Repatha® (evolocumab) Clinical Fact Sheet (Page 1 of 2)

Indications[1]

Repatha® is a PCSK9i indicated:

- In adults with established CV disease to reduce the risk of MI, stroke, and coronary revascularization
- As an adjunct to diet, alone or in combination with other LDL-C–lowering therapies, in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C
- As an adjunct to diet and other LDL-C–lowering therapies in pediatric patients aged 10 years and older with HeFH to reduce LDL-C
- As an adjunct to other LDL-C–lowering therapies in adults and pediatric patients aged 10 years and older with HoFH to reduce LDL-C

The safety and effectiveness of Repatha® have not been established in pediatric patients with HeFH or HoFH who are younger than 10 years or in pediatric patients with other types of hyperlipidemia[1]

Recent Clinical Practice Recommendations – Key Points

2018 AHA/ACC Multisociety Guideline on Blood Cholesterol Management:[2]

- "Lower is better" for LDL-C in ASCVD patients. In VHR ASCVD, LDL-C ≥ 70 mg/dL is the trigger to intensify LLT, adding nonstatin (ezetimibe ± PCSK9i) therapy to maximally tolerated statins.[2]
- PCSK9is should be considered in addition to maximally tolerated statin ± ezetimibe in patients with:[2]
  - VHR ASCVD with LDL-C ≥ 70 mg/dL
  - HeFH (baseline [BL] LDL-C ≥ 190 mg/dL), 30–75 years of age, who achieved LDL-C ≥ 100 mg/dL
  - Primary severe hypercholesterolemia (BL LDL-C ≥ 220 mg/dL), 40–75 years of age, who achieved LDL-C ≥ 130 mg/dL

2022 ACC Expert Consensus Decision Pathway (ECDP)* – endorsed by the NLA:[3]

- Prospective trials and observational studies show that absolute LDL-C reduction is directly associated with ASCVD risk reduction.
- The ECDP says that for ASCVD patients, "there appears to be no LDL-C level below which benefit ceases".
- The ECDP recommends a 50% reduction in LDL-C and a lower LDL-C threshold of 55 mg/dL for adults with ASCVD at VHR and 70 mg/dL for adults with ASCVD not at VHR.
- PCSK9i mAbs, like Repatha®, are preferred by the 2022 ACC ECDP as the initial PCSK9i of choice for adults with ASCVD on maximally-tolerated statin therapy, based on the demonstrated safety profile, efficacy, and cardiovascular outcomes data from outcomes trials.
- PCSK9i mAbs, like Repatha®, may be preferred as the initial nonstatin agent when > 25% additional LDL-C lowering is required.
- PCSK9i mAbs may also be used in patients with primary hyperlipidemia (LDL-C ≥ 190 mg/dL), with or without ASCVD, including patients with FH, and in those with statin-associated side effects.

Dyslipidemia Unmet Medical Need in Patients with ASCVD

Real-world evidence from observational research and registry data indicated that despite receiving statins ± ezetimibe, most patients with ASCVD have LDL-C ≥ 70 mg/dL, placing them at an increased risk of recurrent CV events[4-8]

Summaries of Key Clinical Trials From the Repatha® PROFICIO Clinical Development Program:
(Program to Reduce LDL-C and CV Outcomes Following Inhibition of PCSK9 In Different POpulations)
Repatha® has been studied in 50 clinical trials involving > 51,000 patients in both the Repatha® and comparator groups[9]

Study of CV Outcomes in Adult Patients With Established CV Disease

FOURIER (N = 27,564); a double-blind, placebo-controlled, event-driven RCT; median duration: 2.2 years. Patients with LDL-C ≥ 70 mg/dL or non–HDL-C ≥ 100 mg/dL despite high-intensity (69%) or moderate-intensity (30%) statins received Repatha® (140 mg Q2W or 420 mg QM) or placebo.[1]

