Baptist Health
HEART INSTITUTE

What's New in Cardiac Pharmacology in 2019

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Disclosures: None

Review

- 2016:
  - NOACs/NVKAs
  - P2Y12 Inhibitors
  - Neprilysin Inhibitors
  - PCSK9 Inhibitors
  - If (Funny) Current Inhibitors
- 2017
  - Beta blockers
  - Statins
  - DAPT
- 2018
  - Statins
  - Triglyceride Rx
- 2019
  - Review of new data on existing drugs
  - Brief overview of drugs on the horizon

Selected Drugs

- Existing drugs:
  - Aspirin
  - NOACs
  - PCSK9 Inhibitors
  - SGLT-2 Inhibitors
- New Agents:
  - siRNA for HLD
  - Anti-inflammatory agents for ASCVD
  - CCB for SVT
  - Tafamidis for TTR Amyolid

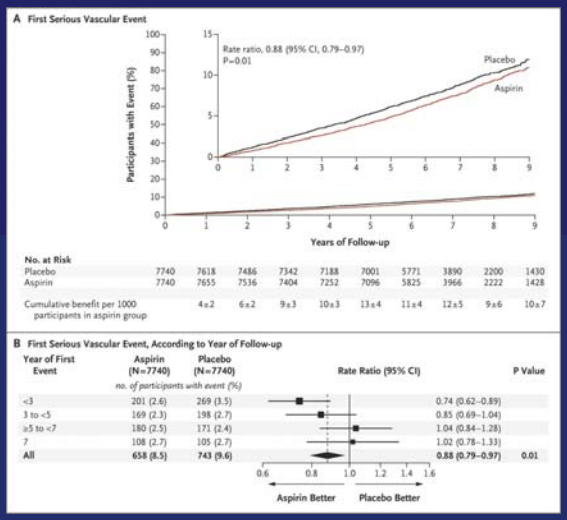
ASA for Primary Prevention

- Benefits of ASA for Secondary Prevention are incontrovertible
- 3 recent Primary Prevention Trials
  - ASCEND – Diabetes without CVD
  - ASPREE – Healthy Elderly
  - ARRIVE – Nondiabetics with Moderate Risk

ASCEND Trial

- 15,480 Diabetics but NO overt CVD
- ASA (100mg/d) vs. Placebo; Mean F/U ~7.4 yrs
- Primary Endpoint – MI, CVA, TIA or Vasc Death
  - 8.5% ASA vs. 9.6% Placebo - HR 0.88
- Safety – Major Bleeding
  - 4.1% ASA vs. 3.2% placebo – HR 1.29
- Interpretation: 12% lower risk of events at the expense of 29% higher risk of bleeding (few PPI's)

ASCEND
First Serious Vascular Event during Follow-up.



The ASCEND Study Collaborative Group. N Engl J Med 2018;379:1529-1539.

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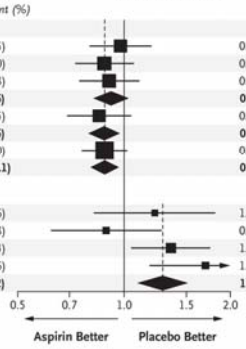
ASCEND
Effect of Aspirin vs. Placebo on Serious Vascular Events

Type of Event	Aspirin (N=7740)	Placebo (N=7740)	Rate Ratio (95% CI)	P Value
	no. of participants with event (%)			
Vascular Outcomes				
Nonfatal myocardial infarction	191 (2.5)	195 (2.5)	0.98 (0.80–1.19)	
Nonfatal presumed ischemic stroke	202 (2.6)	229 (3.0)	0.88 (0.73–1.06)	
Vascular death excluding intracranial hemorrhage	197 (2.5)	217 (2.8)	0.91 (0.75–1.10)	
Any serious vascular event excluding TIA	**542 (7.0)**	**587 (7.6)**	**0.92 (0.82–1.03)**	
TIA	168 (2.2)	197 (2.5)	0.85 (0.69–1.04)	
Any serious vascular event including TIA	**658 (8.5)**	**743 (9.6)**	**0.88 (0.79–0.97)**	**0.01**
Any arterial revascularization	340 (4.4)	384 (5.0)	0.88 (0.76–1.02)	
Any serious vascular event or revascularization	**833 (10.8)**	**936 (12.1)**	**0.88 (0.80–0.97)**	
Major Bleeding				
Intracranial hemorrhage	55 (0.7)	45 (0.6)	1.22 (0.82–1.81)	
Sight-threatening bleeding in eye	57 (0.7)	64 (0.8)	0.89 (0.62–1.27)	
Serious gastrointestinal bleeding	137 (1.8)	101 (1.3)	1.36 (1.05–1.75)	
Other major bleeding	74 (1.0)	43 (0.6)	1.70 (1.18–2.44)	
Any major bleeding	**314 (4.1)**	**245 (3.2)**	**1.29 (1.09–1.52)**	**0.003**



The ASCEND Study Collaborative Group. N Engl J Med 2018;379:1529-1539.

