How do we implement new therapeutics to change the paradigm?

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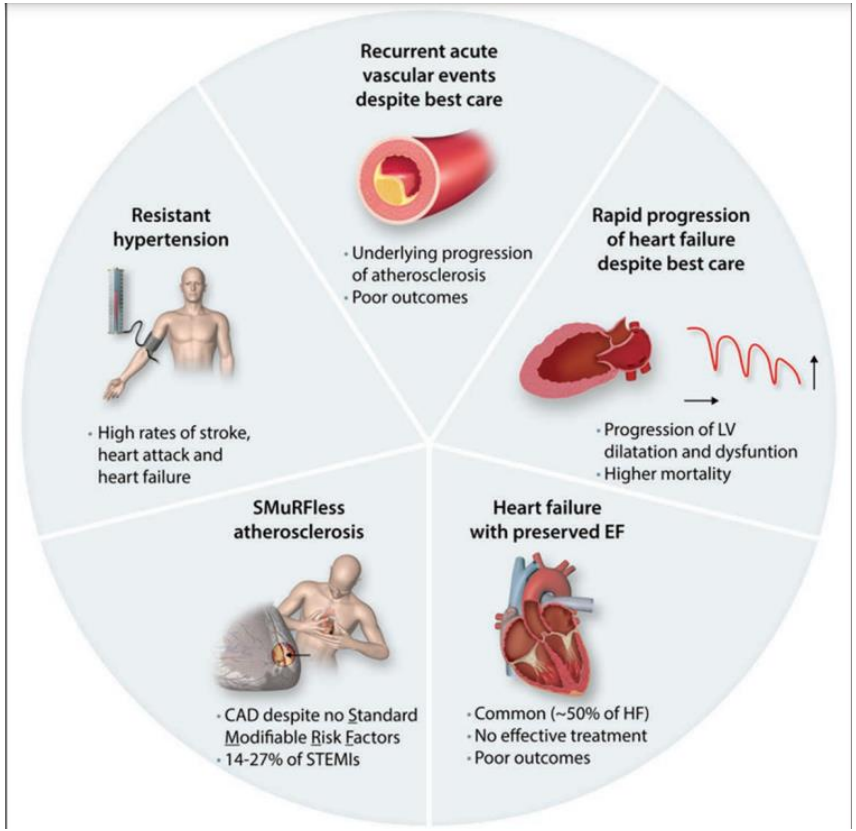
Unmet needs in Cardiology



Circulation. 2021;144:159–169

Unmet needs in lipid lowering therapy

Getting to LDL-C goal

Adherence to medication

Side effects / Statin intolerance

Residual lipid risk from other apoB containing lipoproteins- Lp(a), TRL and other nontraditional RF

Therapies started too late !

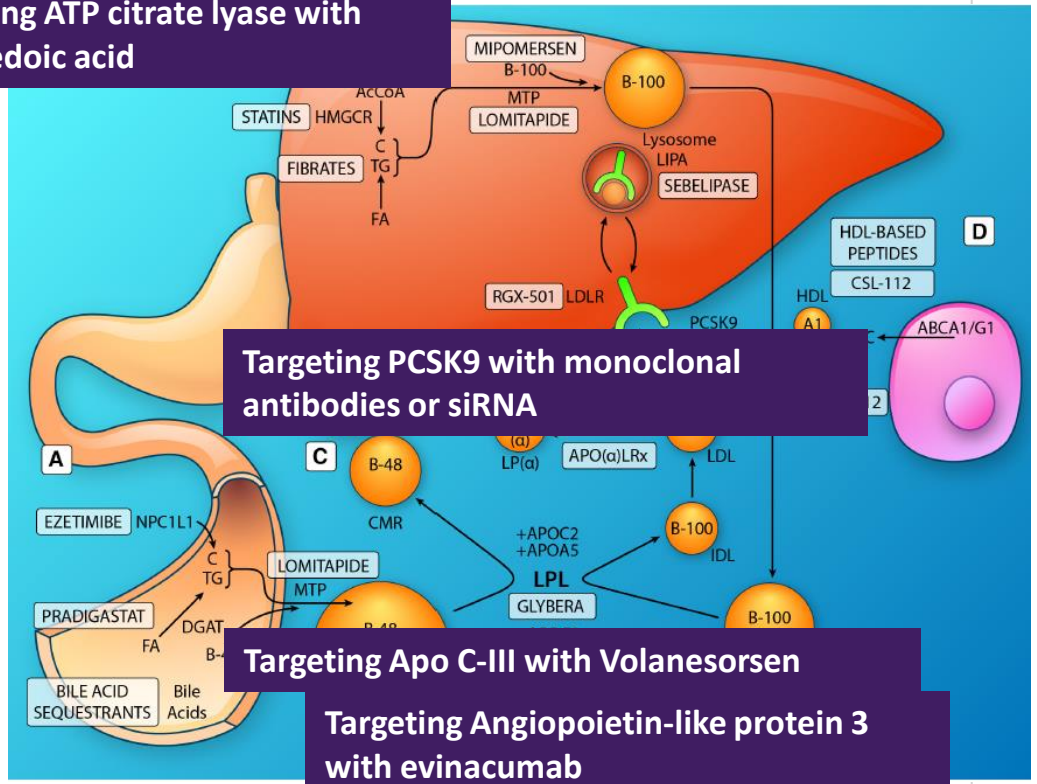
Technology to target novel biology

Discovery of new targets in lipid metabolism via genetic evidence
Advances in analytical techniques

