Late Breaking Clinical Trials: 2019

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Wayne N. Leimbach, Jr. MD, FACC,

Clinical Associate Professor of Medicine
University of Oklahoma College of Medicine - Tulsa

Director of the Cardiac Catheterization Laboratories
Oklahoma Heart Institute at Hillcrest Medical Center

Medical Director of Cardiology
Oklahoma Heart Institute

Oklahoma Heart Institute

Late Breaking Clinical Trials

REDUCE – It Trial

The Value of Lowering Triglycerides with Icosapent Ethyl (Omega - 3 Fish Oils).

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Late Breaking Clinical Trials

reduce-it

Reduction in Total Ischemic Events in the Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial

Deepak L. Bhatt, MD, MPH, Ph. Gabriel Steg, MD, Michael Miller, MD, Eliot A. Brinton, MD, Terry A. Jacobson, MD, Steven B. Ketchum, PhD, Ralph T. Doyle, Jr., BA, Rebecca A. Juliano, PhD, Lixia Jiao, PhD, Craig Granowitz, MD, PhD, Jean-Claude Tardif, MD, John Gregson, PhD, Stuart J. Pocock, PhD, Christie M. Ballantyne, MD, on Behalf of the REDUCE-IT Investigators

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Is There Risk With LDL-C at Target But Triglycerides Elevated?

reduce-it

1. Age ≥45 years with established CVD (Secondary Prevention Cohort) *or* ≥50 years with diabetes with ≥1 additional risk factor for CVD (Primary Prevention Cohort)
2. Fasting TG levels ≥135 mg/dL and <500 mg/dL
3. LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

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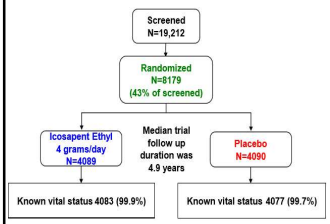
REDUCE-IT Design

reduce-it



LDL-C > 40 and < 100

Fasting TG >135 and < 500

Primary Endpoint Events: CV death, nonfatal MI, nonfatal stroke, coronary revasc, hospitalization for unstable angina

Key Secondary Endpoint Events: CV death, nonfatal MI, nonfatal stroke

Double-blind study; Events adjudicated by CEC that was blinded to treatment during adjudication

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22.

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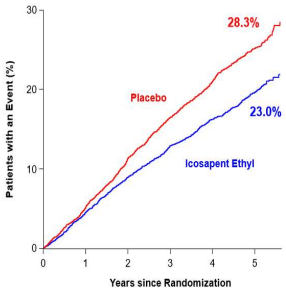
Primary End Point:
CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

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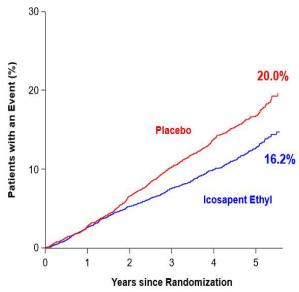
Key Secondary End Point:
CV Death, MI, Stroke



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

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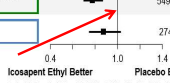
Prespecified Hierarchical Testing

Endpoint	Hazard Ratio (95% CI)	Icosapent Ethyl n/N (%)	Placebo n/N (%)	Hazard Ratio (95% CI)	RRR	P-value
Primary Composite (ITT)		705/4089 (17.2%)	901/4090 (22.0%)	0.75 (0.68–0.83)	25%▼	<0.001
Key Secondary Composite (ITT)		459/4089 (11.2%)	606/4090 (14.8%)	0.74 (0.65–0.83)	26%▼	<0.001
Cardiovascular Death or Nonfatal Myocardial Infarction		392/4089 (9.6%)	507/4090 (12.4%)	0.75 (0.66–0.86)	25%▼	<0.001
Fatal or Nonfatal Myocardial Infarction		250/4089 (6.1%)	355/4090 (8.7%)	0.69 (0.58–0.81)	31%▼	<0.001
Urgent or Emergent Revascularization		216/4089 (5.3%)	321/4090 (7.8%)	0.65 (0.55–0.78)	35%▼	<0.001
Cardiovascular Death		174/4089 (4.3%)	213/4090 (5.2%)	0.80 (0.66–0.98)	20%▼	0.03
Hospitalization for Unstable Angina		108/4089 (2.6%)	157/4090 (3.8%)	0.68 (0.53–0.87)	32%▼	0.002
Fatal or Nonfatal Stroke		98/4089 (2.4%)	134/4090 (3.3%)	0.72 (0.55–0.93)	28%▼	0.01
Total Mortality, Nonfatal Myocardial Infarction, or Nonfatal Stroke		549/4089 (13.4%)	690/4090 (16.9%)	0.77 (0.69–0.86)	23%▼	<0.001
Total Mortality		274/4089 (6.7%)	310/4090 (7.6%)	0.87 (0.74–1.02)	13%▼	0.09



