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The Current Clinical Trial Landscape in Cardiovascular Medicine

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Disclosures

None

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Education Need / Practice Gap

A major education gap exists in the awareness of current cardiology clinical trials. Providers need to be aware of recent cardiovascular clinical trials and how they can effect daily practice

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Objectives

Upon completion of this learning activity, you will be able to:

1. Discuss latest advances in medical and interventional clinical research in cardiovascular medicine.

2. Review the findings of the most relevant clinical trials in cardiovascular medicine in 2018-2019.

3. Discuss the impact of clinical research findings and how it can change daily practice.

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Expected Outcome

The desired change/result in practice is to be aware of leading-edge cardiovascular treatment approaches which stem from current clinical trials and how these benefits can be passed on to cardiovascular patients.

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Cardiovascular Medicine is Changing Fast

Progress and Paradigm Shifts Can Only be Based on High Quality Data

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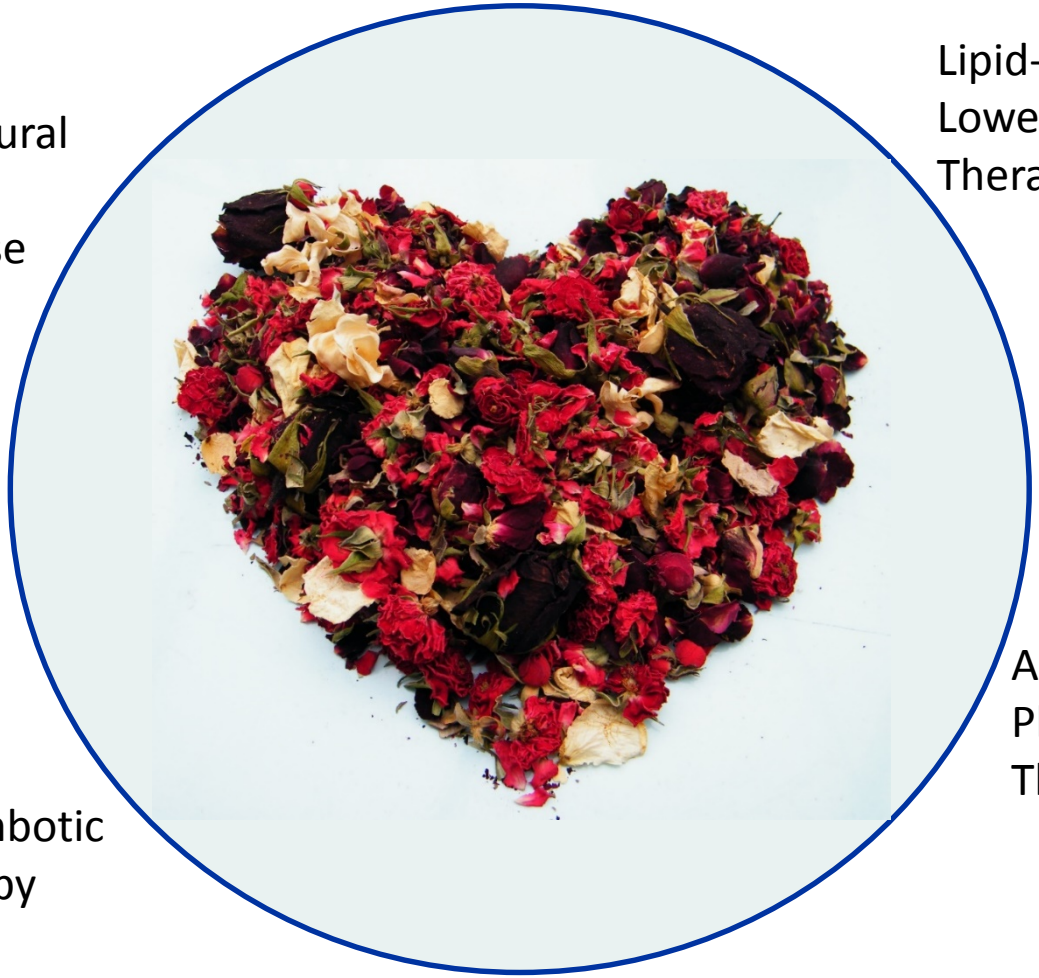
Structural Heart Disease

Lipid-Lowering Therapy



Anti-Thrombotic Therapy

Anti-Platelet Therapy

Diagnostic Coronary Imaging

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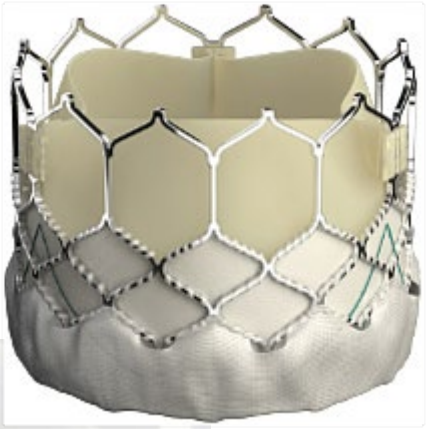
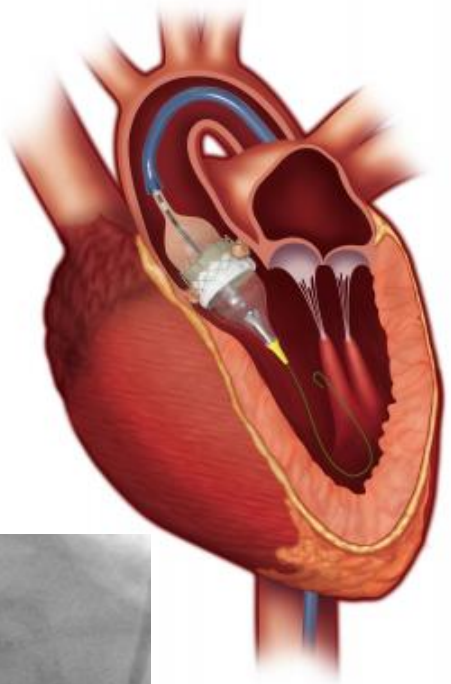
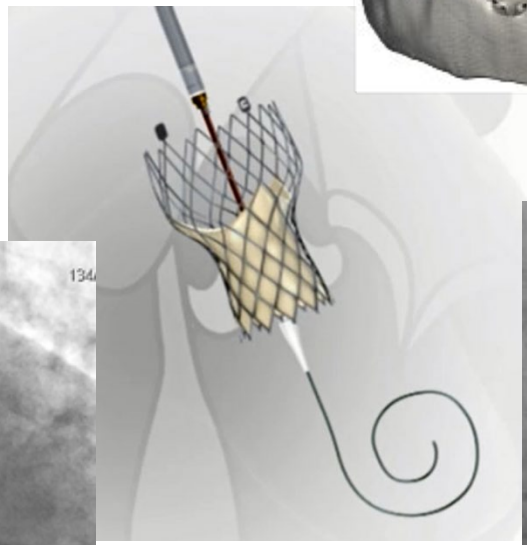
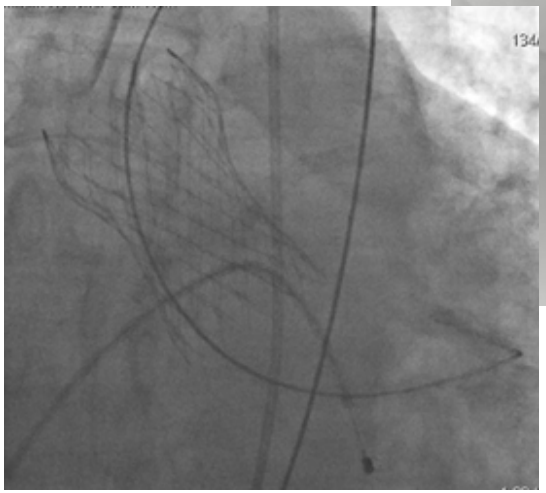
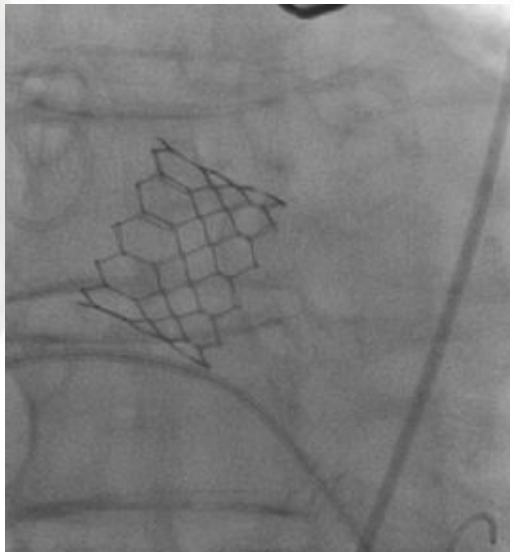
Transcutaneous Aortic Valve Replacement (TAVR)











