Baptist Health
HEART INSTITUTE

Pharmacology Potpourri

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Disclosures: None

Pharmacology Potpourri 2026

- BB after MI (Reboot and Betami/Danblock Trials, Meta-analysis)
- PCSK9-I in patients without prior MI/CVA
- Fish oil in Hemodialysis
- Olezarsen for hypertriglyceridemia
- Antiplatelet with DOAC
- Clopidogrel vs ASA
- Flu Vaccine in CHF
- Caffeine after AFib Cardioversion

2017 CV SYMPOSIUM

- Beta blockers in Coronary Heart Disease
  – Who, When and How long?

2017 CV SYMPOSIUM

- Robust evidence for patients with STEMI treated without reperfusion (fibrinolysis or PCI)
  - Randomized trials performed **before** the use of reperfusion consistently showed a reduction in cardiovascular mortality of 10 to 25 percent.
  - Data are less well-defined for STEMI patients treated **with** reperfusion or for NSTEMI patients but still apply
  - Impact of routine use of antiplatelets and statins?
  - Regardless of revascularization, beta blockers reduce short-term complications and improve long-term survival in patients with Acute MI.
- All patients who have sustained an acute MI should be treated with oral beta blockers (No consistent evidence of benefit from **routine** use of IV beta blockers prior to primary PCI)

2017 CV SYMPOSIUM

Recommendation	Class of Recommendation	Level of Evidence
2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation ACS		
Initiate oral beta-blockers within the first 24 hours in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta-blockade.	I	A
Use of sustained-release metoprolol succinate, carvedilol, or bisoprolol is recommended for beta-blocker therapy with concomitant ACS without ST-segment elevation, stabilized HF, and reduced systolic function.	I	C
It is reasonable to continue beta-blocker therapy in patients with normal LV function with ACS without ST-segment elevation.	**IIa**	**C**
Initiate oral beta-blockers within the first 24 hours in patients with ST-segment elevation MI in the absence of HF, low-output state, risk for cardiogenic shock, or other contraindications to beta-blockade.	I	B
Beta-blockers should be continued during and after hospitalization for all patients with ST-segment elevation MI and with no contraindications to their use.	**I**	**B**

2017 CV SYMPOSIUM

AHA/ACCF Secondary Prevention Guidelines for Beta Blockade

- **Class I**
  - 1. Beta blocker therapy should be used in all patients with left ventricular systolic dysfunction (ejection fraction 40%) with heart failure or prior myocardial infarction, unless contraindicated. (Use should be limited to carvedilol, metoprolol succinate, or bisoprolol, which have been shown to reduce mortality.) (Level of Evidence: A)
  - 2. Beta blocker therapy should be started and continued for 3 years in all patients with normal left ventricular function who have had myocardial infarction or ACS. (Level of Evidence: B)
- **Class IIa**
  - 1. It is reasonable to continue -blockers beyond 3 years as chronic therapy in all patients with normal left ventricular function who have had myocardial infarction or ACS. (Level of Evidence: B)
  - 2. It is reasonable to give -blocker therapy in patients with left ventricular systolic dysfunction (ejection fraction 40%) without heart failure or prior myocardial infarction. (Level of Evidence: C)
- **Class IIb**
  - 1. Beta blockers may be considered as chronic therapy for all other patients with coronary or other vascular disease. (Level of Evidence: C)

Beta-Blockers after Myocardial Infarction 2026

- Current guideline recommendations for the use of beta-blockers after myocardial infarction without reduced ejection fraction are based on trials conducted before routine reperfusion, invasive care, complete revascularization, and contemporary pharmacologic therapies became standard practice.
- 3 recent trials (2025) address BB use after MI
  - REBOOT
  - BETAMI/DANBLOCK
  - Meta-analysis of 5 different trials from the Beta-Blocker Trialists' Collaboration Study Group:
    - REBOOT (7459 patients), REDUCE-AMI (4967 patients), BETAMI (2441 patients), DANBLOCK (2277 patients), and CAPITAL-RCT (657 patients)

Beta-Blockers after Myocardial Infarction without Reduced Ejection Fraction (REBOOT Trial)

(Ivanez, et al. NEJM 2025; 393:1889-900)

- PROBE Trial Design (Prospective, Randomized, Open-label, with Blinded end-point Evaluation) to evaluate the effect of BB vs. no BB in patients with AMI, (STEMI & NSTEMI) and a LVEF >40%.
- Median f/u 3.7 years
- The primary outcome was a composite of death from any cause, reinfarction, or hospitalization for heart failure.

REBOOT Trial: Outcomes

Table 2. Primary, Secondary, and Other Outcomes.