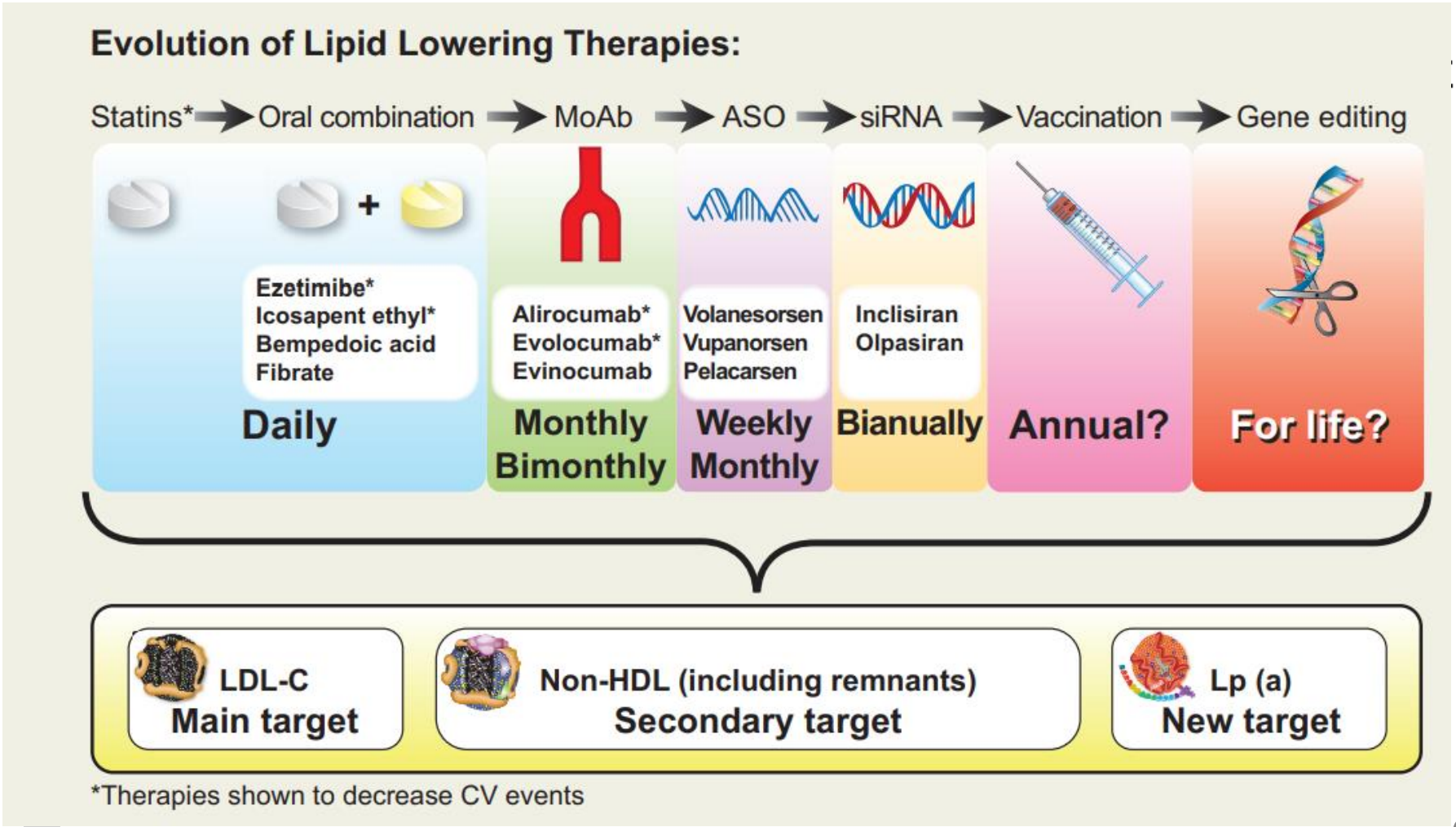
Increased understanding of signaling molecules

Intelligent targeted biological/ chemical therapies

PCSK9,ANGPTL3,Apo C3, Lp(a) major targets

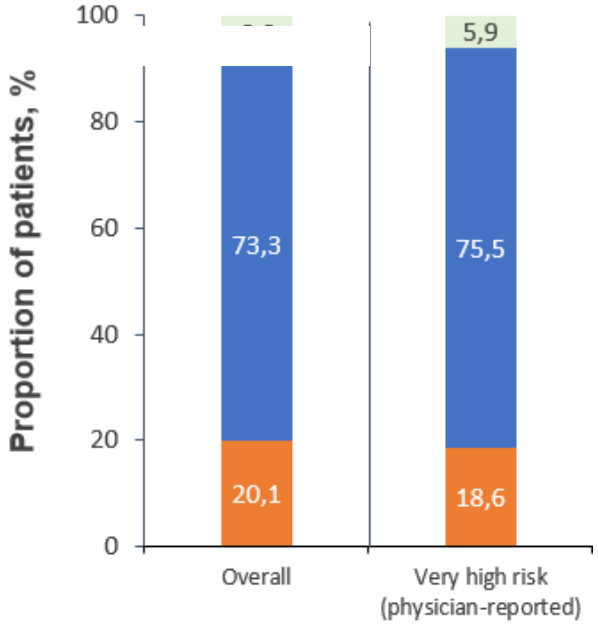


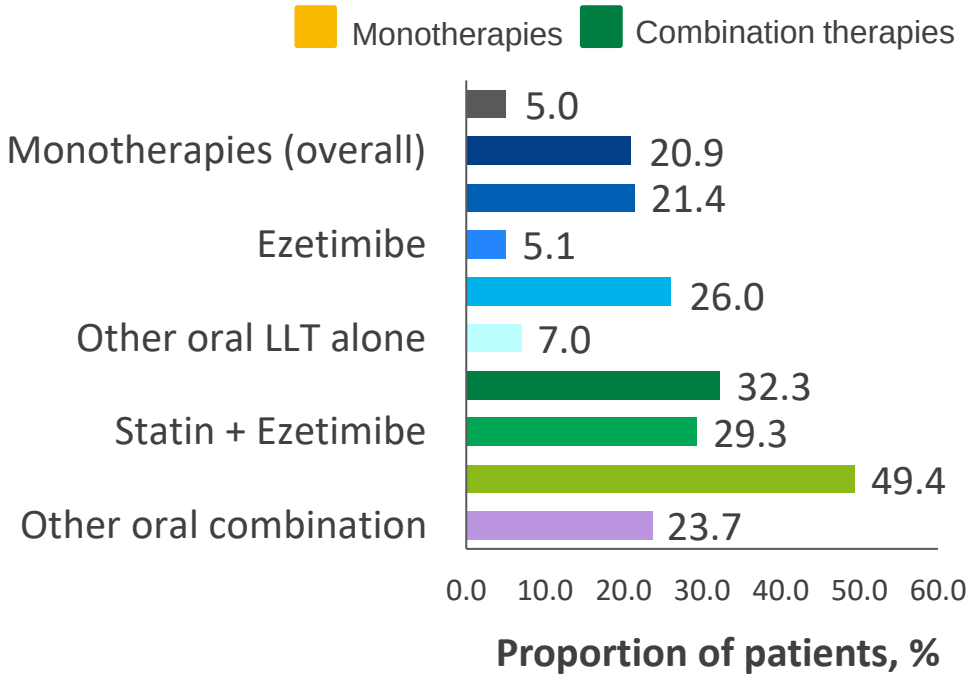
Circ Res. 2019;124:386



Tokgozoglu European Heart **Journal** 2022;ehab841

LDL-C Goal Attainment : The SANTORINI Study





Data on attainment of recommended LDL-C goals in real-world practice supports the need for more intensive LLT regimens worldwide

Lancet Reg Health Eur. 2023;29:100624

Opportunities for new therapies

More potent lipid lowering: Real-world practice on LDL goal attainment supports the need for more intensive LLT regimens

Less side effects ?

More compliance likely with less frequent administration?

Meet patient expectations better

Adress other atherogenic lipids: TGRL, Lp(a)

Help personalise therapy

Help patients with recurrent events

Deescalation of former therapies ?