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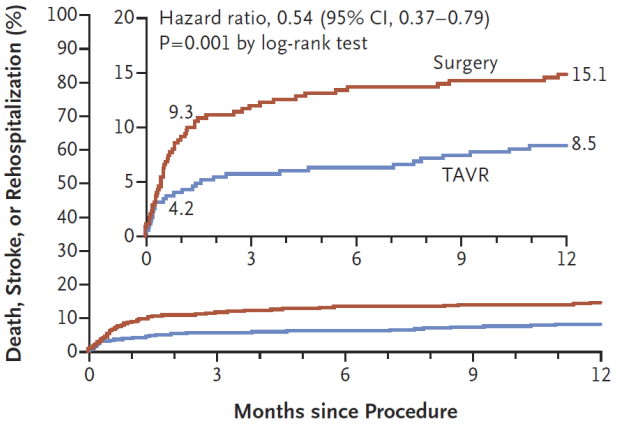
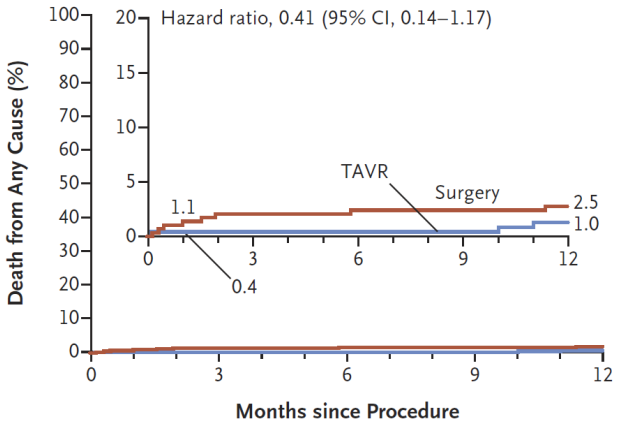
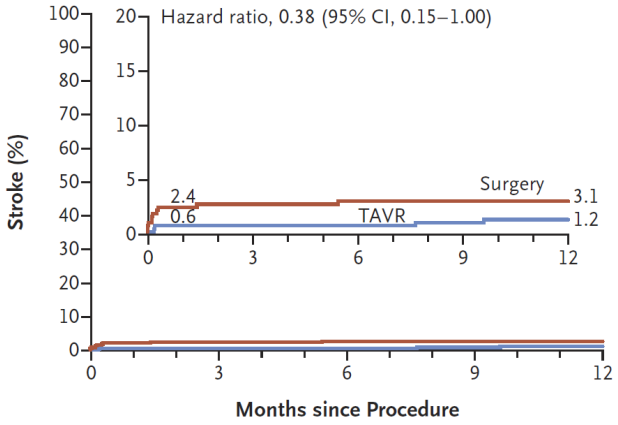
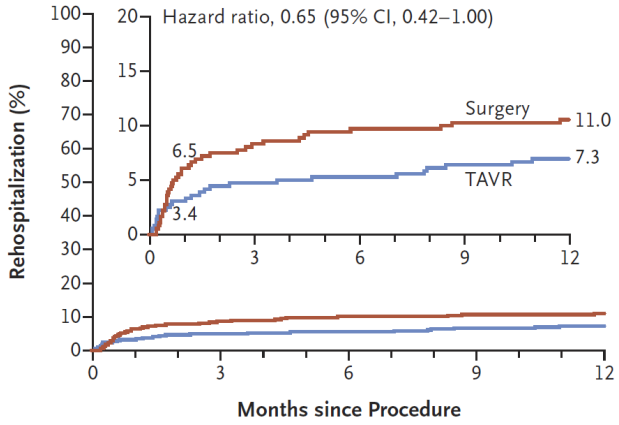
TAVR for Low Risk Patients

- **PARTNER 3 Trial** compared outcomes of TAVR vs SAVR in 1000 low risk AS patients
- Many exclusion criteria
- At 1 year of f/u, TAVR was associated with superior outcomes (death, stroke and rehospitalization)
- Peri-op Afib only 5% with TAVR
- >95% TAVR discharged home; shorter LOS









Mack MJ et al. N Engl J Med 2019; online March 16th

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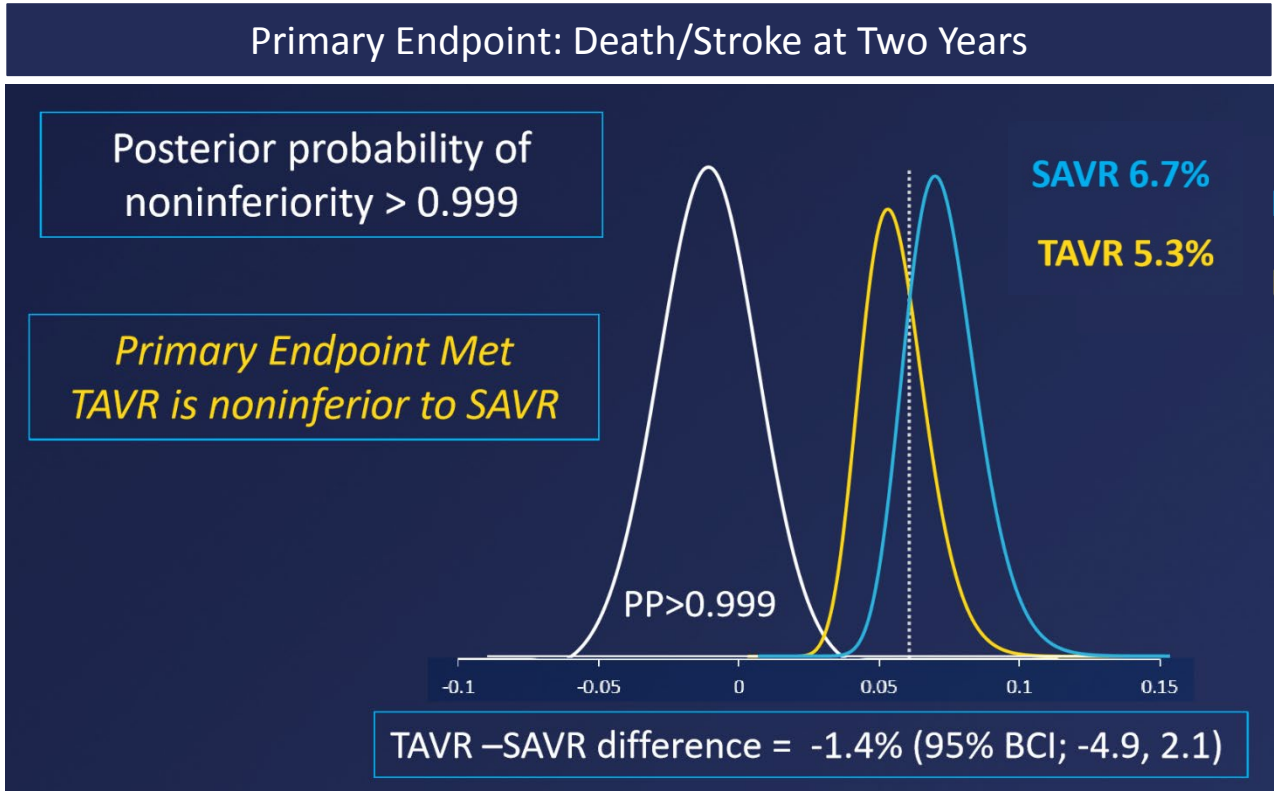
TAVR for Low Risk Patients

- **Evolut Low Risk Trial** compared outcomes of TAVR vs SAVR in 1403 low risk AS patients
- Many exclusion criteria
- At 2 years of f/u, TAVR was not inferior to SAVR
- 30-day outcomes better with TAVR (safety)
- Need for PPM 17.4% with TAVR
- Hemodynamics and QOL better with TAVR



