



# Molecular (M), Clinical (C) and Population (P) Bases of Cardiovascular Disease and Health

## MCP BASES OF THE TRANSITION FROM DISEASE TO HEALTH, 2019

### New Frontiers

# The Historical Evolution of Beta-Blockers & ACEi / ARBs / ARNI

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*Molecular (M), Clinical (C), Population (P)  
Bases of Cardiovascular Disease and Health, 2019*

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*1). MCP Bases of Transition from Disease to Health*

*1. Two Critical Tools – Imaging, Genetics*

*2. Three Behavioral Ages - Elderly, Mid Life, Children*

*3. Two Historical Paths – B. Blockers, ACE / ARBs / ARNI*

*4. Two Historical Paths – Statins / PCSK9i, SGLT2i / GLP1-RA*

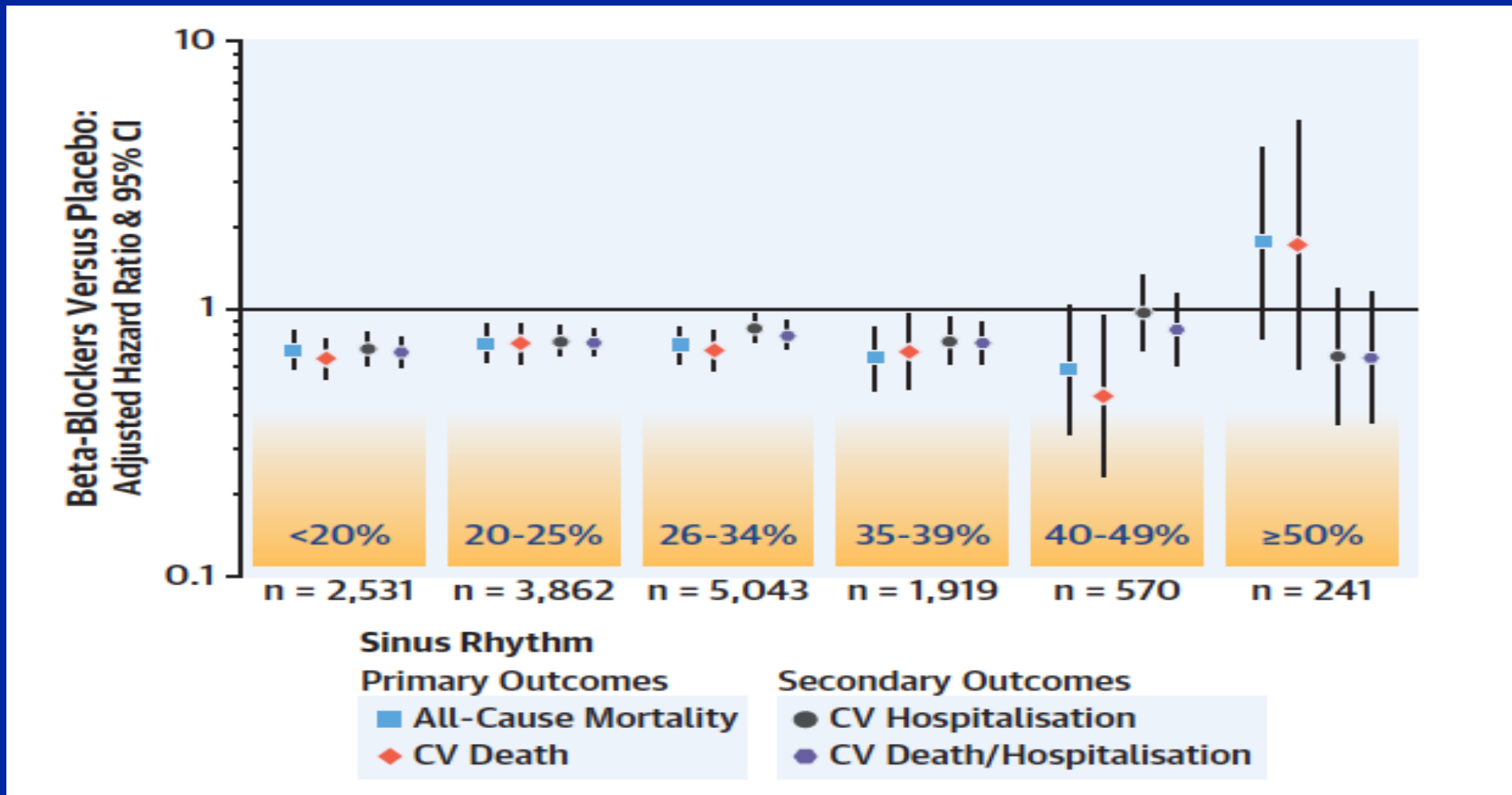
# Pharmacologic Properties of Common Prescribed $\beta$ -Blockers

Drug	$\beta_1/\beta_2$ Selectivity (Cardio-Selectivity)	ISA	Half-Life	Additional Properties
Second generation				
Bisoprolol	++	0	9-12	
Metoprolol	++	0	3-7	
Atenolol	+	0	6-9	
Third generation				
Carvedilol	0	0	7-10	$\alpha_1$ -receptor inhibition mediated vasodilation
Nebivolol	+++	0	8-27	L-arginine/nitric oxide mediated vasodilation