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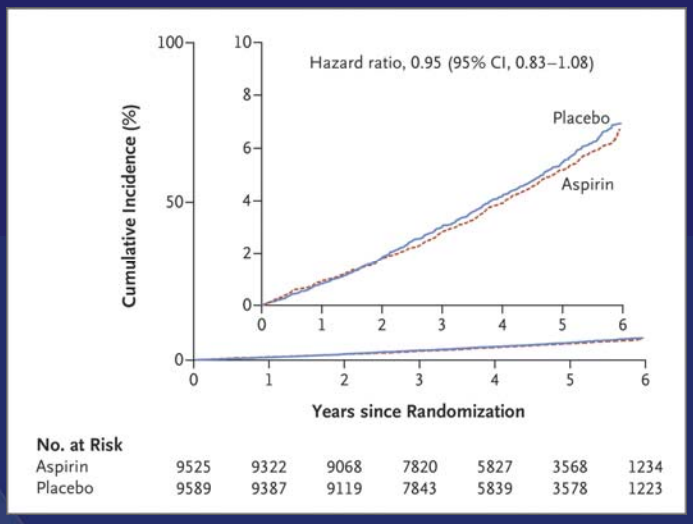
ASPREE Trial

- 19,114 "Healthy" Elderly (mean age 74):
  - No CVD, Dementia or Disability
    - EC-ASA 100mg/day vs. Placebo
    - Mean follow up ~4.7 years
- Endpoints
  - 1^0: Death, Dementia, Physical Disability
  - 2^0: Hemorrhage and CVD (Fatal CHD, Non-fatal MI, CVA or CHF)
- Results
  - CV Disease: 10.7% vs. 11.3% per 1000 person-years (HR 0.95)
  - Bleeding 8.6% vs. 6.2% per 1000 person-years (HR 1.38)
- Interpretation: Higher bleeding risk (38%) without significantly reduced risk (5%) of cardiovascular disease

ASPREE
Cumulative Incidence of Cardiovascular Disease.



JJ McNeil et al. N Engl J Med 2018;379:1509-1518.

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ARRIVE trial

- 12,546 Moderate Risk patients
  - Median age 64
  - No prior clinical CVD
  - ≥3 CV risk factors, 10-year ASCVD risk 10-20%, mean 17%.
  - 100 mg ASA/day vs. Placebo, median f/u 60 mos.
- Outcomes: ASA vs. Placebo
  - 1^0 – Combined risk of CV Death, MI, USA, CVA or TIA
    - 4.3% vs. 4.5%
  - 2^0 - Individual risks of MI (1.4% vs. 1.6%) and CVA (1.2% vs. 1.1%)
  - Safety outcomes: GI Bleeding
    - 0.97% ASA vs. 0.46% Placebo (p=0.0007)
- Interpretation
  - Use of ASA for primary prevention in moderate risk patients not beneficial
  - Low event rate in the era of Statins, decreased smoking, etc.

NOAC
ASCVD Prevention

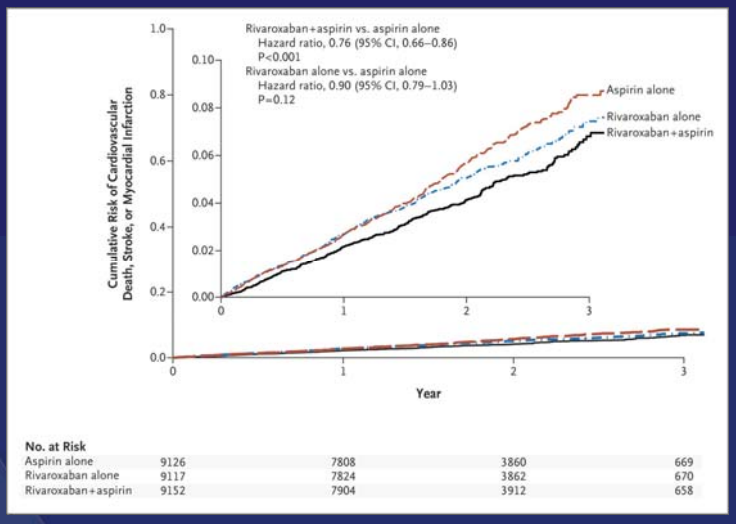
- Stable CVD
  - COMPASS Trial
- Unstable Angina
  - ATLAS ACS 2-TIMI 51 Trial
- CHF
  - COMMANDER HF Trial
- Post-op Myocardial Injury
  - MANAGE Trial