Pompa J et al. N Engl J Med 2019; online March 16th

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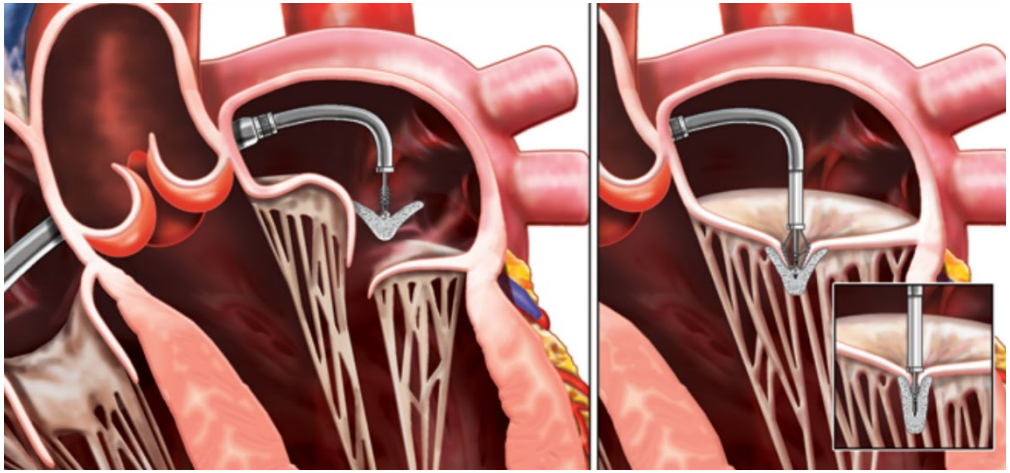
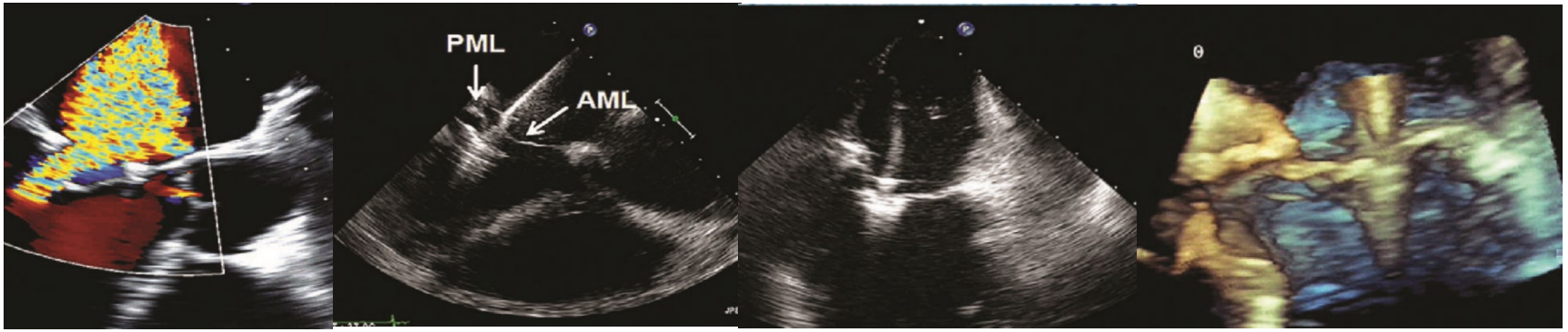
TAVR for Low Risk Patients

- Paradigm shift in management of AS –
  - An estimated 150-200,000 patients are diagnosed with AS and are at low risk for surgery every year in US, Europe and Japan
- Reduction in stroke risk and LOS have been striking
- Many exclusion criteria remain
- Long term outcomes will need further study

Percutaneous Mitral Repair
“Mitra-Clip System”

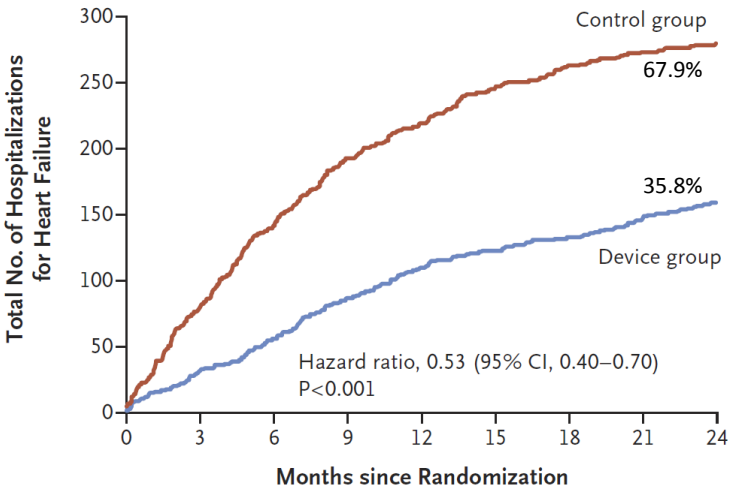


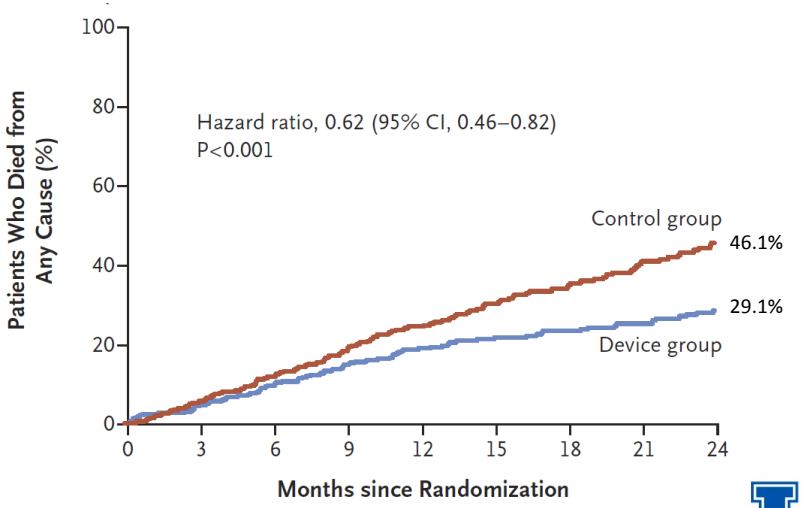


Percutaneous Mitral Repair

The COAPT Trial

- 614 patients with 3+ or 4+ secondary MR with symptomatic CHF despite OMT
- 1:1 Randomization to MitraClip (device) or OMT alone (control)
- Primary endpoint: All CHF hospitalizations at 24 months





Stone GW et al. N Engl J Med 2018;379:2307-18

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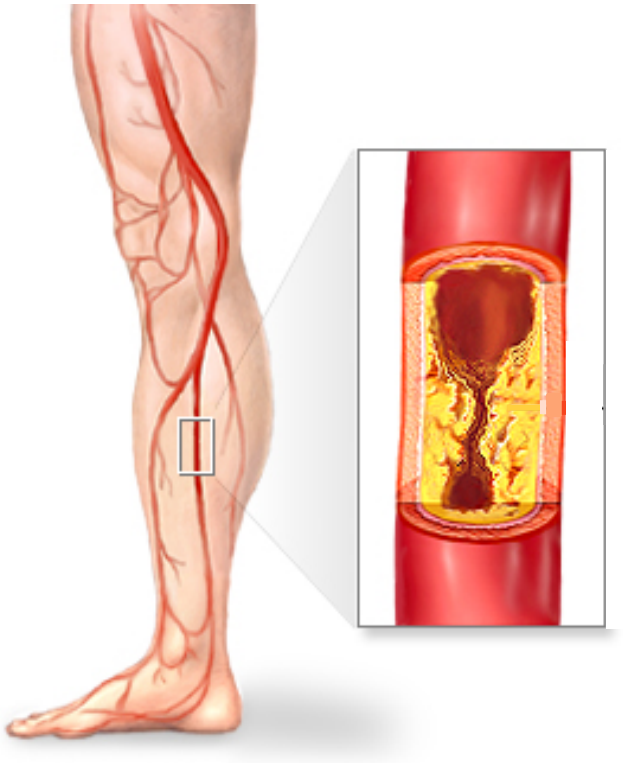
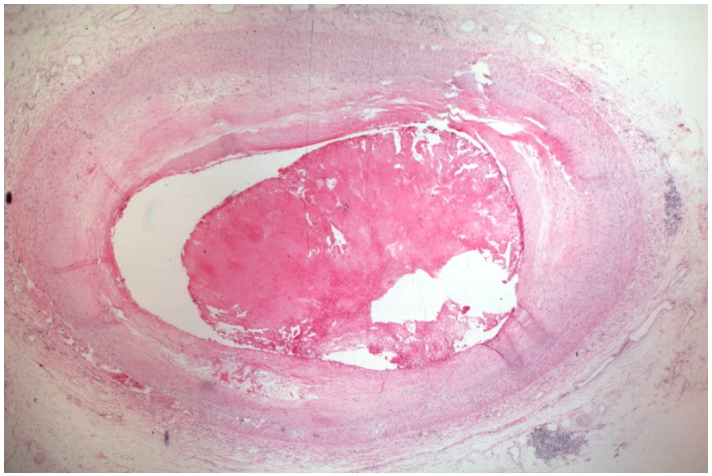
Percutaneous Mitral Repair