# *Effects of $\beta$ -Blockers in Heart Failure*

Cardiac Disease	Effects of $\beta$ -Blockers Based on RCTs	Recommendations
Heart failure with reduced ejection fraction	<ul style="list-style-type: none"><li>• Reduces mortality</li><li>• Reduces hospitalizations</li></ul>	<ul style="list-style-type: none"><li>• Use widely</li></ul>
Heart failure with mid-range or preserved ejection fraction	<ul style="list-style-type: none"><li>• Insufficient data on major adverse cardiac outcomes</li></ul>	<ul style="list-style-type: none"><li>• No data to support use without a secondary indication (i.e. atrial fibrillation, hypertension)</li><li>• Large RCTs needed</li></ul>

# $\beta$ -Blockers and Clinical Outcomes by EF in a Patient-Level Meta-Analysis of 11 RCTs



# Effects of $\beta$ -Blockers in Coronary Disease

## Post ACS

### Immediate effect:

- Reduces mortality (pre-reperfusion era data)
- Reduces re-infarction
- Can increase risk of heart failure and cardiogenic shock (mainly observed in patients at higher risk)

### Longer-term effect:

- Reduces mortality (pre-reperfusion era data)

- Initiate post-ACS in patients without a low blood pressure or clinical evidence of decompensated heart failure
- Start at low doses, and titrate gradually to avoid adverse effects.
- Continue treatment for up to 3 years (or permanently if heart failure with reduced ejection fraction)
- Large contemporary RCTs in progress to study long-term effect in patients without left ventricular dysfunction

## Stable CAD (without recent ACS, and with normal left ventricular function)

- Insufficient data on major adverse cardiac outcomes

- Use for angina
- No data to support routine use
- Large RCTs needed

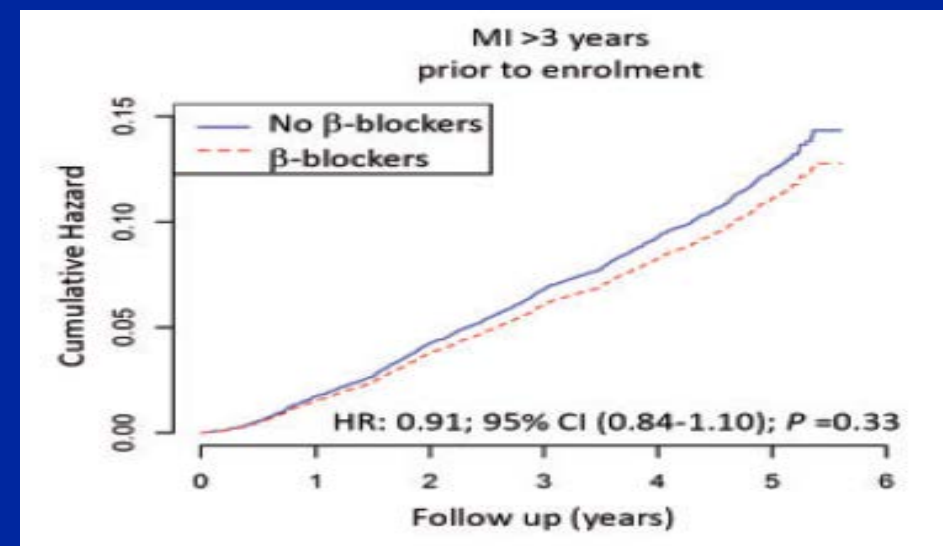
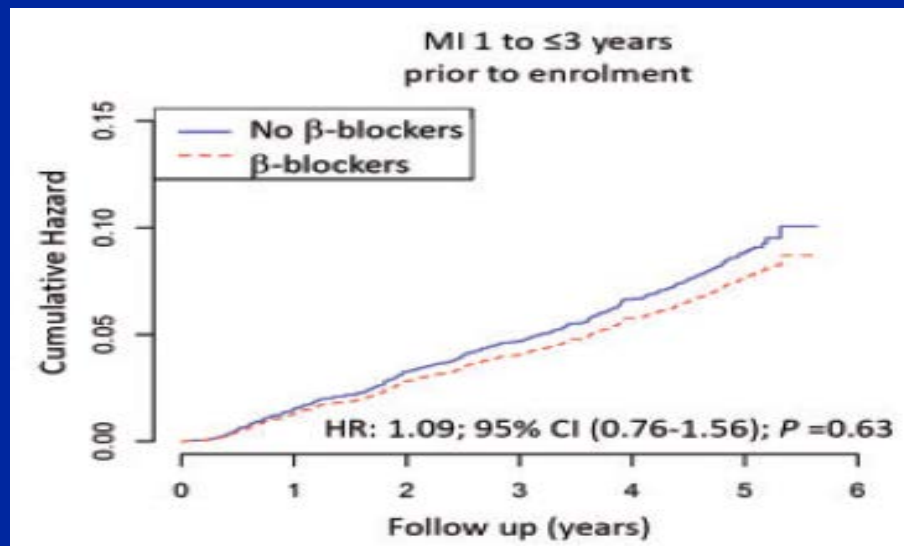
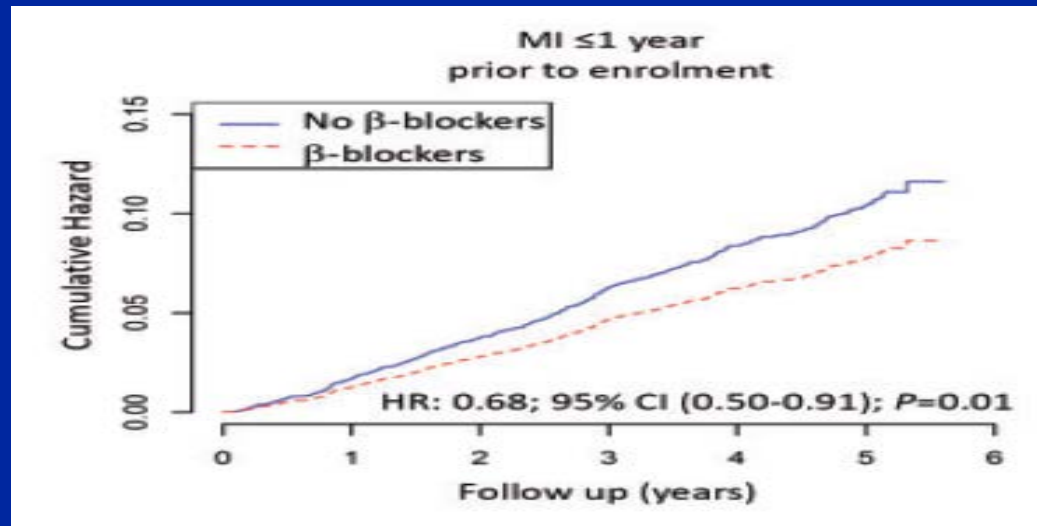
## *$\beta$ -Blockers, Calcium Antagonists, and Mortality in Stable CAD - An International Cohort Study*