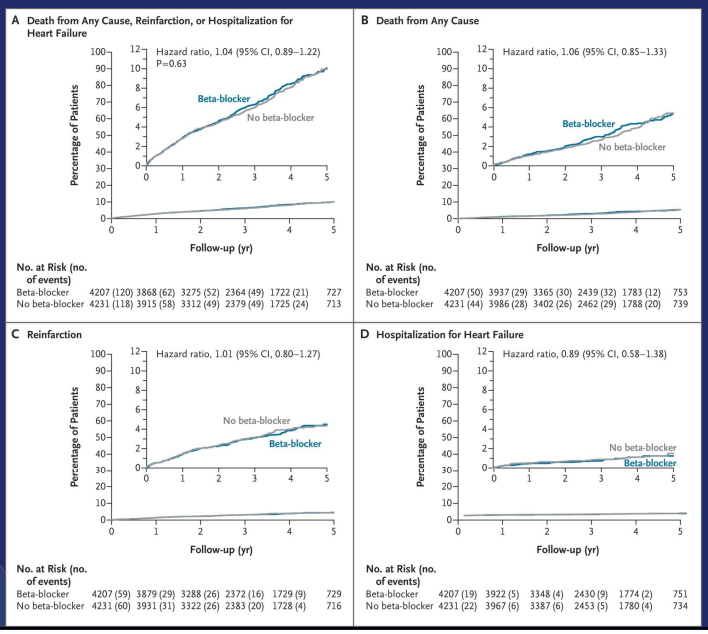
Outcome	Beta-Blocker	No Beta-Blocker	Rate Difference (95% CI)	Hazard Ratio (95% CI)*
	no. of patients (event rate per 1000 patient-yr)			
Primary outcome				
Death from any cause, reinfarction, or hospitalization for heart failure	316 (22.5)	307 (21.7)	0.84 (−2.63 to 4.32)	1.04 (0.89 to 1.22)†
Secondary outcomes				
Death from any cause	161 (11.2)	153 (10.5)	0.66 (−1.75 to 3.07)	1.06 (0.85 to 1.33)
Reinfarction	143 (10.2)	143 (10.1)	0.09 (−2.26 to 2.43)	1.01 (0.80 to 1.27)
Hospitalization for heart failure	39 (2.7)	44 (3.0)	−0.32 (−1.56 to 0.92)	0.89 (0.58 to 1.38)
Death from cardiac causes	65 (4.5)	57 (3.9)	0.60 (−0.90 to 2.10)	1.15 (0.81 to 1.64)
Sustained ventricular tachycardia	3 (0.2)	2 (0.1)	0.07 (−0.23 to 0.38)	1.52 (0.25 to 9.08)
Ventricular fibrillation	3 (0.2)	5 (0.3)	−0.14 (−0.52 to 0.25)	0.61 (0.14 to 2.53)
Resuscitated cardiac arrest	4 (0.3)	4 (0.3)	0.00 (−0.38 to 0.39)	1.01 (0.25 to 4.05)
Tertiary outcomes				
Death from cardiac causes, stroke, or myocardial infarction	235 (16.8)	216 (15.3)	1.51 (−1.45 to 4.47)	1.10 (0.91 to 1.32)
Unplanned revascularization	170 (12.1)	171 (12.1)	0.02 (−2.55 to 2.59)	1.00 (0.81 to 1.24)
Safety outcomes				
Hospitalization for symptomatic advanced atrioventricular block	7 (0.5)	6 (0.4)	0.07 (−0.42 to 0.56)	1.18 (0.40 to 3.50)
Hospitalization for stroke	37 (2.6)	25 (1.7)	0.86 (−0.21 to 1.93)	1.50 (0.90 to 2.49)

* Hazard ratios were estimated with the use of Cox proportional-hazards models to compare the effect of beta-blocker therapy with that of no beta-blocker therapy. No adjustment for multiplicity was made for the analyses of the secondary and tertiary outcomes. The widths of the confidence intervals should not be used to infer a treatment effect.

† P=0.63 for the comparison of the beta-blocker group with the no-beta-blocker group. The P value was calculated with the use of a log-rank test.

Ibanez B et al. N Engl J Med2025;393:1889-1900

REBOOT Trial:
Kaplan–Meier Curves for the Primary Outcome and Its Components.



REBOOT Trial: Conclusions

Among patients discharged after invasive care for AMI, with a left ventricular ejection fraction >40%, beta-blocker therapy appeared to have no effect on the incidence of death from any cause, reinfarction, or hospitalization for heart failure during a median follow-up of 3.7 years.

Beta-Blockers after Myocardial Infarction without Heart Failure (BETAMI–DANBLOCK Trials)

Munkhaugen, et al. N Engl J Med 2025;393:1901-1911

- PROBE Trial Design (prospective, randomized, open-label, with blinded end-point evaluation) conducted in Denmark and Norway
- Patients who had a myocardial infarction with LVEF of at least 40%, randomized in a 1:1 ratio to receive long-term BB therapy within 14 days after the event or no BB therapy.
- The primary end point was a composite of death from any cause or major adverse cardiovascular events (new myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias).

Beta-Blockers after Myocardial Infarction without Heart Failure (BETAMI–DANBLOCK Trials)

Munkhaugen, et al. N Engl J Med 2025;393:1901-1911

- Two trials, conducted at 25 sites in Denmark and 19 sites in Norway, that had almost identical designs and inclusion/exclusion criteria.
- Because recruitment was lower than expected, owing partially to the COVID 19 pandemic, the executive steering committees decided to combine the trials in May 2021 to ensure sufficient power to detect a possible effect of beta-blocker therapy on clinical outcomes.