COMPASS Trial

Cardiovascular **O**utco**M**es for **P**eople Using **A**nticoagulation **S**trategie**S**

- 27,395 pts with Stable CVD
  - 3 treatment arms:
    - Rivaroxaban 2.5 mg BID + ASA 100 mg/d vs.
    - Rivaroxaban 5 mg BID vs.
    - ASA 100 mg/day
  - 1^0 outcome: composite of CV death/MI/CVA
  - Study stopped **prematurely @ 23 months**
    - Rivaroxaban 2.5 mg + ASA
      - Superior to ASA alone (4.1% vs. 5.4%; HR 0.76)
      - Major Bleeding worse (3.1% vs. 1.9%; HR 1.70)
    - Rivaroxaban 5 mg BID vs. ASA – no diff

COMPASS Trial - PRIMARY OUTCOME:
Rivaroxaban +ASA vs. Rivaroxaban Alone vs. Aspirin Alone.



Eikelboom JW et al. N Engl J Med 2017;377:1319-1330.

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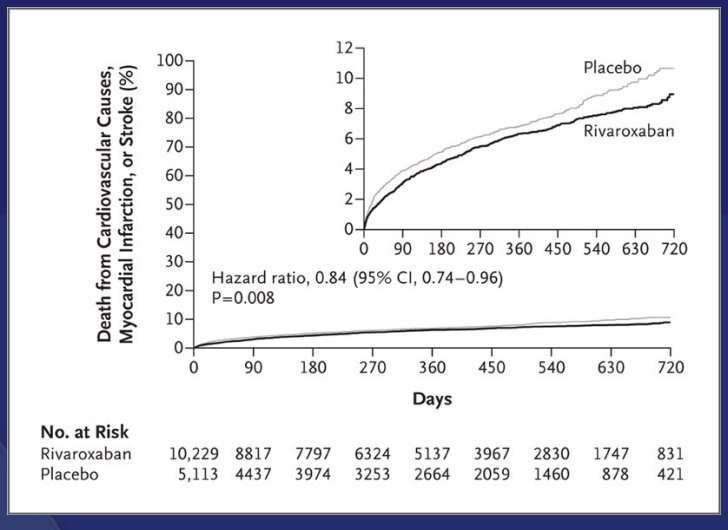
ATLAS ACS 2-TIMI 51 Trial

- 15,526 pts with recent ACS (≤ 7 days)
  - Rivaroxaban 2.5 mg BID vs. 5 mg BID vs. Placebo(>98% on ASA)
  - Results
    - 1^0 Endpoint – Composite of CV death, MI or CVA
      - Rivaroxaban vs. placebo – 8.9% vs. 10.7%; HR 0.84
      - 2.5 mg dose - 9.1%, 5 mg dose - 8.8%, placebo - 10.7%
    - 2.5 mg dose superior to placebo for
      - CV Death: 2.7% vs. 4.1% and Total Mortality 2.9% vs. 4.5%
    - 5 mg dose - no survival benefit (> fatal bleeding than 2.5 mg or placebo)
    - Major Bleeding
      - Rivaroxaban 2.1% vs. Placebo 0.6%
- Conclusions:
  - In patients with recent ACS, rivaroxaban reduced the risk of CV Death, MI and CVA at the expense of major and intracranial but not fatal bleeding

ATLAS ACS 2-TIMI 51 Trial: Cumulative Incidence of the Primary End Point



Mega JL et al. N Engl J Med 2012;366:9-19.

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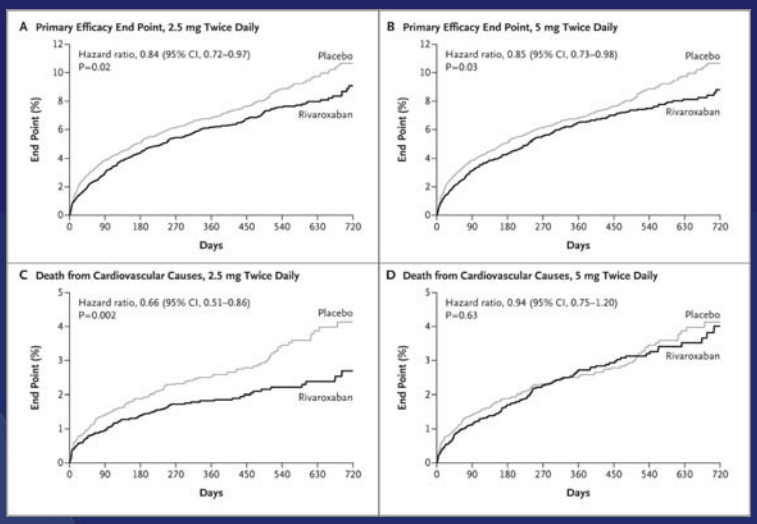
ATLAS ACS 2-TIMI 51 Trial: Dose-related cumulative Incidence of Efficacy End Points



Mega JL et al. N Engl J Med 2012;366:9-19.