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**We analysed the use of  $\beta$ -blockers or calcium antagonists (baseline and annually) and outcomes in 22,006 stable CAD patients (enrolled 2009-2010) followed annually to 5 years, in the CLARIFY registry (45 countries). Primary outcome was all-cause death. Secondary outcomes were CVD death and the composite of CVD death/non-fatal MI. In this contemporary cohort of stable CAD,  $\beta$ -blocker use was associated with lower 5-year mortality (all cause 7% vs 10%; CV 4.5% vs 8.5%) only in patients enrolled in the year following MI. Use of calcium antagonists was of no benefit associated with**

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# All-cause Mortality According To $\beta$ -blocker Use, Time Elapsed Since The Index MI Prior To Enrolment





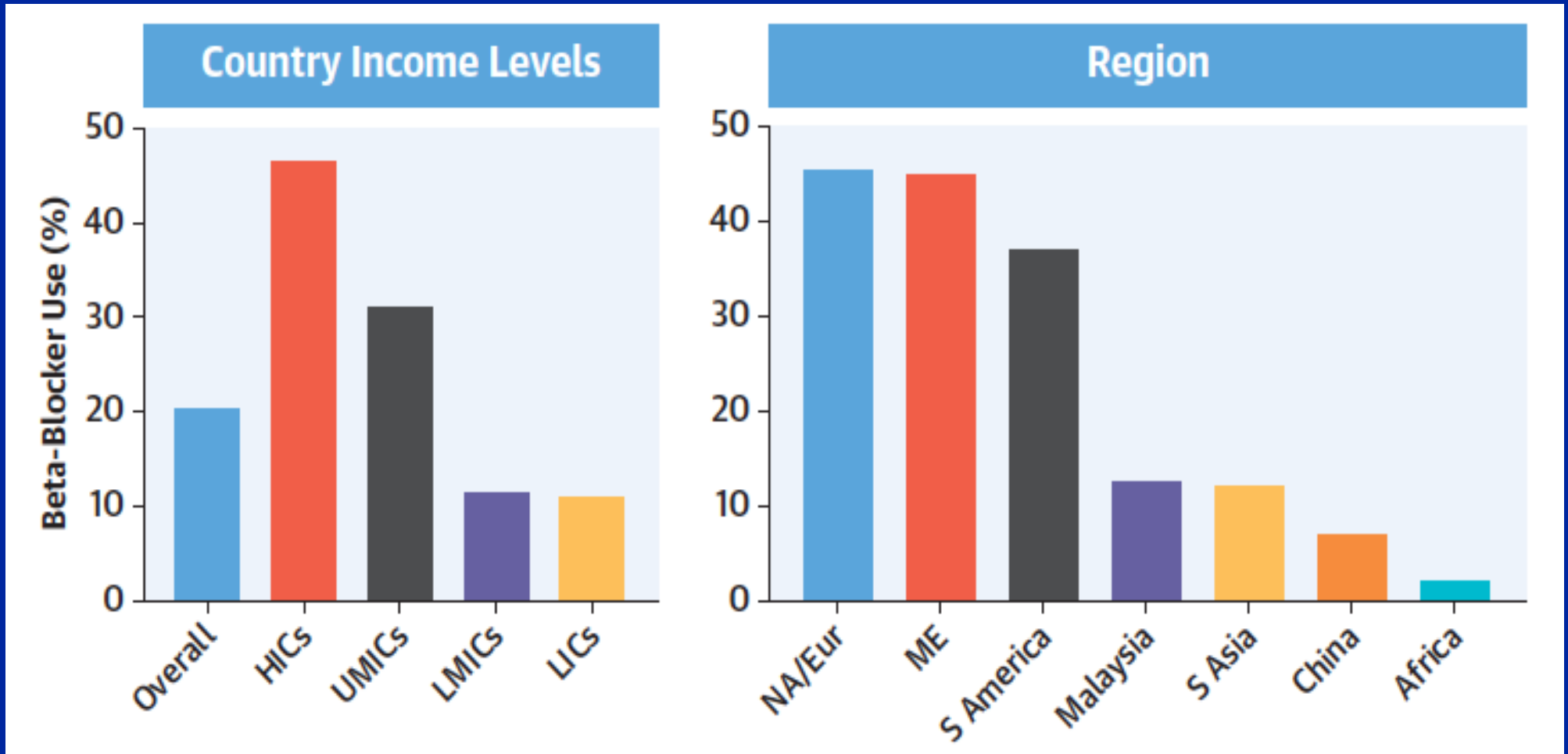
## The Evolution of $\beta$ -Blockers in Coronary Artery Disease and Heart Failure (Part I)