We still need patient adherence and implementation of guidelines

Challenges for new therapies

Off target effects

Immunogenicity

Unpredictable side effects

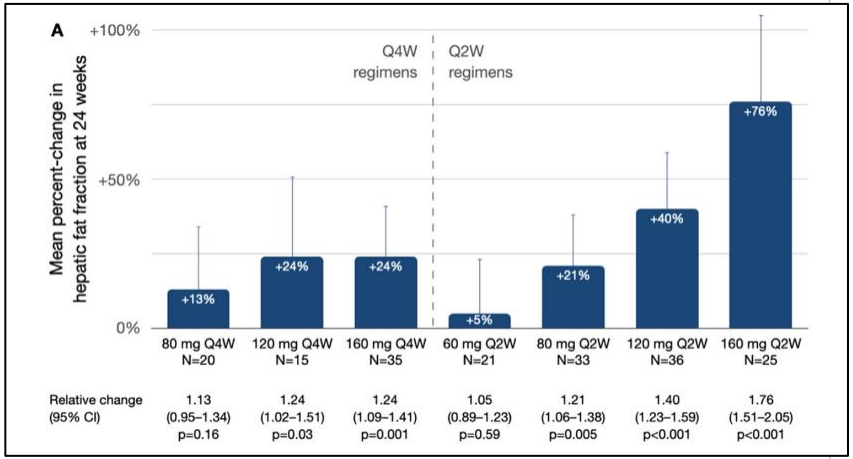
Regulatory challenges

Ethical considerations

Reproductive system effects

Germline editing

Hepatic fat changes with antisense oligonucleotide therapy targeting ANGPTL3: TIMI 70



J Clinical Lipidol December 28, 2023;16:12]

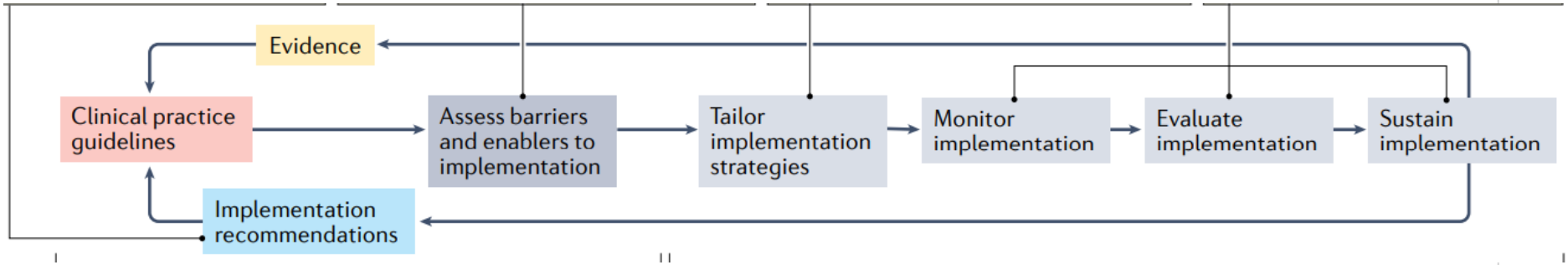
Great scientific progress

Effective therapies

Evidence based guidelines

≠ **Real life**

Systematic uptake of research findings into routine practice to improve the quality and effectiveness of health services.



Barriers to implementation in clinical practice

Healthcare system:

- Administrative barriers to drug prescription
- Cost of novel therapies
- Barriers to reimbursement
- Limited availability of cardiac rehabilitation programmes
- Poor coordination among healthcare stakeholders
- Limited time for patient

Physician:

- Inadequate LLT prescription at discharge
- Lack of knowledge/adherence to guideline recommendations
- Lack of structured clinical pathway
- Therapeutic inertia
- Knowledge gap between levels of care
- Complex medication regime

Patient:

- Poor treatment adherence
- Poor health literacy
- Lack of education during hospital admission
- Fear of side effects
- Cost
- Social problems
- Multiple morbidities
- Polypharmacy

How can we change practice?

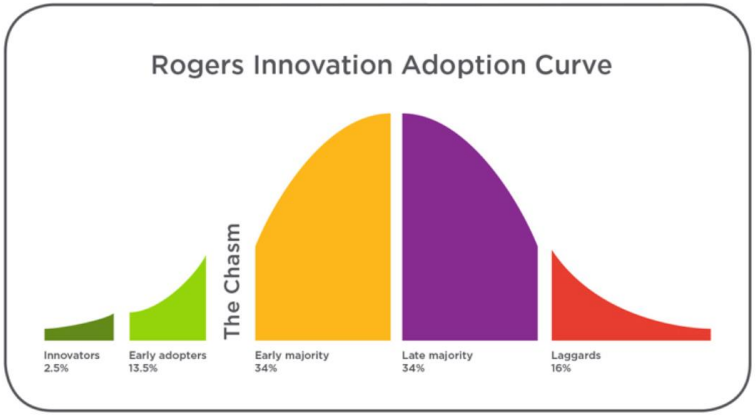
Strong scientific support: Efficacy safety-sp important for nucleic acid based

Adress physician / patient / policymaker related barriers

Provide support for practice change in a structured and organized manner to accelerate the pace

How do we change practice ?

Practice change may happen without support, in a haphazard, slow and disorganized manner.



Rapid adoption of therapy if:

Treatment addresses an unmet need

Demonstrates clear benefits improving patient outcome, QOL or comfort

Safe

Accessible

Diverse stakeholders are addressed and supported to overcome inertia

Physician related

Provide clear protocols for treatment

Identify which patient will benefit most

Educate and enpower physican

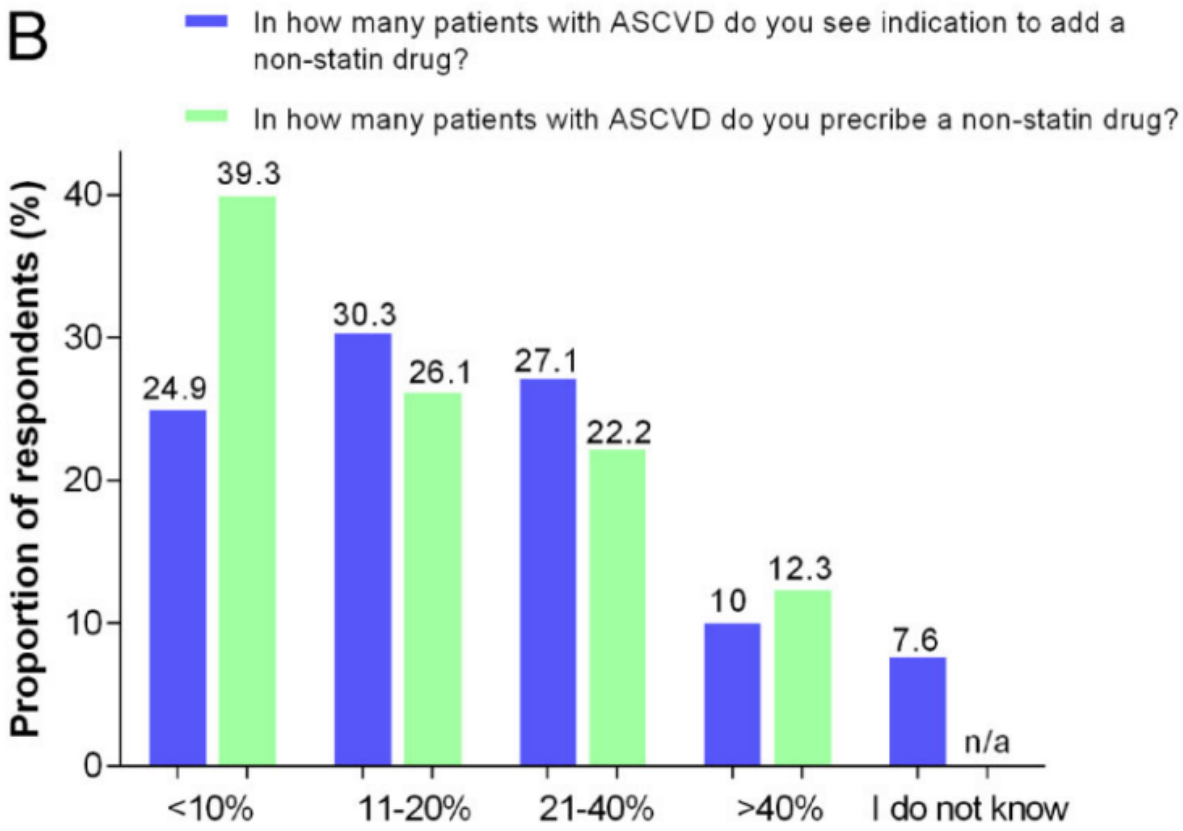
Ensure necessary infrastructure

Optimise delivery system

Some implementation methods already have been shown to be useful

More studies on implementation science needed to see what works

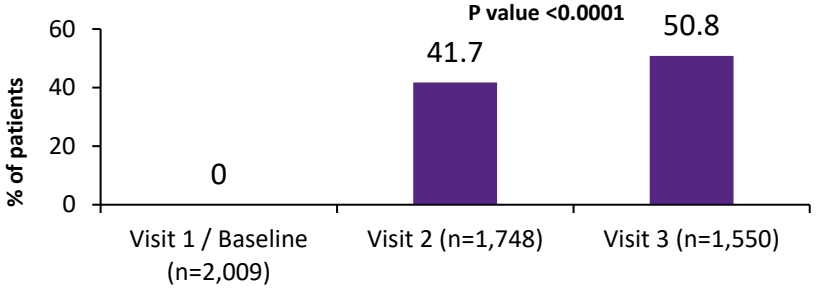
Inertia on prescribing non-statin drugs

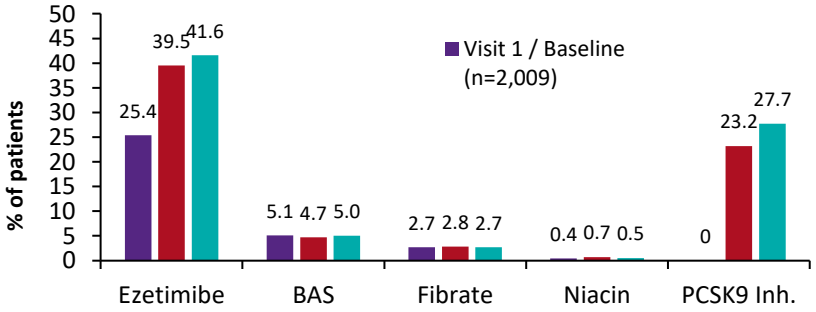


European Journal of Preventive Cardiology, Volume 28, December 2021, Pages 2030–2037

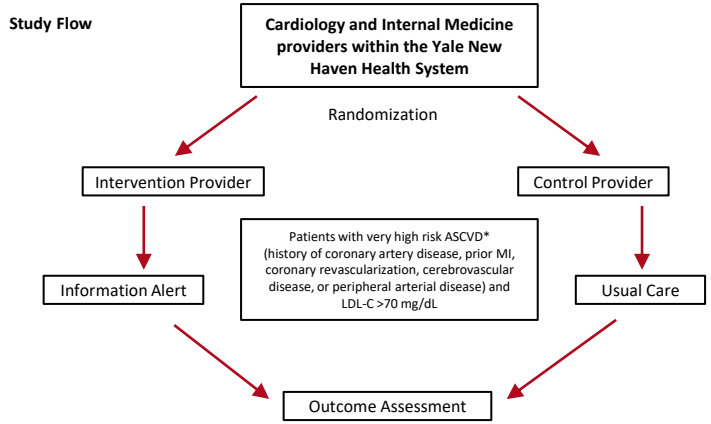
Programs that remind and educate physicians

GOAL Canada: Physician education and support can improve patient management[1]





PROMPT-LIPID: Effectiveness of an electronic alert built into EHR[2]



* Based on 2018 ACC/AHA/Multisociety Lipid Guidelines

Primary outcome: Proportion of patients who have intensified LLT at 90 days

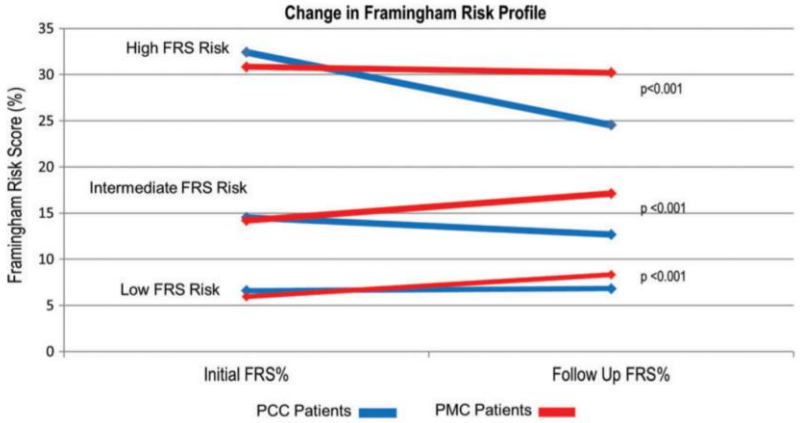
Secondary outcomes: Achieved LDL-C goal at 6 months and rates of CV hospitalization

ACC/AHA, American College of Cardiology/American Heart Association; ASCVD, atherosclerotic cardiovascular disease; BAS, bile acid sequestrant; EHR, electronic health record; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor

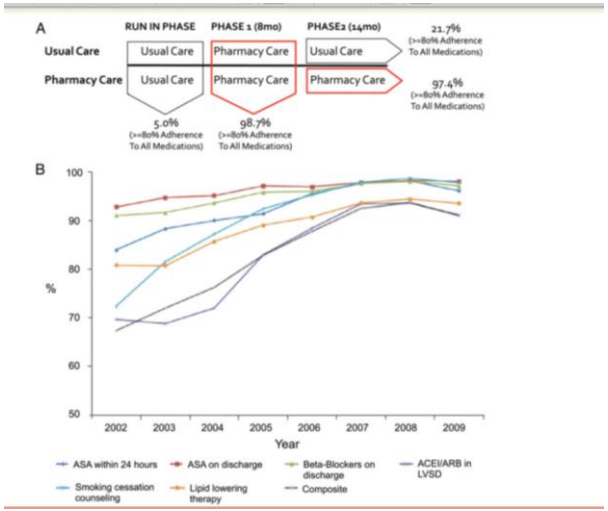
1. Langer A, et al. CJC Open. 2020;2:49-54; 2. Shah N, et al. Am Heart J. 2022. DOI: 10.1016/j.ahj.2022.07.002 Epub ahead of print