- Significant reduction in morbidity and mortality in a difficult patient population
- Many questions remain
  - MITRA FR, a similar randomized trial in Europe did not show same results
  - Inclusion criteria were very narrow – highly selected population
  - Mortality benefit maybe too good to be true or reproduce

Novel Application of Anti-Thrombotics





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Xa Inhibitor Rivaroxaban for 2ry Prevention

The COMPASS Trial

- A large randomized controlled trial examining Rivaroxaban as an additional 2ry prevention measure in outpatients with CAD or PAD
- 1:1:1 randomization to rivaroxaban (2·5 mg bid) plus aspirin (100 mg qd), rivaroxaban alone (5 mg bid), or aspirin alone (100 mg qd).
- CAD study : >24,800 patients (stable or unstable angina, h/o multivessel CAD, h/o multivessel CABG, h/o multivessel PCI)
- PAD study: >7400 patients with
  - LE PAD – h/o surgery or PTA, amputation, claudication with objective evidence of PAD,
  - Carotid disease – h/o revascularization or ≥50% stenosis, or
  - CAD with an ankle–brachial index of <0·90.

Connolly SG et al. Lancet 2018; 391: 205–18

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Xa Inhibitor Rivaroxaban for 2ry Prevention

COMPASS CAD Cohort

	Low-dose rivaroxaban plus aspirin (n=8313)	Rivaroxaban alone (n=8250)	Aspirin alone (n=8261)	Low-dose rivaroxaban plus aspirin *vs* aspirin alone		Rivaroxaban alone *vs* aspirin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Myocardial infarction, stroke, or cardiovascular death*	347 (4%)	411 (5%)	460 (6%)	0·74 (0·65–0·86)	<0·0001	0·89 (0·78–1·02)	0·094
Myocardial infarction, ischaemic stroke, coronary heart disease death, or acute limb ischaemia	299 (4%)	357 (4%)	411 (5%)	0·72 (0·62–0·83)	<0·0001	0·87 (0·75–1·00)	0·048
Myocardial infarction, ischaemic stroke, cardiovascular death, or acute limb ischaemia*	349 (4%)	406 (5%)	470 (6%)	0·73 (0·64–0·84)	<0·0001	0·86 (0·76–0·98)	0·029
Death*	262 (3%)	316 (4%)	339 (4%)	0·77 (0·65–0·90)	0·0012	0·93 (0·80–1·09)	0·37
Cardiovascular death*	139 (2%)	175 (2%)	184 (2%)	0·75 (0·60–0·93)	0·010	0·95 (0·77–1·17)	0·63
Non-cardiovascular death	123 (2%)	141 (2%)	155 (2%)	0·79 (0·62–1·00)	0·048	0·91 (0·73–1·15)	0·43
Myocardial infarction	169 (2%)	176 (2%)	195 (2%)	0·86 (0·70–1·05)	0·15	0·90 (0·74–1·11)	0·33
Myocardial infarction or sudden cardiac death†	234 (3%)	273 (3%)	273 (3%)	0·85 (0·71–1·01)	0·065	1·00 (0·85–1·18)	1·00
Myocardial infarction, coronary heart disease death, sudden death, resuscitated cardiac arrest, or unstable angina*†	264 (3%)	314 (4%)	314 (4%)	0·83 (0·71–0·98)	0·028	1·00(0·86–1·17)	1·00
Stroke*	74 (1%)	105 (1%)	130 (2%)	0·56 (0·42–0·75)	<0·0001	0·81 (0·62–1·05)	0·10
Ischaemic stroke or unspecified site	60 (1%)	79 (1%)	120 (2%)	0·50 (0·36–0·67)	<0·0001	0·66 (0·50–0·87)	0·0037
Haemorrhagic stroke	14 (<1%)	27 (<1%)	10 (<1%)	1·39 (0·62–3·32)	0·43	2·70 (1·31–5·59)	0·0051

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Xa Inhibitor Rivaroxaban for 2ry Prevention

COMPASS PAD Cohort

	Low-dose rivaroxaban plus aspirin (n=2492)	Rivaroxaban alone (n=2474)	Aspirin alone (n=2504)	Low-dose rivaroxaban plus aspirin versus aspirin alone		Rivaroxaban alone versus aspirin alone	
				HR (95% CI)	p value	HR (95% CI)	p value
Primary and secondary outcomes							
Cardiovascular death, stroke, myocardial infarction*	126 (5%)	149 (6%)	174 (7%)	0·72 (0·57–0·90)	0·0047	0·86 (0·69–1·08)	0·19
Coronary heart disease death, myocardial infarction, ischaemic stroke, acute limb ischaemia†	115 (5%)	147 (6%)	169 (7%)	0·68 (0·53–0·86)	0·0011	0·88 (0·70–1·10)	0·25
Cardiovascular death, myocardial infarction,	142 (6%)	168 (7%)	198 (8%)	0·71 (0·57–0·88)	0·0019	0·86 (0·70–1·05)	0·14
Prespecified limb outcomes							
Acute limb ischaemia‡	19 (1%)	19 (1%)	34 (1%)	0·56 (0·32–0·99)	0·042	0·57 (0·32–1·00)	0·046
Chronic limb ischaemia‡	16 (1%)	18 (1%)	24 (1%)	0·67 (0·35–1·26)	0·21	0·76 (0·41–1·40)	0·37
Major adverse limb event‡	30 (1%)	35 (1%)	56 (2%)	0·54 (0·35–0·84)	0·0054	0·63 (0·41–0·96)	0·032
All vascular amputations	11 (<1%)	17 (1%)	28 (1%)	0·40 (0·20–0·79)	0·0069	0·61 (0·33–1·11)	0·10
Major amputation‡	5 (<1%)	8 (<1%)	17 (1%)	0·30 (0·11–0·80)	0·011	0·46 (0·20–1·08)	0·068
Major adverse limb event plus major amputation§	32 (1%)	40 (2%)	60 (2%)	0·54 (0·35–0·82)	0·0037	0·67 (0·45–1·00)	0·046
Key composite outcomes for PAD							
Cardiovascular death, stroke, myocardial infarction or major adverse limb event	155 (6%)	184 (7%)	222 (9%)	0·69 (0·56–0·85)	0·0004	0·83 (0·68–1·01)	0·065
Cardiovascular death, stroke, myocardial infarction or major adverse limb event including major amputation	157 (6%)	188 (8%)	225 (9%)	0·69 (0·56–0·85)	0·0003	0·84 (0·69–1·02)	0·077

Anand SS et al. Lancet 2018; 391: 219–29

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Xa Inhibitor Rivaroxaban for 2ry Prevention

- The combination of low-dose Rivaroxaban + low dose ASA reduced adverse ischemic outcomes including death, stroke, MI and amputations.
- The relative reduction in vascular amputations for those with PAD was striking, but the absolute event rates were low
- There is a significant increase in risk of major bleeding
    - 1% absolute and 66% relative increase in bleeding
    - Mostly GI, not ICH
- In the CAD cohort ---> significant reduction in cv death & stroke
- In the PAD cohort ---> significant reduction in amputations in addition to cv death and stroke

