Δευτερογενής πρόληψη στεφανιαίας νόσου

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Αθήνα, 19 Οκτωβρίου 2018
Conflict of Interest

• None
Update and future of secondary prevention

• A changing epidemiology, worldwide
Trends in Age-Adjusted Mortality Rates From Coronary Heart Disease – USA 1980 to 2005

The most frequent causes of death in ACS survivors are now noncardiac.

Temporal trends in incidence of cause-specific mortality after PCI for ACS.

Spoon D B et al. *Circulation* 2014;129:1286-1294
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real
Long-term event rates after ACS
The UK–Belgian GRACE experience

5-year death rates

<table>
<thead>
<tr>
<th>% of patients</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>UA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>19</td>
<td>22</td>
<td>17</td>
</tr>
</tbody>
</table>

Proportion of post-discharge deaths

<table>
<thead>
<tr>
<th>% of patients</th>
<th>STEMI</th>
<th>NSTEMI</th>
<th>UA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>68</td>
<td>86</td>
<td>97</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome;
NSTEMI, non–ST segment elevation myocardial infarction;
STEMI, ST segment elevation myocardial infarction

Mortality 10 years after MI in the FAST-MI 2005 registry

FAST-MI 2005 – 3,670 patients hospitalised for ACS

Mortality (%) vs. Time (years)

- Dead
- Alive
- Lost to follow-up

1 yr: 10%, 90%, 0%
2 yrs: 15%, 85%, 0%
3 yrs: 25%, 75%, 0%
4 yrs: 28%, 72%, 0%
5 yrs: 32%, 68%, 0%
6 yrs: 35%, 65%, 0%
7 yrs: 38%, 62%, 0%
8 yrs: 40%, 60%, 0%
9 yrs: 42%, 58%, 0%
10 yrs: 42%, 58%, 0%

ACS, acute coronary syndrome; MI, myocardial infarction

CV event rates are high in the 1st year post-MI...

CV events during the first 365 days

- Discharged alive

97,254 patients admitted with 1st MI between July 2006 and June 2011

Sweden

...and remain high in the following 3.5 years

CV events between 1 and 4.5 years

- 20.0%

76,687 patients surviving during 365 days after MI with recurrent MI or stroke


CV, cardiovascular; MI, myocardial infarction
Cumulative event probability at 8 years for first recurrent myocardial infarction related to non-culprit, culprit and indeterminate lesions

Higher risk for non-culprit related recurrent MIs than culprit related recurrent MIs

SWEDHEART
N=108,615 pts
2006-2014

Varenhorst et al J Am Heart Assoc. 2018 Jan; 7(1)
Even patients with stable atherosclerotic disease experience high event rates

4-year event rates in the REACH registry

*All event rates adjusted for age and gender.

CV, cardiovascular; MI, myocardial infarction

Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized
GDMT for secondary prevention

**β blockers**
- Initiate orally within 24 h if no contraindications; avoid IV without knowledge of LVEF*
- Decrease myocardial oxygen demand; improve myocardial remodelling
- Reduce angina, infarct size, myocardial infarction, mortality

Guidelines advise 3 years of use after myocardial infarction; indefinite if other indication (ie, heart failure)

Major studies: COMMIT, TIMI II, numerous meta-analyses

**ACE inhibitors or ARBs**
- Initiate orally within 24 h if no contraindications†; consider ARB if intolerance or allergy
- Reduce afterload; myocardial remodelling
- Benefit largest in anterior STEMI, heart failure, LVEF <40%
- Less benefit if low risk, no heart failure, revascularised
- Angiotensin receptor-neprilysin inhibitor reduces death or hospitalisation in heart failure

Major studies: SAVE, HOPE, EUROPA, PARADIGM-HF, numerous meta-analyses

**Aldosterone antagonists**
- Consider in patients with heart failure, LVEF <35–40%, already on adequate doses of β blocker and ACE inhibitor or ARB
- Limited data on benefit without reduced LVEF
- Improve myocardial remodelling; may reduce all-cause and cardiovascular mortality, and rehospitalisation

Major studies: EPHESUS, RALES, meta-analyses

**Lipid-lowering therapy**
- Initiate high-intensity statin therapy (ie, atorvastatin 80 mg) in all patients after acute myocardial infarction
- Consider ezetimibe for goal LDL <70 mg/dL (ideally ~50 mg/dL)
- Reduce mortality, subsequent cardiovascular events, and may reduce readmission‡

Major studies: A-to-Z, PROVE-IT, IMPROVE-IT

**Antiplatelet therapy (aspirin, P2Y12 inhibitor):‡**
- Aspirin—indefinite low dose (81–100 mg), reduces mortality
- DAPT (aspirin + clopidogrel/prasugrel/ticagrelor)—reduces ischaemic events and mortality (ticagrelor only)

Major studies: CURE, CREDO, TRITON-TIMI 38, PLATO, CHARISMA, DAPT, PEGASUS

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*LVEF*: left ventricular ejection fraction
†Low LVEF
‡High risk subtype
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized...but is often not sustained...
Use of cardiac medication in the PCI and CABG arms of the SYNTAX trial

Mortality as a function of adherence to Optimal Medical Therapy (OMT)

OMT: antiplatelet, statin, β-blocker, ACEi/ARB

RRR: 36% at 5-yrs
P=0.002

Iqbal et al. *Circulation* 2015;131:1269-1277
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized...but is often not sustained...and some components may be unnecessary...
Medical treatment at discharge and 1-year mortality in MI

Tomas Jernberg et al SWEDEHEART Registry
ECC 27 August 2018
Beta-Blockers are associated with improved outcomes only in pts with prior MI

The Kaiser Permanente study

Andersson et al; *J Am Coll Cardiol* 2014;64:247-52.

