Collaborative Pragmatic Trials in Action: EVOLVE-MI

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Conventional vs Pragmatic Trials

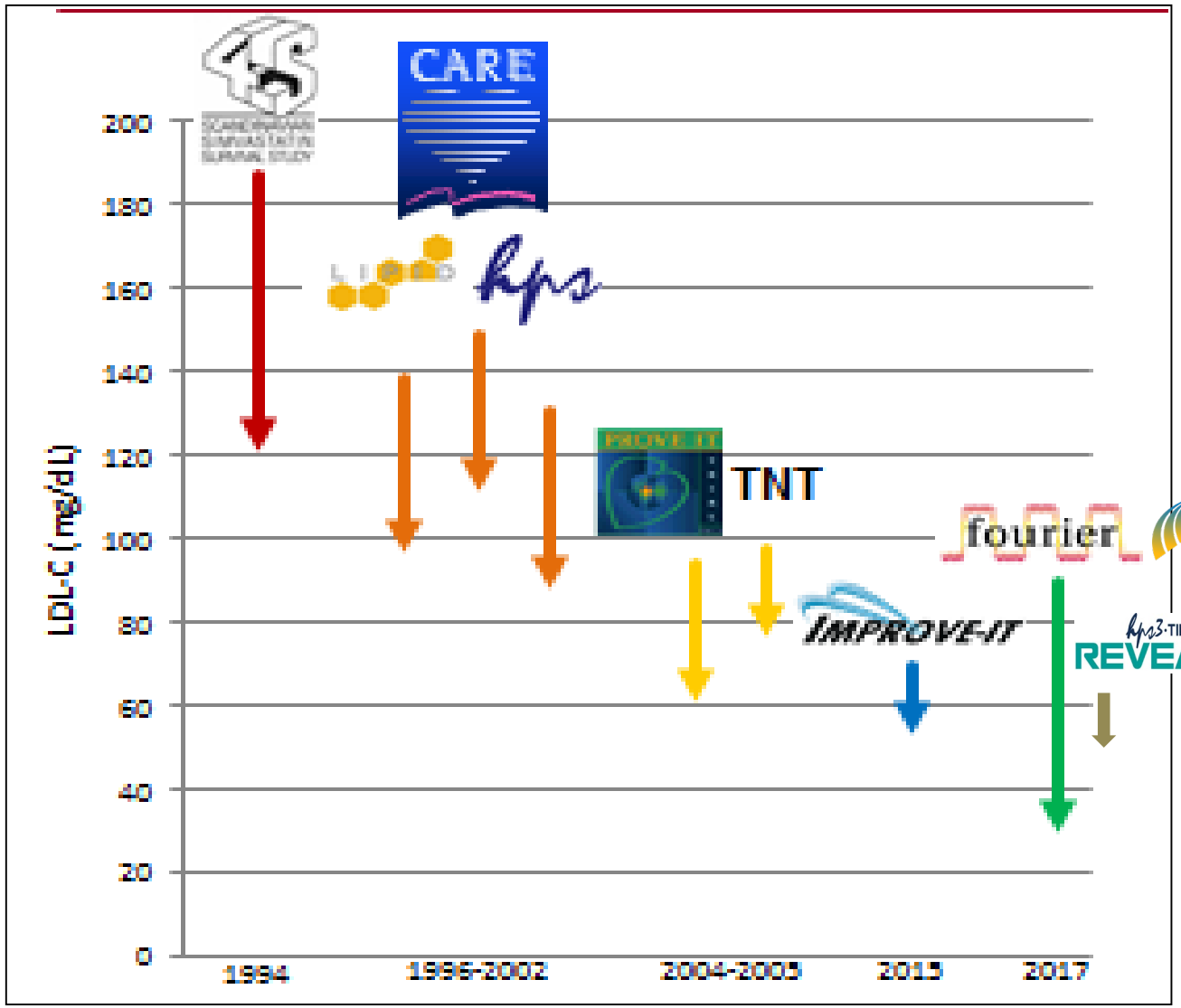
- Conventional RCTs confirm a physiological or clinical hypothesis
  - Typically performed in highly selected participants, long, expensive, less generalizable

- Pragmatic trials should be strongly integrated with standard care, can use routinely collected clinical data, maximize efficiency, minimize duration and cost