BETAMI/DANBLOCK:
Primary, Secondary, and Safety End Points

Table 2. Primary, Secondary, and Safety End Points.*

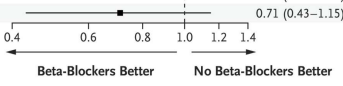
End Point	Beta-Blockers (N=2783)	No Beta-Blockers (N=2791)	Hazard Ratio (95% CI)
		number (percent)	
Primary end point†			
Composite of death from any cause, myocardial infarction, unplanned coronary revascularization, ischemic stroke, heart failure, or malignant ventricular arrhythmias‡	394 (14.2)	454 (16.3)	0.85 (0.75–0.98)
Secondary end points			
Death from any cause	118 (4.2)	124 (4.4)	0.94 (0.73–1.21)
Myocardial infarction	138 (5.0)	186 (6.7)	0.73 (0.59–0.92)
Unplanned coronary revascularization	108 (3.9)	110 (3.9)	0.99 (0.76–1.29)
Ischemic stroke	45 (1.6)	35 (1.3)	1.30 (0.84–2.03)
Heart failure	42 (1.5)	52 (1.9)	0.78 (0.52–1.18)
Malignant ventricular arrhythmias‡	15 (0.5)	18 (0.6)	0.82 (0.42–1.64)
Implantation of a pacemaker or second- or third-degree atrioventricular block	49 (1.8)	49 (1.8)	1.00 (0.67–1.49)
Safety end point			
Composite of death from any cause, myocardial infarction, heart failure, or malignant ventricular arrhythmia at 30 days	21 (0.8)	32 (1.1)	

* For all end points except the primary composite end point and the secondary end point of death from any cause, death before an event occurred was counted as a competing risk, and cause-specific hazards are shown. The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis tests.
† P=0.03 for the comparison of beta-blocker therapy with no beta-blocker therapy.
‡ Malignant ventricular arrhythmias include ventricular arrhythmia and resuscitated cardiac arrest of cardiac origin.

Munkhaugen J et al. N Engl J Med2025;393:1901-1911

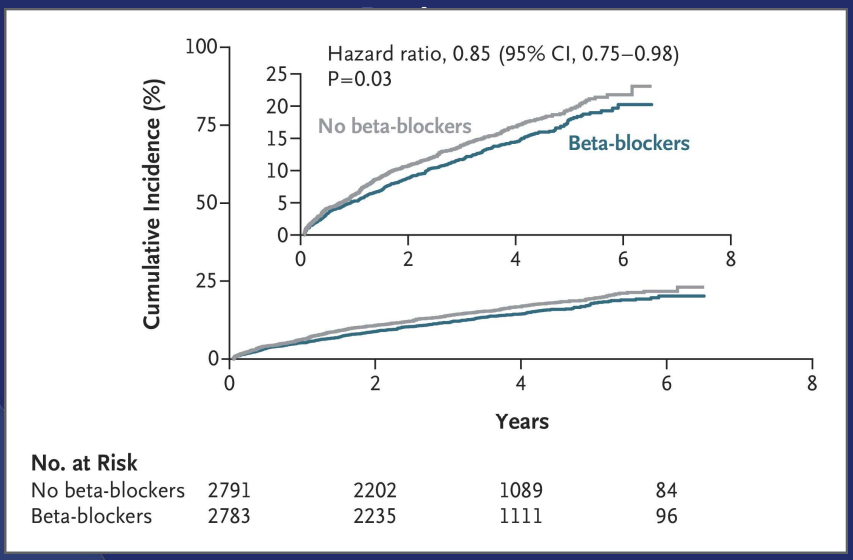
BETAMI/DANBLOCK: Primary End

Subgroup	Beta-Blockers	No Beta-Blockers	Hazard Ratio (95% CI)
	no. of events/total no. of patients (%)		
All patients	394/2783 (14.2)	454/2791 (16.3)	0.85 (0.75–0.98)
Sex			
Female	89/601 (14.8)	107/561 (19.1)	0.77 (0.62–0.96)
Male	305/2182 (14.0)	347/2230 (15.6)	0.91 (0.81–1.03)
Age			
<70 yr	225/2001 (11.2)	281/2029 (13.8)	0.82 (0.71–0.95)
≥70 yr	169/782 (21.6)	173/762 (22.7)	0.85 (0.59–1.21)
Country			
Norway	204/1431 (14.3)	235/1436 (16.4)	0.86 (0.72–1.02)
Denmark	190/1352 (14.1)	219/1355 (16.2)	0.84 (0.67–1.04)
Type of myocardial infarction			
NSTEMI	230/1453 (15.8)	246/1475 (16.7)	0.93 (0.79–1.11)
STEMI	164/1330 (12.3)	208/1316 (15.8)	0.81 (0.69–0.96)
Left ventricular ejection fraction			
40–49%	82/446 (18.4)	95/406 (23.4)	0.82 (0.65–1.02)
≥50%	312/2333 (13.4)	359/2385 (15.1)	0.93 (0.85–1.01)
Beta-blocker dose			
<50 mg	112/801 (14.0)	454/2791 (16.3)	0.88 (0.71–1.08)
≥50 mg	257/1813 (14.2)	454/2791 (16.3)	0.85 (0.73–1.00)
Hypertension			
No	198/1656 (12.0)	232/1642 (14.1)	0.83 (0.71–0.98)
Yes	196/1127 (17.4)	222/1149 (19.3)	0.86 (0.66–1.13)
Diabetes			
No	326/2451 (13.3)	364/2428 (15.0)	0.88 (0.77–1.00)
Yes	68/332 (20.5)	90/363 (24.8)	0.71 (0.43–1.15)