26,793 patients
3.7 yrs FU
CHARISMA: β-blockers are associated with improved outcomes in pts with prior MI

Outcomes in propensity-matched patients on and not on β-blockers in the prior MI cohort
(P values from Cox proportional hazards model)

CHARISMA: β-blockers are NOT associated with improved outcomes in pts with known CAD

Outcomes in propensity-matched patients on and not on β-blockers in the known CAD cohort.

(P values from Cox proportional hazards model)

No association between prescription of b-blockers and survival in AMI survivors without HF or LVSD

A MINAP analysis of 179,810 survivors of hospitalization with AMI without HF or LVSD, between January 1, 2007, and June 30, 2013

Use of β-blockers was not associated with a lower risk of death at any time point up to 1 year

Dondo TB et al. J Am Coll Cardiol 2017;69:2710-20
B-blockers and mortality after MI in patients without heart failure: multicentre prospective cohort study

A FAST MI analysis

In contrast, 5-yr mortality was lower in pts continuing statins at 1-yr (HR 0.42, 0.25 to 0.72) compared with those discontinuing statins

Puymirat E et al. BMJ 2016;354:i4801
**β-blockers in CLARIFY**

**β-blockers use and all-cause mortality**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.94</td>
<td>(0.84-1.06)</td>
<td>0.30</td>
</tr>
<tr>
<td>MI ≤ 1 year prior to enrollment</td>
<td>0.68</td>
<td>(0.50-0.91)</td>
<td>0.01</td>
</tr>
<tr>
<td>MI 1 to ≤ 3 years prior to enrollment</td>
<td>1.09</td>
<td>(0.76-1.56)</td>
<td>0.63</td>
</tr>
<tr>
<td>MI &gt; 3 years prior to enrollment</td>
<td>0.91</td>
<td>(0.84-1.10)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

_Sorbets E at al: ECC 2018_

**ESC Congress Munich 2018**

Survival analysis from Cox proportional hazards models
Multivariable adjustment for SBP, DBP, LVEF, histories of PCI, CABG, PAD, asthma/COPD and the REACH cardiovascular event risk score
Common sense: β-Blocker use

➢ Short term (6 m – 1y?) use to reduce risk of AMI

➢ Long term use:
  ▪ *Heart Failure / Left ventricular dysfunction*
  ▪ To control Arrhythmias, Hypertension, Angina
  ▪ High risk patients?
    • re-MI
    • incomplete revascularization
Renin angiotensin system inhibitors for patients with stable coronary artery disease without heart failure: systematic review and meta-analysis of randomized trials

Sripal Bangalore,1 Robert Fakheri,1 Simon Wandel,3 Bora Toklu,2 Jasmin Wandel,4 Franz H Messerli5,6,7

24 trials with 198.275 patient years of follow-up were included

BMJ 2017;356:j4 | doi: 10.1136/bmj.j4
RASi vs placebo or active controls
All cause mortality

<table>
<thead>
<tr>
<th>Trials</th>
<th>No of events/total</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APRES</td>
<td>2/80</td>
<td>0.61 (0.05 to 1.16)</td>
</tr>
<tr>
<td>CAMELOT</td>
<td>8/673</td>
<td>1.23 (0.45 to 3.74)</td>
</tr>
<tr>
<td>CATS</td>
<td>2/149</td>
<td>0.46 (0.11 to 1.99)</td>
</tr>
<tr>
<td>Cal et al</td>
<td>47/678</td>
<td>6.19 (0.24 to 0.48)</td>
</tr>
<tr>
<td>EUROPA</td>
<td>375/6110</td>
<td>10.43 (0.78 to 1.63)</td>
</tr>
<tr>
<td>HOPE</td>
<td>482/4645</td>
<td>10.78 (0.75 to 0.96)</td>
</tr>
<tr>
<td>IMAGINE</td>
<td>28/1280</td>
<td>3.82 (1.00 to 1.68)</td>
</tr>
<tr>
<td>JAMP</td>
<td>47/422</td>
<td>1.07 (0.41 to 0.02)</td>
</tr>
<tr>
<td>Kondo et al</td>
<td>16/308</td>
<td>2.95 (0.34 to 1.10)</td>
</tr>
<tr>
<td>PRACTICAL</td>
<td>12/150</td>
<td>10.09 (0.76 to 1.04)</td>
</tr>
<tr>
<td>PREMAI</td>
<td>40/631</td>
<td>4.69 (0.68 to 1.66)</td>
</tr>
<tr>
<td>QUIET</td>
<td>27/878</td>
<td>3.73 (0.58 to 1.69)</td>
</tr>
<tr>
<td>QUO VADIS</td>
<td>0/75</td>
<td>0.10 (0.02 to 0.05)</td>
</tr>
<tr>
<td>ROADMAP (CHD subgroup)</td>
<td>13/564</td>
<td>0.90 (1.18 to 14.56)</td>
</tr>
<tr>
<td>SCAT</td>
<td>8/229</td>
<td>1.61 (0.73 to 1.62)</td>
</tr>
<tr>
<td>TRANSCEEND</td>
<td>364/2954</td>
<td>10.28 (0.91 to 1.22)</td>
</tr>
</tbody>
</table>