Both types of studies must be of high quality

McGinnis. NEJM 2021;385:1. Ford I. NEJM 2016; 375:454

Lowering LDL and CV Risk Reduction



High is bad

Average is not good

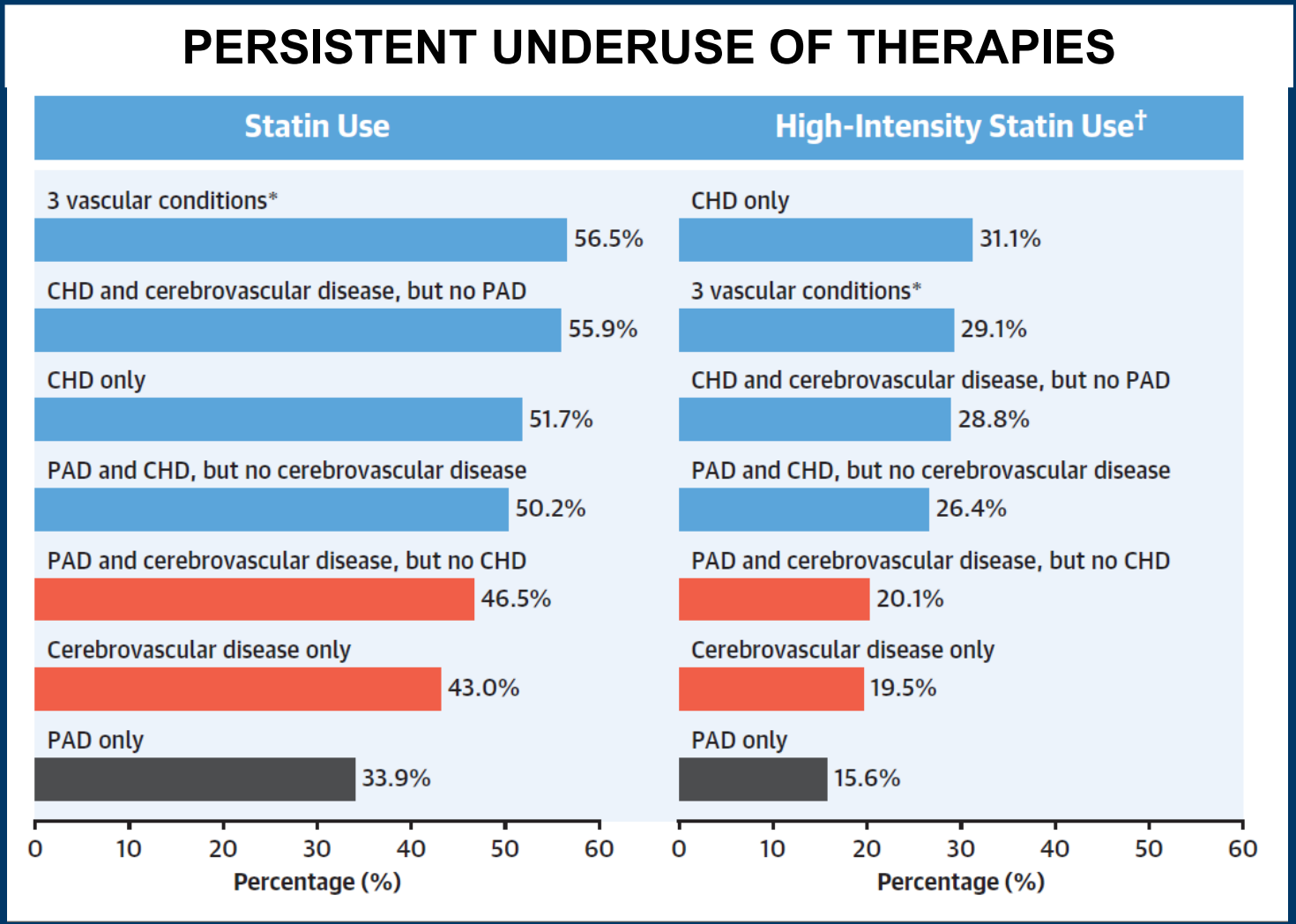
Lower is better

Even lower is even better

Lowest is best

LDL is the Problem…and is it Solved? NO!

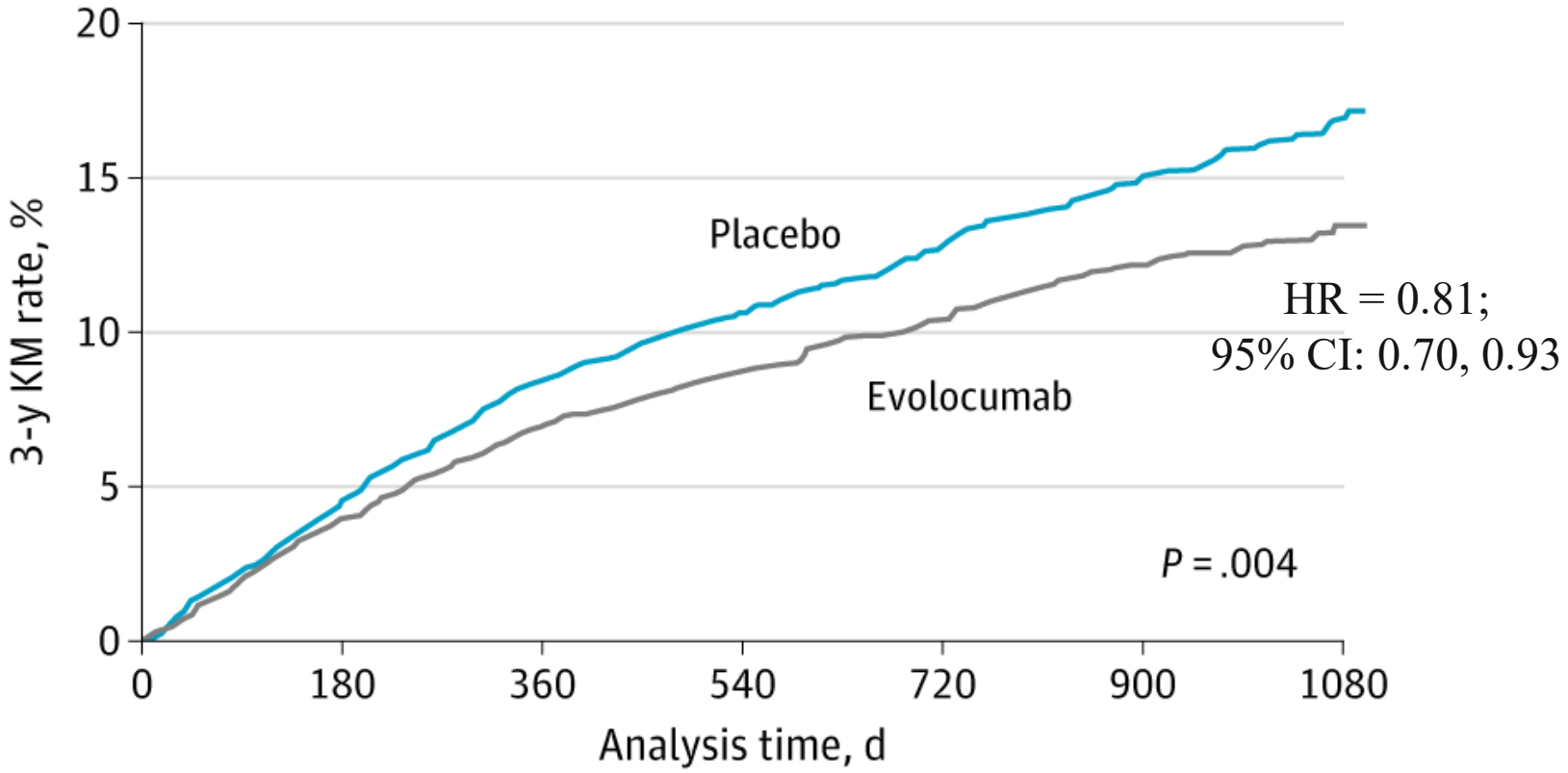
- LDL-C proven to be a risk factor (not just marker)
- No lower limit for safety
- Multiple drugs that can be used in combination with excellent safety profile
- Multiple trials show predictable outcomes benefit (based on absolute reduction in LDL-C)



Colantonio et al. JACC 2020

FOURIER - Efficacy of Evolocumab in Patients with Recent MI (<12 Months)