- Key BL characteristics:[1]
  - Mean age: 63 years (≥ 65 years, 45%); 25% female
  - BL LDL-C: 92 mg/dL (median); 98 mg/dL (mean)
  - History of CV disease: prior MI (81%); prior nonhemorrhagic stroke (19%); symptomatic PAD (13%)
  - Additional CV risk factors: HTN (80%); type 2 DM (36%); current daily cigarette smoking (28%); New York Heart Association class I or II congestive heart failure (23%); eGFR < 60 mL/min per 1.73 m^2 (6%)
  - Other background CV therapies included ezetimibe (5%), antiplatelet agents (93%), beta-blockers (76%), ACEis (56%), and ARBs (23%)
- Difference between Repatha® and placebo in mean % change from BL in LDL-C was –63% at week 12 and –57% at week 72.[1]
- At week 48 in FOURIER, the median (Q1, Q3) LDL-C was 26 (15, 46) mg/dL in the Repatha® group, with 47% of Repatha® patients having LDL-C < 25 mg/dL.[1]
- Repatha® significantly reduced the risk of the primary composite endpoint (time to first occurrence of CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization; *P* < 0.0001) and the key secondary composite endpoint (time to first occurrence of CV death, MI, or stroke; *P* < 0.0001; **Figures 1** and **2**).[1]
- Results for primary and key secondary composite endpoints were driven by reductions in MI (HR: 0.73), stroke (HR: 0.79), and coronary revascularization (HR: 0.78).[1,10] None of these HRs were statistically significant.
- **Observed HR for CV death: 1.05 (95% CI: 0.88–1.25); observed HR for hospitalizations due to unstable angina: 0.99 (95% CI: 0.82–1.18)[1]**

Cumulative Incidence of Primary and Key Secondary Composite Endpoints in FOURIER Over Time [1,10]

Figure 1. Primary Composite Endpoint

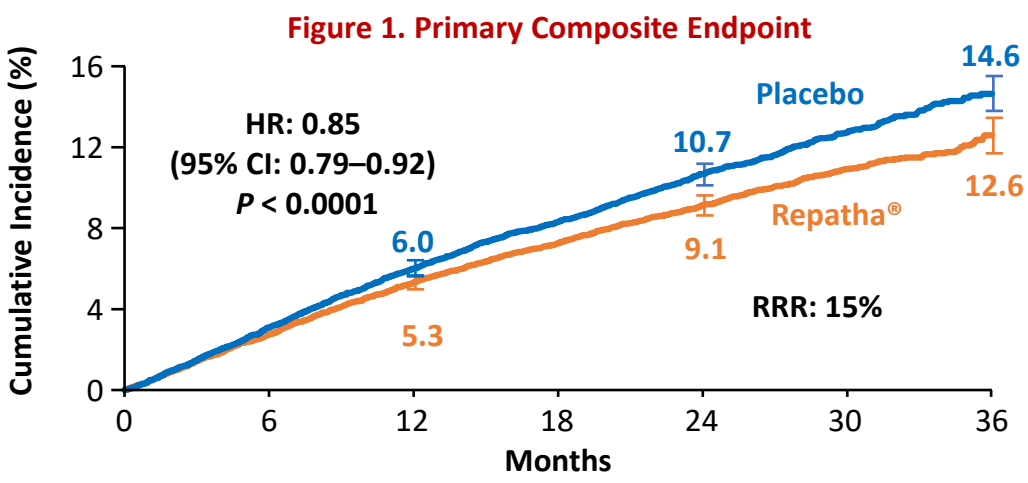
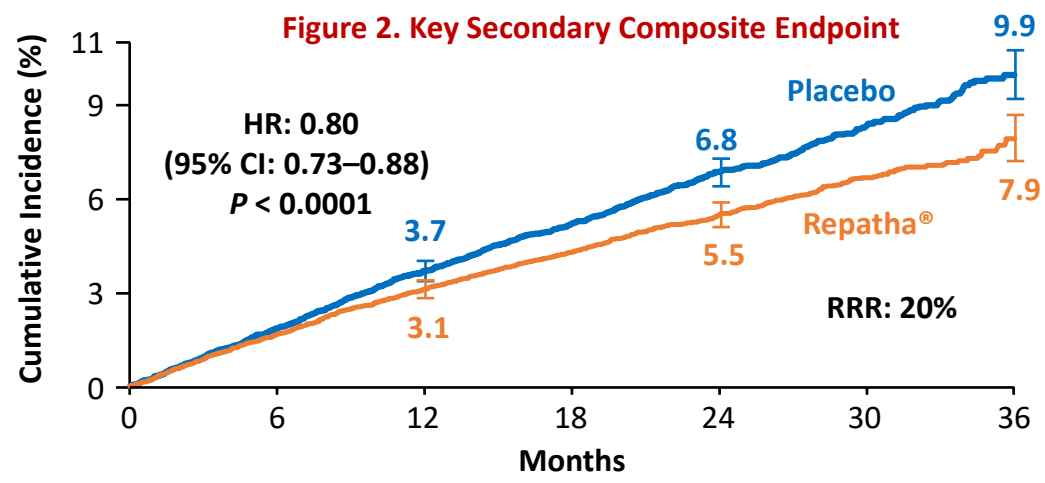