**D+L subtotal:** $P=0$, $I^2=66.8%$

<table>
<thead>
<tr>
<th><strong>Active</strong></th>
<th>No of events/total</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALLHAT (CHD subgroup)</td>
<td>407/2270</td>
<td>10.9 (0.92 to 1.16)</td>
</tr>
<tr>
<td>CAMELOT</td>
<td>8/673</td>
<td>1.33 (0.41 to 3.31)</td>
</tr>
<tr>
<td>CARP</td>
<td>7/90</td>
<td>1.17 (0.44 to 3.90)</td>
</tr>
<tr>
<td>HIJ-CREATE</td>
<td>69/1024</td>
<td>6.18 (0.83 to 1.66)</td>
</tr>
<tr>
<td>JMIC-B</td>
<td>15/822</td>
<td>2.19 (0.59 to 2.69)</td>
</tr>
<tr>
<td>NAGOYA HEART (CHD subgroup)</td>
<td>6/158</td>
<td>1.23 (0.29 to 1.38)</td>
</tr>
<tr>
<td>OLIVUS</td>
<td>4/126</td>
<td>0.75 (0.24 to 3.84)</td>
</tr>
</tbody>
</table>

**D+L overall:** $P=0$, $I^2=59.9%$

<table>
<thead>
<tr>
<th><strong>I-V overall</strong></th>
<th>Weight (%)</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Favors RASi</strong></td>
<td>100.00</td>
<td>0.89 (0.79 to 1.01)</td>
</tr>
<tr>
<td><strong>Favors control</strong></td>
<td>0.92</td>
<td>0.88 (0.88 to 0.98)</td>
</tr>
</tbody>
</table>

*Fig 2 | Bayesian meta-regression analysis of the influence of baseline risk (control event rate) on the effect size of RASt versus placebo on all cause mortality.*

*Fig 1 | Forest plot showing effect of renin angiotensin system inhibitors (RASI) versus placebo or active controls on all cause mortality in patients with stable coronary artery disease without heart failure. D+L=DerSimonian and Laird; I-V=inverse variance; CHD=coronary heart disease.*
RASi vs placebo or active controls
CV mortality

Fig 3 | Forest plot showing effect of renin angiotensin system inhibitors (RASi) versus placebo or active controls on cardiovascular mortality in patients with stable coronary artery disease without heart failure. D+L=DerSimonian and Laird; I-V=inverse variance; CHD=coronary heart disease

Fig 4 | Bayesian meta-regression analysis of the influence of baseline risk (control event rate) on the effect size of RASi versus placebo on cardiovascular mortality

BMJ 2017;356:j4 | doi: 10.1136/bmj.j4
RASi vs placebo or active controls
MI

Fig 5 | Forest plot showing effect of renin angiotensin system inhibitors (RASi) versus placebo or active controls on myocardial infarction in patients with stable coronary artery disease without heart failure. D-L=DerSimonian and Laird; I-V=inverse variance; CHD=coronary heart disease.
Fig 9 | Forest plot showing effect of renin angiotensin system inhibitors (RASI) versus placebo or active controls on heart failure in patients with stable coronary artery disease without heart failure on trial entry.

RASi vs placebo or active controls
Heart failure
The lack of advantage of RASi over active controls for CV events could be due to three reasons.

1. The active controls are as good as RASi, and the effect is mediated mainly by a reduction in BP.

2. The enrolled cohort (unlike patients with HF) might not have had an activated RAAs, resulting in less benefit.

3. In this cohort, the RAAs could have had a role in delaying the chronic process of atherogenesis and the benefit might not have been apparent during the short follow-up in these trials.

BMJ 2017;356:j4 | doi: 10.1136/bmj.j4
Benefit of statins but not ACEI/ARBs in stable CAD without CHF

CV death, MI and Stroke in the REACH registry subset of 20,909 pts with CAD but without CHF

Adjusted event curves after correction for propensity


4 year FU
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized...but is often not sustained...and some components may be unnecessary...

• New treatments are coming up!
How can we do better?

1. Improved antithrombotic therapy
   - Improved or prolonged antiplatelet therapy (*PEGASUS, DAPT*)
   - Monotherapy? (*GLOBAL LEADERS*)
   - Combining anticoagulation and antiplatelet therapy (*COMPASS*)

2. More potent LDL-lowering (*FOURIER, ODYSSEY*)

3. Alternative lipid-modifying therapies (*REVEAL*)

4. Targeting inflammation (*CANTOS*)
**PEGASUS-TIMI 54**

Long-term use of ticagrelor in patients with prior myocardial infarction.


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**DAPT Trial**

Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents.


Cardiovascular death, MI or stroke

N = 21,162
Median follow-up 33 months

CV Death, MI, or Stroke (%)

0 1 2 3 4 5 6 7 8 9 10

Months from Randomization

0 3 6 9 12 15 18 21 24 27 30 33 36

Ticagrelor 90 mg
HR 0.85 (95% CI 0.75 - 0.96)
P = 0.003

Ticagrelor 60 mg
HR 0.84 (95% CI 0.74 - 0.95)
P = 0.004

Thienopyridine
Placebo

Bonaca MP et al. NEJM 2015;372:1791-800

Primary Analysis Period
12-30 Months:
HR 0.71 (0.59-0.85)
4.3% vs. 5.9%
P < 0.001

~ 46% with history of MI

Mauri et al. NEJM 2014
EU label: Continuing on long-term after MI patients ≤2 yrs from MI or 1 Yr from P2Y$_{12}$

