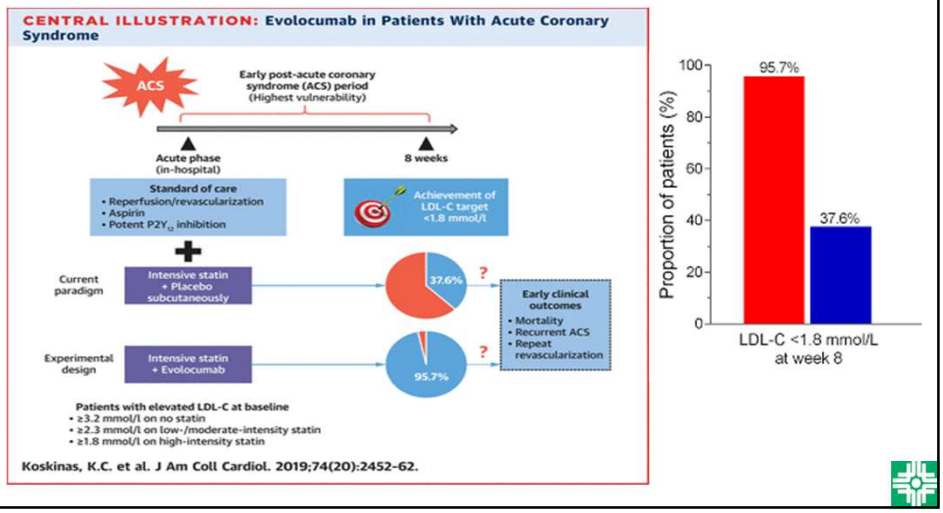
PCSK9 INHIBITORS- EVOPACS TRIAL



PCSK9 INHIBITORS- EVOPACS TRIAL



PCSK9 INHIBITORS- EVOPACS TRIAL

- Most patients (78.2%) had not been on previous statin treatment. Mean LDL-C levels decreased from 3.61 to 0.79 mmol/l at week 8 in the evolocumab group, and from 3.42 to 2.06 mmol/l in the placebo group; the difference in mean percentage change from baseline was −40.7% (95% confidence interval: −45.2 to −36.2; $p < 0.001$). LDL-C levels <1.8 mmol/l were achieved at week 8 by 95.7% of patients in the evolocumab group versus 37.6% in the placebo group. Adverse events and centrally adjudicated cardiovascular events were similar in both groups.
- **Conclusions** In this first randomized trial assessing a PCSK9 antibody in the very high-risk setting of ACS, evolocumab added to high-intensity statin therapy was well tolerated and resulted in substantial reduction in LDL-C levels, rendering >95% of patients within currently recommended target levels. (EVOlocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes [EVOPACS]; NCT03287609)

COLCOT TRIAL

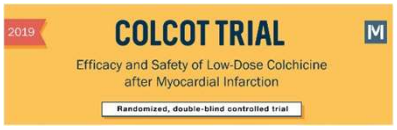
Benefits of colchicine in the treatment of acute MI (January 2020)

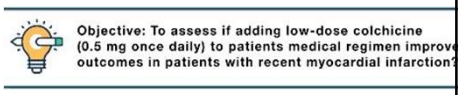
- Anti-inflammatory therapy for patients with acute myocardial infarction (MI) has shown some promise but has been limited by side effects.
- The efficacy and safety of colchicine were evaluated in a trial of over 4700 patients within 30 days of an acute MI who were randomly assigned to this agent (0.5 mg daily) or placebo .
- After a median follow-up of nearly two years, the risk of the primary composite endpoint (death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization) was approximately 25 percent lower in the colchicine group, a result primarily driven by lower rates of stroke and angina.
- Adverse events were similar between the two groups.
- Pending additional supporting evidence, we do not treat acute MI with colchicine.

COLCOT TRIAL

Benefits of colchicine in the treatment of acute MI (January 2020)

- There is a critical role for inflammation in the process of atherosclerotic heart disease.
- The CANTOS study was the first large cardiovascular outcomes trial to demonstrate a role for immunomodulation in reducing cardiovascular events. In CANTOS, IL-1B inhibitor canakinumab resulted in a 15% lower risk of cardiovascular events when compared to placebo in individuals with established atherosclerotic heart disease.
- Identification of an effective immunosuppressant with a safer adverse effect profile with the potential to reduce cardiovascular events in individuals with residual inflammatory risk represents a major unmet need.

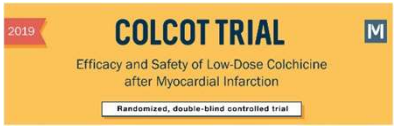


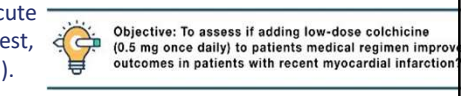


COLCOT TRIAL

Benefits of colchicine in the treatment of acute MI (January 2020)

- Colchicine is an inexpensive, orally administered, potent anti-inflammatory medication with a long history of use for indications such as gouty arthritis and pericarditis.
- Results from a small, uncontrolled trial of 532 patients, which was not placebo controlled known as Low-Dose Colchicine (LoDoCo) trial evaluated 0.5 mg once daily in stable coronary artery disease
- The study documented a reduction in the primary outcome measure which was a composite of acute coronary syndrome, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke ($p<0.001$).
- These findings, however, merited confirmation with a larger, randomized controlled trial.