Figure 2. Key Secondary Composite Endpoint



Important Safety Information (continued on Page 2)

Contraindication: Repatha® is contraindicated in patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in Repatha®. Serious hypersensitivity reactions, including angioedema, have occurred in patients treated with Repatha®

Hypersensitivity Reactions: Hypersensitivity reactions, including angioedema, have been reported in patients treated with Repatha®. If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with Repatha®, treat according to the standard of care, and monitor until signs and symptoms resolve

Adverse Reactions in Adults With Primary Hyperlipidemia: The most common adverse reactions (> 5% of patients treated with Repatha® and more frequently than placebo) were nasopharyngitis, upper respiratory tract infection, influenza, back pain, and injection site reactions

From a pool of the 52-week trial and seven 12-week trials: Local injection site reactions occurred in 3.2% and 3.0% of Repatha®-treated and placebo-treated patients, respectively. The most common injection site reactions were erythema, pain, and bruising. Hypersensitivity reactions occurred in 5.1% and 4.7% of Repatha®-treated and placebo-treated patients, respectively. The most common hypersensitivity reactions were rash (1.0% versus 0.5% for Repatha® and placebo, respectively), eczema (0.4% versus 0.2%), erythema (0.4% versus 0.2%), and urticaria (0.4% versus 0.1%)

*Note that this process did not involve formal systematic reviews, grading of evidence, or synthesis of evidence. The goal was to provide practical guidance in situations not covered by the 2018 AHA/ACC/Multisociety cholesterol guideline until the next round of guidelines has the opportunity to formally review recent scientific evidence.

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Summaries of Key Repatha® Clinical Trials

Studies in Primary Hyperlipidemia:

LAPLACE-2 (N = 1,896); RCT; patients received Repatha® 140 mg Q2W or 420 mg QM, placebo, or ezetimibe as add-on to daily statins; mean BL LDL-C ranged from 77 to 127 mg/dL. Difference between Repatha® and placebo in mean % change in LDL-C from BL to week 12 was -71% and -63% for the 140 mg Q2W and 420 mg QM groups, respectively; difference between Repatha® and ezetimibe was -45% and -41% for the 140 mg Q2W and 420 mg QM groups, respectively.[1]

DESCARTES (N = 901); RCT; patients received Repatha® 420 mg QM or placebo in addition to diet alone, statin, or statin plus ezetimibe; mean BL LDL-C: 90–117 mg/dL across groups. Difference between Repatha® and placebo in mean % change from BL to week 52 in LDL-C was -55%.[1]

MENDEL-2 (N = 614); RCT; patients not on LLT received Repatha® 140 mg Q2W or 420 mg QM, ezetimibe, or placebo; mean BL LDL-C was 143 mg/dL. Difference in mean % change in LDL-C from BL to week 12 between Repatha® and placebo was -55% and -57% for the 140 mg Q2W and 420 mg QM groups, respectively; difference in mean % change in LDL-C from BL to week 12 between Repatha® and ezetimibe was -37% and -38% for the 140 mg Q2W and 420 mg QM groups, respectively.[1]

OSLER-1; OLE up to 5 years; efficacy analysis (n = 1,151); safety analysis (n = 1,255); patients were enrolled from Repatha® parent studies; mean % change in LDL-C from BL per year ranged from -56% to -57% across the 5 years. Incidence of AEs remained consistent or tracked lower over the 5 years; the percentage of patients discontinuing Repatha® due to AEs was 1.4% per year (range: 0.2%–2.9%).[11]

Studies in FH:[1]

RUTHERFORD-2 (N = 329); **HeFH**; RCT; adult patients on LLT received Repatha® 140 mg Q2W or 420 mg QM, or placebo; 76% were on high-intensity statin; mean BL LDL-C was 156 mg/dL. Difference in mean % change from BL to week 12 in LDL-C between Repatha® and placebo was -61% and -60% for the 140 mg Q2W and 420 mg QM groups, respectively.