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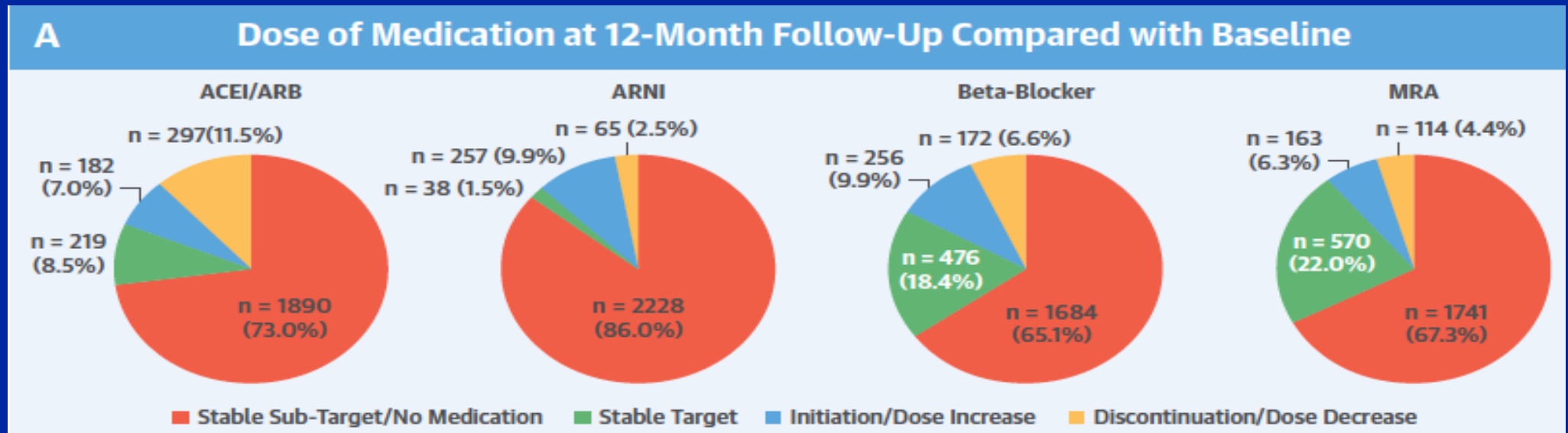
*We examine the current evidence supporting  $\beta$ -blocker use in HFpEF, HFmEF and HFrEF, post ACS & in stable CAD.  $\beta$ -Blockers remain essential in HFrEF, but limited evidence supports their use in HFmEF or HFpEF. Are considered routinely following ACS, but there is a need for contemporary trials in patients without LV dysfunction, as well as in stable CAD. From a global perspective, more studies are needed to characterize the extent of  $\beta$ -blocker use in CAD and HF, and how evidence-based use can be improved in these conditions.*

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# $\beta$ -Blocker Use in Participants With Established CAD - the PURE Study



# Changes in Use & Dose of GDMT Over 12 Months Among Patients With Chronic HFrEF in U.S. Outpatient Practice



**Among 2,588 U.S. outpatients with chronic HFrEF in the CHAMP-HF registry with complete medication data and no contraindications to medical therapy, use and dose were examined at baseline and at 12-month follow-up. Most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time.**