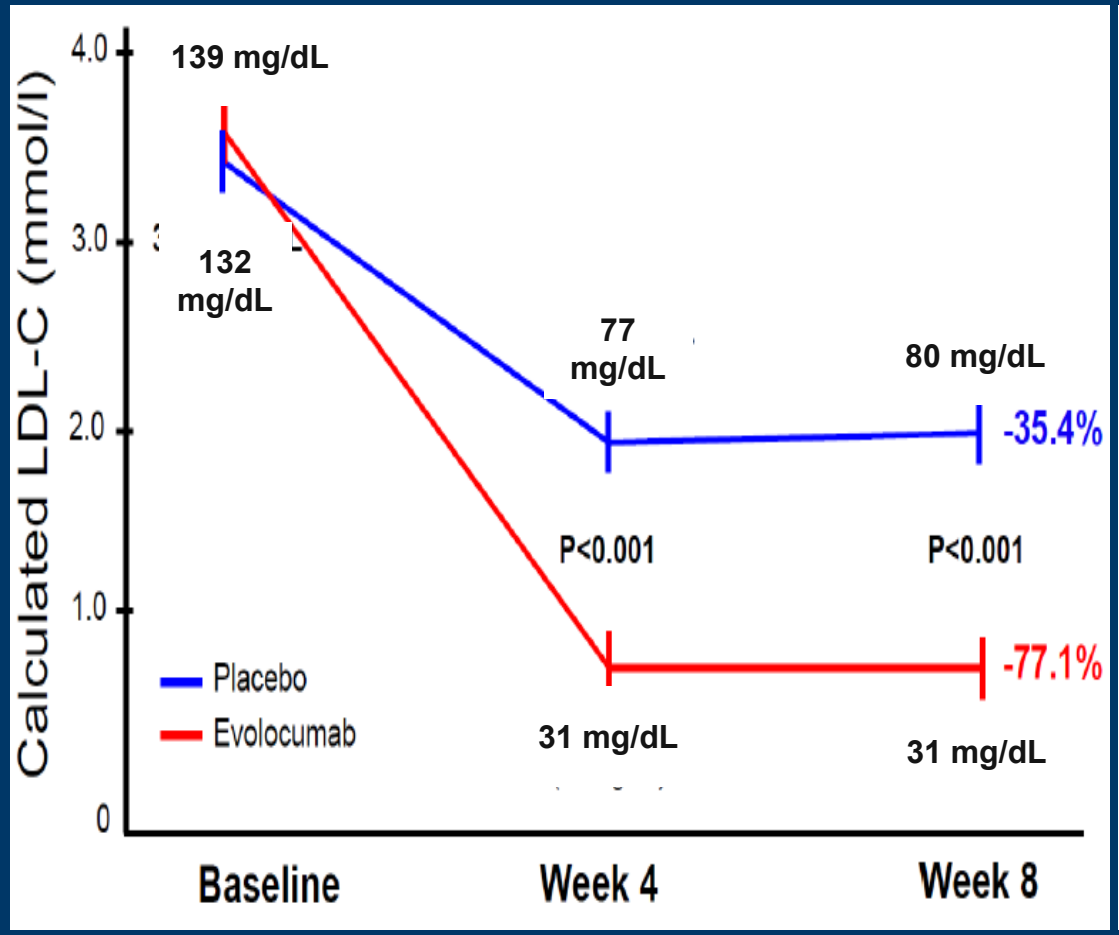
Primary endpoint: CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization

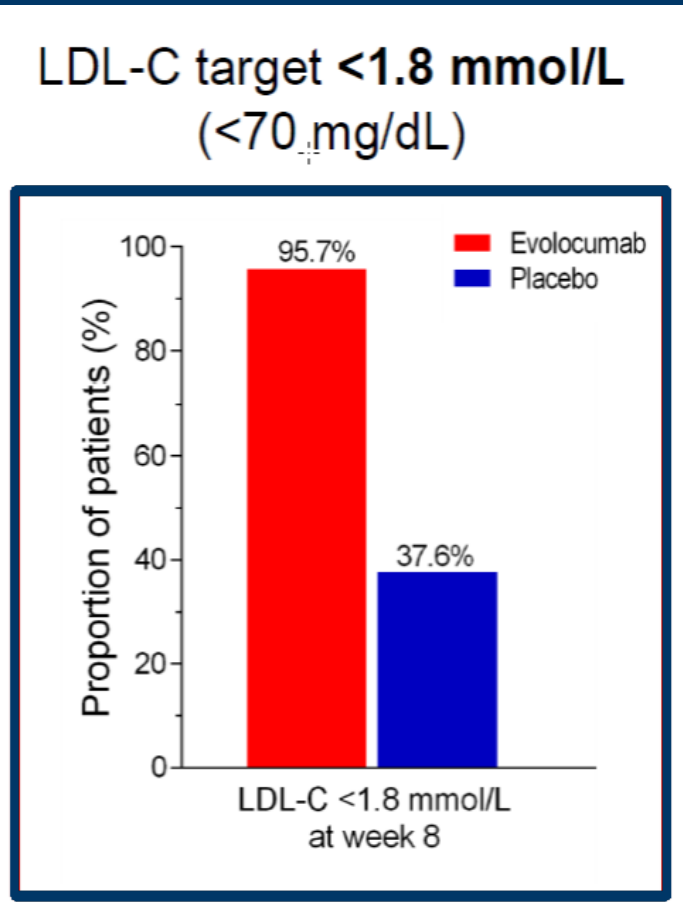


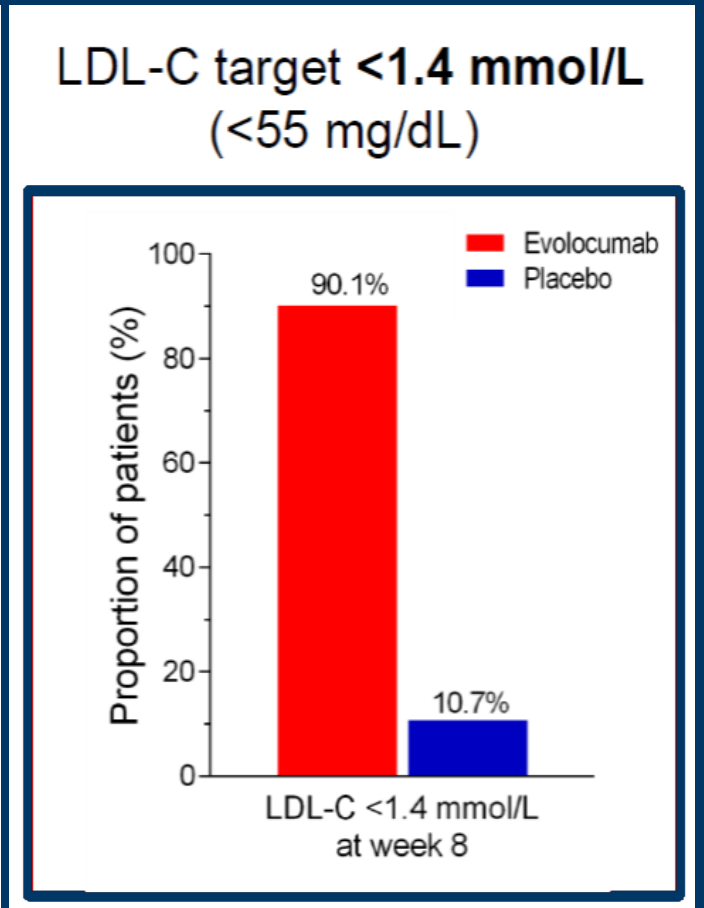
Gencer B, et al. JAMA Cardiol. 2020;5:952-957