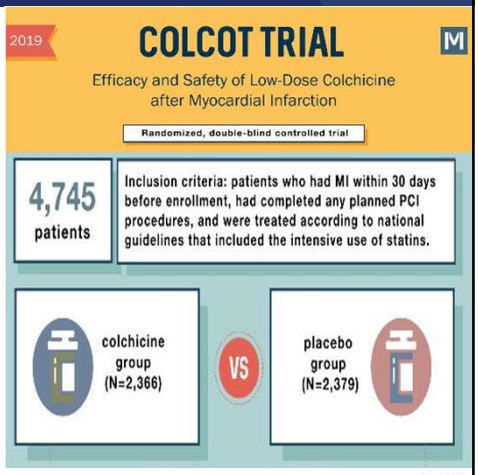




COLCOT TRIAL

Benefits of colchicine in the treatment of acute MI (January 2020)

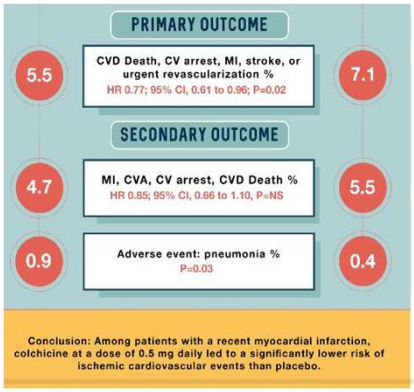
- Total of 4745 patients were enrolled
- 2366 patients were assigned to the colchicine group, and 2379 to the placebo group.
- Patients were followed for a median of 22.6 months. Colchicine group and in 0.4% of those in the placebo group (P = 0.03).



COLCOT TRIAL

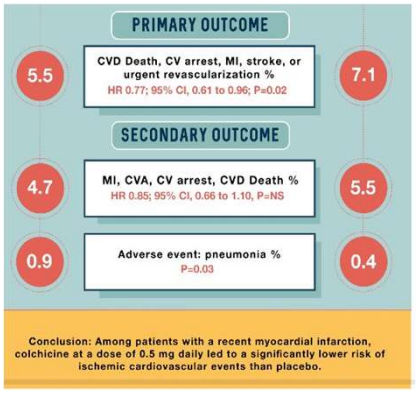
Benefits of colchicine in the treatment of acute MI (January 2020)

- The primary end point occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group (hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; P = 0.02).
- 94% Patients got PCI



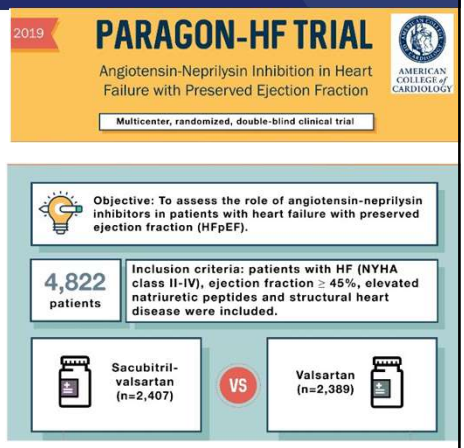
COLCOT TRIAL

- The hazard ratios were 0.84 (95% CI, 0.46 to 1.52) for death from cardiovascular causes, 0.83 (95% CI, 0.25 to 2.73) for resuscitated cardiac arrest, 0.91 (95% CI, 0.68 to 1.21) for myocardial infarction, 0.26 (95% CI, 0.10 to 0.70) for stroke, and 0.50 (95% CI, 0.31 to 0.81) for urgent hospitalization for angina leading to coronary revascularization.
- Diarrhea was reported in 9.7% of the patients in the colchicine group and in 8.9% of those in the placebo group (P = 0.35). Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group and in 0.4% of those in the placebo group (P = 0.03).



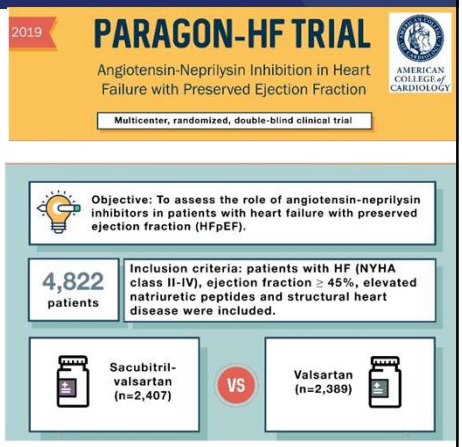
PARAGON-HF TRIAL

- The angiotensin receptor–neprilysin inhibitor sacubitril–valsartan led to a reduced risk of hospitalization for heart failure or death from cardiovascular causes among patients with heart failure and reduced ejection fraction.
- The effect of angiotensin receptor–neprilysin inhibition in patients with heart failure with preserved ejection fraction was unclear.