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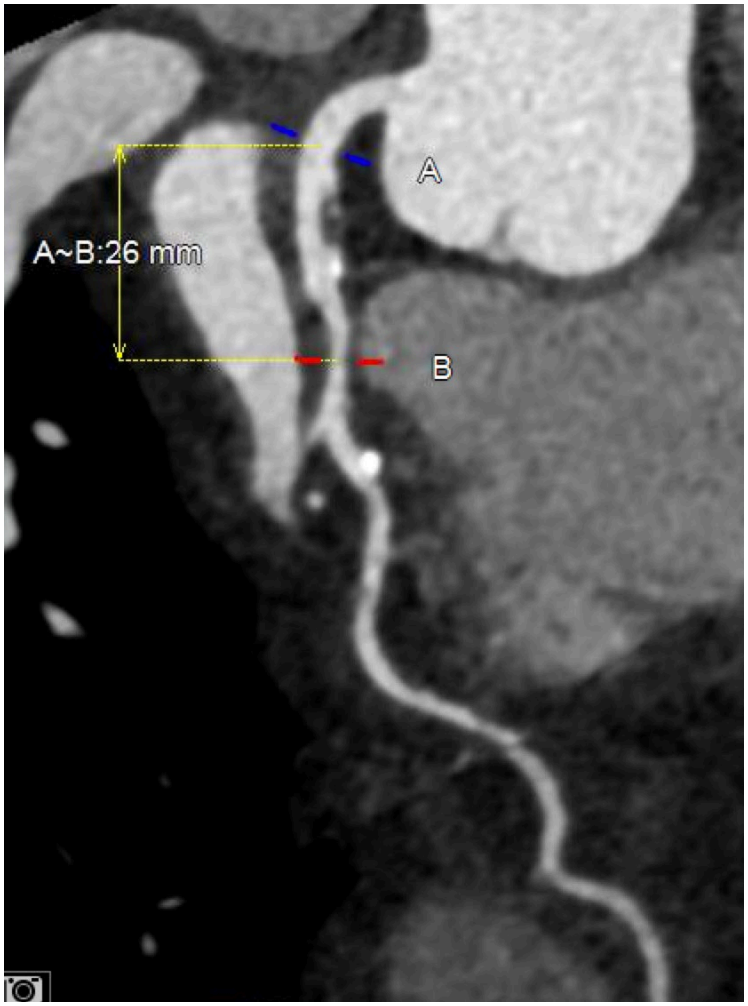
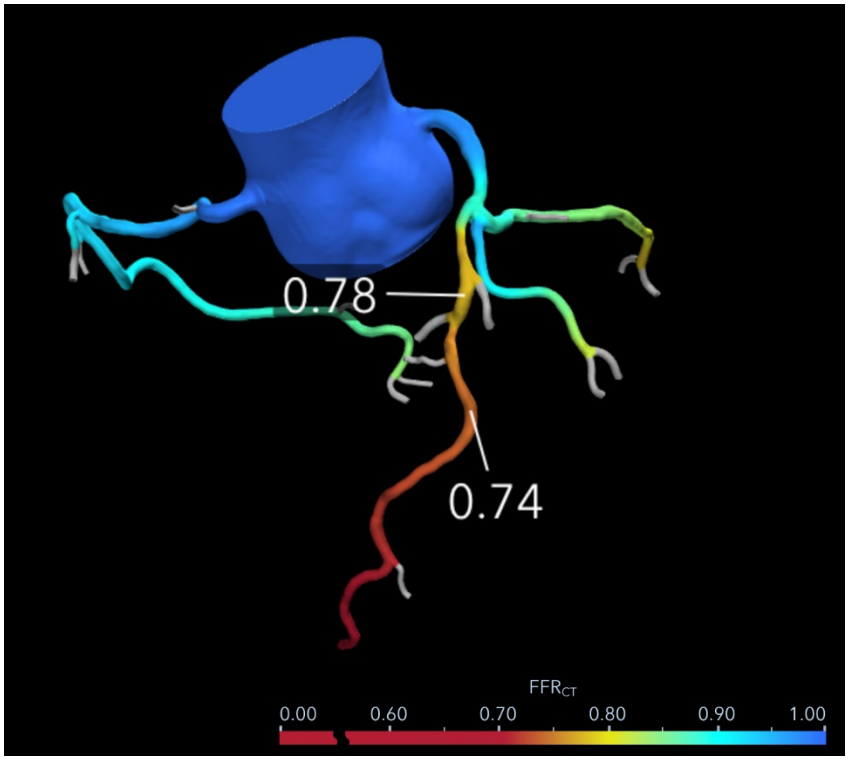
Diagnostic Coronary Imaging – CTA and CTFFR for Myocardial Ischemia Workup





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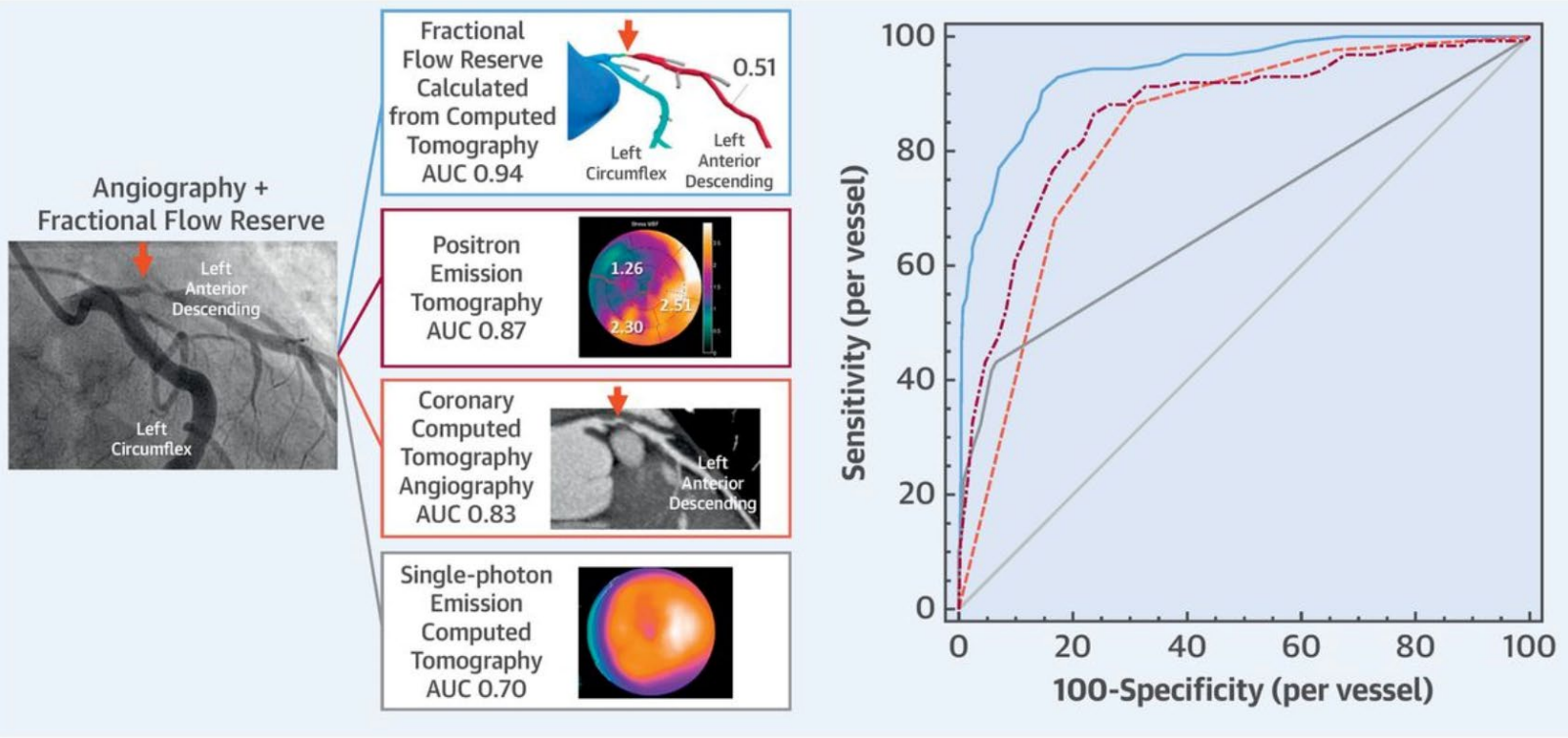
Diagnostic Coronary Imaging – CTA and CTFFR

- Post-hoc analysis of the PACIFIC Trial – 505 of 612 (83%) vessels
- Invasive FFR <0.80 as the gold standard for ischemia