- CV Death/MI/Stroke:
  - HR 0.80 (0.70 - 0.91), P=0.001, ARR = 1.7%
  - Placebo 9.6%, Ticagrelor 7.9%

- CV Death:
  - HR 0.71 (0.56 - 0.90), P=0.0041, ARR = 1.0%
  - Placebo 3.6%, Ticagrelor 2.6%

- TIMI Major Bleeding:
  - HR 2.36 (1.65 - 3.39), P<0.001, ARI = 1.4%
  - Placebo 1.1%, Ticagrelor 2.5%

- ICH or Fatal Bleeding:
  - HR 0.17 (0.68 - 2.01), P=0.58, ARI = NA
  - Placebo 0.7%, Ticagrelor 0.8%

- Mortality:
  - HR 0.80 (0.67 - 0.96), P=0.018, ARR = 1.0%
  - Placebo 5.4%, Ticagrelor 4.4%

Dellborg et al. ESC 2017
DAPT: Prior MI and efficacy for MACE

Yeh et al. JACC 2015

Cumulative incidence of MACE

- Thienopyridine vs. Placebo, 3.9% vs. 6.8%; Hazard Ratio 0.56, p<0.001

- Thienopyridine vs. Placebo, 4.4% vs. 5.3%; Hazard Ratio 0.83, p=0.08

GUSTO Mod/Sev Bleeding

HR = 2.38 (1.27-4.43) P = 0.005

1.9% vs. 0.8%

Yeh et al. JACC 2015
A framework for optimizing DAPT duration

**Who**
- Patients with prior MI at high risk:
  - Diabetes mellitus
  - Multiple prior MIs
  - Renal dysfunction
  - MVD
  - PAD
  - Recent MI/on P2Y₁₂
- Without bleeding risk factors including:
  - Prior/risk of ICH
  - Recent major Bleeding
  - Bleeding diathesis
  - On anticoagulation
  - Hx of Hosp for Bleed
  - Anemia

**When**
- Continue after started for MI and re-evaluate at each visit:
  - Recent bleeding?
  - Are they tolerating?
  - Are they adherent?
  - Contraindications (e.g. new dx of AF requiring anticoagulation)

**Why**
- To reduce long-term ischemic risk including:
  - New spontaneous MI including STEMI
  - Ischemic stroke including disabbling events
  - Limb ischemic events in PAD
  - CV mortality as predominant cause of death
Experimental strategy

ACS + Stable CAD
- ASA 75-100 mg/d
- Ticagrelor 90 mg bid

Reference strategy

ACS: UA+NSTEMI+STEMI
- ASA 75-100 mg/d
- Ticagrelor 90 mg bid

Stable CAD
- Clopidogrel 75 mg/d

“All-comers” PCI population
N = 15,991
1:1 Randomisation, open-label design, 130 centers worldwide

- Any type of lesions: Left main, SVG, CTO bifurcation, ISR, etc.
- Unrestricted use of DES (number, length)

Bivalirudin-supported
BioMatrix DES by default

ECG discharge
ECG 90D
ECG 2Y
Adherence to treatment strategies

Primary and secondary outcomes at 12 months (Intention to treat)

<table>
<thead>
<tr>
<th></th>
<th>Experimental group</th>
<th>Reference group</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or new Q-wave MI*</td>
<td>1.95 %, (156)</td>
<td>2.47 %, (197)</td>
<td>0.79 (0.64-0.98)</td>
<td>0.028</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.35 %, (108)</td>
<td>1.64 %, (131)</td>
<td>0.82 (0.64-1.06)</td>
<td>0.138</td>
</tr>
<tr>
<td>New Q-wave MI</td>
<td>0.60 %, (46)</td>
<td>0.86 %, (69)</td>
<td>0.70 (0.48-1.00)</td>
<td>0.052</td>
</tr>
</tbody>
</table>

* Mantel-Cox method based on time of death or diagnosis of new Q wave MI
** Mantel-Cox log-rank method for secondary safety endpoints
Adherence to treatment strategies

- Discharge
  - Experimental arm: 98%
  - Reference arm: 97%

- Follow-up 1 M
  - Experimental arm: 96%
  - Reference arm: 96%

- Follow-up 3 M
  - Experimental arm: 86%
  - Reference arm: 94%

- Follow-up 6 M
  - Experimental arm: 85%
  - Reference arm: 92%

- Follow-up 12 M
  - Experimental arm: 82%
  - Reference arm: 89%

- Follow-up 18 M
  - Experimental arm: 79%
  - Reference arm: 92%

- Follow-up 24 M
  - Experimental arm: 78%
  - Reference arm: 93%

Primary and secondary outcomes at 24 months (Intention to treat)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Experimental group</th>
<th>Reference group</th>
<th>Risk Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or new Q-wave MI</td>
<td>3.81%, 304</td>
<td>4.37%, 349</td>
<td>0.87 (0.75-1.01)</td>
<td>0.073</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.81%, 224</td>
<td>3.17%, 253</td>
<td>0.88 (0.74-1.06)</td>
<td>0.18</td>
</tr>
<tr>
<td>New Q-wave MI</td>
<td>1.04%, 83</td>
<td>1.29%, 103</td>
<td>0.80 (0.60-1.07)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

- Blue: Ticagrelor monotherapy in ACS and SA
- Orange: ASA monotherapy in ACS and SA
Kaplan Meier estimate of mortality and safety outcome at 2 years

All-cause death

- Reference arm
- Experimental arm (Ticagrelor monotherapy)

RR (95%CI) = 0.88 (0.74-1.06)  
P = 0.182

BARC 3 or 5 bleeding

- Reference arm
- Experimental arm (Ticagrelor monotherapy)

RR (95%CI) = 0.97 (0.78-1.20)  
P = 0.766
GLOBAL-LEADERS trial

— Conclusions —

• GLOBAL-LEADERS trial is a well designed and conducted study

• It is a formally **negative trial** that may have a positive impact on the overall value of ticagrelor therapy in patients with CAD and PCI

**Questions that need an answer after GLOBAL-LEADERS trial**

• Is 1-month of aspirin absolutely required after PCI in patients on ticagrelor?