TESLA (N = 49); **HoFH**; RCT; patients (not on lipid apheresis; all were on statins; 92% were on ezetimibe) received Repatha® 420 mg QM or placebo; mean BL LDL-C: 349 mg/dL. Difference between Repatha® and placebo in mean % change in LDL-C from BL to week 12 was -31%.

TAUSSIG (N = 106); **HoFH**; 5-year OLE; patients (including 14 patients aged 13-17 years) on LLT received Repatha® 420 mg QM; those on lipid apheresis began Repatha® 420 mg Q2W. Mean % change from BL at week 12 in LDL-C was -30% to -20% for Repatha® 420 mg Q2W and Repatha® 420mg QM groups, respectively.

HAUSER (N = 157); **pediatric HeFH** (10-17 years); RCT; patients (mean age, 14 years) on a low-fat diet and LLT received Repatha® 420 mg QM or placebo; mean BL LDL-C was 184 mg/dL. Mean % change from BL to week 24 in LDL-C was -44% and -6% for the Repatha® 420 mg QM and placebo groups, respectively. Difference between Repatha® 420 mg QM and placebo in mean % change from BL to week 24 in LDL-C was -38%.

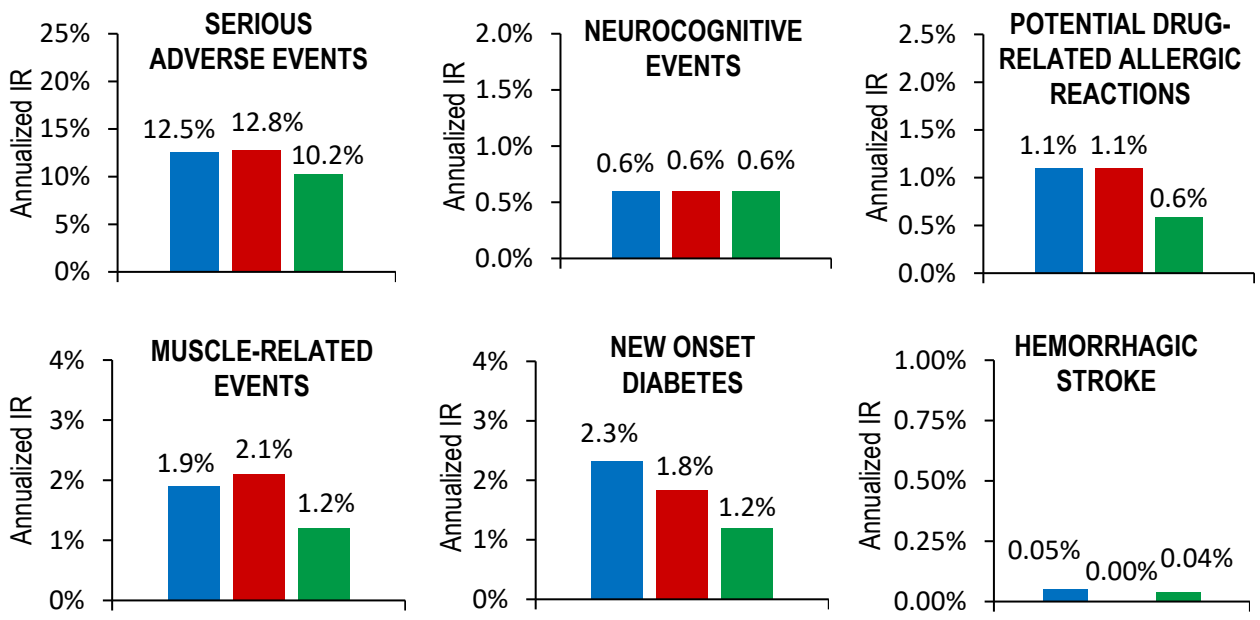
HAUSER-OLE (N = 12); **pediatric HoFH** (age 10-17 years); OLE; patients on a low-fat diet and LLT received 420 mg Repatha® QM; median BL LDL-C was 398 mg/dL. Median % change in LDL-C from BL to week 80 was -14%.