Structured, team based, patient centered intervention

Usual care versus advanced team care in primary prevention: n=1190

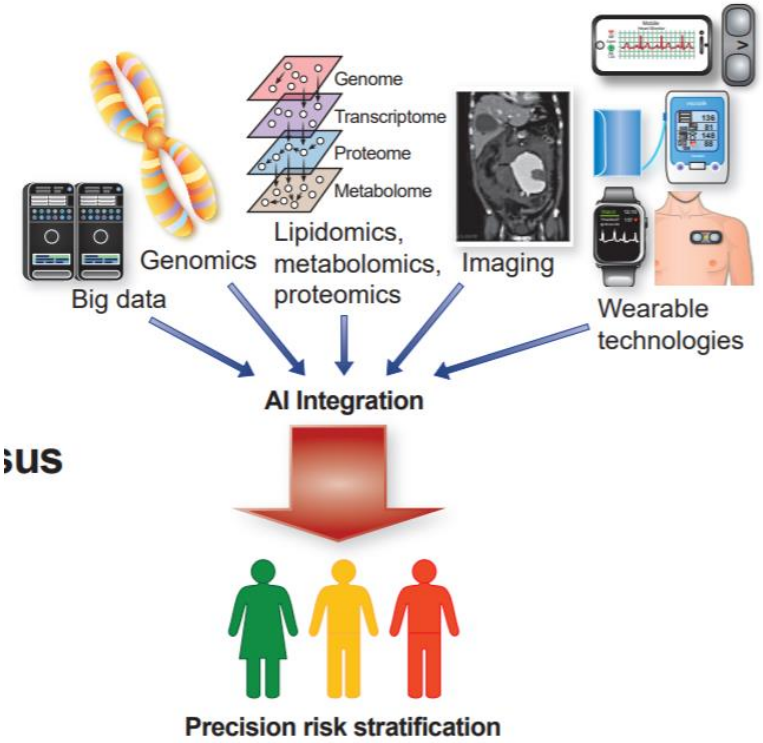


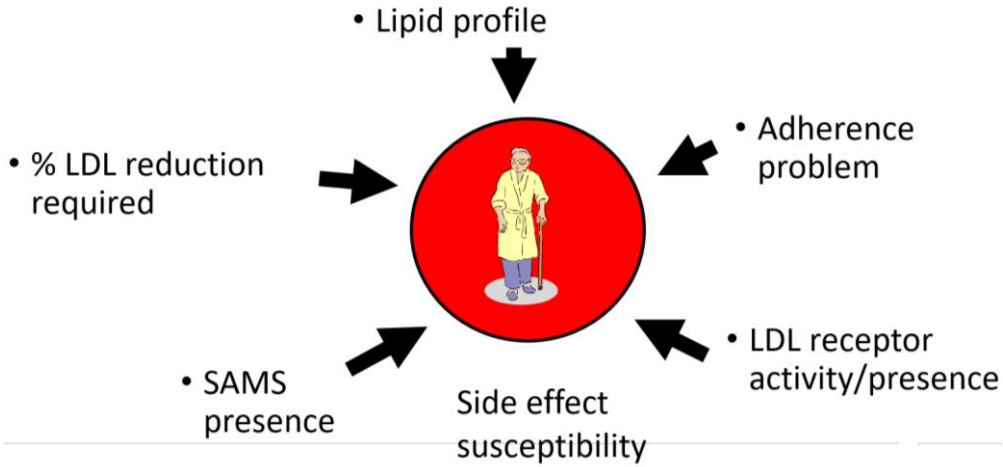
Pharmacy care improves adherence



Clinical Cardiology. 2018;41:817–824
Eur Heart J 2014; 35:3267

Personalised risk prediction and management





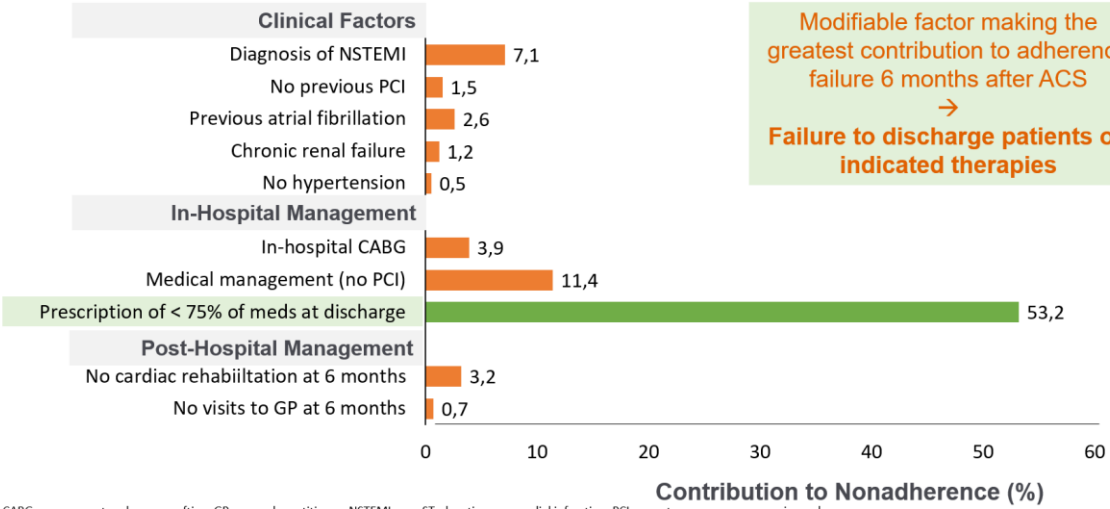
Tokgozoglu, Eur Heart J 2021;42:2468

Prioritise those at highest risk

- **ACS patients have high risk of recurrence**
- **Implementation studies show optimal time to ensure adherence is starting therapy during hospitalisation**
- **After safety and efficacy proven in high risk patients, threshold for testing these therapies on less ill patients may be progressively reduced**

Predictors of Adherence 6 Months After ACS

CONCORDANCE ACS Registry (n = 6595)



Modifiable factor making the greatest contribution to adherence failure 6 months after ACS

→

Failure to discharge patients on indicated therapies

- CABG, coronary artery bypass grafting; GP, general practitioner; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary angiography.

Brieger D, et al. Intern Med J. 2018;48:541-549.