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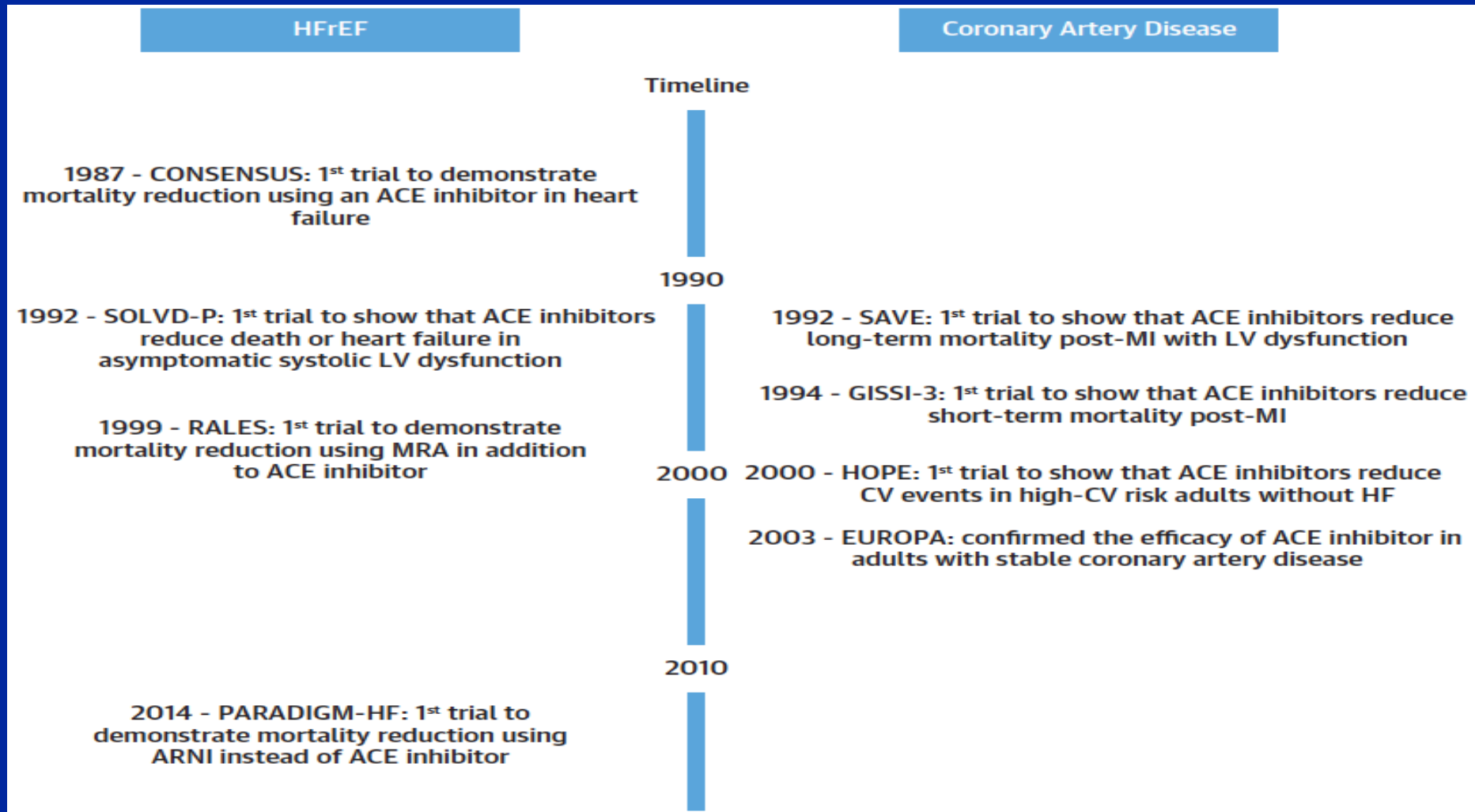
*3. Two Historical Paths – B. Blockers, ACE / ARBs / ARNI*

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# From ACE Inhibitors/ARBs to ARNIs in Coronary Artery Disease and Heart Failure (Part I)

*The pharmacological inhibition of the RAAS is one of the most significant advances in the treatment and prevention of HFrEF and in CAD. Recently, the addition of neprilysin inhibition to ARB or ARNI has been shown to be even more effective than ACEI inhibition alone in HFrEF. This review summarizes the major trials that have informed the clinical role of inhibition of the RAA and neprilysin pathways, as well as the limitations of these strategies.*

# Chronology of Landmark Trials Involving RAAS/ACEI in HFrEF & CAD



# Evidence for Use of ACEI, ARB, MCRA & ARNI in Coronary Artery Disease and Heart Failure



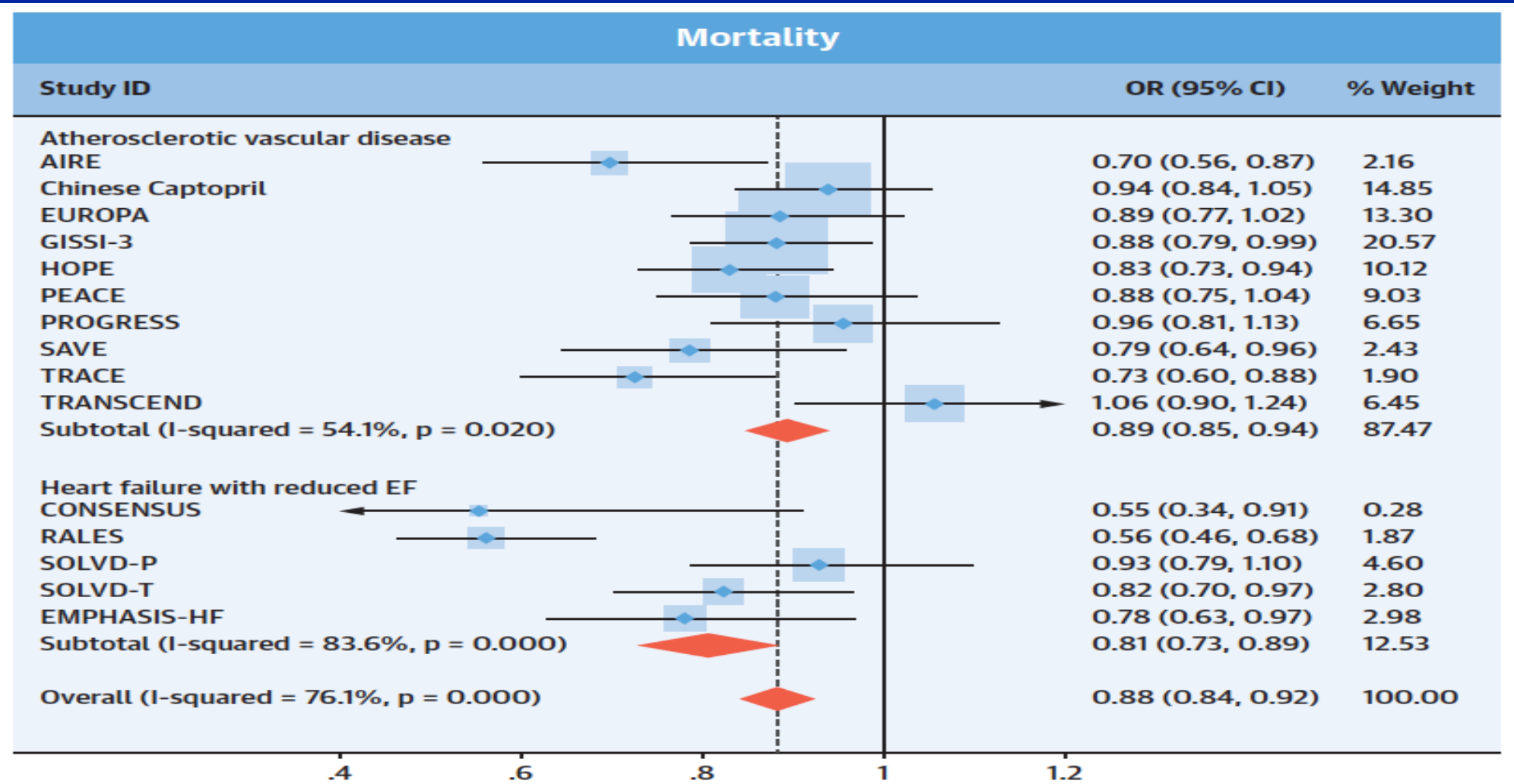
Atherosclerotic Coronary Disease - Increasing Risk