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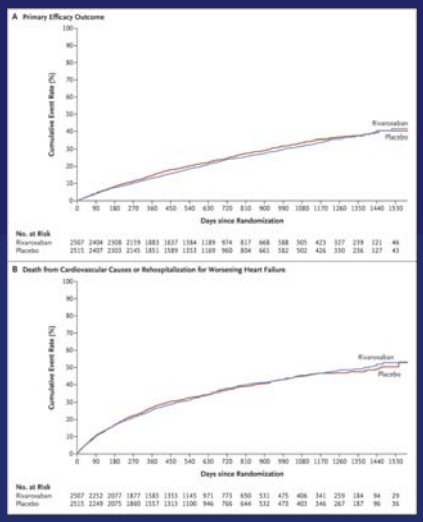
COMMANDER HF Trial

- 5022 pts with chronic CHF and a recent exacerbation
  - EF <40%, known CAD, elevated BNP, no Atrial Fibrillation,
  - Rivaroxaban 2.5 mg BID vs. Placebo + standard of care GDMT followed for ~21 mos
- Results:
  - 1^0 Endpoint – composite of Death/MI/CVA
    - Rivaroxaban 25% vs. Placebo 26% (p=0.27)
  - 1^0 Safety – fatal or disabling nonfatal bleeding
    - No significant difference
- Conclusions
  - No benefit of rivaroxaban in this patient population

COMMANDER HF Trial: Primary Efficacy Outcomes



F Zannad et al. N Engl J Med 2018;379:1332-1342.

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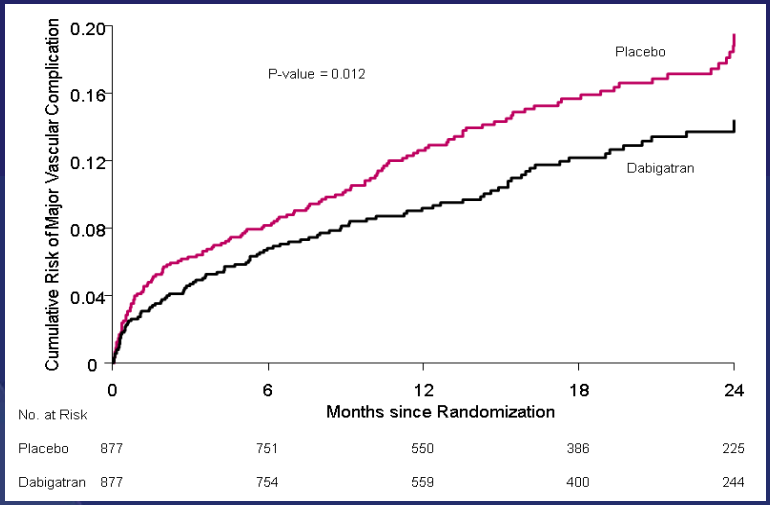
MANAGE Trial

- Myocardial Injury after Non-cardiac Surgery (MINS)
  - Carries an increased risk of CV Events and Death
- MANAGE Trial: 1754 patients ≤ 35 days following MINS
- Randomized to dabigatran 110 mg BID vs. Placebo for up to 2 years
- 1^0 Endpoint – Major Vascular Complication – defined as a composite of vascular mortality, non-fatal MI, non-hemorrhagic CVA, peripheral arterial thrombosis, amputation and symptomatic DVT
- RESULTS:
  - Dabigatran 11% vs Placebo 15% (HR 0.72)
- CONCLUSIONS – among patients with MINS, dabigatran 110 mg BID lowered the risk of Major Vascular Complications without increased bleeding.