Bhatt DL, Steg PG, Miller M, et al. *N Engl J Med.* 2019; 380:11-22. Bhatt DL. AHA 2018, Chicago.

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REDUCE It Trial

- **Original Analysis based only on reduction of 1st events (AHA 2018)**
- **Secondary analysis based on reduction in total events (ACC 2019)**

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Methods – Subsequent and Total Events

First events were significantly reduced, including CV death

- However, patients with non-fatal events are at increased risk for subsequent ischemic events

Multiple validated statistical models used to examine subsequent events

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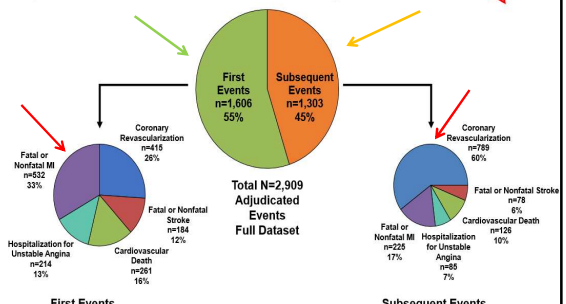
Proportions of First and Subsequent Events



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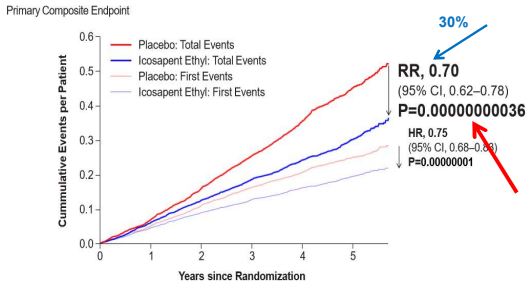
Total (First and Subsequent) Events

Primary: CV Death, MI, Stroke, Coronary Revasc, Unstable Angina



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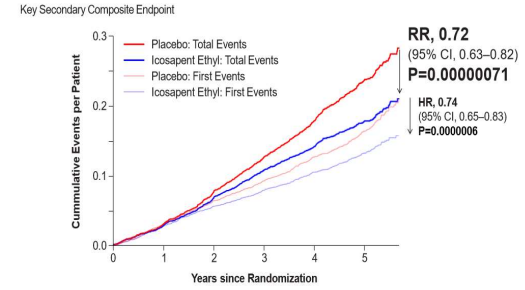
Total (First and Subsequent) Events

Key Secondary: CV Death, MI, Stroke



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Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events

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Conclusions

Compared with placebo, icosapent ethyl 4g/day significantly reduced total cardiovascular events by **30%**, including:

- **25%** reduction in first cardiovascular events
- **32%** reduction in second cardiovascular events
- **31%** reduction in third cardiovascular events
- **48%** reduction in fourth or more cardiovascular events

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Reduce It Trial

Analysis of first, recurrent, and total events demonstrates the large burden of ischemic events in statin-treated patients with baseline triglycerides > ~100 mg/dL and the potential role of icosapent ethyl in reducing this residual risk

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Late Breaking Clinical Trials

COAPT Trial

- **MitraClip for Mitral Regurgitation and Heart Failure from Functional Mitral Regurgitation.**

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COAPT TRIAL

COAPT

A Randomized Trial of Transcatheter Mitral Valve Leaflet Approximation in Patients with Heart Failure and Secondary Mitral Regurgitation

Gregg W. Stone, MD

On behalf of Michael Mack, William Abraham, JoAnn Lindenfeld and the COAPT Investigators

TCT 2018

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COAPT TRIAL

Background (i)