Munkhaugen J et al. N Engl J Med2025;393:1901-1911

BETAMI/DANBLOCK: Primary End



No. at Risk

No beta-blockers	2791	2202	1089	84
Beta-blockers	2783	2235	1111	96

The NEW ENGLAND JOURNAL of MEDICINE

Munkhaugen J et al. N Engl J Med2025;393:1901-1911

BETAMI–DANBLOCK Conclusions

Munkhaugen, et al. N Engl J Med 2025;393:1901-1911

- The authors conclude: "Among patients with a myocardial infarction and a left ventricular ejection fraction of at least 40%, beta-blocker therapy led to a lower risk of death **OR** major adverse cardiovascular events than no beta-blocker therapy."
- BUT…They also conclude: "Beta-blocker therapy may have decreased the cumulative incidence of new myocardial infarction, but there was no apparent difference between patients who received beta-blockers and those who did not in the risk of death from any cause, heart failure, malignant ventricular arrhythmias, unplanned coronary revascularization, or ischemic stroke. "

BETAMI–DANBLOCK Limitations

Munkhaugen, et al. N Engl J Med 2025;393:1901-1911

- And, they acknowledge limitations of the study:
- Open Label Trial design
- Different eligibility criteria
  - BETAMI: Type 1 MI; DANBLOCK either a Type 1 or Type 2 MI
  - LVEF of at least 40% (BETAMI) or more than 40% (DANBLOCK).
  - The BETAMI trial included only patients who underwent coronary revascularization, whereas the DANBLOCK trial did not impose this criterion.
- DANBLOCK and BETAMI trials were combined partway through the study period
- BB treatment used metoprolol XL at a median starting dose of 50 mg and therefore the findings may not be generalizable to other beta-blocker classes and higher doses

Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

(A.M.D. Kristensen, et al. NEJM 2025)

- Meta-analysis from five open-label trials that randomly assigned patients with recent myocardial infarction, no other indications for beta-blocker therapy, and an LVEF of at least 50% to receive beta-blocker therapy or no beta-blocker therapy.
- The primary end point was a composite of death from any cause, myocardial infarction, or heart failure.

Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

(A.M.D. Kristensen, et al. NEJM 2025)

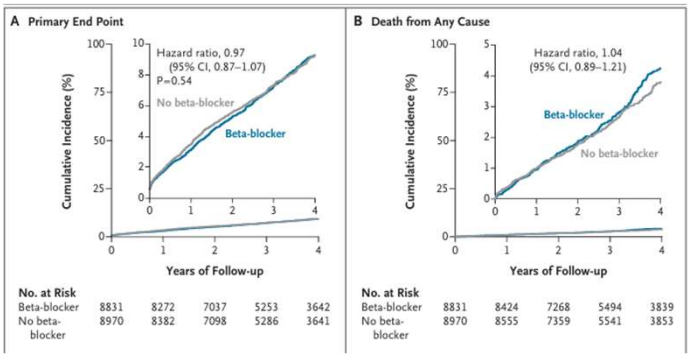


Figure 1. Kaplan–Meier Curves for the Primary End Point and Its Components.

Shown are the Kaplan–Meier curves of the cumulative incidence of death from any cause, myocardial infarction, or heart failure (the composite primary end point) (Panel A) and of the individual components of the primary end point (the secondary end points) (Panels B, C, and D). The widths of the confidence intervals for the secondary end points have not been adjusted for multiplicity and should not be used in place of hypothesis testing. The insets show the same data on an expanded y axis.

Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

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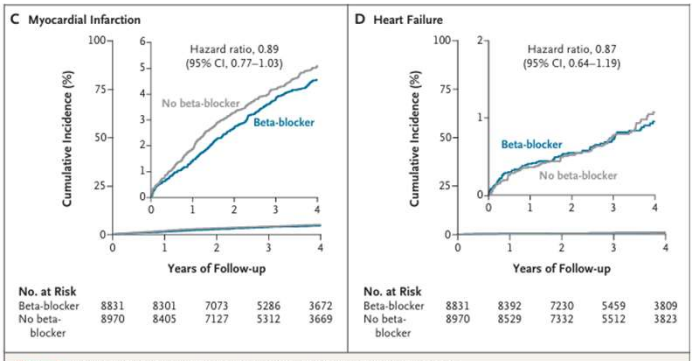

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Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

(A.M.D. Kristensen, et al. NEJM 2025)