EVOPACS

Change in LDL-C and Target achievement



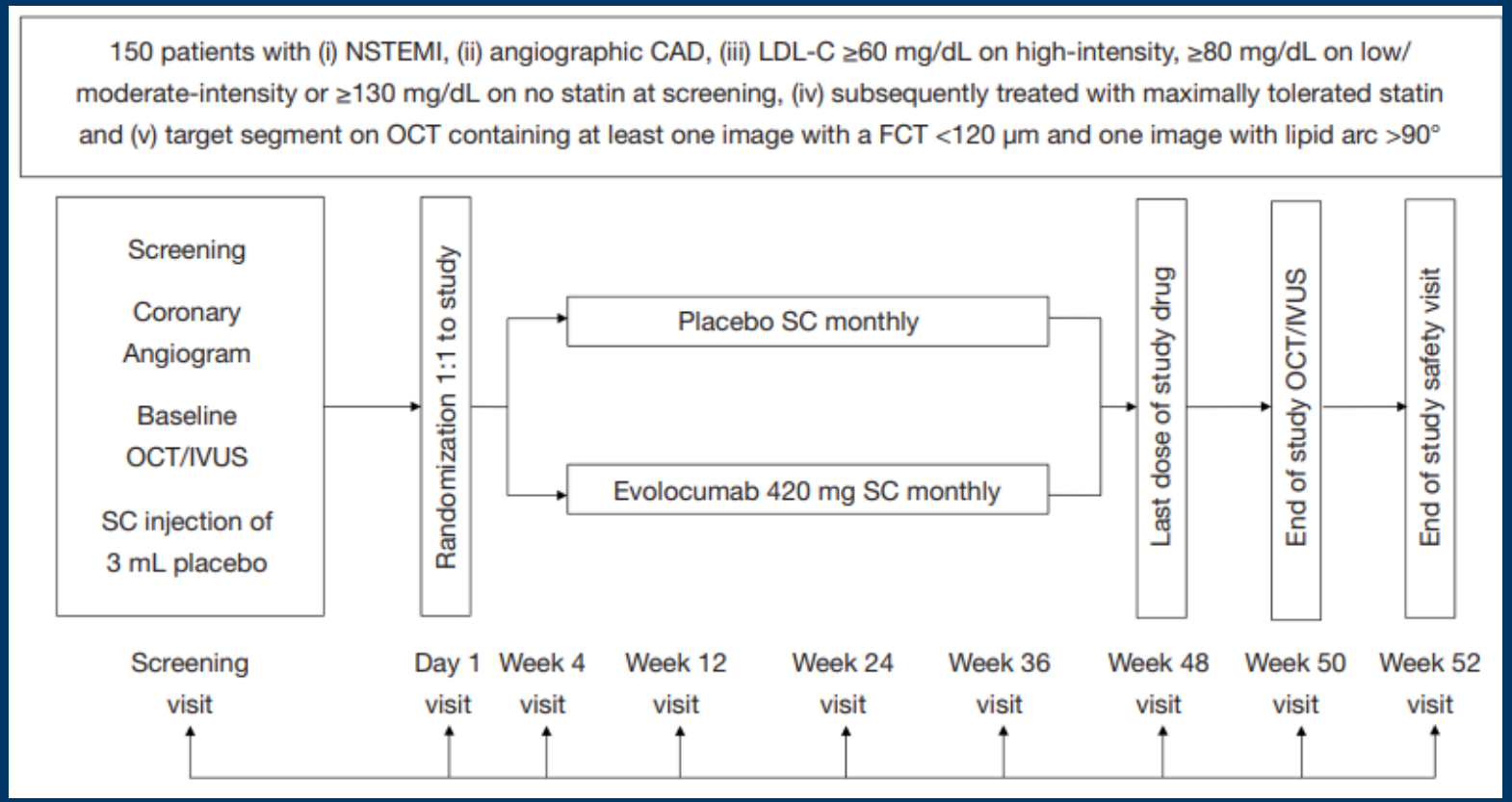




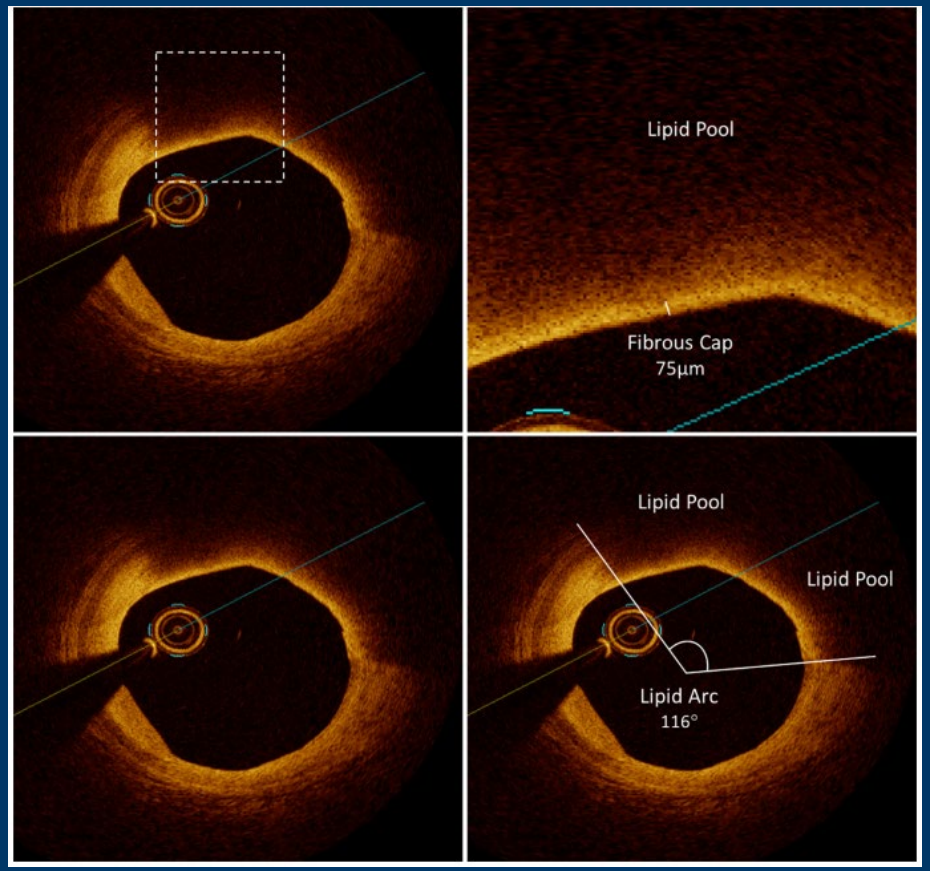
Koskinas KC, et al. J Am Coll Cardiol. 2019;74:2452-2462.