- Pts with heart failure (HF) in whom mitral regurgitation (MR) develops secondary to left ventricular dysfunction have a poor prognosis, with reduced quality-of-life, frequent hospitalizations for heart failure and decreased survival
- There are no proven therapies for secondary MR in HF
  - Guideline-directed medical therapy (GDMT) and cardiac resynchronization therapy (CRT) may provide symptomatic relief in some pts
- Whether correcting secondary MR improves the prognosis of pts with HF is unknown
  - Surgery with a downsized annuloplasty ring has not been demonstrated to be beneficial for secondary MR, and has a high recurrence rate

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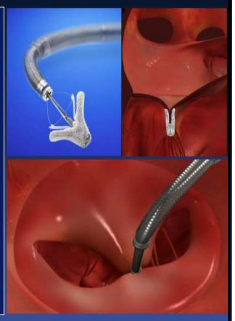
COAPT TRIAL

Background (ii)

- By approximating the anterior and posterior mitral leaflets and forming a double-orifice valve, the MitraClip device reduces MR
- Registries have suggested that the MitraClip is safe and may provide symptomatic benefit to HF pts with secondary MR
- We therefore performed the COAPT randomized trial to evaluate the safety and effectiveness of transcatheter mitral leaflet approximation in HF pts with secondary MR who remained symptomatic despite GDMT



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COAPT TRIAL

The COAPT Trial

Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in ~610 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

Randomize 1:1*

MitraClip + GDMT N=305

GDMT alone N=305

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site

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COAPT TRIAL

Key Inclusion Criteria

1. Ischemic or non-ischemic cardiomyopathy with LVEF 20%-50% and LVESD ≤70 mm
2. Moderate-to-severe (3+) or severe (4+) secondary MR confirmed by an independent echo core laboratory prior to enrollment (US ASE criteria)
3. NYHA functional class II-IVa (ambulatory) despite a stable maximally-tolerated GDMT regimen and CRT (if appropriate) per societal guidelines
4. Pt has had at least one HF hospitalization within 12 months and/or a BNP ≥300 pg/ml* or a NT-proBNP ≥1500 pg/ml*
5. Not appropriate for mitral valve surgery by local heart team assessment
6. IC believes secondary MR can be successfully treated by the MitraClip

Adjusted by a 4% reduction in the BNP or NT-proBNP cutoff for every increase of 1 kg/m² in BMI >20 kg/m²

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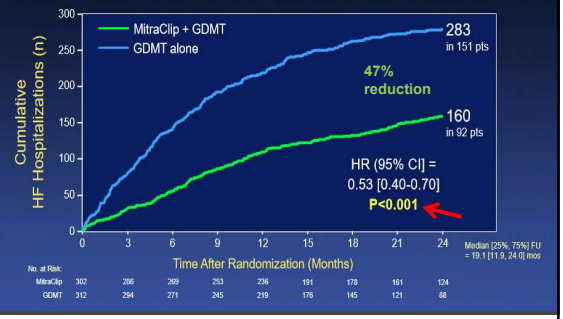
COAPT TRIAL

Primary Effectiveness Endpoint

All Hospitalizations for HF within 24 months



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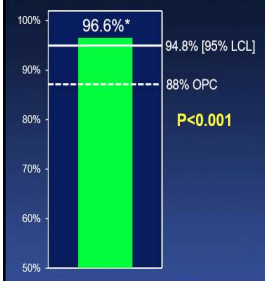
Primary Safety Endpoint

Freedom from Device-related Complications within 12 months



MitraClip procedure attempted	N=293
Device-related complications	9 (3.4%)
- Single leaflet device attachment	2 (0.7%)
- Device embolization	1 (0.3%)
- Endocarditis requiring surgery	0 (0.0%)
- Mitral stenosis requiring surgery	0 (0.0%)
- Left ventricular assist device implant	3 (1.2%)
- Heart transplant	2 (0.8%)
- Any device-related complication requiring non-elective CV surgery	1 (0.3%)

*KM estimate; **Calculated from Z test with Greenwood's method of estimated variance against a pre-specified objective performance goal of 88%