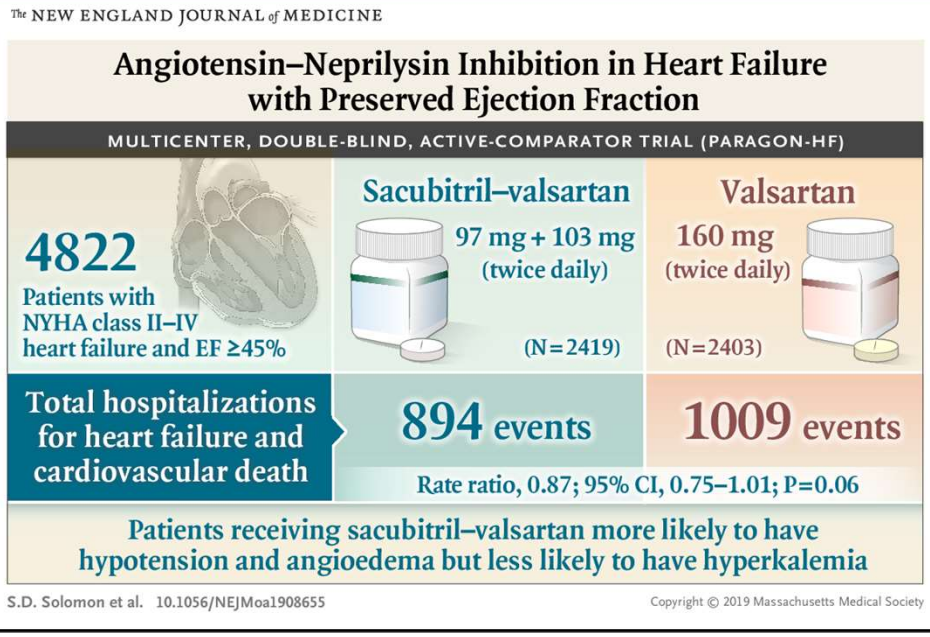


PARAGON-HF TRIAL

- 4822 patients with New York Heart Association (NYHA) class II to IV heart failure, ejection fraction of 45% or higher, elevated level of natriuretic peptides, and structural heart disease to receive sacubitril–valsartan (target dose, 97 mg of sacubitril with 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily).
- Primary outcome was a composite of total hospitalizations for heart failure and death from cardiovascular causes.
- Secondary outcomes including NYHA class change, worsening renal function, and KCCQ



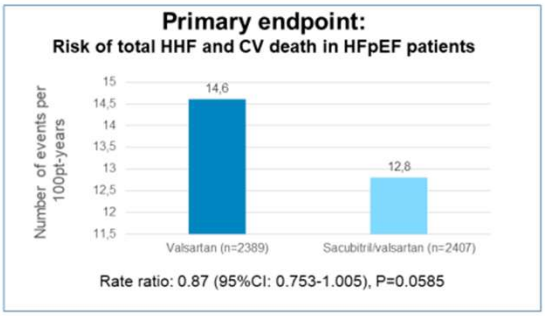
PARAGON-HF TRIAL



PARAGON-HF TRIAL

Primary endpoint just missed significance in trial evaluating ARNI in HFpEF patients

Randomized, double-blind, active comparator PARAGON-HF trial, in HF patients with LVEF ≥45%

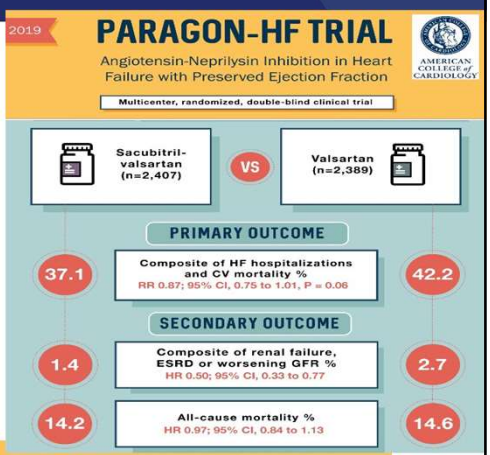


ARNI: angiotensin neprilysin inhibitor; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; HHF: hospitalization for heart failure

PACE-CME

PARAGON-HF TRIAL

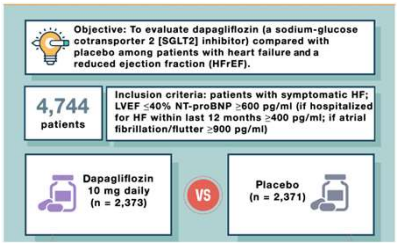
- There were 894 primary events in 526 patients in the sacubitril–valsartan group and 1009 primary events in 557 patients in the valsartan group (rate ratio, 0.87; 95% confidence interval [CI], 0.75 to 1.01; P=0.06).
- The incidence of death from cardiovascular causes was 8.5% in the sacubitril–valsartan group and 8.9% in the valsartan group (hazard ratio, 0.95; 95% CI, 0.79 to 1.16); there were 690 and 797 total hospitalizations for heart failure, respectively (rate ratio, 0.85; 95% CI, 0.72 to 1.00).



Conclusion: Sacubitril-valsartan did not result in a significantly lower rate of total hospitalizations for HF and death from CV causes among patients with HFpEF (EF ≥ 45%).