HUYGENS Imaging Study
Effect of Evolocumab on Atherosclerotic Plaque

- Phase 3, multicenter, double-blind study will assess the impact of incremental lipid lowering with evolocumab on plaque features using serial OCT imaging, in statin-treated patients with NSTEMI ACS (N = 150)



OCT Plaque Measurements

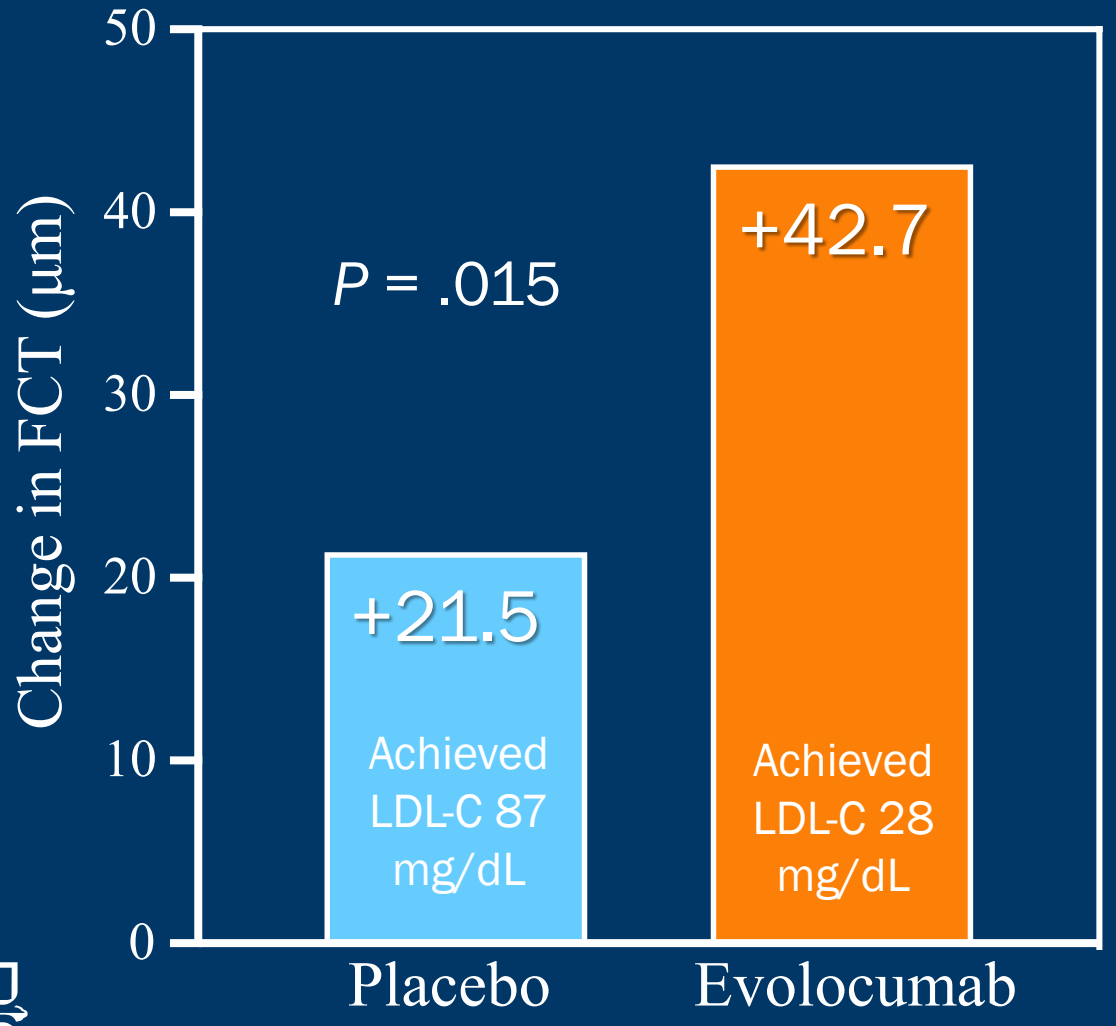


FCT, fibrous cap thickness; OCT, optical coherence tomography.

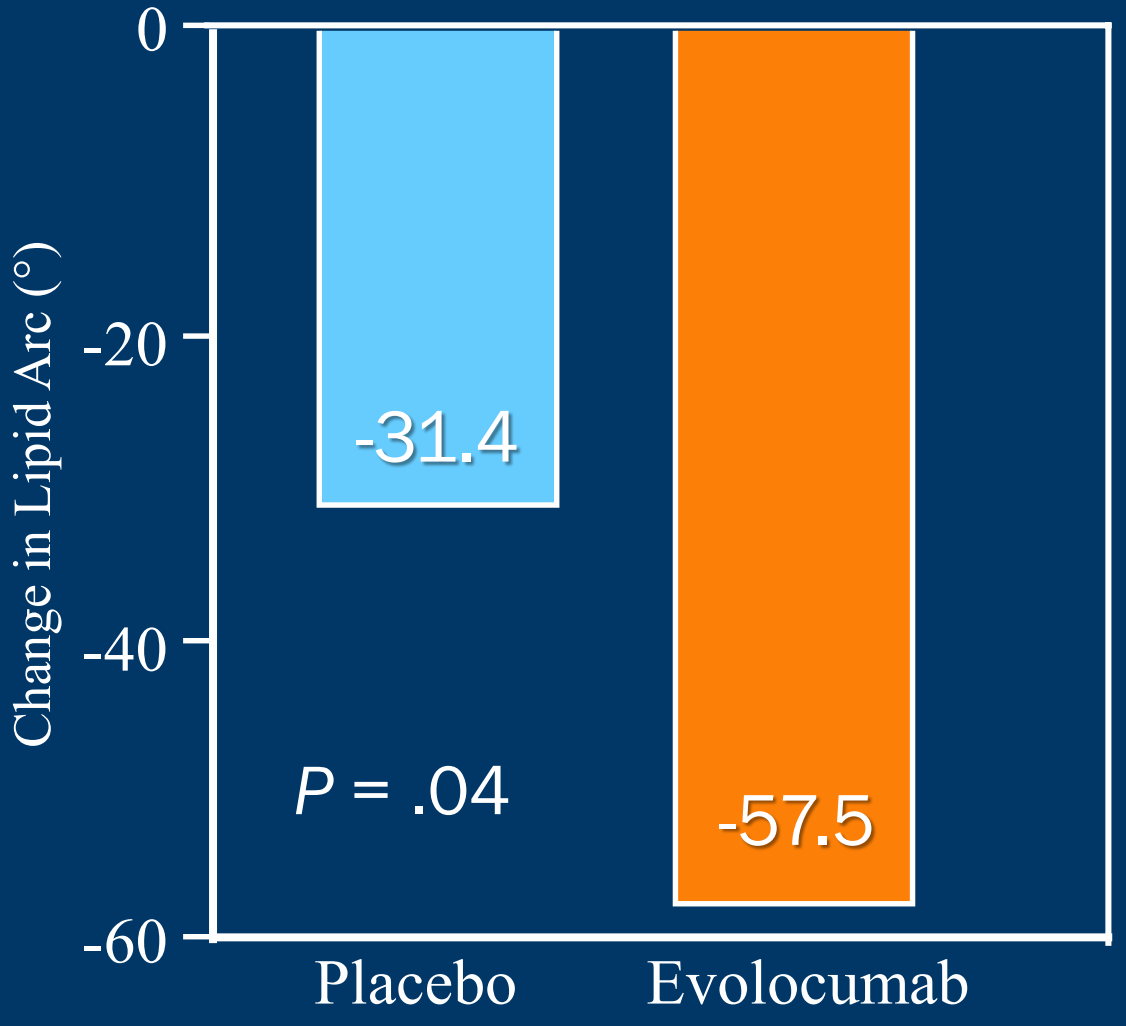
Nicholls SJ, et al. Cardiovasc Diagn Ther. 2021;11:120-129.