MANAGE Trial
Primary Endpoint



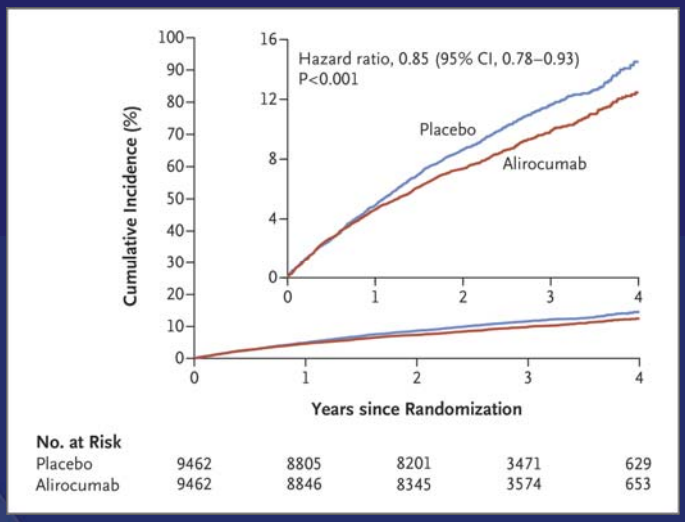
NOAC ASCVD Prevention
SUMMARY

- Low dose rivaroxaban + ASA lowers CV risk in **Stable ASCVD** patients
- Low dose rivaroxaban lowers CV risk in patients with **Recent ACS**
- Low dose rivaroxaban does not lower CV risk in patients with **Stable CHF**
- Dabigatran lowers CV risk in patients with recent **MINS**

PCSK9 Inhibitors: ODYSSEY OUTCOMES Trial

- **Odyssey Trial**: PCSK9 Inhibitors reduce LDL and CV Events in stable patients with Hyperlipidemia not controlled on HIST (High Intensity Statin Therapy)
- **Odyssey Outcomes Trial** (18,924 pts)
  - ACS 1-12 mos prior, already on HIST, LDL ≥ 70, randomized to alirocumab 75 mg q 2 wks vs. placebo. Mean f/u 2.8 yrs
- 1^0 Endpoint – Composite of CHD Death, NFMI, Ischemic CVA or USA
  - Alirocumab 9.5% vs. Placebo 11.1%; HR 0.85
- Death alone
  - Alirocumab 3.5% vs. Placebo 4.1%; HR 0.85
- Conclusions – In patients with recent ACS on maximally-tolerated HIST and LDL ≥ 70, treatment with alirocumab lowered the risk of recurrent ischemic CV Events and Total Mortality

Cumulative Incidence of the Composite Primary End Point.



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

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Novel Treatment of Hyperlipidemia: Small Interfering RNA (siRNA)

- Background
  - PCSK9 degrades LDL receptors
  - Inhibition of PCSK9 increases LDL receptor expression and hence LDL clearance
  - Alirocumab & Evolocumab are monoclonal antibodies directed towards PCSK9, dramatically lower LDL and improve outcomes

Novel Treatment of Hyperlipidemia: Small Interfering RNA (siRNA)

- RNA Interference and RNA Silencing Pathways provide a mechanism to regulate gene expression
- siRNA Selectively and Catalytically silence the Translation of their target mRNAs in a sequence-specific manner through the formation of Effector RNA Silencing Complexes
- Inclisiran is a synthetic siRNA that has produced sustained hepatocyte-specific, PCSK9-specific RNA silencing in healthy volunteers

ORION-1 Trial

- Phase 2, Multicenter, DBPC, Ascending Dose trial of SQ inclisiran in patients with elevated LDL at high risk for CVD
- Single Doses (200, 300, 500 mg)
- Two Doses (100, 200, 300 mg @ days 1 & 90)
- 1^0 Endpoint - Δ LDL @ 180 days; data on PCSK9 levels also available.

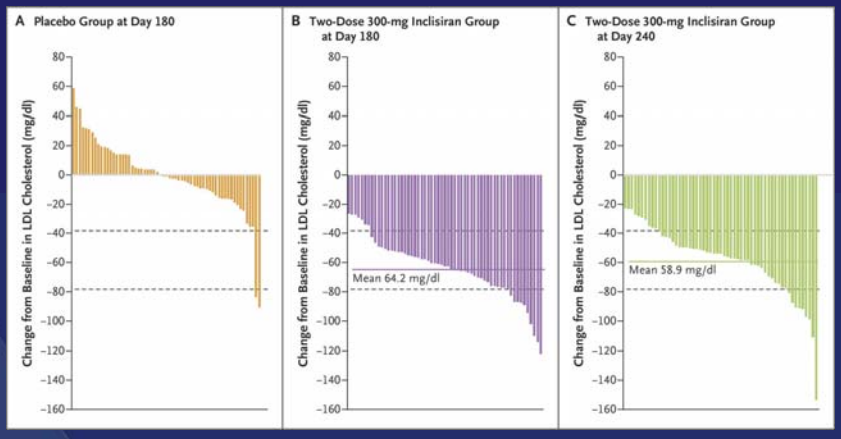
ORION-1 Trial Results

- Mean LDL reduction:
  - Single doses
    - Mean 27.9-41.9%, nadir 60 days
  - Two doses
    - Mean 35.5 – 52.6%, nadir 150 days
    - Maximum reduction was with two 300 mg doses – 48% of patients had LDL<50 mg/dl
  - Benefit was durable through 240 days (28.2-36.6%)
- Maximum PCSK9 level reduction was 66.2-74% and was durable through 240 days
- SAEs – 11% drug, 8% placebo