Driessen RS et al. J Am Coll Cardiol 2019

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Diagnostic Coronary Imaging – CTA and CTFFR

- Improved diagnostic accuracy over routinely used tests, leading to better triage in and out of the catheterization laboratory
- Currently the first line test recommended in the United Kingdom for ischemia work up. Gill and UK ED are implementing an optimal care pathway for triaging CP patients based on CTA and HsTn. The PRECISE trial can expand that approach across the US
- Requires comprehensive logistic programming and individual expertise (physician readers and technical staff)
- High quality scans may not be feasible in 10-15% of cases
- Not recommended in
    - Heavily calcified arteries
    - Previous stenting
    - Renal insufficiency
- <u>CCTA and CTFFR are the future – SYNTAX III Trial will be pivotal</u>

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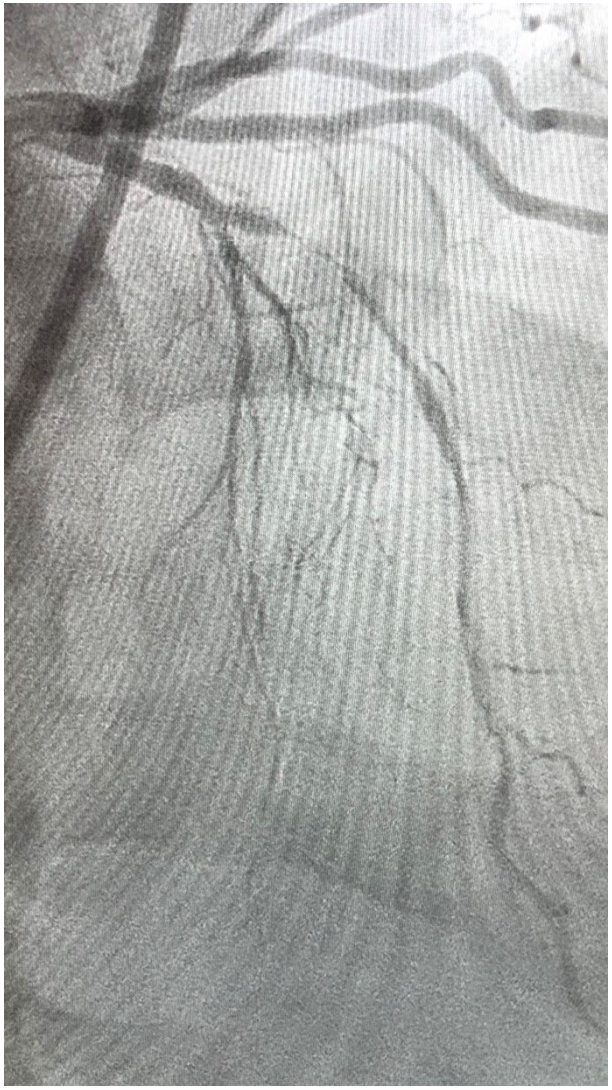
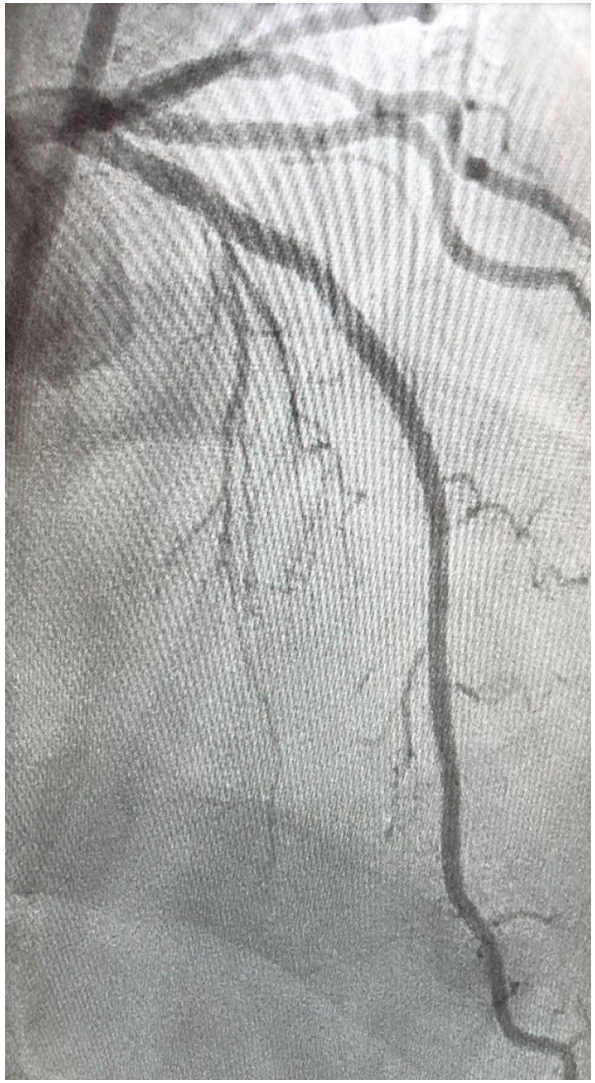
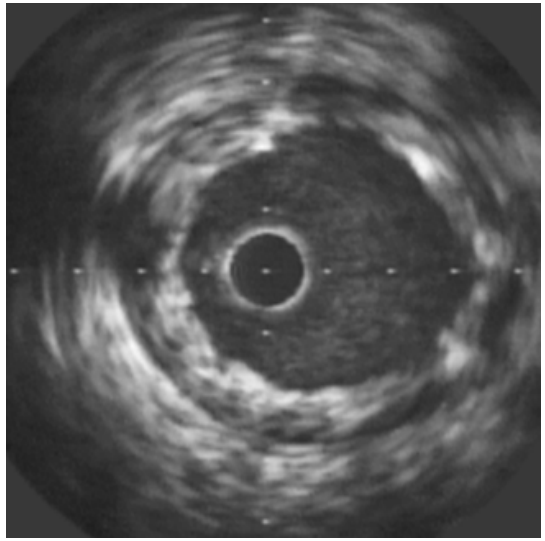
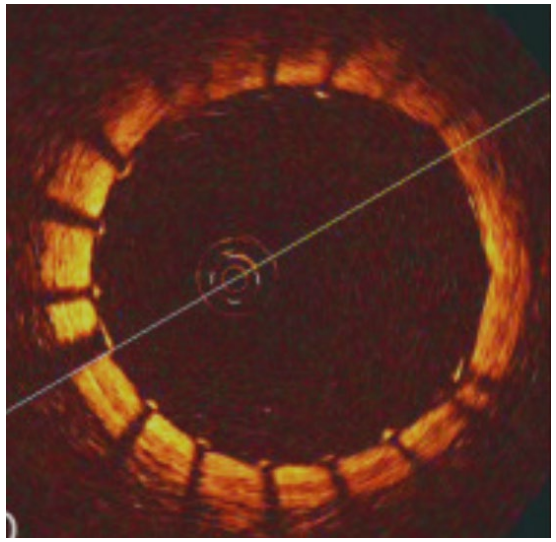
Anti-Platelet Therapy Following Coronary Stenting