HUYGENS

Primary Endpoint: Minimum Fibrous Cap Thickness



Secondary Endpoint: Maximum Lipid Arc

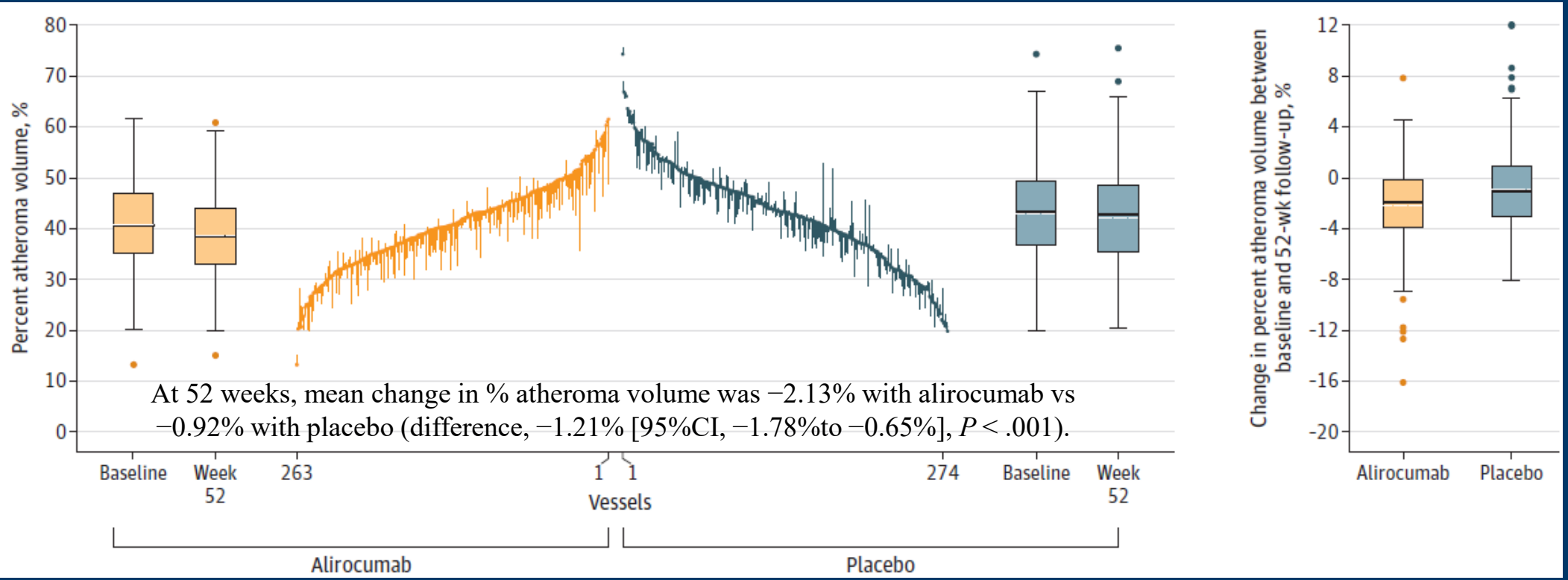


Nicholls S, et al. J Am Coll Cardiol Img 2022; online March)

PACMAN-AMI

- Design: 300 patients with AMI randomized to biweekly alirocumab or placebo < 24 h of PCI, for 52 weeks in addition to high-intensity statin (rosuvastatin, 20 mg) at 9 academic European hospitals
- Objective: Determine the effects of alirocumab on coronary atherosclerosis using serial multimodality IVUS imaging

Changes in Percent Atheroma Volume via IVUVS in Patients Treated With Alirocumab vs Placebo Added to High-Intensity Statin Therapy



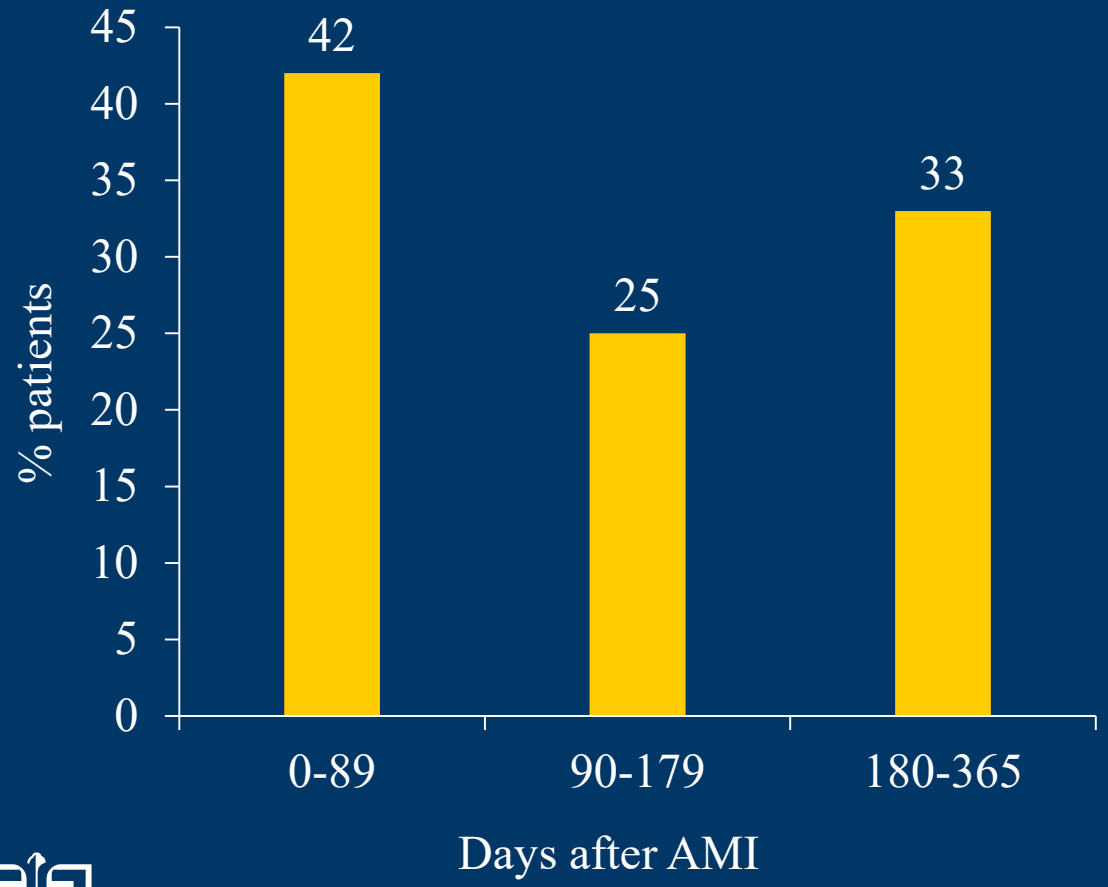
Räber L, et al. JAMA. 2022 Apr 3:e225218.