Table 2. Treatment Estimates for the Primary, Secondary, and Safety End Points.*

End Point	Beta-Blockers (N=8831)	No Beta-Blockers (N=8970)	Hazard Ratio† (95% CI)
	number/total number (percent)		
Primary end point			
Composite of death from any cause, myocardial infarction, or heart failure	717/8831 (8.1)	748/8970 (8.3)	0.97 (0.87 to 1.07)‡
Key secondary end points			
Death from any cause	335/8831 (3.8)	326/8970 (3.6)	1.04 (0.89 to 1.21)
Myocardial infarction	360/8831 (4.1)	407/8970 (4.5)	0.89 (0.77 to 1.03)
Heart failure	75/8831 (0.8)	87/8970 (1.0)	0.87 (0.64 to 1.19)
Other secondary end points			
Cardiac death§	97/7624 (1.3)	78/7736 (1.0)	1.26 (0.94 to 1.70)
Unplanned coronary revascularization¶	315/6346 (5.0)	315/6488 (4.9)	1.03 (0.88 to 1.20)
Malignant ventricular arrhythmias¶‖	16/6025 (0.3)	23/6152 (0.4)	0.71 (0.37 to 1.34)
Safety end points			
Ischemic stroke	115/8831 (1.3)	94/8970 (1.0)	2.6 (−0.73 to 4.4)
Advanced atrioventricular block‖	69/8510 (0.8)	68/8634 (0.8)	1.03 (0.73 to 1.44)

Beta-Blockers after Myocardial Infarction with Normal Ejection Fraction

(A.M.D. Kristensen, et al. NEJM 2025)

- In this meta-analysis including individual-patient data from five randomized trials, beta-blocker therapy did not reduce the incidence of death from any cause, myocardial infarction, or heart failure in patients with an LVEF of at least 50% after myocardial infarction without other indications for beta-blockers

PCSK9-Inhibitors in Patients Without Prior MI/CVA

- The FOURIER Trial demonstrated that in patients with established ASCVD and prior MI/CVA/PAD, intense LDL lowering (~30 mg/dl) with evolocumab on a background of statin therapy resulted in a significant reduction in CV Events (composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization)
- More recently, the VESALIUS CV Trial evaluated evolocumab in patients WITHOUT prior MI/CVA

VESALIUS CV Trial

- PRDBPC Trial of evolocumab vs. placebo in patients **with** atherosclerosis or diabetes but **without** a previous myocardial infarction or stroke
- LDL of at least 90 mg per deciliter
- Two primary end points
  - 3-point MACE: a composite of death from coronary heart disease, myocardial infarction, or ischemic stroke
  - 4-point MACE a composite of 3-point MACE or ischemia-driven arterial revascularization
- 87% on statin therapy (68% HIST)
- Median LDL 122 mg/dl @ Baseline
- Median LDL 45 mg/dl @ 48 weeks with evolocumab
- The median follow-up was 4.6 years

VESALIUS CV Trial: Primary and Secondary End Points

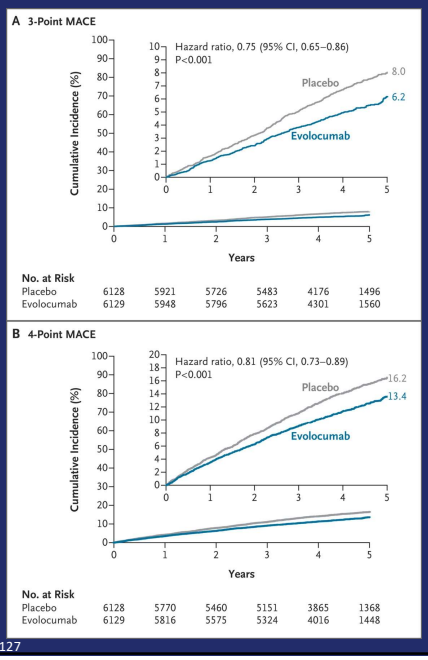
Table 2. Primary and Secondary End Points.*

End Point	Evolocumab (N=6129)	Placebo (N=6128)	Hazard Ratio (95% CI)	P Value
	no. (5-yr Kaplan–Meier estimate, %)			
Primary end points†				
3-Point MACE	336 (6.2)	443 (8.0)	0.75 (0.65–0.86)	<0.001
4-Point MACE	747 (13.4)	907 (16.2)	0.81 (0.73–0.89)	<0.001
Secondary end points‡				
Myocardial infarction, ischemic stroke, or ischemia-driven arterial revascularization	674 (12.2)	834 (15.0)	0.79 (0.72–0.88)	<0.001
Death from coronary heart disease, myocardial infarction, or ischemia-driven arterial revascularization	664 (11.9)	819 (14.6)	0.79 (0.72–0.88)	<0.001
Death from cardiovascular causes, myocardial infarction, or ischemic stroke	374 (6.8)	503 (9.1)	0.73 (0.64–0.84)	<0.001
Death from coronary heart disease or myocardial infarction	232 (4.2)	313 (5.6)	0.73 (0.62–0.87)	<0.001
Myocardial infarction	149 (2.7)	229 (4.1)	0.64 (0.52–0.79)	<0.001
Ischemia-driven arterial revascularization	561 (10.1)	699 (12.5)	0.79 (0.70–0.88)	<0.001
Death from coronary heart disease	105 (1.9)	117 (2.1)	0.89 (0.68–1.16)	0.39
Death from cardiovascular causes	156 (2.8)	195 (3.6)	0.79 (0.64–0.98)	NA
Death from any cause	434 (7.9)	539 (9.7)	0.80 (0.70–0.91)	NA
Ischemic stroke	115 (2.3)	144 (2.7)	0.79 (0.62–1.01)	NA

* Shown are the numbers of patients with a first event and the Kaplan–Meier estimate at 5 years in the intention-to-treat population, which included all the patients who had undergone randomization. NA denotes not applicable.
† The two primary end points were the composites of death from coronary heart disease, myocardial infarction, or ischemic stroke (3-point major adverse cardiac events [MACE]) and of 3-point MACE or ischemia-driven arterial revascularization (4-point MACE).
‡ Secondary end points are listed in the order of hierarchical testing (see the Supplementary Appendix). The widths of the confidence intervals for secondary end points that were not tested statistically were not adjusted for multiplicity and thus should not be used to infer treatment effect.