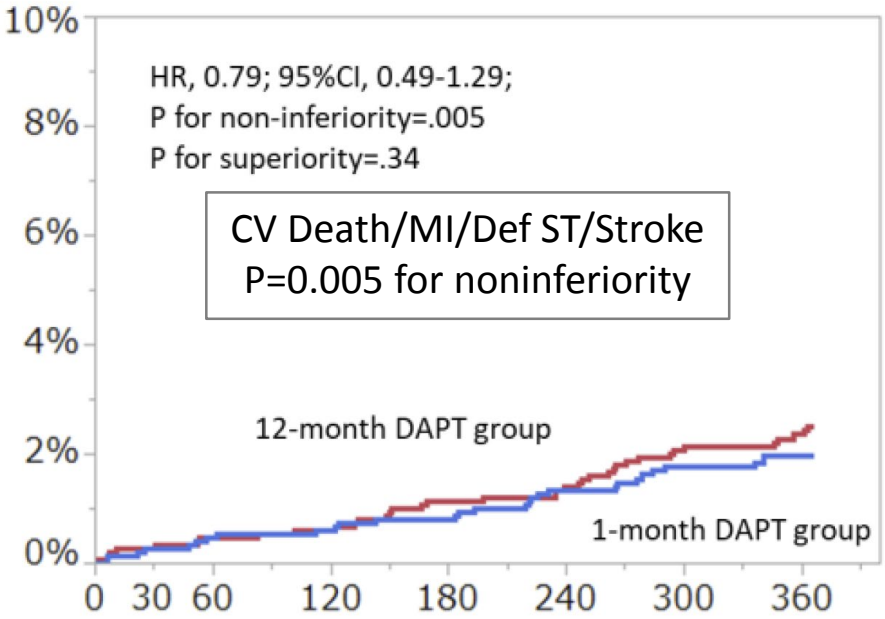


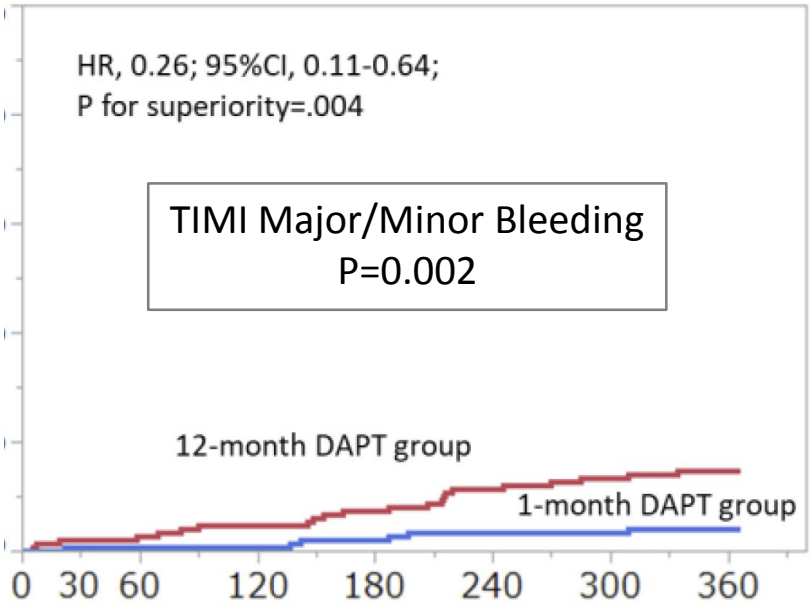


Anti-Platelet Therapy Following Coronary Stenting- ASA Discontinuation

STOP-DAPT-2 Trial

- 3009 pts undergoing stenting using everolimus-eluting stent
- 1:1 randomized to DAPT x 12 mons or DAPT x 1 mon followed by clopidogrel therapy (ASA discontinuation)
- Primary endpoint: CV death/MI/Def ST/Stroke/TIMI bleeding





Watanabe H et al. ACC March 2019

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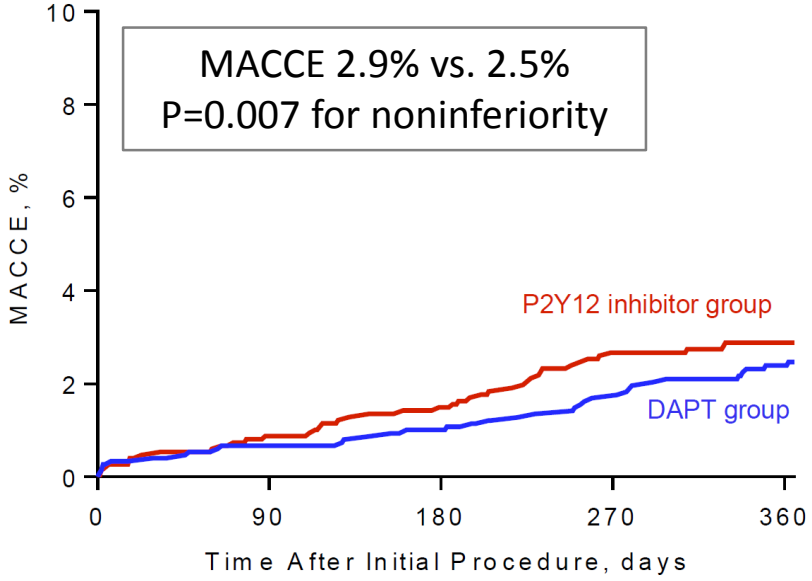
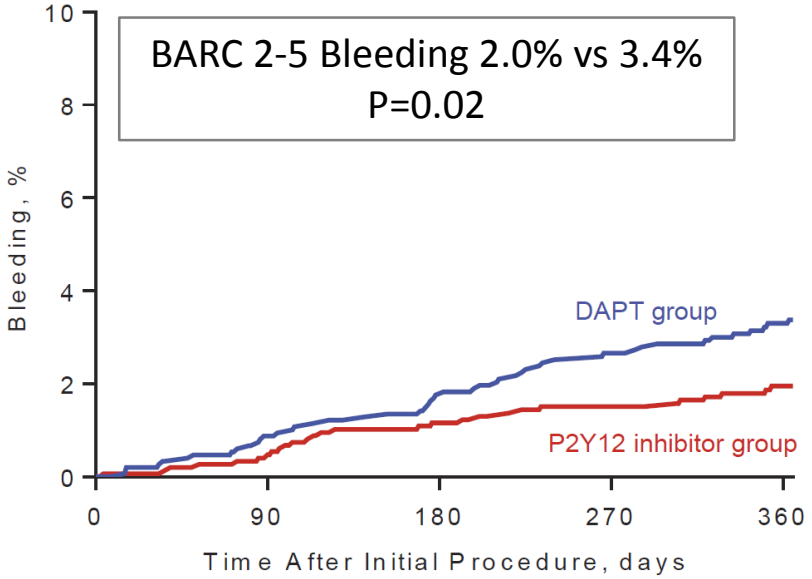
Anti-Platelet Therapy Following Coronary Stenting- ASA Discontinuation

SMART CHOICE Trial





- 2993 pts undergoing stenting using current generation DES
- 1:1 randomized to DAPT x 12 mons or DAPT x 3 mon followed by clopidogrel therapy (ASA discontinuation)
- Primary endpoint: MACCE at 12 months, BARC bleeding for safety

Hahn JY et al. ACC March 2019

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Anti-Platelet Therapy Following Coronary Stenting- ASA Discontinuation

- Early discontinuation of DAPT has not been advocated due to fear of stent thrombosis and other ischemic events
- Second and third generation stents are much safer before, hence risk of thrombosis is dramatically lower – consistently under 0.5-0.7%
- Shorter DAPT regimens followed by P2Y12 inhibitor monotherapy can reduce bleeding without compromising ischemic events
- However, it is important to identify patients who are eligible for these regimens – both SMART CHOICE and STOP-DAPT may have selected lower risk patients and results may not be generalizable
- TWILIGHT is a larger study that focuses on higher risk patients and will hopefully answer the question regarding safety of short DAPT regimens and early discontinuation of ASA

Lipid Lowering Therapy: Beyond Statins

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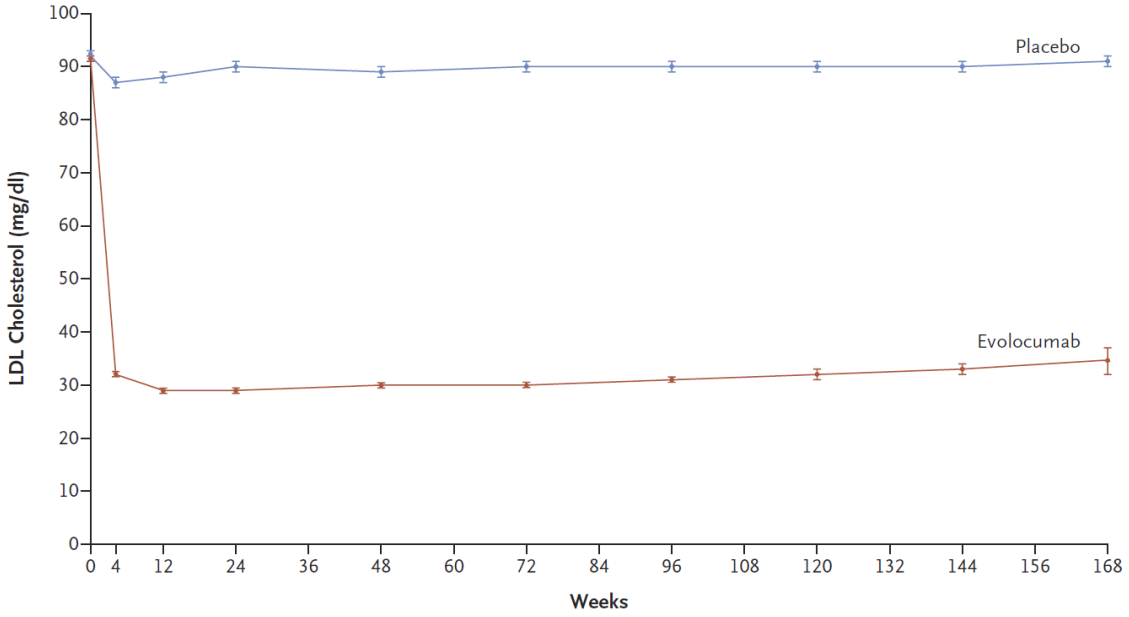
PCSK9 Inhibitors Effectively Lower LDL-C



- Reduction of LDL-C up to ~60% lower than in statin treated patients
- Absolute LDL-C levels down to 20-30 mg/dL
- Sustained effect over several years of therapy

Sabatine MS et al. N Engl J Med. 2017;376:1713-1722.