• Do all patients need the same 90 mg dose of ticagrelor after PCI?

• Should all patients be treated with ticagrelor beyond 1 year after PCI?
DUAL PATHWAYS OF CLOTTING

Platelet Pathway

- Collagen
- ADP
- TxA2

Platelet activation

Platelet aggregation

Plaque Rupture

- Tissue Factor
- Plasma Clotting cascade
- Prothrombin

Thrombin

Fibrinogen → Fibrin

Coagulation Pathway

Coronary artery THROMBUS

Welsh RC et al. Am Heart J 2016;181:92
Objective: efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in CAD or PAD

Population: Documented CAD or PAD

Rivaroxaban 2.5 mg bid + ASA 100 mg od
± pantoprazole 40 mg od

30-day run-in, ASA 100 mg

Rivaroxaban 5.0 mg bid
± pantoprazole 40 mg od

Final follow-up visit*

ASA 100 mg od
± pantoprazole 40 mg od

Final washout period visit

30-day washout period*

N~21,000

1:1:1

Slide by C. Michael Gibson, M.S., M.D.

www.clinicaltrials.gov/show/NCT01776424
COMPASS: CV Death, Stroke, MI

Rivaroxaban + Aspirin vs. Aspirin
HR: 0.76, 95% CI 0.66-0.86, P<0.0001

Rivaroxaban vs. Aspirin
HR: 0.90, 95% CI 0.79-1.03, P = 0.12

ASA 100mg
Riva 5mg BID
Riva 2.5 BID + ASA

Cumulative Hazard Rate

No. at Risk
Rivaroxaban + Aspirin 9152
Rivaroxaban 9117
Aspirin 9126
Year
0 1 2 3
No. at Risk
7964
7024
3912
659
7806
670
3862
669
3800

Eikelboom et al. for the COMPASS investigators, NEJM 2017
## COMPASS: Primary Components

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A N=9,152</th>
<th>A N=9,126</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CV death</td>
<td>160 (1.7%)</td>
<td>203 (2.2%)</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td>Stroke</td>
<td>83 (0.9%)</td>
<td>142 (1.6%)</td>
<td>0.58 (0.44-0.76)</td>
</tr>
<tr>
<td>MI</td>
<td>178 (1.9%)</td>
<td>205 (2.2%)</td>
<td>0.86 (0.70-1.05)</td>
</tr>
</tbody>
</table>

*Eikelboom et al. for the COMPASS investigators, NEJM 2017*
Key Points

- The addition of riva 2.5 mg BID to ASA reduces the risk of MACE in pts with CAD and PAD, but with increased bleeding

- A strategy of replacing ASA with riva 5mg BID appears less beneficial

- Pts with polyvascular disease likely derive more benefit from intensification of antiplatelet Rx or addition of anticoagulant

- Strategies to facilitate appropriate patient selection will help to overcome inertia to modify existing regimens
FOURIER
Further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017
**Trial Design**

- High-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in

High or moderate intensity statin therapy (± ezetimibe)

- LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

**RANDOMIZED DOUBLE BLIND**

- Evolocumab SC 140 mg Q2W or 420 mg QM
- Placebo SC Q2W or QM

FU median 26 months (22-30)

Follow-up Q 12 weeks

**Patient Disposition**

**ODYSSEY OUTCOMES**

**Post ACS pts (1-12 months)**

- Randomized 18,924 patients

- Alirocumab (N=9462)
  - 8242 (44%) patients with potential follow-up ≥3 years
  - 1955 patients experienced a primary endpoint
  - 726 patients died

- Placebo (N=9462)
  - Follow-up*: median 2.8 (Q1-Q3 2.3–3.4) years

- Premature treatment discontinuation
- Blinded switch to placebo (2 consecutive LDL-C values <15 mg/dL)
- Patients lost to follow-up (vital status)

- 1343 (14.2%)
- 730 (7.7%)
- 14

- 1496 (15.8%)
- Not applicable
- 9

*Ascertainment was complete for 99.1% and 99.8% of potential patient-years of follow-up for the primary endpoint and all-cause death, respectively

LDL-C was significantly reduced in the evolocumab group (median: 30 mg/dL) including 42% who achieved levels ≤ 25 mg/dL vs < 0.1% in the placebo group.