PCSK9i after ACS - Background

- PCSK9i reduce athero-thrombotic events in patients with ASCVD
- Previous trials of PCSK9i excluded patients hospitalized with ACS - a population at the highest risk of recurrent events
- Traditional RCTs enrolled select participants and required optimal lipid-lowering therapy at baseline - which is infrequently achieved in the real-world practice
- Consequently, the absolute (and possibly relative) risk reductions seen with PCSK9i may have been underestimated
- Although PCSK9i may provide substantial benefits immediately post-ACS, there are no dedicated trials evaluating their effects on meaningful CV outcomes in ACS and use in immediate post-ACS setting is extremely low

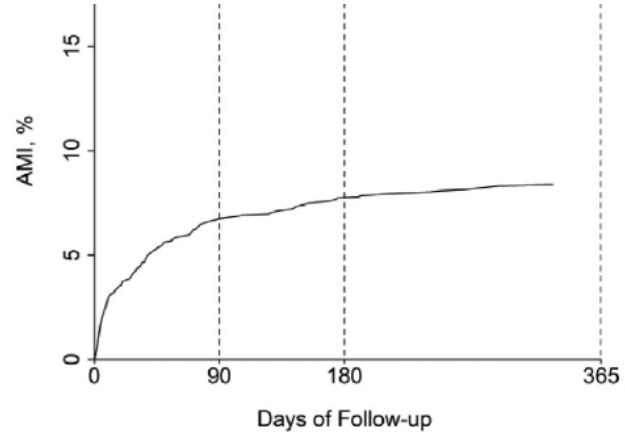
PCSK9 Inhibitor Use After Acute MI

N=1705 pts
Median time to initiation 114 days



Cumulative incidence of CV events prior to initiation of PCSK9i

Characteristics	Follow-up period		
	90 days	180 days	365 days
ASCVD event	8.0%	10.5%	12.5%
Acute myocardial infarction	6.7%	7.7%	8.4%
Coronary heart disease	7.7%	10.1%	12.0%
Peripheral artery disease event	0.3%	0.4%	0.5%



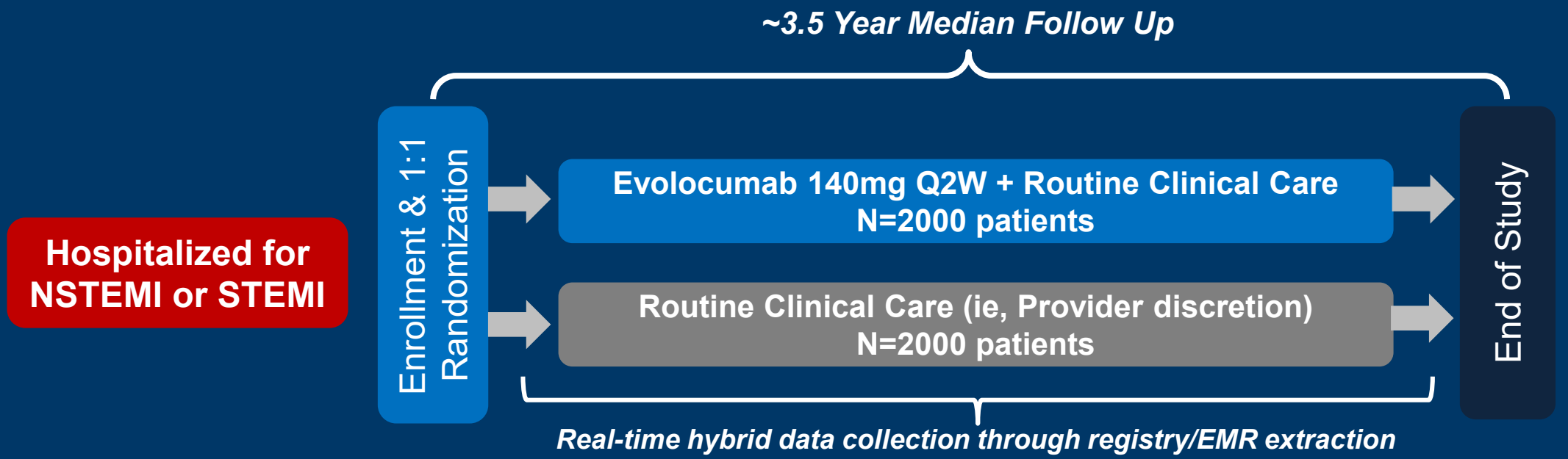
McKinley et al J Clin Lipidology 2022;16:75–82

Barriers & Solutions

BARRIERS	SOLUTIONS
Focus on “titration” approach	Prove that “just treating” works
Perception that LDL-lowering is not urgent; can wait for outpatient	Prove that getting lower earlier improves outcomes
Perception that practical translation in hospital challenging	Prove feasible in real-world practice

EVOLVE MI

Pragmatic Effectiveness Study in ACS



- Evolocumab dosed within 10 days of index MI vs SOC (open-label study)
- 1° endpoint: total (first and subsequent) MI, ischemic stroke, any arterial revascularization, all-cause death

CPC Clinical Research
ALBERT EINSTEIN
SOCIEDADE BENEFICENTE ISRAELITA BRASILEIRA
UCR
Uppsala Clinical Research Center