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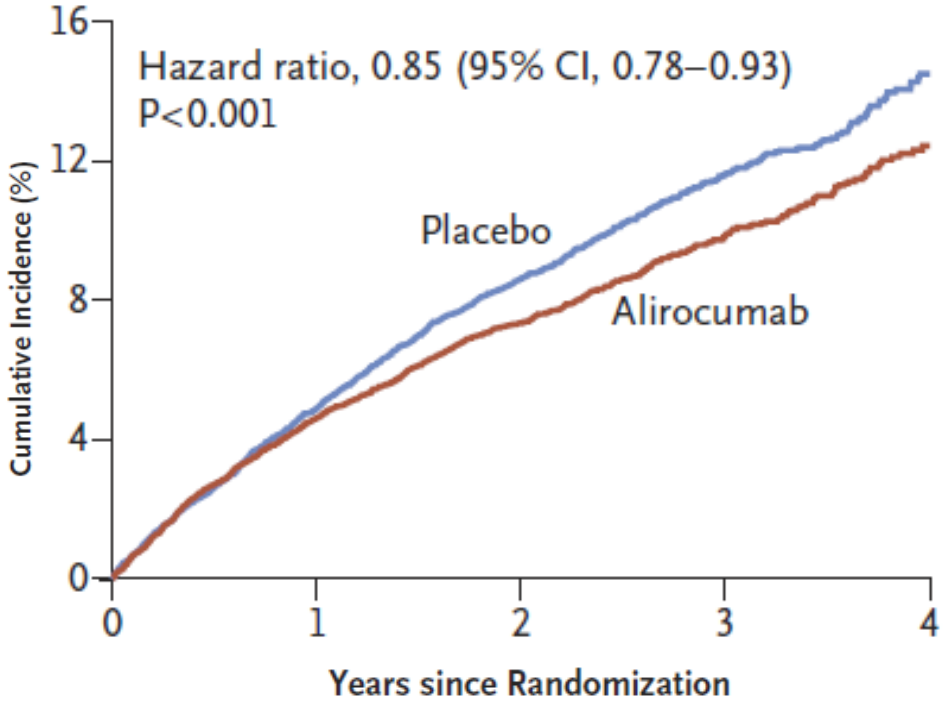
Improved Clinical Outcomes with PSCK9 Inhibitors:

The ODYSSEY OUTCOMES Trial

- Randomized double blinded trial of ~19,000 pts with h/o ACS within 1-12 months
- All on statin therapy, but LDL >70mg/dL
- Aliroocumab vs. placebo injections q 2 weeks, with blinded dose adjustment
- Primary composite efficacy endpoint: cardiovascular death, stroke, myocardial infarction or hospitalization due to UA
- Median duration of follow up was 2.8 years



Schwartz GG et al. N Engl J Med. 2018;379:2097-2107.

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2018 Cholesterol Management Guidelines Update

In very high-risk ASCVD, use a LDL-C threshold of 70 mg/dL to consider addition of non-statins to statin therapy.

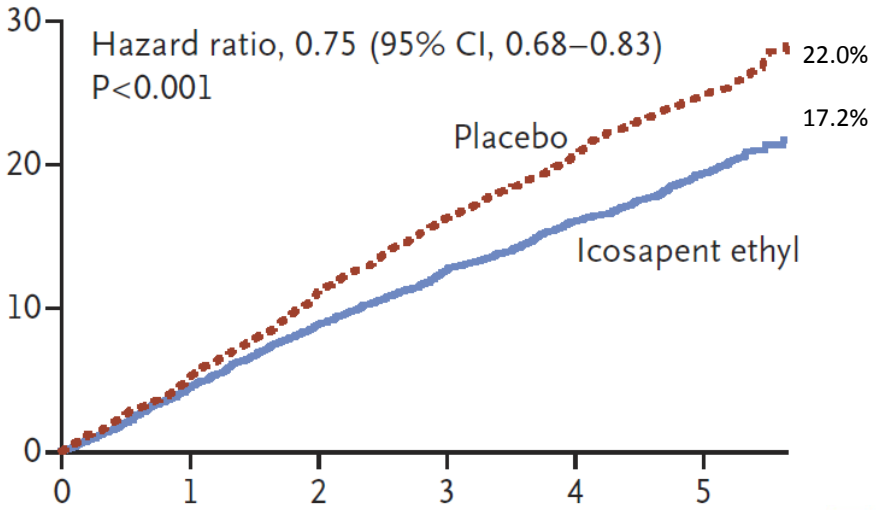
- Very high-risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions.
- In very high-risk ASCVD patients, it is reasonable to add ezetimibe to maximally tolerated statin therapy when the LDL-C level remains ≥70 mg/dL.
- In patients at very high risk whose LDL-C level remains ≥70 mg/dL on maximally tolerated statin and ezetimibe therapy, adding a PCSK9 inhibitor is reasonable, although the long-term safety (>3 years) is uncertain and cost- effectiveness is low at mid-2018 list prices.

Grundy SM et al.2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol. J Am Coll Cardiol 2018. https://doi.org/10.1016/j.jacc.2018.11.003.

Lipid Lowering Therapy: Beyond Statins

The REDUCE-IT Trial

- >8000 patients with established CVD or DM+Risk factors who are on statin therapy and have hypertriglyceridemia
- 1:1 Randomization to Icosapent Ethyl 2g bid or mineral oil matching placebo
- Primary endpoint: CV death, MI, stroke, coronary revascularization
- CV death was significantly reduced (4.3% vs. 5.2%, p= 0.03)
- Afib was more common (3.1% vs. 2.1%, p= 0.004)



Bhatt DL et al. N Engl J Med 2019;380:11-22

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Lipid Lowering Therapy: Beyond Statins

- Statins will continue to be the mainstay for lipid lowering and risk reduction, but the field is expanding in new directions
- PCSK9 inhibitors are effective and possibly more effective, but issues remain, primarily cost and safety
- N-3 fatty acid products have been tested before without success, but REDUCE-IT provides evidence for clear CV benefit
- The difference maybe in the proprietary product, the dose or patient selection. The mechanism of action remains unclear and the effect of mineral oil placebo has been difficult to understand
- More studies are on the way with other n-3 fatty acid products, hoping to answer some of the questions

Many More Trials In Other Areas of CV Medicine

- New TAVR devices
- New Mitral regurgitation devices and valves
- New LAA Occluders
- Resistant hypertension
- Triple vs. Dual antithrombotic therapy
- Pulmonary Hypertension
- Pulmonary Embolism
- Peripheral Arterial Interventions

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Conclusions

- Several novel concepts and disruptive technologies are shaping up to change the practice of CV medicine.
- The interventional approaches to structural heart disease are maturing and encroaching on what has traditionally been surgical domain – stay tuned for TMVR
- Fast paced advances in diagnostic imaging over last 10 years are beginning to impact daily practice – reducing cath, earlier d/c from ED
- Novel applications of anti-thrombotics and anti-platelet regimen integrated with more advanced coronary devices and techniques are shown to improve outcomes
- Lipid lowering is no longer synonymous with statin therapy. Newer agents are proving themselves in well conducted trials

Thank You

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