Excludes LDL-C values after premature treatment discontinuation or blinded switch to placebo. Approximately 75% of months of active treatment were at the 75 mg dose.
Primary Endpoint: Composite of CV Death, MI, Stroke, Hospitalization for UA, or Coronary Revascularization

1344 patients [9.8%] vs. 1563 patients [11.3%]  
HR 0.85 [95% CI 0.79 to 0.92]; P < 0.001

Key Secondary Endpoint: Composite of CV Death, MI, or Stroke

816 [5.9%] vs. 1013 [7.4%]
HR 0.80 (95% CI 0.73 to 0.88); P < 0.001

NNT=74

**REVEAL:**
Randomized placebo-controlled trial of **anacetrapib** in 30,449 pts with atherosclerotic vascular disease

- **Anacetrapib** is a potent inhibitor of Cholesteryl Ester Transfer Protein (CETP) which doubles HDL-C and lowers LDL-C
- Previous trials of other CETP inhibitors have been stopped after around 2 yrs of FU due to unexpected CV hazards (torcetrapib) or apparent lack of efficacy (dalcetrapib, evacetrapib)
- The REVEAL trial assessed the efficacy and safety of **adding anacetrapib vs placebo** to effective doses of atorvastatin among patients with established occlusive vascular disease
## Effects of anacetrapib on lipids at trial midpoint

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Absolute difference</th>
<th>SI units</th>
<th>Proportional difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDL cholesterol</td>
<td>+43</td>
<td>+1.1 mmol/L</td>
<td>104%</td>
</tr>
<tr>
<td>Apolipoprotein AI</td>
<td>+42</td>
<td>+0.4 g/L</td>
<td>36%</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Direct (Genzyme)</td>
<td>-26</td>
<td>-0.7 mmol/L</td>
<td>-41%</td>
</tr>
<tr>
<td>- Beta-quantification*</td>
<td>-11</td>
<td>-0.3 mmol/L</td>
<td>-17%</td>
</tr>
<tr>
<td>Apolipoprotein B</td>
<td>-12</td>
<td>-0.1 g/L</td>
<td>-18%</td>
</tr>
<tr>
<td>Non-HDL cholesterol</td>
<td>-17</td>
<td>-0.4 mmol/L</td>
<td>-18%</td>
</tr>
</tbody>
</table>

* measured in a random subset of 2000 participants
Primary outcome: Major coronary events
(Coronal death, myocardial infarction, or coronary revascularization)

Rate ratio 0.91 (0.85 to 0.97)  
P=0.004

FU 4.1 yrs median
Mean LDL 61 mg/dl
### Components of the primary outcome

<table>
<thead>
<tr>
<th>Type of Event</th>
<th>Anacetrapib (N=15225)</th>
<th>Placebo (N=15224)</th>
<th>Rate Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of participants with events (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary death</td>
<td>388 (2.5)</td>
<td>420 (2.8)</td>
<td>0.92 (0.80–1.06)</td>
<td>0.25</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>669 (4.4)</td>
<td>769 (5.1)</td>
<td>0.87 (0.78–0.96)</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Coronary death or MI</strong></td>
<td><strong>934 (6.1)</strong></td>
<td><strong>1048 (6.9)</strong></td>
<td><strong>0.89 (0.81–0.97)</strong></td>
<td><strong>0.008</strong></td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>1081 (7.1)</td>
<td>1201 (7.9)</td>
<td>0.90 (0.83–0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Major coronary event</td>
<td><strong>1640 (10.8)</strong></td>
<td><strong>1803 (11.8)</strong></td>
<td><strong>0.91 (0.85–0.97)</strong></td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>

Major coronary event: Coronary death, MI or coronary revascularization

No significant evidence of differential proportional effects among 23 pre-specified subgroup categories.
Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease

- Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

Ridker ACC 2017
From CRP to IL-6 to IL-1
Moving Upstream to Identify novel Targets for Atheroprotection

Plasma levels of inflammatory biomarkers including hsCRP and IL-6 robustly predict first and recurrent CV events, independent of lipid levels.

Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.

In primary prevention, the JUPITER trial demonstrated that those with elevated hsCRP but low levels of LDLC markedly benefit from statin therapy.

In secondary prevention, clinicians now distinguish between those with “residual cholesterol risk” and those with “residual inflammatory risk”
Canakinumab

- **High-affinity human monoclonal anti-human interleukin-1b (IL-1b) antibody** currently indicated for the treatment of IL-1b driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)

- Designed to bind to human IL-1b and functionally neutralize the bioactivity of this pro-inflammatory cytokine

- **Long half-life (4-8 weeks)** with CRP and IL-6 reduction for up to 3 months
Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI) Residual Inflammatory Risk (hsCRP ≥ 2 mg/L)

N = 10,061
39 Countries
April 2011 - June 2017
1490 Primary Events

Randomized
Canakinumab 50 mg SC q 3 months

Randomized
Canakinumab 150 mg SC q 3 months

Randomized
Canakinumab 300 mg SC q 3 months

Randomized
Placebo SC q 3 months

Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Secondary Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)

“Residual Inflammatory Risk”
Baseline LDLC 82mg/dL (2.1mmol/L) but hsCRP 4.1 mg/L

CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

Graphs showing changes in inflammatory biomarkers and lipids over 48 months with different doses of canakinumab compared to placebo.

• Placebo event rates in CANTOS were high, approaching 25% at five years.

• These data thus affirm that statin-treated patients with “residual inflammatory risk” as assessed by baseline hsCRP >2 mg/L have future event rates as high, if not higher, than statin-treated patients with “residual cholesterol risk.”

**CANTOS: Primary Cardiovascular Endpoint (MACE)**

- Placebo SC q 3 months
- Canakinumab 150/300 SC q 3 months

**HR 0.85**

95% CI 0.76-0.96

P = 0.007

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints.