Open Label Extension Study of Long-Term Efficacy and Safety in Adult Patients With Established Cardiovascular Disease

FOURIER-OLE (N = 6,635); All patients in the FOURIER-OLE program received Repatha® (140 mg Q2W or 420 mg QM), regardless of randomization in the FOURIER parent trial (3,355 had been randomized to Repatha® and 3,280 to placebo in the parent trial). Primary endpoint was incidence of TEAEs. Secondary endpoints were % change from BL in LDL-C and achievement of LDL-C < 40 mg/dL. Median follow-up in FOURIER-OLE was 5.0 years; maximum Repatha® exposure in FOURIER plus FOURIER-OLE was **8.4 years.**[12]

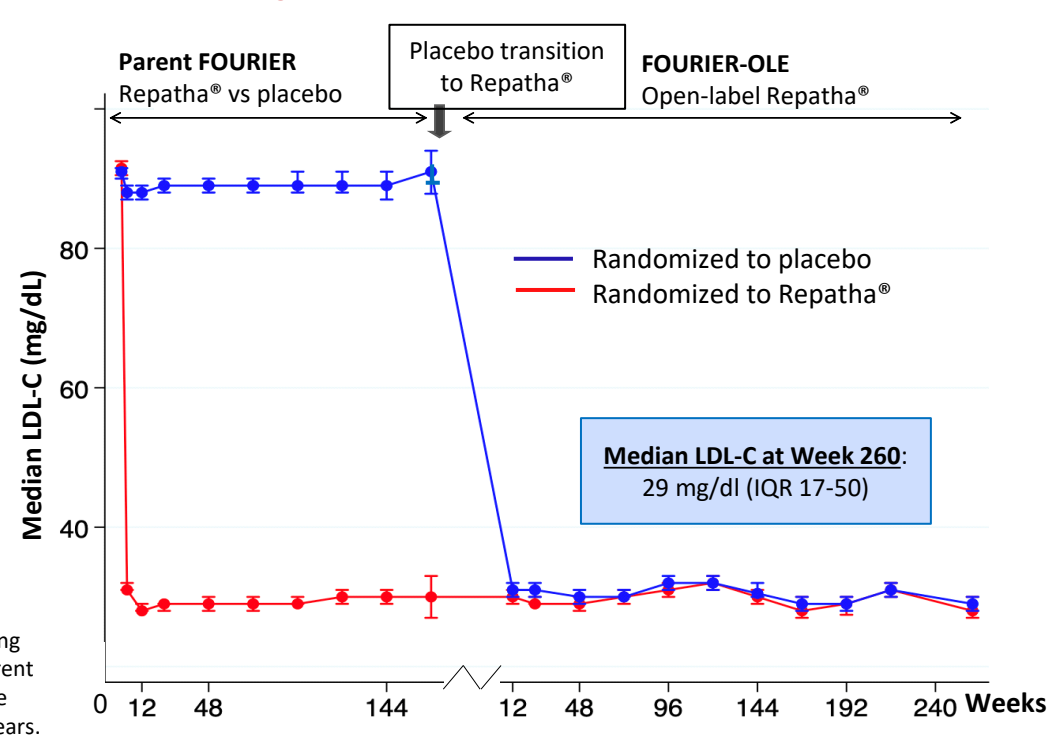
- Safety findings in the longer duration of treatment are consistent with the established safety profile of Repatha®: no new safety signals were detected and incidence of serious AEs did not increase over time (**Figure 3**), including among patients achieving very low LDL-C (< 25 mg/dL). Patients in FOURIER-OLE who had taken Repatha® in FOURIER had longer exposure to Repatha® across both FOURIER and FOURIER-OLE; data for these patients (shown in the green columns below) reflect yearly safety information over the combined FOURIER and FOURIER-OLE studies.
- At 12 weeks in FOURIER-OLE, with all patients on Repatha®, median LDL-C was 30 mg/dL; 80% achieved LDL-C < 55 mg/dL; 63% achieved < 40 mg/dL.
- Intensive LDL-C reduction in FOURIER-OLE was sustained from week 12 throughout week 260 (by 58% to 59%). At week 260, median LDL-C was 29 mg/dL (**Figure 4**).
- Limitations to FOURIER-OLE include but are not limited to the following: all patients in the extension program were treated with open-label Repatha® resulting in no concurrent placebo arm during this period.