Bohula EA et al. N Engl J Med2026;394:117-127

VESALIUS CV Trial: Primary Efficacy End Points over Time



Bohula EA et al. N Engl J Med2026;394:117-127

VESALIUS CV Trial

- **CONCLUSIONS:** PCSK9 inhibition with evolocumab led to a lower risk of first cardiovascular events than placebo among patients with atherosclerosis or diabetes and without a previous myocardial infarction or stroke.

2025 Symposium: Omega 3 FA's

- Lower TG's, may Increase TC/LDL
- Meta-analysis of 55 trials, 1 g/d lowered TG's by 5.9 mg/dl (J Am Coll Cardiol. 2011 Nov;58(20):2047-67)
- Meta-analysis of 7 Trials, 4 g/d Krill Oil:
  - Lowered LDL 15.5 mg/dl
  - Lowered TG's 14 mg/dl
  - Raised HDL 6.6 mg/dl

  (Nutr Rev. 2017;75(5):361)

Fish Oil in ESRD on HD

- Cardiovascular disease is the leading cause of death in patients receiving hemodialysis
- **PISCES Trial**: PRDBPC trial of patients receiving maintenance hemodialysis comparing daily supplementation with fish oil (4 g of n−3 polyunsaturated fatty acids [1.6 g of EPA and 0.8 g of DHA]) or corn-oil placebo (N Engl J Med Volume 394(2):128-137 January 8, 2026)
- 3.5 y follow up
- The primary end point was a composite of all serious cardiovascular events including sudden and nonsudden cardiac death, fatal and nonfatal myocardial infarction, peripheral vascular disease leading to amputation, and fatal and nonfatal stroke

PISCES Trial: Primary and Secondary End Points

Table 2. Primary and Secondary End Points.*

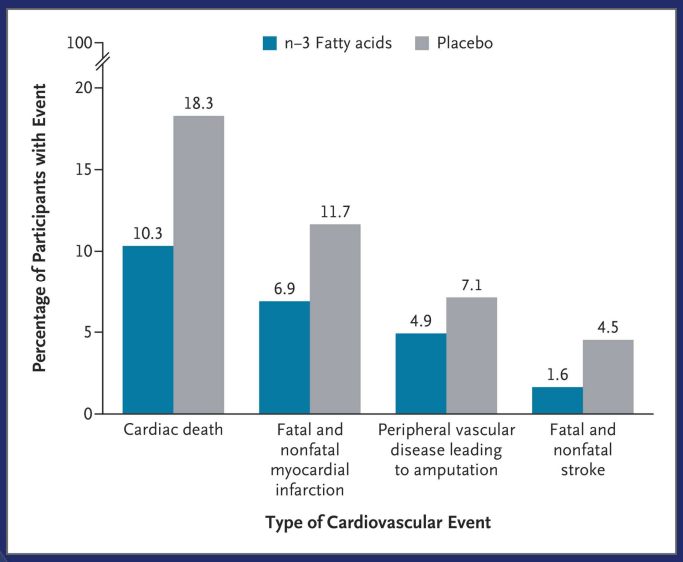
End Point	Fish Oil		Placebo		Hazard Ratio (95% CI)†
	No. of Events	Rate *no. per 1000 patient-days*	No. of Events	Rate *no. per 1000 patient-days*	
Primary end point					
Primary end-point events among all participants	158	0.31	309	0.61	0.57 (0.47–0.70)
Primary end-point events in subgroups based on history of a cardiovascular event at baseline					
Previous cardiovascular event	81	0.43	164	0.91	0.50 (0.37–0.67)
No previous cardiovascular event	77	0.24	145	0.45	0.55 (0.40–0.76)
Secondary end points					
Primary end-point events plus noncardiac death	266	0.52	381	0.76	0.77 (0.65–0.90)
Death from any cause	175	0.34	195	0.39	0.89 (0.73–1.01)
Components of the primary end point					
Cardiac death	63	0.12	113	0.22	0.55 (0.40–0.75)
Fatal and nonfatal myocardial infarction	49	0.10	96	0.19	0.56 (0.40–0.80)
Peripheral vascular disease leading to amputation	35	0.07	66	0.13	0.57 (0.38–0.86)
Fatal and nonfatal stroke	11	0.02	34	0.07	0.37 (0.18–0.76)
First cardiovascular event or death from any cause	215	0.45	270	0.60	0.73 (0.61–0.87)

* The primary end point was serious cardiovascular events, a composite that included all occurrences of any of the following events: cardiovascular death (sudden and nonsudden cardiac death), nonfatal and fatal myocardial infarction, nonfatal and fatal stroke, and peripheral vascular disease leading to amputation. The rates of cardiovascular events were compared between the trial groups with the Prentice–Williams–Peterson gap-time model for the primary end point, the extension of the primary end point to include noncardiac causes of death, and the individual components of the primary end point that were potentially recurrent events. The rates of cardiovascular death, death from any cause, and a first cardiovascular event or death from any cause were compared between the trial groups with the Cox proportional-hazards model.