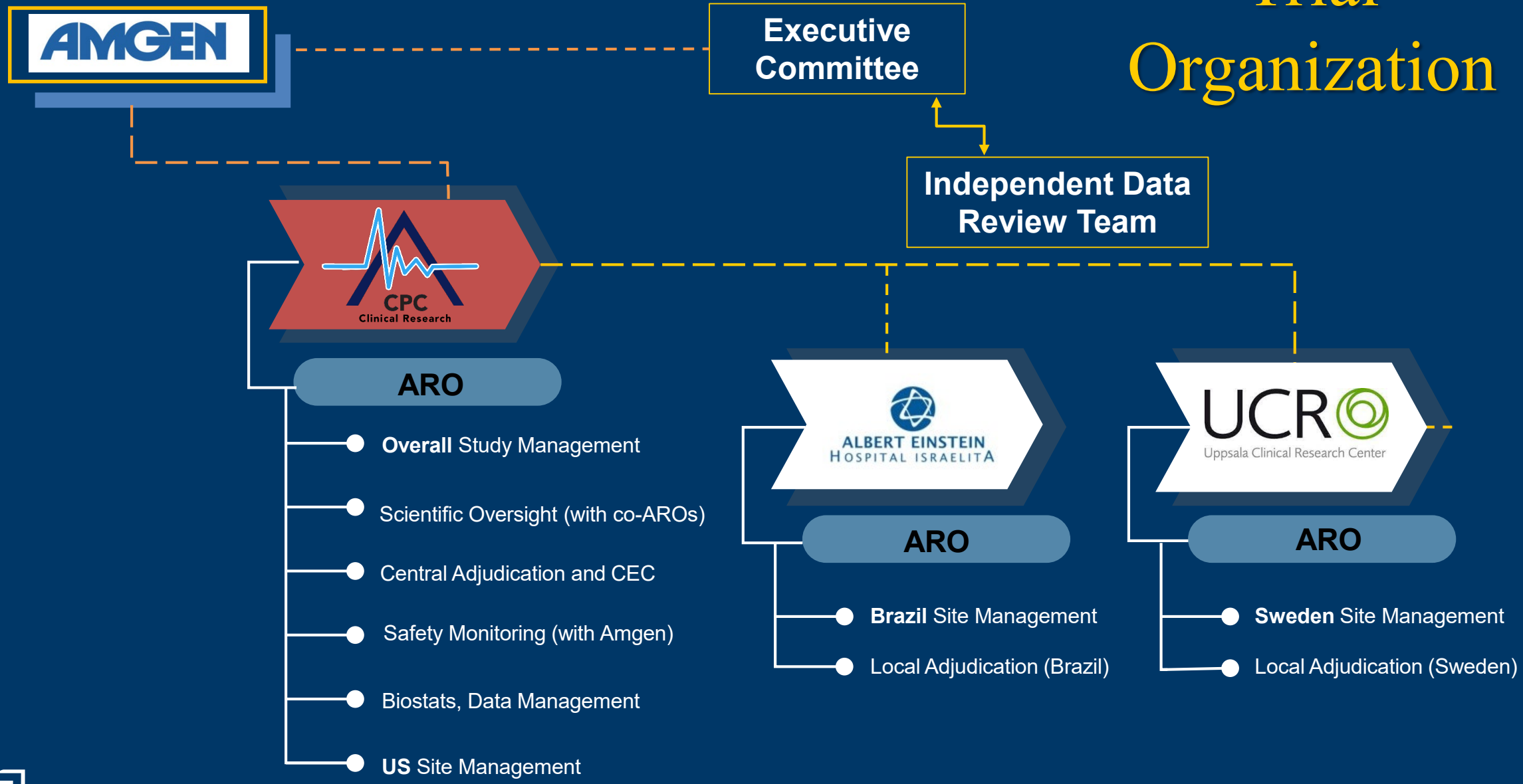
Innovations in Trial Organization

- Collaborative study with Academic-Industry Partnership
- Oversight by an Academic Executive Committee
- Trial Innovation through Academic Research Organizations (who are also enrolling and understand challenges firsthand)
- Patient recruitment through network of sites managed by a collaboration of AROs

EVOLVE-MI

- Regional AROs with diverse health systems
- Study participants managed within health systems in-line with local standard of care
- Automated data collection
- Leverage Swedish registries

Trial Organization



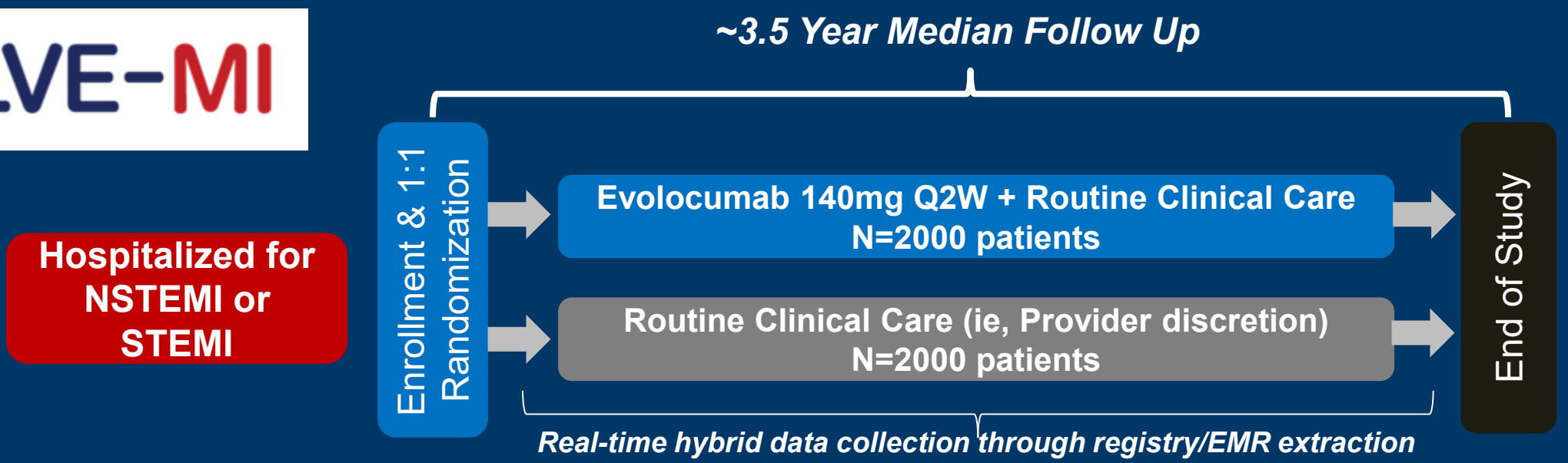
Innovations in Protocol Development

- Minimal inclusion / exclusion
- Minimal procedures and ability to screen/randomize same day
- Simplified schedule of events
- Streamlined safety

Innovations in Trial Operations

Traditional Trial	EVOLVE-MI
Manual entry into eCRF, many fields, complex navigation	Hybrid data collection
Drug dispensed at visits	Hybrid – optimized for each environment
Study labs	Minimal, local lab at baseline
Identification of events via study coordinator/PI	Hybrid endpoint collection
Central event adjudication	Hybrid adjudication
Separate IWRS/IXRS requiring multiple site logins	Randomization directly in EDC

EVOLVE-MI



N=4000

1° endpoint: total (first and subsequent) MI, ischemic stroke, any arterial revascularization, all-cause death

Pragmatic features

- IP self-administration
- Limited visits
- Hybrid endpoint identification, including use of EMR and other methods
- Only required lab: local LDL at baseline
- Streamlined safety reporting

Early Experience

- First sites enrolled within a day of activation
- “Screening & enrollment were smooth, and it was nice to be able to randomize within the EDC.”
- “Patients are interested, almost everyone qualifies, and the data entry is not burdensome.”

Take Home Points

- Pragmatic trials are a reality, here to stay
- Greater “decentralization” of most trials in the future
- Greater use of digital technology over time
- Promise: rapid enrollment and study completion, lower cost, more convenient to patients, greater generalizability
- Not “one size fits all”. As always, approach should be tailored to the clinical question that is being addressed