ORION-1 Trial Results

- Conclusions: In patients on maximally tolerated statin therapy, inclisiran injected either once or twice 90 days apart substantially lowers LDL and PCSK9 levels. The effect is durable at 180 days and partially persists through 240 days
- Phase III trial (300 mg on Day-1 and Day-90 then q6 mos)
  - 1^0 endpoint LDL-C , 2^0 endpoints other atherogenic proteins.
  - Expected results in the second half of 2019.

ORION-1 Trial
Changes in LDL Cholesterol Levels



Ray KK et al. N Engl J Med 2017;376:1430-1440.

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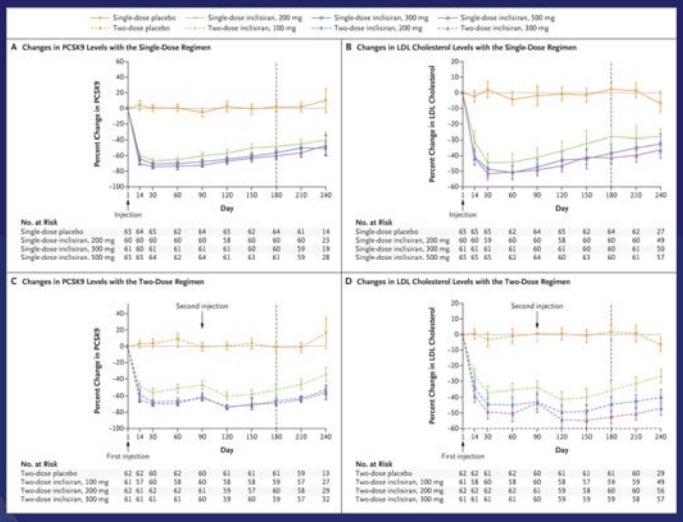
Effect of Inclisiran on PCSK9 and Low-Density Lipoprotein (LDL) Cholesterol Levels.



Ray KK et al. N Engl J Med 2017;376:1430-1440.

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Anti-inflammatory Therapy for ASCVD

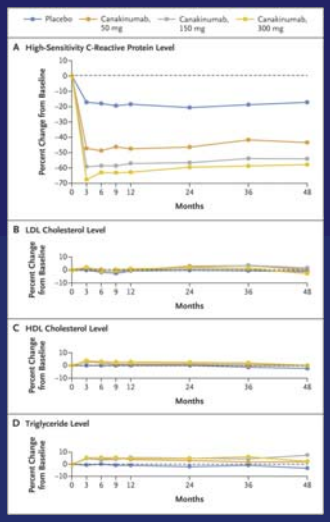
- Experimental data suggest reducing inflammation without lowering lipid levels may reduce ASCVD risk
- CRP and IL-6 are associated with an increased risk of CV events, unrelated to lipid levels
- Interleukin-1β is a cytokine that drives IL-6 signaling
- Canakinumab is a monoclonal antibody targeting Interleukin- 1β approved for use in rheumatologic disorders
- Interleukin- 1β inhibition with canakinumab has been shown to lower CRP and IL-6 unrelated to LDL levels

CANTOS Trial

Canakinumab **AN**ti-inflammatory **T**hrombosis **O**utcome **S**tudy

- Randomized, DBPC trial of 10,061 patients with prior MI and elevated hsCRP
- 3 doses Canakinumab (50mg, 150 mg, 300 mg) SQ every 3 months vs. placebo
- Endpoints (median f/u 3.7 yrs) :
  - 1^0 - Nonfatal MI, nonfatal CVA or CV Death
  - 2^0 – 1^0 endpoint plus Hospitalization for USA with urgent revascularization
- Results
  - Placebo - 4.5 events/100 person-years
  - Canakinumab
    - 50 mg - 4.1 events/100 person-years (HR - 0.93)
    - 150mg – 3.86 events/100 person-years (HR – 0.85)
    - 300 mg – 3.90 events/100 person-years (HR – 0.86)
    - Secondary endpoint only significant with 150 mg dose
- Higher risk of fatal infection; no difference in All-Cause mortality

Effects of Canakinumab, as Compared with Placebo, on Plasma Levels of High-Sensitivity C-Reactive Protein, Low-Density Lipoprotein (LDL) Cholesterol, High-Density Lipoprotein (HDL) Cholesterol, and Triglycerides.