† The 95% confidence intervals for the secondary end points were not adjusted for multiplicity and should not be used for hypothesis testing.

Lok CE et al. N Engl J Med2026;394:128-137

PISCES Trial: Participants with Cardiovascular Events



Lok CE et al. N Engl J Med2026;394:128-137

PISCES Trial Results/Discussion

- The rate of serious cardiovascular events was approximately **40% lower** (**hazard ratio, 0.57; 95% CI, 0.47 to 0.70; P<0.001**) among those who received 4 g of n−3 polyunsaturated fatty acids daily than among those who received placebo
- EPA and DHA have beneficial effects including antithrombotic, anti-inflammatory, anti-lipid, antiarrhythmic, and remodeling on the cardiovascular system
- HD results in metabolic, rheologic, inflammatory, and cardiovascular aberrations whereby cardiac stunning, ischemia, and vascular dysfunction are exacerbated by the rapid fluid and electrolyte shifts. Such circumstances may lead to arrhythmias.
- In the presence of n−3 fatty acids, the stimuli for arrhythmias might be lowered by directly inhibiting cardiomyocyte sarcolemma voltage-dependent sodium and L-type calcium currents, thereby prolonging the refractory period, inhibiting depolarization, and increasing cellular electrical stability

Olezarsen

- Hypertriglyceridemia (HTG) is common and is associated with an increased risk of atherosclerosis; highly effective therapies for reducing TG levels are lacking.
- Moderate HTG is associated with an increased risk of ASCVD and TG-rich lipoproteins are at least as atherogenic as LDL cholesterol
- Apolipoprotein C-III (APOC3) limits the clearance of TG-rich lipoproteins through inhibition of lipoprotein lipase and reducing hepatic uptake of TG-rich lipoprotein remnants
- Olezarsen is an *N*-acetylgalactosamine–conjugated antisense oligonucleotide that binds *APOC3* messenger RNA, inducing its degradation.
- Olezarsen has been shown to decrease TG levels in small phase 2 trials and to reduce TG levels and the risk of acute pancreatitis among patients with familial chylomicronemia syndrome
- The **Essence–TIMI (Thrombolysis in Myocardial Infarction) 73b trial** was designed to evaluate the efficacy and safety of olezarsen in patients with moderate HTG who are at high cardiovascular risk and in those with severe HTG.

Essence–TIMI 73b Trial

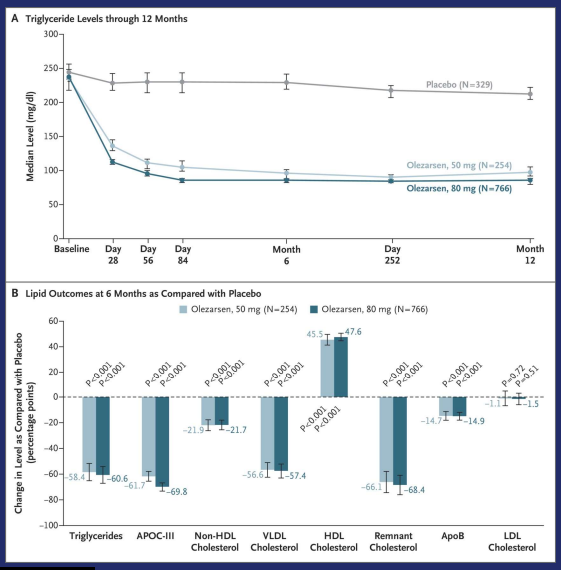
N Engl J Med 2025;393:1279-1291

- Patients were randomly assigned in a 1:3 ratio to a 50-mg or 80-mg cohort and were then randomly assigned in a 3:1 ratio to receive subcutaneous olezarsen or volume-matched placebo within each cohort
- The primary outcome was the least-squares mean percent change in triglyceride level from baseline to 6 months among the patients with moderate hypertriglyceridemia
- Secondary outcomes were
  - the percent change in triglyceride level from baseline to 12 months
  - the proportion of patients who had a triglyceride level of less than 150 mg per deciliter at 6 and 12 months
  - percent changes from baseline to 6 months and 12 months in the fasting levels of apolipoprotein C-III, VLDL, remnant cholesterol, non-HDL, HDL, apolipoprotein B, and LDL.