Figure 3. Long-Term Safety in FOURIER plus FOURIER-OLE[12]



Annualized IRs of AEs are shown for Placebo and Repatha® groups during the parent FOURIER trial. Because patients taking Repatha® in both parent and OLE trials had the longest exposure to Repatha®, annualized IRs are also shown for these patients, who had Repatha® exposure up to 8.4 years.

Figure 4. Effect on LDL-C in FOURIER-OLE[12]



Important Safety Information (continued from Page 1)

Adverse Reactions in the Cardiovascular Outcomes Trial: The most common adverse reactions (> 5% of patients treated with Repatha® and more frequently than placebo) were DM (8.8% Repatha®, 8.2% placebo), nasopharyngitis (7.8% Repatha®, 7.4% placebo), and upper respiratory tract infection (5.1% Repatha®, 4.8% placebo)
Among the 16,676 patients without DM at BL, the incidence of new-onset DM during the trial was 8.1% in patients treated with Repatha® compared with 7.7% in patients who received placebo

Adverse Reactions in Pediatric Patients With HeFH: The most common adverse reactions (> 5% of patients treated with Repatha® and more frequently than placebo) were nasopharyngitis, headache, oropharyngeal pain, influenza, and upper respiratory tract infection

Adverse Reactions in Adults and Pediatric Patients With HoFH: In a 12-week study in 49 patients, the adverse reactions that occurred in at least 2 patients treated with Repatha® and more frequently than placebo were upper respiratory tract infection, influenza, gastroenteritis, and nasopharyngitis. In an OLE study in 106 patients, including 14 pediatric patients, no new adverse reactions were observed

Immunogenicity: Repatha® is a human mAb. As with all therapeutic proteins, there is potential for immunogenicity with Repatha®

Please see full Prescribing Information for Repatha®

Abbreviations: ACC = American College of Cardiology; ACEi = angiotensin-converting enzyme inhibitor; AE = adverse event; AHA = American Heart Association; ARB = angiotensin receptor blocker; ASCVD = atherosclerotic cardiovascular disease; BL = baseline; CI = confidence interval; CV = cardiovascular; DM = diabetes mellitus; ECDP = Expert Consensus Decision Pathway; eGFR = estimated glomerular filtration rate; FH = familial hypercholesterolemia; HDL-C = high-density lipoprotein cholesterol; HeFH = heterozygous familial hypercholesterolemia; HoFH = homozygous familial hypercholesterolemia; HR = hazard ratio; HTN = hypertension; IR = incidence rate; LDL-C = low-density lipoprotein cholesterol; LLT = lipid-lowering therapy; mAb = monoclonal antibody; MACE = major adverse cardiovascular event; MI = myocardial infarction; NLA = National Lipid Association; OLE = open-label extension; PAD = peripheral artery disease; PCSK9 = proprotein convertase subtilisin/kexin type 9; PCSK9i = PCSK9 inhibitor; Q2W = once every 2 weeks; QM = once monthly; RCT = randomized controlled trial; RRR = relative risk reduction; VHR = very high risk.

References: 1. Repatha® (evolocumab) prescribing information, Amgen. 2. Grundy SM, et al. *Circulation*. 2019;139:e1082-e1143. 3. Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2022;4:1366-1418. 4. Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2017;70:1785-1822. 5. Baum SJ, et al. Poster presented at: National Lipid Association Scientific Sessions; May 16-19, 2019; Miami, FL. 6. Cannon CP, et al. Poster presented at: American Heart Association; November 16-18, 2019; Philadelphia, PA. 7. Cannon CP, et al. Slides presented at: American Heart Association; November 13-17, 2020, Virtual Meeting. 8. Gitt AK, et al. *Atherosclerosis.* 2017;266:158-166. 9. Data on file, Amgen; 2021. 10. Sabatine MS, et al. *N Engl J Med*. 2017;376:1713-1722. 11. Koren MJ, et al. *J Am Coll Cardiol*. 2019;74:2132-2146. 12. O'Donoghue ML, et al. *Circulation.* 2022;146:1109-1119.

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