Heart Failure - Increasing Left Ventricular Ejection Fraction

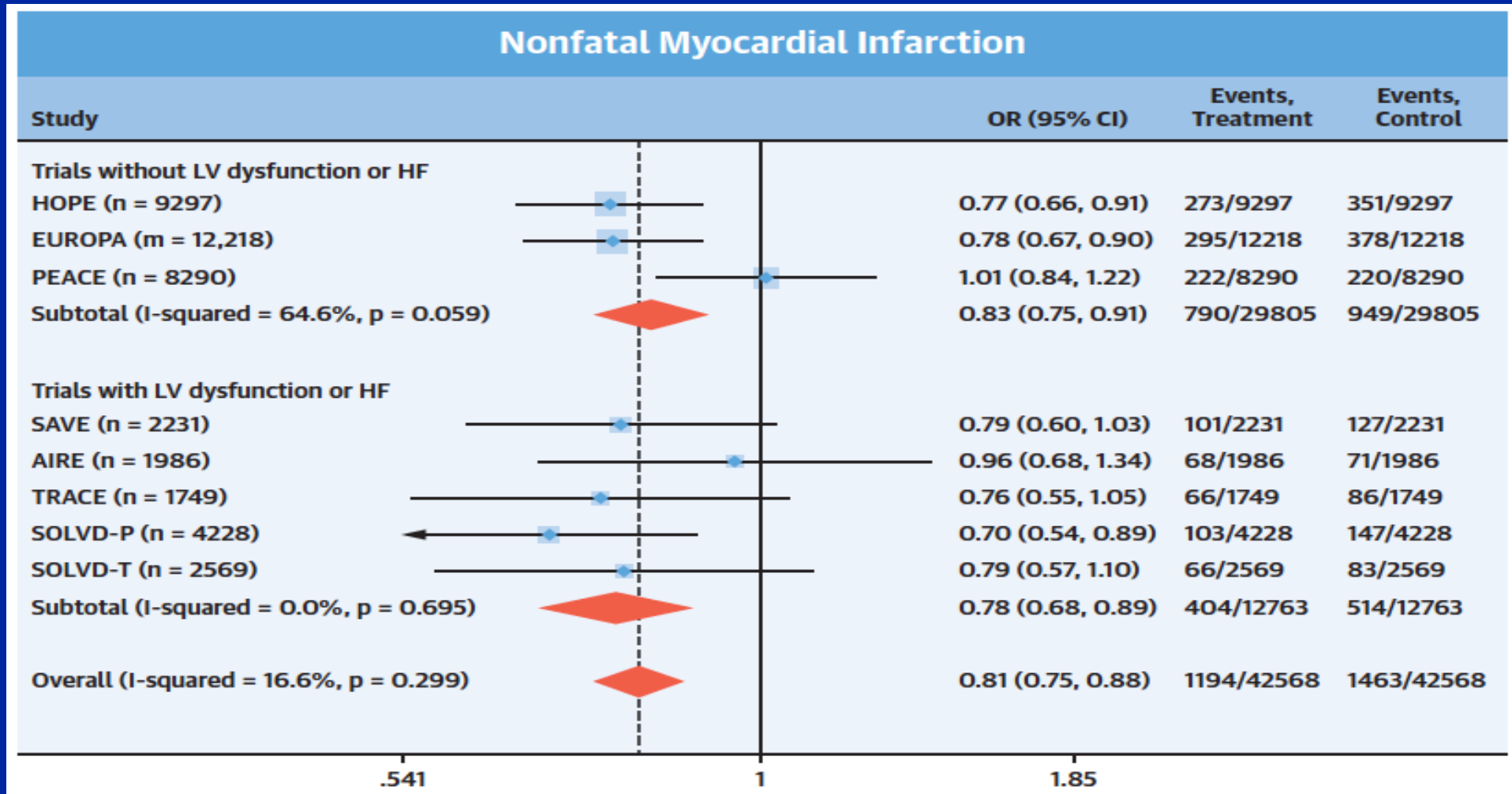
	Stable Atherosclerotic Vascular Disease	High-Risk Post-Myocardial Infarction	Acute Post-Myocardial Infarction	Heart Failure With Reduced Ejection Fraction	Heart Failure With Midrange Ejection Fraction	Heart Failure With Preserved Ejection Fraction
Angiotensin-Converting Enzyme Inhibitor	+	+	+	+	?	-
Angiotensin Receptor Blockers	+	+	+	+	?	-
Mineralocorticoid Receptor Antagonists	?	+	+	+	?	(+)
Angiotensin Receptor-Neprilysin Inhibitors	?	To Be Determined	To Be Determined	+	To Be Determined	To Be Determined