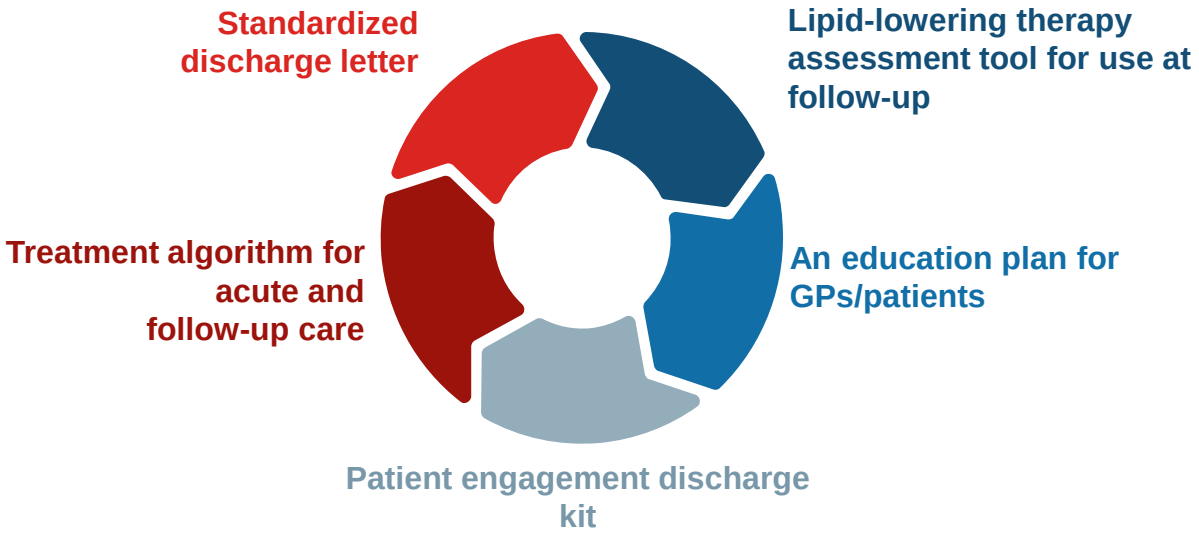
Survey on improving Lipid Management in Patients With ACS

The ACS Lipid EuroPath Tool (EuroPath III)

ESC

Data From 555 Cardiologists, 445 GPs, and 662 Patients

Proposed Solutions

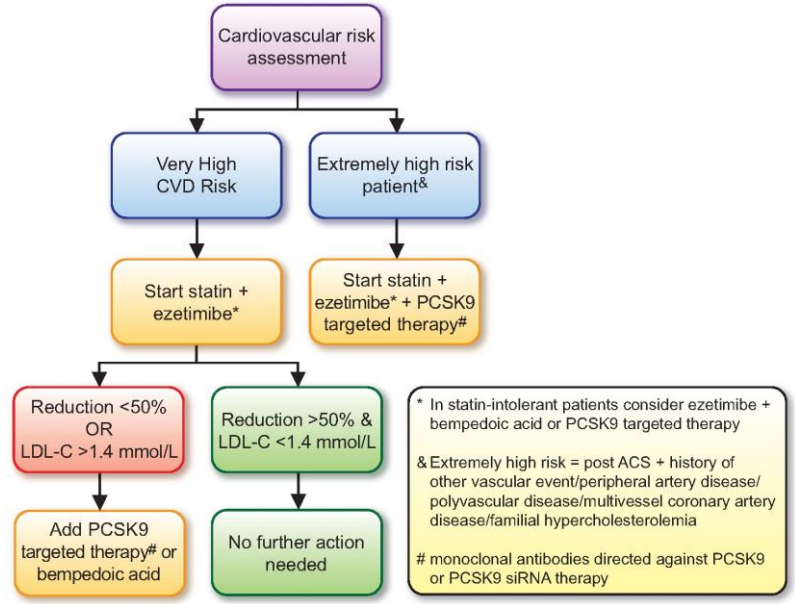


Catapano AL, et al. Clin Cardiol. 2023;46:407-415.

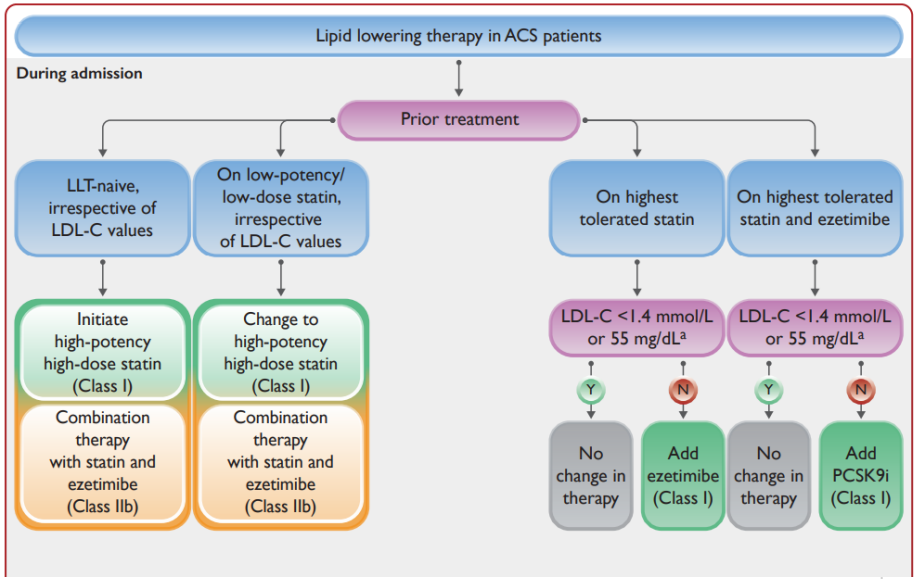
Optimisation of LLT before discharge in ACS

High bar set on mortality vs imaging trials

Combination lipid-lowering therapy as first line strategy in very high-risk patients



2023 ACS Guideline



European Heart Journal (2023) 44, 3720–3826
European Heart Journal *2022;* 43, 830–833,

Patient related

Provide clear, comprehensive information on drug and disease (imaging) with shared decision making

Less number of medications, less frequent administration

Aid in delivery for injectables

Transparent public disclosure of adverse events involving new therapies

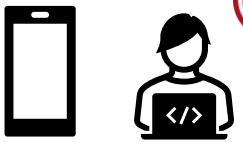
Create awareness and advocacy groups so request comes from patient eg: semaglutide, cholesterol vaccine !