39% reduction in hsCRP

No change in LDLC

15% reduction in MACE
## CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1.00</td>
<td>0.93</td>
<td>0.85</td>
<td>0.86</td>
<td>0.020</td>
</tr>
<tr>
<td>Secondary</td>
<td>1.00</td>
<td>0.90</td>
<td>0.83</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.00</td>
<td>0.94</td>
<td>0.76</td>
<td>0.84</td>
<td>0.028</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>1.00</td>
<td>0.70</td>
<td>0.64</td>
<td>0.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Any Coronary Revascularization</td>
<td>1.00</td>
<td>0.72</td>
<td>0.68</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.00</td>
<td>1.01</td>
<td>0.98</td>
<td>0.80</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>1.00</td>
<td>0.72</td>
<td>0.63</td>
<td>0.46</td>
<td>0.035</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.00</td>
<td>0.89</td>
<td>0.90</td>
<td>0.94</td>
<td>0.62</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>1.00</td>
<td>0.94</td>
<td>0.92</td>
<td>0.94</td>
<td>0.39</td>
</tr>
</tbody>
</table>
CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>(95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>(ref)</td>
<td>(ref)</td>
</tr>
<tr>
<td>On-treatment hsCRP: ≥ 2.0 mg/L</td>
<td>0.95</td>
<td>(0.81, 1.09)</td>
<td>0.48</td>
</tr>
<tr>
<td>On-treatment hsCRP: &lt; 2.0 mg/L</td>
<td>0.75</td>
<td>(0.66, 0.85)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Cumulative Incidence

MACE
25% reduction in risk for those achieving hsCRP < 2 mg/L
5% reduction in risk for those achieving hsCRP ≥ 2 mg/L
(No change in LDL cholesterol)

Follow-up (years)

CANTOS: Cardiovascular Outcomes According to On-Treatment Levels of IL-6 Above or Below the Study Median After the Initial Dose of Canakinumab (MACE)

MACE
36% reduction for those achieving IL-6 below median
No benefit for those achieving IL-6 above median
(No change in LDL cholesterol)

Ridker et al Lancet 2018;391:319-328

70 YEARS OF CARDIOLOGY (HSC)

70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (ΕΚΕ)

PANHELLENIC CARDIOLOGICAL SYNEDEIΡΙΟ

PANHELLENIC CONGRESS OF CARDIOLOGY

WWW.HCS.GR
CANTOS: 31% Reduction in Cardiovascular Mortality and All-Cause Mortality Among Participants with Robust Inhibition of the Inflammatory Response

"lower is better" appears to be true for inflammation as well as LDLC

35 - 40% reductions in hsCRP and IL-6
No change in LDLC

Ridker PM. Circulation 2018;137:1763-1766
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality

- Placebo: HR 1.0 (95% CI: referent, referent)
- Canakinumab 50 mg: HR 0.96 (0.59-1.34) P = 0.42
- Canakinumab 150 mg: HR 0.78 (0.54-1.13) P = 0.19
- Canakinumab 500 mg: HR 0.49 (0.31-0.75) P = 0.0009

P-trend across groups = 0.0007

Canakinumab 300 mg
51% reduction in death from any cancer
P = 0.0009

Follow-up Years

Incident Lung Cancer

- Placebo: HR 1.0 (95% CI: referent, referent)
- Canakinumab 50 mg: HR 0.77 (0.49-1.20) P = 0.25
- Canakinumab 150 mg: HR 0.61 (0.39-0.97) P = 0.034
- Canakinumab 300 mg: HR 0.33 (0.18-0.59) P = 0.00008

P-trend across groups = 0.0003

Canakinumab 300 mg
67% reduction in incident lung cancer
P = 0.00008

Follow-up Years

Ridker et al. Lancet. 2017;390:1833-1842

70 ΧΡΟΝΙΑ ΚΑΡΔΙΟΛΟΓΙΑΣ (ΕΚΕ)
70 YEARS OF CARDIOLOGY (HSC)
ΠΑΝΕΛΛΗΝΙΟ ΚΑΡΔΙΟΛΟΓΙΚΟ ΣΥΝΕΔΡΙΟ
PANHELLENIC CONGRESS OF CARDIOLOGY

WWW.HCS.GR
How Common is Residual Inflammatory Risk?

Following High-Intensity Statins

PROVE-IT

- Residual Inflammatory Risk: hsCRP ≥ 2 mg/L, LDLC < 1.8 mmol/L (44%)
- Residual Cholesterol Risk: hsCRP < 2 mg/L, LDLC ≥ 1.8 mmol/L (29%)
- Both: hsCRP ≥ 2 mg/L, LDLC ≥ 1.8 mmol/L (13%)
- Neither: hsCRP < 2 mg/L, LDLC < 1.8 mmol/L (14%)

Following High-Intensity Statins Plus Ezetimibe

IMPROVE-IT

- Residual Inflammatory Risk: hsCRP ≥ 2 mg/L, LDLC < 1.8 mmol/L (39%)
- Residual Cholesterol Risk: hsCRP < 2 mg/L, LDLC ≥ 1.8 mmol/L (33%)
- Both: hsCRP ≥ 2 mg/L, LDLC ≥ 1.8 mmol/L (14%)
- Neither: hsCRP < 2 mg/L, LDLC < 1.8 mmol/L (14%)

Following High-Intensity Statins Plus PCSK9 Inhibition

SPIRE-1 / SPIRE-2

- Residual Inflammatory Risk: hsCRP ≥ 2 mg/L, LDLC < 1.8 mmol/L (46%)
- Residual Cholesterol Risk: hsCRP < 2 mg/L, LDLC ≥ 1.8 mmol/L (37%)
- Both: hsCRP ≥ 2 mg/L, LDLC ≥ 1.8 mmol/L (10%)
- Neither: hsCRP < 2 mg/L, LDLC < 1.8 mmol/L (7%)

Pradhan et al Circulation 2018 (on line).
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized...but is often not sustained...and some components may be unnecessary...