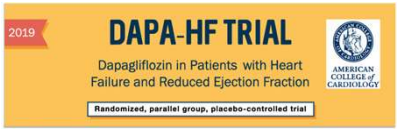
DAPA HF Trial

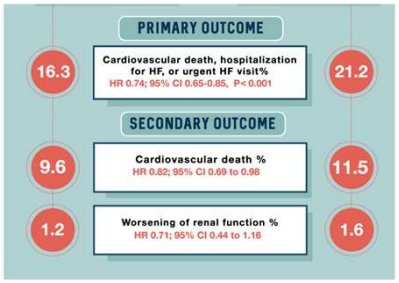
- **Dapagliflozin for heart failure with reduced ejection fraction (October 2019)**
- Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce hospitalization for heart failure (HF) in patients with type 2 diabetes mellitus (DM), but whether they improve outcomes for nondiabetic patients with HF has not been known.
- The DAPA-HF trial evaluated the SGLT2 inhibitor dapagliflozin in nearly 5000 patients with symptomatic heart failure with reduced ejection fraction (HFrEF) and an elevated natriuretic peptide level on optimal drug and device therapy
- Compared with placebo, all-cause mortality and the primary composite outcome (worsening HF or cardiovascular death) was reduced with dapagliflozin, with similar effects in patients with and without type 2 DM.



DAPA HF Trial

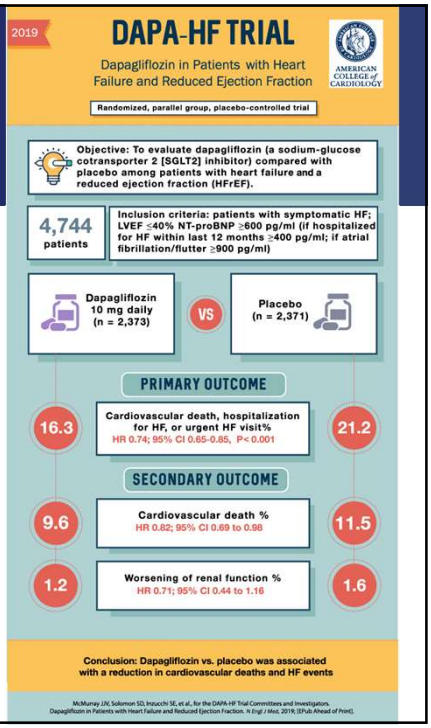
- The frequency of adverse effects was generally similar in the dapagliflozin and placebo groups. Given these findings, we now recommend dapagliflozin for patients with HFrEF with persistent symptoms and an elevated serum natriuretic peptide level despite optimal drug and device therapy (including a mineralocorticoid receptor antagonist and/or cardiac resynchronization therapy, if indicated).
- Dapagliflozin is contraindicated in patients with symptomatic hypotension or systolic blood pressure <95 mmHg, estimated glomerular filtration rate (eGFR) <30 mL per minute per 1.73 m^2, or rapidly declining renal function.



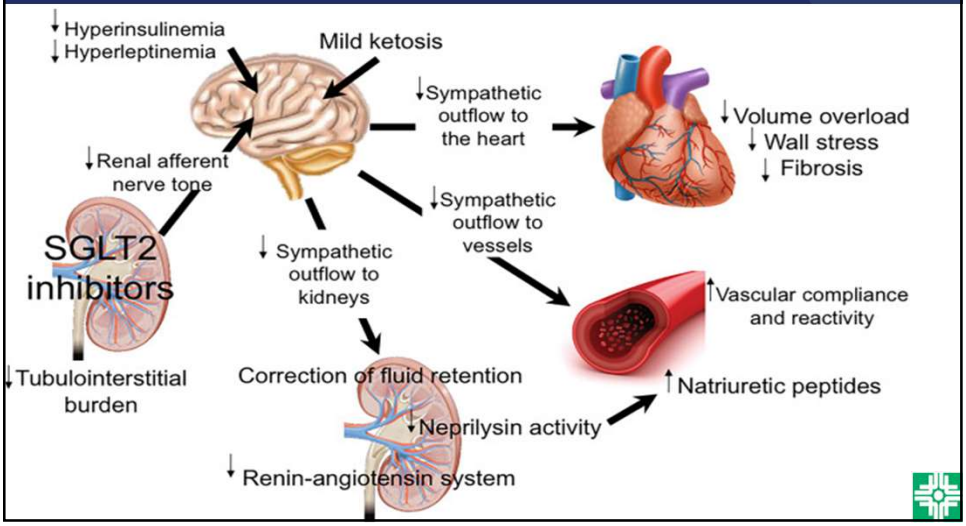


DAPA HF Trial

- Dapagliflozin was also found to reduce death and hospitalization in patients who have HFrEF with and without diabetes.
- The late-breaking results of the DAPA-HF trial were presented in a Hot Line Session at European Society of Cardiology (ESC) in August 2019.
- "The most important finding of all is the benefit in patients without diabetes. This is truly a treatment for heart failure and not just a drug for diabetes,"