Ridker PM et al. N Engl J Med 2017;377:1119-1131.

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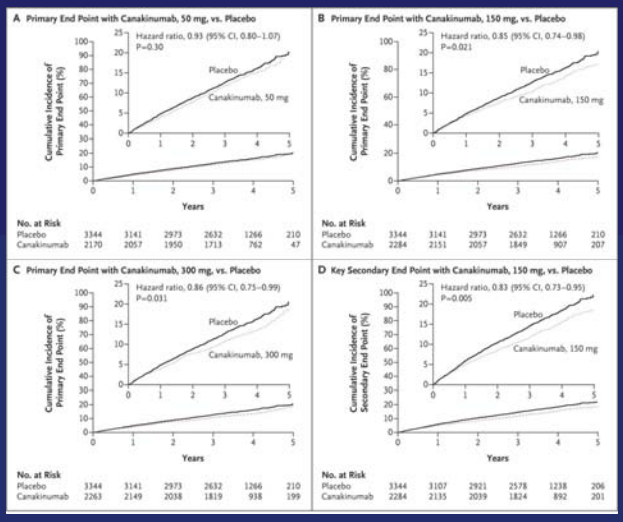
Cumulative Incidence of the Primary End Point and the Key Secondary Cardiovascular End Point.



Ridker PM et al. N Engl J Med 2017;377:1119-1131.

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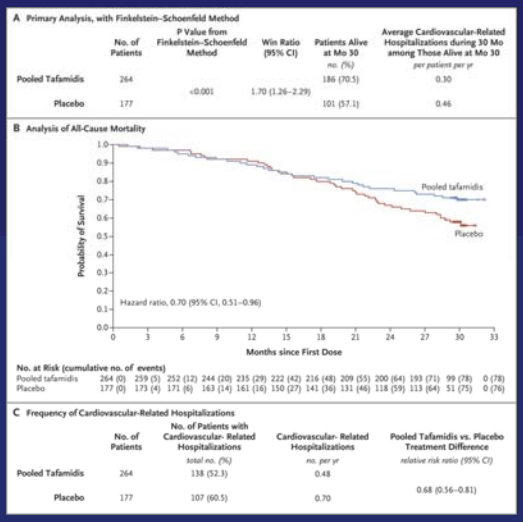
Tafamidis for TTR Amyloid Cardiomyopathy

- Transthyretin amyloid cardiomyopathy is caused by the deposition of transthyretin amyloid fibrils in the myocardium. The deposition occurs when wild-type or variant transthyretin becomes unstable and misfolds. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis.
- Prevalence uncertain
  - 13% pts with HFpEF
  - 16% pts undergoing TAVR
  - 5% pts with presumed HCM
- Median Survival 2.5-3.6 yrs after diagnosis

ATTR-ACT Study

- Multicenter, DBPC, Phase 3 trial
- Tafamidis 80 mg vs. 20 mg vs. Placebo (30 months)
- Endpoints
  - Mortality 29.5% vs. 42.9% (HR 0.70)
  - CV-related hospitalizations (RR 0.68)
  - Functional Capacity/QOL
    - both better (p<0.001)

Primary Analysis and Components.



A Primary Analysis, with Finkelstein–Schoenfeld Method

	No. of Patients	P Value from Finkelstein–Schoenfeld Method	Win Ratio (95% CI)	Patients Alive at Mo 30 no. (%)	Average Cardiovascular-Related Hospitalizations during 30 Mo among Those Alive at Mo 30 per patient per yr
Pooled Tafamidis	264	<0.001	1.70 (1.26–2.29)	186 (70.5)	0.30
Placebo	177			101 (57.1)	0.46

B Analysis of All-Cause Mortality

No. at Risk (cumulative no. of events)

Pooled tafamidis	264 (0)	259 (5)	252 (12)	244 (20)	235 (29)	222 (42)	216 (48)	209 (55)	200 (64)	193 (71)	99 (78)	0 (78)
Placebo	177 (0)	173 (4)	171 (6)	163 (14)	161 (16)	150 (27)	141 (36)	131 (46)	118 (59)	113 (64)	51 (75)	0 (76)

C Frequency of Cardiovascular-Related Hospitalizations

	No. of Patients	No. of Patients with Cardiovascular- Related Hospitalizations total no. (%)	Cardiovascular- Related Hospitalizations no. per yr	Pooled Tafamidis vs. Placebo Treatment Difference relative risk ratio (95% CI)
Pooled Tafamidis	264	138 (52.3)	0.48	0.68 (0.56–0.81)
Placebo	177	107 (60.5)	0.70	

MS Maurer et al. N Engl J Med 2018;379:1007-1016.