• New treatments are coming up!

• Therefore there is a need to risk stratify and individualize Rx
Stable CAD is a heterogeneous group

- Patients with prior MI/ACS
- Pts with prior PCI or CABG
- Pts with angina pectoris (and evidence of ischemia)
- Patients with silent myocardial ischemia
- Patients with « significant » coronary artery disease
- Patients with coronary artery disease

ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized...but is often not sustained...and some components may be unnecessary...

• New treatments are coming up!

• Therefore there is a need to risk stratify and individualize Rx
  ➢ The extent and severity of CAD and other locations of atherothrombosis are important determinants of risk
Nonobstructive CAD and risk of MI

Time-to-event plots for 1-year myocardial infarction, mortality, and combined myocardial infarction and mortality, by CAD extent

Polyvascular Disease Increases Risk

1-year cardiovascular event rates as function of number of symptomatic disease locations in atherothrombosis

All p-values <0.001
*Patients with three risk factors but no symptoms are counted as 0, even in the presence of asymptomatic carotid plaque or reduced ABI

ABI, ankle–branchial index

Steg PG et al, JAMA 2007;297:1197–1206
Update and future of secondary prevention

• A changing epidemiology, worldwide

• Residual risk is real

• Secondary prevention therapy is standardized...but is often not sustained...and some components may be unnecessary...

• New treatments are coming up!

• **Therefore there is a need to risk stratify and individualize Rx**
  - The extent and severity of CAD and other locations of atherothrombosis are important determinants of risk
  - Formal assessment of risk scores or net clinical benefit scores can be useful
Predicting the risk of events in stable outpatients with atherothrombosis

The REACH risk score calculator

### Risk score sheet

2 year CV death/MI/stroke

<table>
<thead>
<tr>
<th>Step</th>
<th>Factor</th>
<th>Status and Points Assigned</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age (years)</td>
<td>30-39 -4 40-49 -2 50-59 0 60-69 2 70-79 4 80-89 6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Smoking</td>
<td>No 0 Yes 2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Diabetes mellitus</td>
<td>No 0 Yes 3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Number of vascular beds</td>
<td>One 0 Two 1 Three 3</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CV event in past year</td>
<td>No 0 Yes 2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Congestive heart failure</td>
<td>No 0 Yes 3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Statin therapy</td>
<td>No 0 Yes -2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Aspirin therapy</td>
<td>No 0 Yes -1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>TOTAL POINTS</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL Pts</th>
<th>2 Year Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7</td>
<td>1.1%</td>
</tr>
<tr>
<td>-6</td>
<td>1.3%</td>
</tr>
<tr>
<td>-5</td>
<td>1.5%</td>
</tr>
<tr>
<td>-4</td>
<td>1.8%</td>
</tr>
<tr>
<td>-3</td>
<td>2.1%</td>
</tr>
<tr>
<td>-2</td>
<td>2.6%</td>
</tr>
<tr>
<td>-1</td>
<td>3.1%</td>
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<td>6.2%</td>
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<td>6</td>
<td>10.3%</td>
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<tr>
<td>7</td>
<td>12.3%</td>
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<tr>
<td>8</td>
<td>14.6%</td>
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<td>17.1%</td>
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<td>10</td>
<td>20.1%</td>
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<td>23.5%</td>
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<td>12</td>
<td>27.5%</td>
</tr>
<tr>
<td>13</td>
<td>31.9%</td>
</tr>
<tr>
<td>14</td>
<td>36.9%</td>
</tr>
<tr>
<td>15</td>
<td>42.4%</td>
</tr>
<tr>
<td>16</td>
<td>48.3%</td>
</tr>
<tr>
<td>17</td>
<td>54.6%</td>
</tr>
<tr>
<td>18+</td>
<td>&gt; 60%</td>
</tr>
</tbody>
</table>
REACH score: predicting events in post-ACS patients in the IMPROVE-IT trial

Prespecified analysis, including 18.144 patients stabilized after ACS, randomized to EZE/simva or simva alone

May E, et al. ACC 2015. Presentation 1125M-07
Conclusions

• The incredible progress made in secondary prevention will continue but will require
  ➢ Dropping some treatments that are unnecessary
  ➢ Tailoring therapy to patients risk and profile
  ➢ Improving long term adherence

• A challenge will be to ensure access to these therapies on a global scale, given the burden of cardiovascular disease in low and middle income countries
Medical therapy for secondary prevention after ACS

1. Aspirin 81 mg/d for life
2. 3rd Gen. DAPT (P2Y12) for at least a year
3. β-Blockade
4. LDL-C Lowering with Statin (high-intensity) + ezetimibe or PCSK9 for target LDL <50 (even lower is event better)
5. ACEI if CHF, EF<0.40, HTN, DM; ? in all CAD
6. Aldo antag if EF <40% & CHF
7. Nitrates if sx, prn for all
8. Ranolazine if sx
9. For DM – SGLT-2 or GLP-1 added to metformin for CV risk reduction
10. Emerging role for anti-inflammatory therapy