Essence–TIMI 73b Trial

- Nearly 90% of the patients with moderate hypertriglyceridemia who received olezarsen had normal triglyceride levels at 6 months and 12 months
- Mean change in triglyceride level was −50.7%
- 6-month TG levels <150 mg/dl:
  - 85.0% of the patients in the olezarsen 50-mg group
  - 88.7% of those in the olezarsen 80-mg group
  - 12.5% of those in the placebo group
- 12-month TG levels <150 mg/dl:
  - 82.8% of the patients in the olezarsen 50-mg group
  - 85.0% of those in the olezarsen 80-mg group
  - 20.6% of those in the placebo group
- Treatment resulted in significant reductions in remnant cholesterol levels (up to nearly 70%) as well as in the total number of atherogenic lipoproteins as assessed on the basis of the apolipoprotein B level, with no change in LDL cholesterol level.

Triglyceride Levels through 12 Months and Lipid Outcomes at 6 Months



The NEW ENGLAND JOURNAL of MEDICINE

Bergmark BA et al. N Engl J Med2025;393:1279-1291

Aspirin in Patients with Chronic Coronary Syndrome Receiving Oral Anticoagulation

- Patients with an indication for oral anticoagulation (OAC) who undergo percutaneous coronary intervention (PCI) often receive combination antithrombotic therapy (ie, OAC plus an antiplatelet medication) indefinitely; however, it is uncertain whether long-term antiplatelet therapy is necessary.
- AFIRE Trial (rivaroxaban) – we discussed in 2020
- AQUATIC Trial (any anticoagulant) 2025
- ADAPT AF-DES – (DOAC/Clopidogrel only) 2025

AFIRE Trial

Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

- Noninferiority trial of patients with A Fib, remote PCI or CABG > 1 yr prior, or angiographically confirmed CAD not requiring revascularization
  - Randomized to receive monotherapy with rivaroxaban or combination therapy with rivaroxaban plus a single antiplatelet agent (~75% ASA, 25% clopidogrel).
- 1^{O} efficacy end point was a composite of CVA, systemic embolism, MI, unstable angina requiring revascularization, or death from any cause;
- 1^{O} safety end point was major bleeding

AFIRE Trial
Results

- The trial was stopped early because of increased mortality in the combination therapy group.
- Rivaroxaban monotherapy was noninferior ($P<0.001$) to combination therapy for the 1^{O} efficacy end point
- Rivaroxaban monotherapy was superior ($P = 0.01$) to combination therapy for the 1^{O} safety end point

AQUATIC Trial

N Engl J Med Volume 393(16):1578-1588 October 23, 2025

- Multicenter, PRDBPC trial in patients with chronic coronary syndrome with previous stent implantation (>6 months prior), at high atherothrombotic risk, on long-term oral anticoagulation.
- The patients were randomly assigned in a 1:1 ratio to receive aspirin (100 mg once daily) or placebo. The trial was **stopped early** on the advice of the DSMB after a median follow-up of 2.2 years because of an **excess of deaths from any cause in the aspirin group**.

ADAPT AF-DES

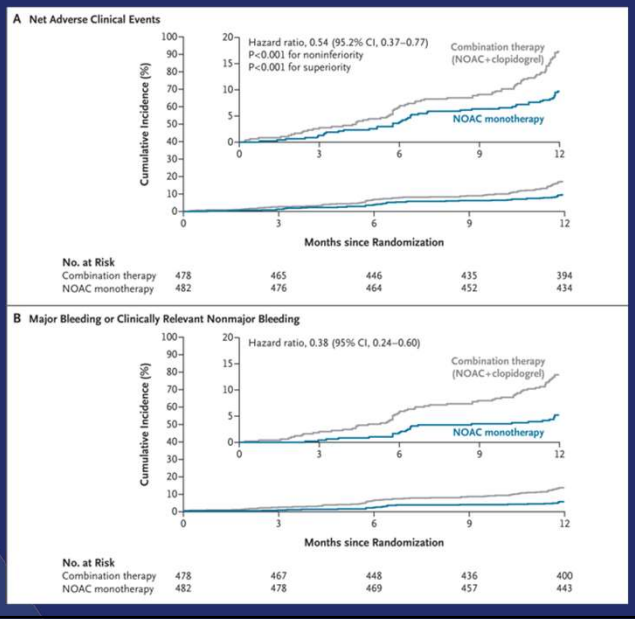
(NEJM 2025)

- Multicenter, randomized, open-label, noninferiority trial in South Korea.
- Patients with atrial fibrillation & placement of a drug-eluting stent at least 1 year earlier
- Randomized to NOAC monotherapy or combination therapy (NOAC plus clopidogrel)
- The primary end point was net adverse clinical events: a composite of death from any cause, MI, stent thrombosis, CVA, systemic embolism, or major bleeding or clinically relevant nonmajor bleeding at 12 months

ADAPT AF-DES

- Monotherapy was found to be noninferior to combination therapy for the composite of death from any cause, myocardial infarction, stent thrombosis, stroke, systemic embolism, or major bleeding or clinically relevant nonmajor bleeding at 12 months.
- In a prespecified analysis, monotherapy was also found to be superior to combination therapy for this same end point.

ADAPT AF-DES



Parting Shots

- Clopidogrel > ASA for Chronic CAD
- Routine flu vaccine vs no vaccine during hospitalization for CHF reduces all cause mortality (10% vs 12.8%) and rehospitalization for CHF (35.4% vs 40.5%)
- Caffeine vs no caffeine following cardioversion for atrial fibrillation reduces risk of recurrent A Fib (47% versus 64%)

Thank You!