DAPA HF TRIAL



DECLARE-TIMI 58 Study

- **About DECLARE-TIMI 58 Study**
- DECLARE (Dapagliflozin Effect on Cardiovascular Events)-TIMI 58 is the largest CV outcomes trial conducted for a selective inhibitor of SGLT2 to date in a broad patient population. It is an AstraZeneca-sponsored, Phase III, randomized, double-blind, placebo-controlled, multicenter trial designed to evaluate the effect of dapagliflozin compared with placebo on CV outcomes in adults with T2D at risk of CV events, including patients with multiple CV risk factors or established CV disease and also assessed key renal secondary endpoints. The trial included more than 17,000 patients across 882 sites in 33 countries and was independently run in collaboration with academic investigators from the TIMI study group (Boston) and the Hadassah Hebrew University Medical Center (Jerusalem, Israel).
- DECLARE-TIMI 58 showed that dapagliflozin significantly reduced the risk of the primary composite endpoint of hHF or CV death versus placebo by 17% (4.9% vs. 5.8%; HR 0.83 [95% CI 0.73-0.95], p=0.005). This finding was driven by a significant 27% reduction in the risk of hHF (2.5% vs. 3.3%; HR 0.73 [95% CI 0.61, 0.88]). The treatment benefit was consistent across patient subgroups. The Phase III DECLARE-TIMI 58 trial confirmed the well-established safety profile of dapagliflozin.
- The full results of the DECLARE-TIMI 58 trial were published in The New England Journal of Medicine in January 2019.[2]

DECLARE-TIMI 58 Study

- The U.S. Food and Drug Administration (FDA) has granted market clearance for AstraZeneca's dapagliflozin (Farxiga) to reduce the risk of hospitalization for heart failure (HF) in adults with type 2 diabetes (T2D) and established cardiovascular disease (CVD) or multiple cardiovascular (CV) risk factors.
- The approval is based on results from the landmark DECLARE-TIMI 58 CV outcomes trial (CVOT).[1] It is the largest sodium-glucose co-transporter 2 (SGLT2) inhibitor CVOT conducted to date to evaluate T2D patients with multiple CV risk factors or established CV disease. The
- "DECLARE-TIMI 58 is a landmark trial, offering compelling evidence that dapagliflozin can reduce the risk of heart failure in patients living with type 2 diabetes with multiple risk factors for or established cardiovascular disease," explained **Stephen Wiviott, M.D.,** associate professor of cardiovascular medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, and a senior investigator with the TIMI Study Group and co-principal investigator of the trial. "These data could help change the way we approach diabetes management – going beyond a singular focus on glucose control to help address the risk of heart failure in a diverse population of patients."
- The drug is the first SGLT2 inhibitor approved in the United States to reduce the risk of hospitalization for heart failure in type 2 diabetes patients with established cardiovascular disease or multiple cardiovascular risk factors, said Ruud Dobber, executive vice president, AstraZeneca, BioPharmaceuticals Business Unit. He explained this is promising news for the 30 million people living with type 2 diabetes in the U.S., as heart failure is one of the earliest cardiovascular complications for them, before heart attack or stroke.
- In August, the **FDA granted Fast Track designation for dapagliflozin** to reduce the risk of cardiovascular death, or the worsening of heart failure in adults with heart failure with reduced ejection fraction (HFrEF) or preserved ejection fraction (HFpEF). This was based on the Phase III trials, DAPA-HF and DELIVER.[2-5] and Fast Track designation to delay the progression of renal failure and prevent CV and renal death in patients with chronic kidney disease (CKD) based on the Phase III DAPA-CKD trial. The drug is not indicated to reduce the risk of heart failure, CV death or kidney disease.

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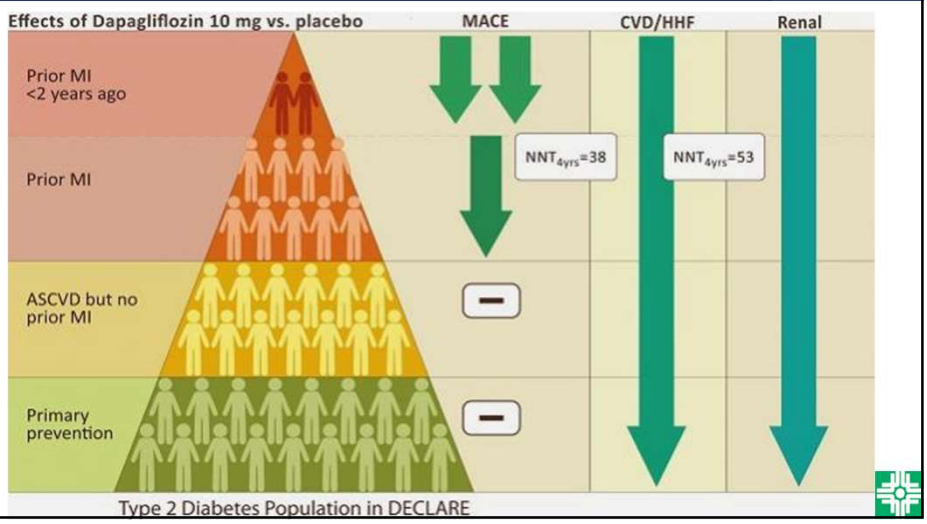
Table. DECLARE-TIMI 58: Results