# The Effects of RASI or MCRI on Mortality in Stable Vascular Disease or HFrEF

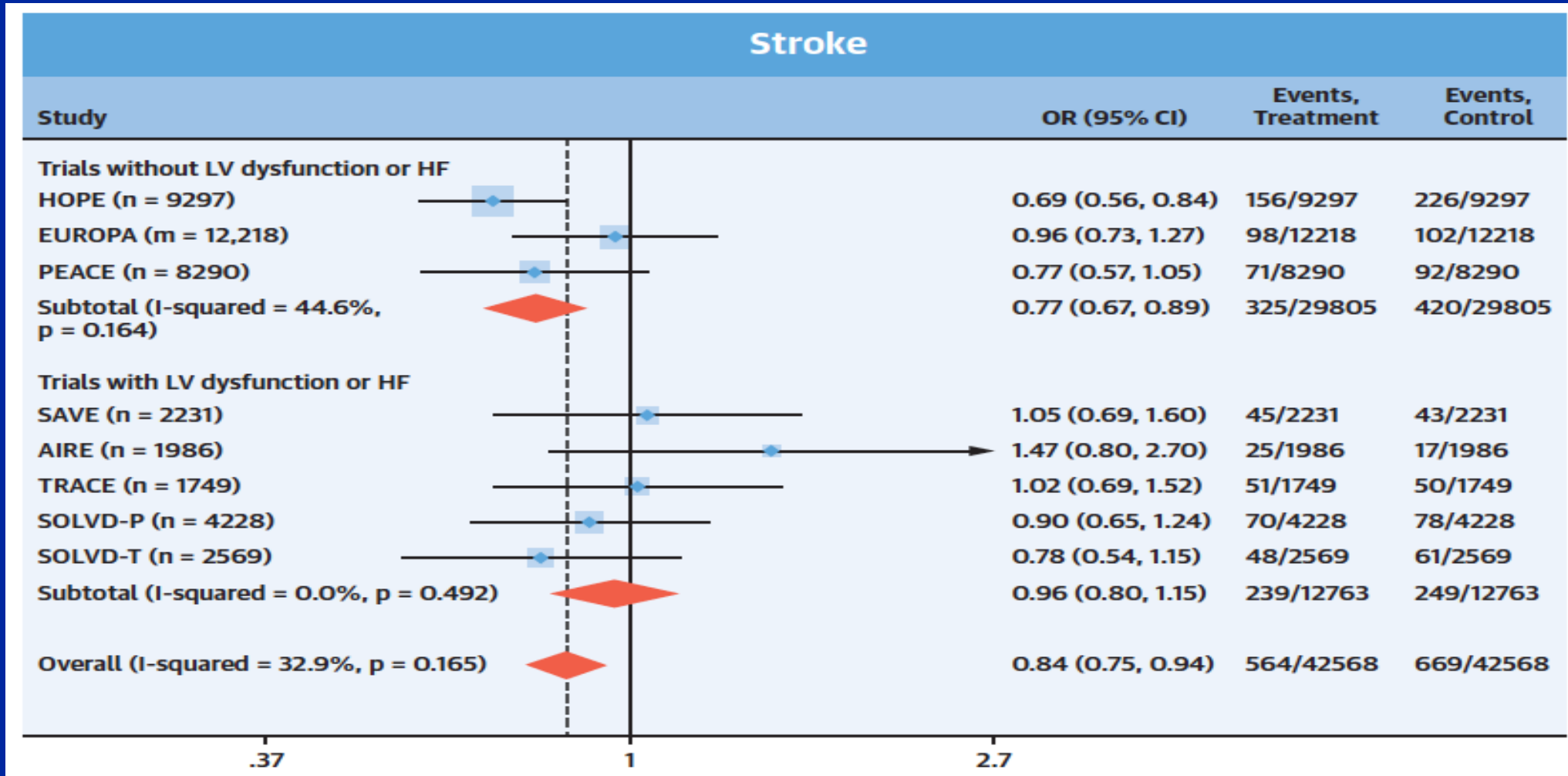




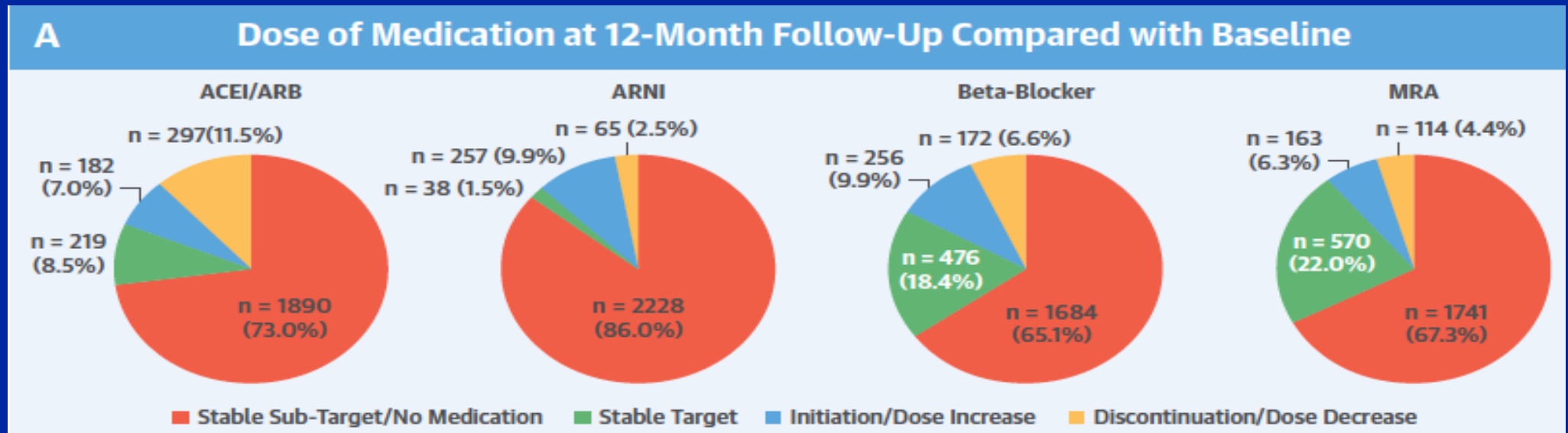
# The Effects of RASI on MI in Stable Vascular Disease or HFrEF



# The Effects of RASI on Stroke in Vascular Disease or HFrEF



# Changes in Use & Dose of GDMT Over 12 Months Among Patients With Chronic HFrEF in U.S. Outpatient Practice



**Among 2,588 U.S. outpatients with chronic HFrEF in the CHAMP-HF registry with complete medication data and no contraindications to medical therapy, use and dose were examined at baseline and at 12-month follow-up. Most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time.**

# Cardiovascular Medications in Pregnancy

Arrhythmias	Hypertension
<p>Adenosine <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Metoprolol/propranolol <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Digoxin <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> F </p> <p>Lidocaine <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span></p> <p>Verapamil <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Diltiazem <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Procainamide <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Sotalol <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span> F</p> <p>Flecainide <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> F</p> <p>Propafenone <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Amiodarone <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> D <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span></p> <p><small># may be used if other therapies fail</small></p>	<p>Labetalol <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Nifedipine <span style="display: inline-block; 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width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Isosorbide dinitrate <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Amlodipine <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Furosemide <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Hydrochlorothiazide <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span></p> <p>Clonidine <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p>
Heart Failure	Pulmonary Hypertension
<p>Metoprolol <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Carvedilol <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Furosemide <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Bumetanide <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Dopamine <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Dobutamine <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Norepinephrine <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Hydralazine <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span></p> <p>Nitroglycerin <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Isosorbide dinitrate <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Torsemide <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Metolazone <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p>	<p>Iloprost <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Epoprostenol <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Sildenafil <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Treprostinil <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p>
Anticoagulants/Antiplatelets/Thrombolytics	Contraindicated in Pregnancy