Enpower patient support groups

Patient organisations: FH Europe

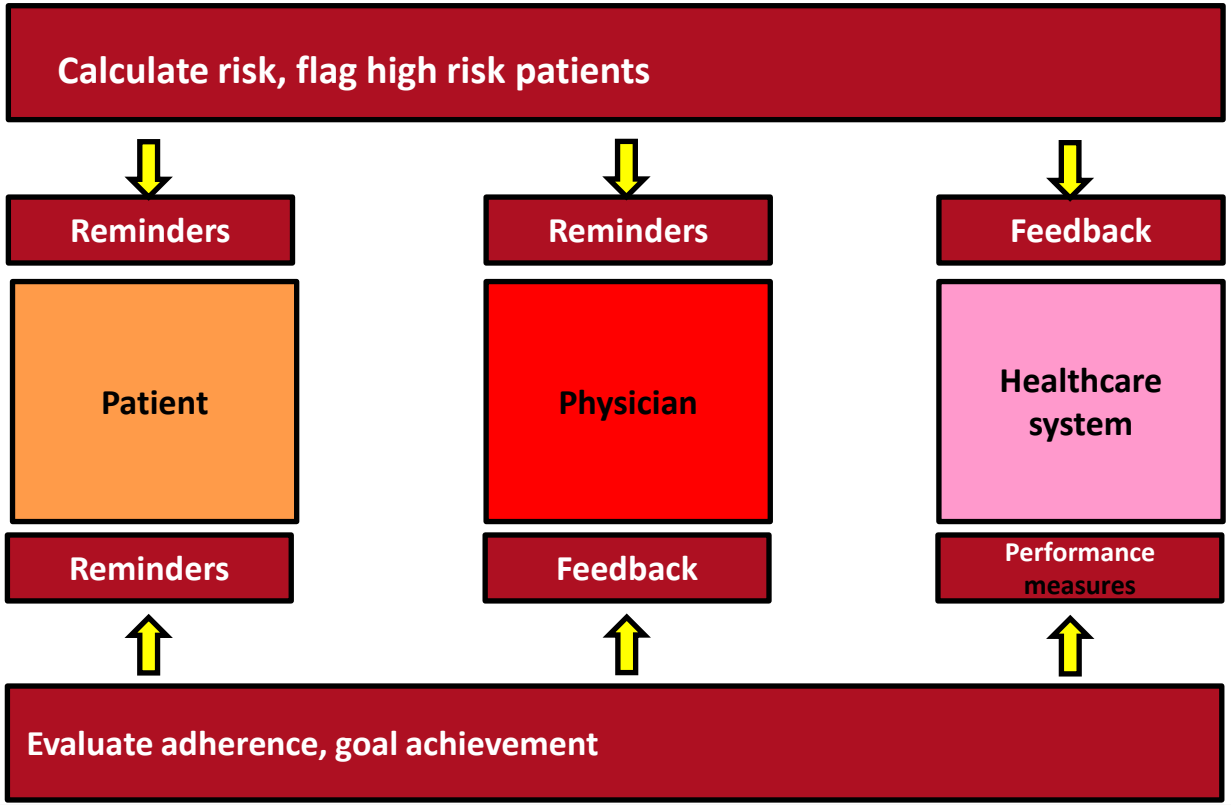
- Improve health literacy
- Create awareness
- Lobby at EU level to improve early identification and treatment of very high risk patients
- Support patients

Adherence improving tools



- Medication reminder apps
- Health tracking apps
- SMS / text reminders
- Wearables
- Smart medication packages
- Electronic dispensers
- Remote patient monitoring, telehealth
- Electronic health records
- Digital health coaches
- Health related social media platforms and literacy interventions

Technology can link the patient, physician and healthcare system



Healthcare policy related

Balance short term cost with potential benefits

Explore ways to make medication accessible

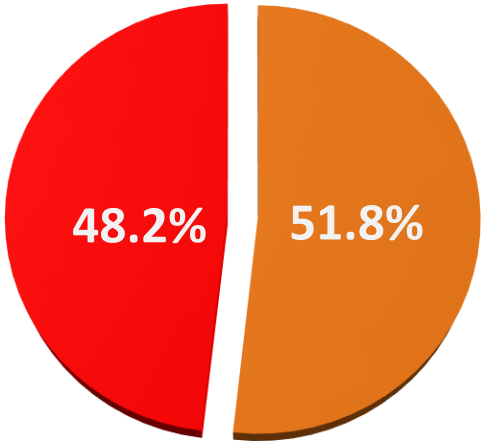
Reimbursement issues: Cost effectiveness and benefit to society

Start with highest risk but expand to lower risk patients

Shifting focus from the volume of services provided to the patient outcomes achieved

Predictors of LDL-C Target Achievement: DYSIS Study

- Higher statin dose
- Specialist treatment
- Combination therapy

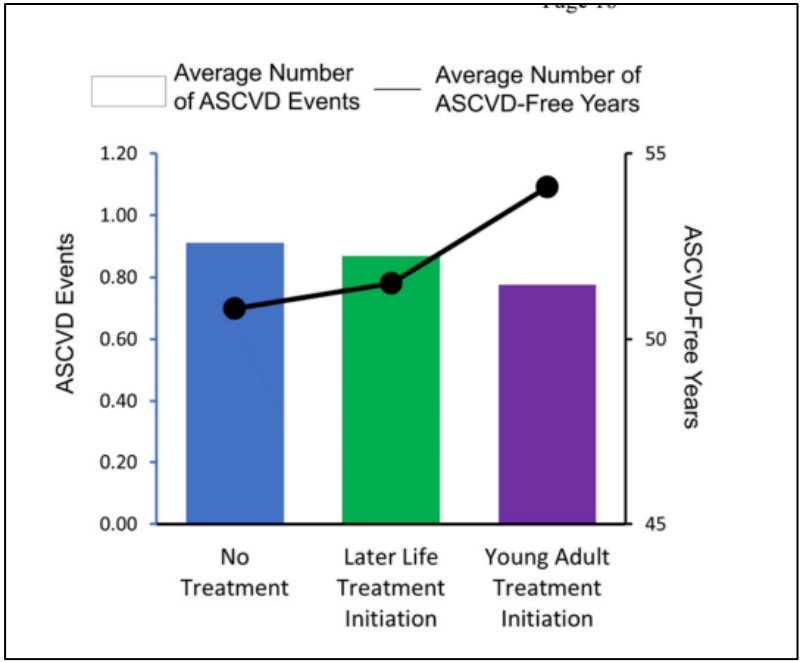


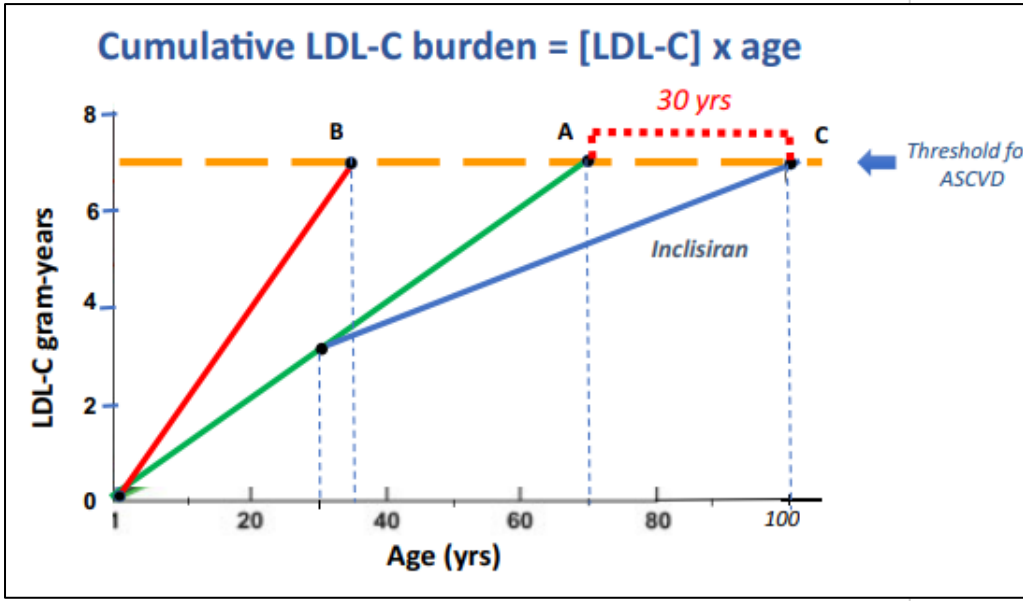
Incentive-driven reimbursement system:

LDL-C at goal 42% in Germany vs 79% in UK[2]

Eur J Prev Cardiol. 2012;19:221-30
Eur Heart J. 2013; 34:3689

Earlier LDL-C lowering to change trajectory of ASCVD once safety confirmed

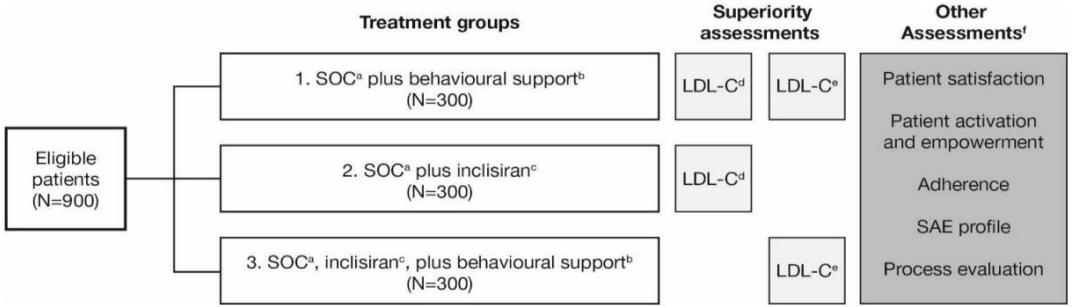




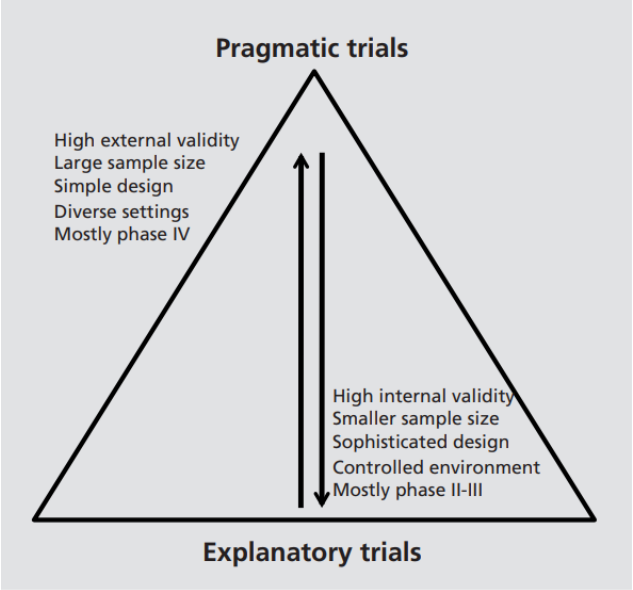
Modeling studies need confirmation !

J Am Coll Cardiol. 2021 November 16; 78(20): 1954–1964
European Heart Journal 2022; 43, 249–250,

More evidence on what works
Pragmatic trials eg: VICTORION-Spirit



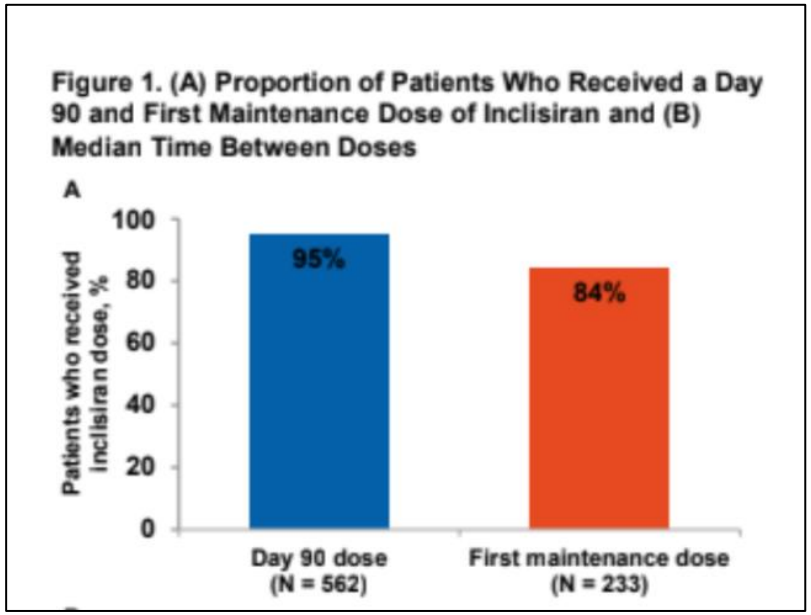
Implementation of inclisiran in UK primary care for patients with atherosclerotic cardiovascular disease or ASCVD-risk equivalents



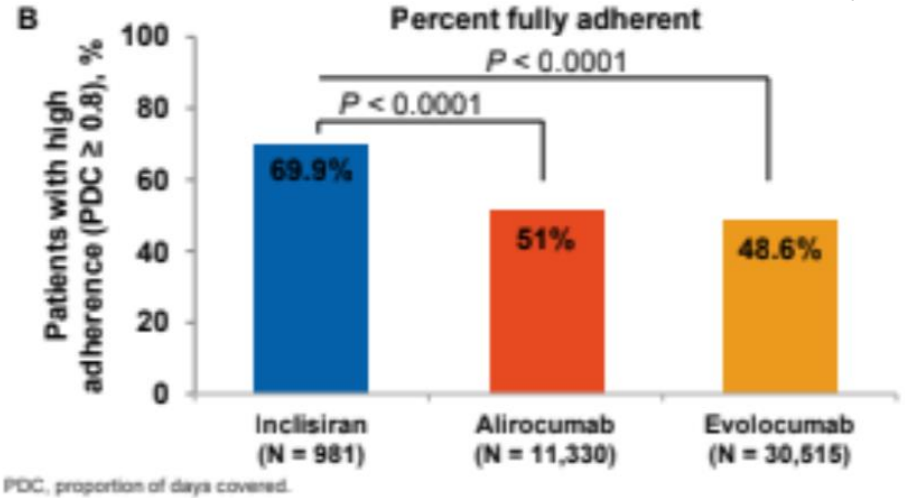
Int J Clin Trials. 2023 May;10(2):156-165
Dialogues Clin Neurosci. 2011;13:217-224

Is adherence improved with inclisiran ?
Real world evidence

Metro infusion center n=562



US Komodo Health database n= =981



- After propensity score matching, patients receiving inclisiran had significantly higher PDC by treatment at 6 months vs those receiving alirocumab or evolocumab ($P < 0.0001$; **Table 2** and **Figure 3**)
- Results were similar for the 1:3 propensity score–matched cohorts

We will need a paradigm shift !

Rethinking healthcare policies where value is defined as health outcomes

Systemwide changes enabling high risk patients to receive early and potent therapy

Personalise therapy better

Structured, team based, patient centered individually tailored intervention involving family, pharmacist ,other healthcare workers

Incorporating technology to connect/educate/alert all stakeholders

More work on implementation science to see what works