Efficacy outcomes		
MACE	Similar rates	8.8% vs 9.4% ; HR 0.93; P=0.17
Composite of CV death or hospitalization for HF	Lower for dapagliflozin	4.9% vs. 5.8%; HR 0.83; P=0.005
Renal composite	24% lower risk with dapagliflozin	4.3% vs 5.6%, respectively, HR 0.76
Death from CV cause	Similar	2.9% vs 2.9% HR 0.98
Death from any cause	Similar	6.2% vs 6.6%, HR 0.93
Safety outcomes		
MACE	Dapagliflozin no worse vs placebo	P<.001 for noninferiority

DECLARE TIMI 58 TRIAL



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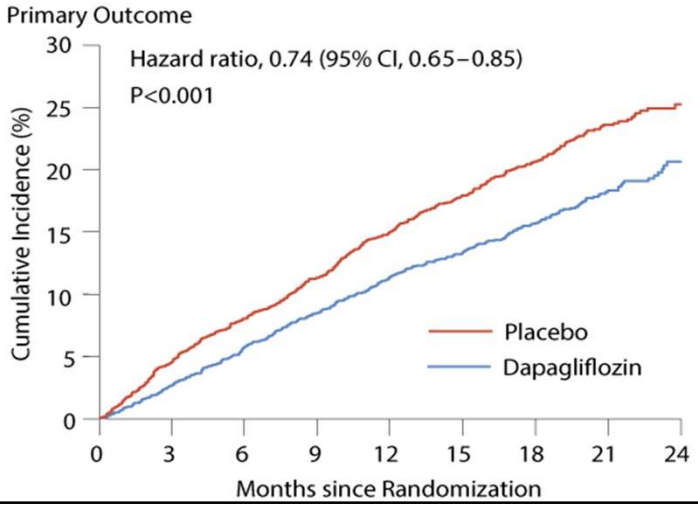

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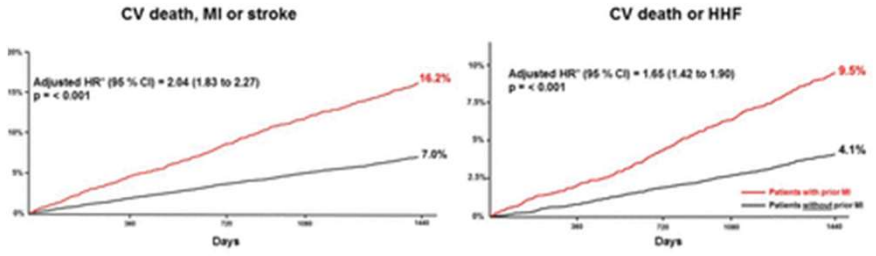


Figure: Event rates for patients with prior MI (n = 3,584) versus patients without prior MI (n = 13,576)

CV – cardiovascular; HHF – hospitalization for heart failure; MI – myocardial infarction

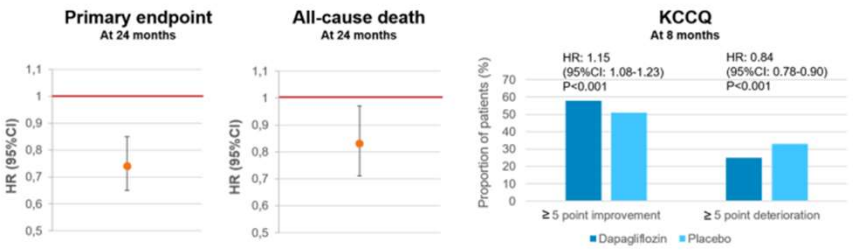
* Adjusted for: age ≥ vs. < 65 yo, sex, race, smoking, BMI ≥ vs. < 30 kg/m², DM duration > vs. ≤ 10 yrs, HbA1c > vs. ≤ 8 %, eGFR ≥ vs. < 60 mL/min/1.73m², region, baseline insulin, Hx of HF, Hx of dyslipidemia, Hx of hypertension, Hx of stroke

DECLARE TIMI 58 TRIAL

SGLT2 inhibitor reduces CV death and worsening HF events in HFrEF patients

DAPA-HF trial, in HFrEF patients (EF ≤40%) both with and without T2DM (n=4744)

Outcomes with dapagliflozin 10 mg once daily on top of standard care



Primary endpoint: worsening of HF events (unplanned HHF or an urgent HF visit requiring intravenous therapy) and CV death

HFrEF: heart failure with reduced ejection fraction; HHF: hospitalization for heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire

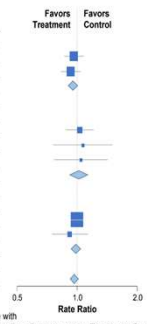
REDUCE IT TRIAL

Multiple epidemiologic studies have established elevated triglyceride (TG) levels as an important risk factor for atherosclerotic cardiovascular events.

However, in randomized trials, medications that reduce TG levels, such as niacin, fibrates, and n-3 fatty acid products, have not reduced cardiovascular events when added to appropriate medical therapy including statins.