<p><b>Anticoagulants</b></p> <p>Warfarin <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> D <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span></p> <p>Unfractionated Heparin <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span></p> <p>Enoxaparin <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span></p> <p>Fondaparinux <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Argatroban <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Bivalirudin <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p><b>Antiplatelets</b></p> <p>Aspirin (low dose) <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> N <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Clopidogrel <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span></p> <p>Prasugrel <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> B <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Ticagrelor <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p><b>Thrombolytics</b></p> <p>Alteplase <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Streptokinase <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> C <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p></p>	<p>Atenolol <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> D <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> ** </p> <p>ACE-I class <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> D <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> **</p> <p>ARB class <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> D <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span></p> <p>Aldosterone antagonists <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> X <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span></p> <p>Statin class <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> X <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span></p> <p>DOACs <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> X <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span></p> <p>ERAs (e.g. bosentan) <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> X <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span></p> <p><small>## captopril, benazepril and enalapril are considered safe during lactation. *Variable designation according to specific drug.</small></p>
<p><b>Safety in pregnancy</b> <span style="display: inline-block; width: 15px; height: 15px; border: 1px solid black; border-radius: 50%;"></span> <b>FDA category</b> <span style="display: inline-block; width: 15px; height: 15px; border: 1px solid black; border-radius: 50%;"></span> <b>Safety in lactation</b> <span style="display: inline-block; width: 15px; height: 15px; border: 1px solid black; border-radius: 50%;"></span> <b>Used also for fetal treatment</b> <span style="display: inline-block; width: 15px; height: 15px; border: 1px solid black; border-radius: 50%; text-align: center; font-size: 8px;">F</span></p> <p><span style="display: inline-block; width: 15px; height: 15px; background-color: green; border-radius: 50%;"></span> Considered safe  <span style="display: inline-block; width: 15px; height: 15px; background-color: orange; border-radius: 50%;"></span> Limited data/to be used with caution  <span style="display: inline-block; width: 15px; height: 15px; background-color: red; border-radius: 50%;"></span> Contraindicated  <span style="display: inline-block; width: 15px; height: 15px; background-color: blue; border-radius: 50%;"></span> Conflicting data/unknown</p>	

*Molecular (M), Clinical (C), Population (P)  
Bases of Cardiovascular Disease and Health, 2019*

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*1). MCP Bases of Transition from Disease to Health*

*1. Two Critical Tools – Imaging, Genetics*

*2. Three Behavioral Ages - Elderly, Mid Life, Children*

*3. Two Historical Paths – B. Blockers, ACE / ARBs / ARNI*

*4. Two Historical Paths – Statins / PCSK9i, SGLT2i / GLP1-RA*