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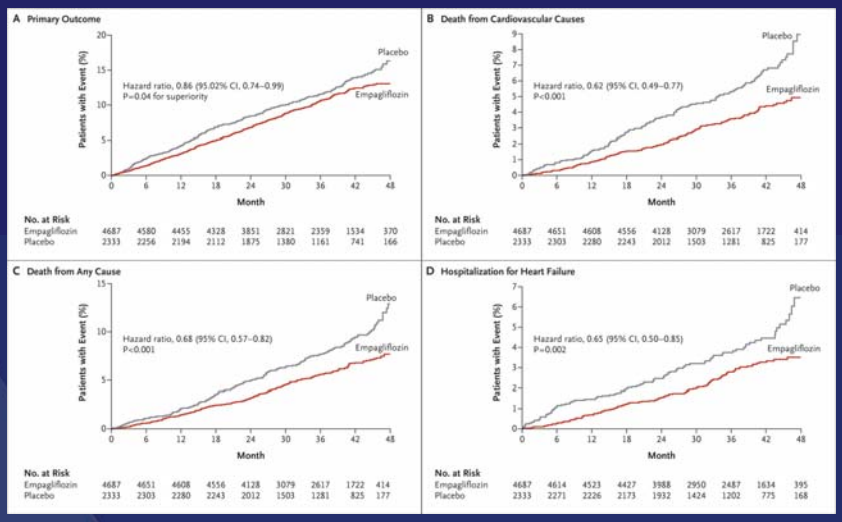
Etripamil Nasal Spray for Conversion of Supraventricluar Tachycardia

- No Non-parenteral medication for rapid termination of PSVT
- Etripamil nasal spray is a short-acting CCB
- 104 pts in EP lab, with SVT >5 min
  - Placebo vs. 4 different doses of Etripamil
  - 1^0 Endpoint – Conversion within 15 min
    - 35% placebo
    - 65-95% with drug
- Effective treatment needing further study

SGLT-2 Inhibitors

- Empagliflozin – Pts with Established CV disease
  - Lower risk of CVD, MI and CVA (HR 0.86)
- Canagliflozin – Pts with high CV risk
  - Lower risk of CVD, MI and CVA (HR 0.86)
- Dapagliflozin – known CVD or at risk
  - No difference
- All 3 agents were associated with a lower risk of hospitalization for CHF

Cardiovascular Outcomes and Death from Any Cause.



Zinman B et al. N Engl J Med 2015;373:2117-2128.

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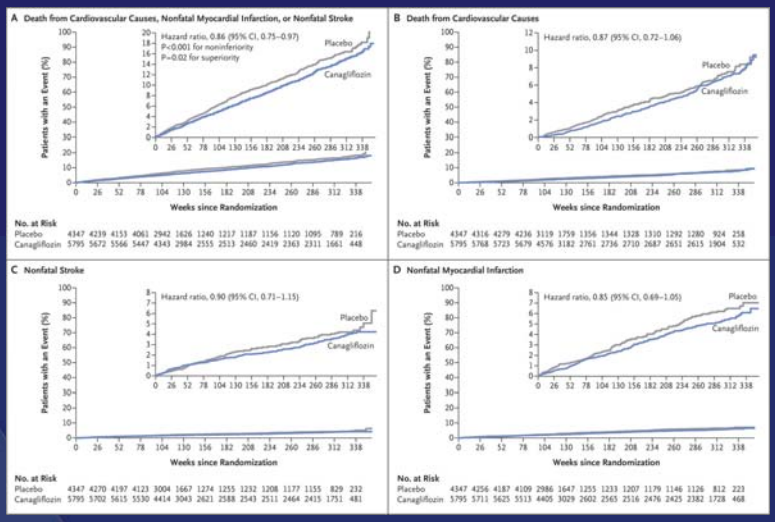
Cardiovascular Outcomes in the Integrated CANVAS Program.



Neal B et al. N Engl J Med 2017;377:644-657.

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SUMMARY

- New applications of existing medications
- Agents to watch for in the future
  - RNA interference
  - Anti-inflammatory therapy for ASCVD
  - Novel delivery systems
  - Novel treatments for untreatable diseases

Thank You!