Low Dose Omega-3 Mixtures Show No Significant Cardiovascular Benefit

Source	No. of Events (%) Treatment	Control	Rate Ratios (CI)
Coronary heart disease			
Nonfatal myocardial infarction	1121 (2.9)	1155 (3.0)	0.97 (0.87–1.08)
Coronary heart disease	1301 (3.3)	1394 (3.6)	0.93 (0.83–1.03)
Any	3085 (7.9)	3188 (8.2)	0.96 (0.90–1.01)
			P=.12
Stroke			
Ischemic	574 (1.9)	554 (1.8)	1.03 (0.88–1.21)
Hemorrhagic	117 (0.4)	109 (0.4)	1.07 (0.76–1.51)
Unclassified/other	142 (0.4)	135 (0.3)	1.05 (0.77–1.43)
Any	870 (2.2)	843 (2.2)	1.03 (0.93–1.13)
			P=.60
Revascularization			
Coronary	3044 (9.3)	3040 (9.3)	1.00 (0.93–1.07)
Noncoronary	305 (2.7)	330 (2.9)	0.92 (0.75–1.13)
Any	3290 (10.0)	3313 (10.2)	0.99 (0.94–1.04)
			P=.60
Any major vascular event	5930 (15.2)	6071 (15.6)	0.97 (0.93–1.01)
			P=.10



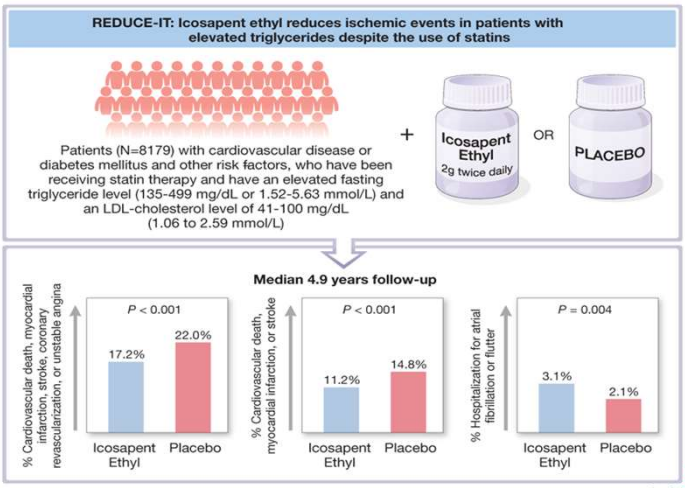
Adapted with permission from Aung T, Halsey J, Kromhout D, et al. Associations of omega-3 fatty acid supplement use with cardiovascular disease risks: Meta-analysis of 10 trials involving 77917 individuals. *JAMA Cardiol.* 2018;3:225-234. [https://creativecommons.org/licenses.org/by-nc/4.0/]

REDUCE IT TRIAL

- Bhatt DL, et al. "Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia". *The New England Journal of Medicine*. 2018.
- Clinical Question-In patients with established atherosclerotic heart disease, or diabetes with an additional risk factor, on pre-existing statin therapy with residual hypertriglyceridemia (fasting triglyceride level 135-499 mg/dL), does icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, reduce cardiovascular events compared to placebo?
- In patients with established atherosclerotic heart disease, or diabetes and an additional risk factor, on pre-existing statin therapy with residual hypertriglyceridemia (fasting triglyceride level 135-499 mg/dL), icosapent ethyl was associated with an absolute 4.8% reduction in cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina), with a 0.9% absolute reduction in cardiovascular death, at 4.9 years.

REDUCE IT TRIAL

- More recently, however, the JELIS trial demonstrated a 19% relative risk reduction in cardiovascular events when 1.8g daily of eicosapentaenoic acid (EPA) was added to low-intensity statin therapy



REDUCE IT TRIAL

Multicenter, randomized, double-blind, placebo-controlled
N=8179
- Icosapent ethyl (N=4089)
- Placebo (N=4090)

Setting: 473 sites in 11 countries

Enrollment: November 28, 2011 - August 4, 2016

Median follow-up: 4.9 years

Analysis: Intention-to-treat

Primary Outcome: Cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, unstable angina

REDUCE IT TRIAL

Inclusion Criteria

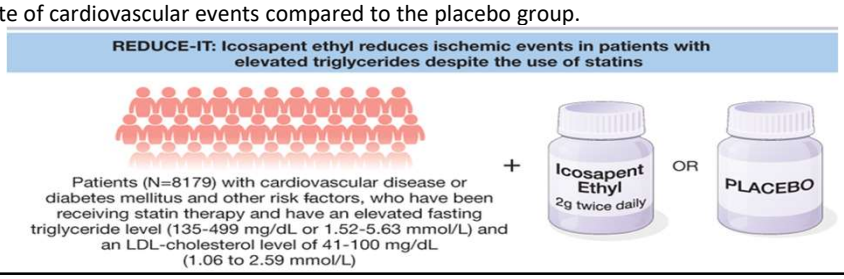
Age ≥ 45 years with established atherosclerotic heart disease (Documented multivessel coronary artery disease (≥ 50% stenosis in at least two major epicardial coronary arteries), prior MI, or hospitalization for NSTEACS)

Age ≥ 50 years with diabetes and ≥ 1 of the following
- Age ≥ 55 (men) or ≥ 65 (women)
- HTN
- Active smoker or quit within 3 months
- HDL-C ≤ 40 (men) or ≤ 50 (women)
- hs-CRP > 3 mg/dL
- creatinine clearance > 30 and < 60 mL/min

Fasting TG levels ≥ 150 mg/dL and < 500 mg/dL

REDUCE IT TRIAL

- Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT) trial randomized 8,179 patients with established atherosclerotic heart disease or diabetes and an additional risk factor, on baseline statin therapy, to icosapent ethyl (a highly purified and stable EPA ethyl ester) or placebo, and assessed for major cardiovascular events (cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina).
- The majority of enrolled individuals (70%) had established atherosclerotic heart disease. At median 4.9 years, patients randomized to receive icosapent ethyl had an absolute 4.8% lower rate of cardiovascular events compared to the placebo group.

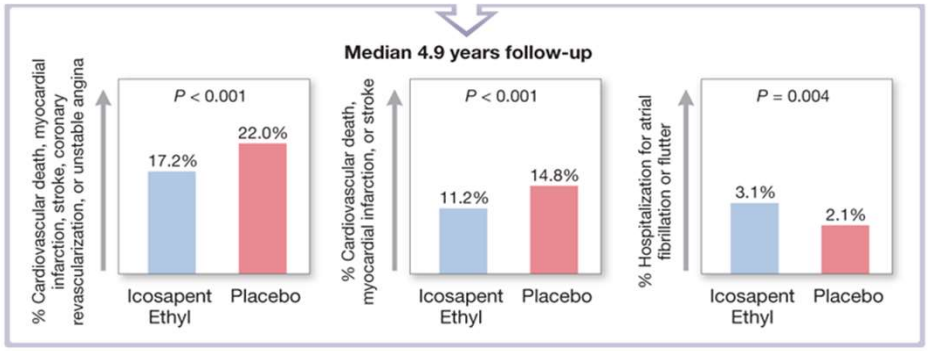


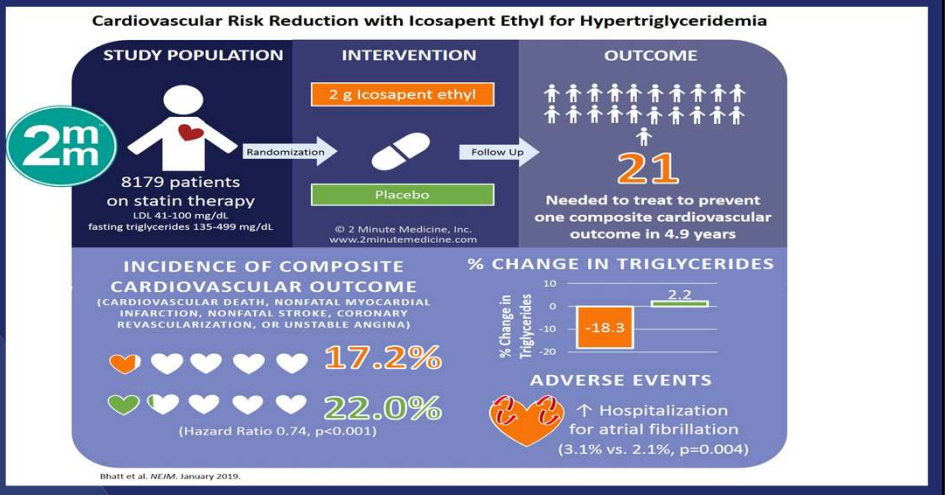
REDUCE IT TRIAL

- There were symmetric reductions in the key components of the primary endpoint, including a 20% relative risk reduction in cardiovascular death with icosapent ethyl.
- Median TG levels were reduced by 18% in the icosapent ethyl group and rose by 2.2% in the placebo group. LDL levels rose in both groups, although to a lesser degree in the icosapent ethyl group.
- There was a trend towards increased bleeding (2.7% with eicosapent ethyl versus 2.1% with placebo, p=0.06) with icosapent ethyl, although the absolute rates were low. There was also a modest increase in hospitalizations for atrial fibrillation or flutter with icosapent ethyl (3.1% versus 2.1%).

REDUCE IT TRIAL

In summary, the REDUCE-IT trial provides confirmatory evidence that targeting residual elevated TG with icosapent ethyl reduces cardiovascular events, including cardiovascular death





REDUCE IT TRIAL

Criticisms

- Most patients enrolled (70%) had established atherosclerotic disease, and although the subgroup interaction was not significant the benefit was somewhat attenuated in the smaller primary prevention cohort. Thus, whether there is truly substantial benefit with icosapent ethyl in the latter group is somewhat unclear.
- Ezetimibe and PCSK9 use was very low in the trial. Whether the benefit of icosapent ethyl persists in patients receiving these drugs on top of baseline statin therapy is unclear.
- The benefit observed with icosapent ethyl persisted even in patients with very modest TG elevation (150-200 mg/dL), and did not closely correlate with the degree of TG reduction observed.

Thank You!