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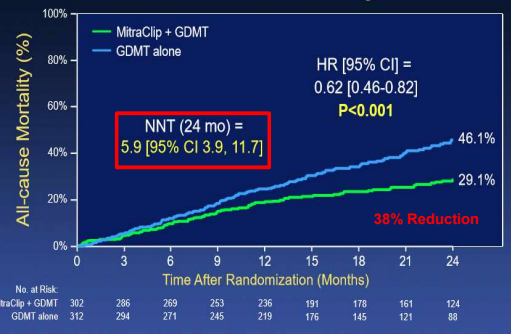
All-cause Mortality



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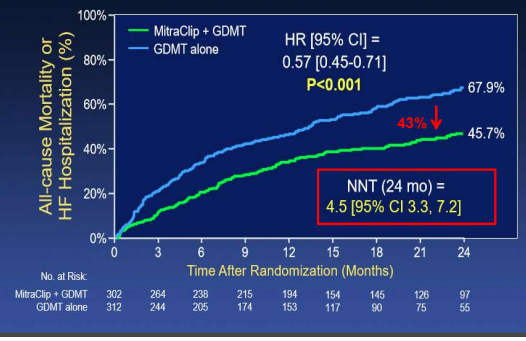
Death or HF Hospitalization



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24-Month Death or HF Hospitalization

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Conclusions

- In pts with HF and moderate-to-severe or severe secondary MR who remain symptomatic despite maximally-tolerated GDMT, transcatheter mitral leaflet approximation with the MitraClip was safe, provided durable reduction in MR, reduced the rate of HF hospitalizations, and improved survival, quality-of-life and functional capacity during 24-month follow-up
- As such, the MitraClip is the first therapy shown to improve the prognosis of patients with HF by reducing secondary MR due to LV dysfunction

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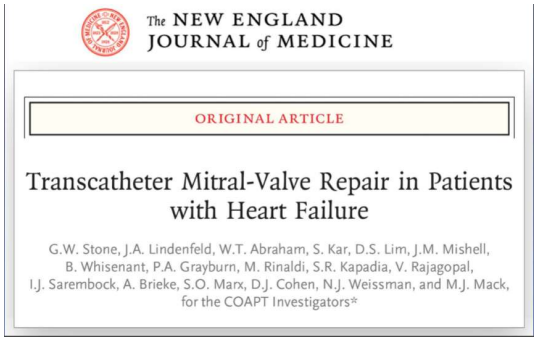

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Late Breaking Clinical Trials

PARTNER 3 and Evolut- Low Risk Trials

Aortic Stent Valves (TAVR) in Low Surgical Risk patients with Severe Aortic Stenosis

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THE PARTNER 3 TRIAL

PARTNER 3

Transcatheter or Surgical Aortic Valve Replacement in Low Risk Patients with Aortic Stenosis

Martin B. Leon, MD &
Michael J. Mack, MD
on behalf of the PARTNER 3 Trial Investigators

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THE PARTNER 3 TRIAL

SAPIEN Valve Evolution

	SAPIEN	SAPIEN XT	SAPIEN 3
Valve Technology			
Sheath Compatibility	 22-24F	 16-20F	 14-16F
Available Valve Sizes	 23 mm, 26 mm	 23 mm, 26 mm, 29 mm	 20 mm, 23 mm, 26 mm, 29 mm
FDA Approval of Valve:	PARTNER 1 2011	PARTNER 2 2014	PARTNER 3 2015

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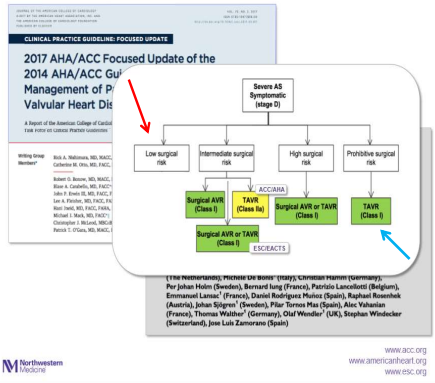

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THE PARTNER 3 TRIAL

PARTNER 3 Study Design

Symptomatic Severe Aortic Stenosis

Low Risk/TF ASSESSMENT by Heart Team (STS < 4%)

1:1 Randomization 1000 Patients

TAVR (SAPIEN 3 THV) | Surgery (Surgical Bioprosthetic Valve)

Follow-up: 30 day, 6 mos, and annually through 10 years

PRIMARY ENDPOINT:
Composite of all-cause mortality, stroke, or CV re-hospitalization at 1 year post-procedure

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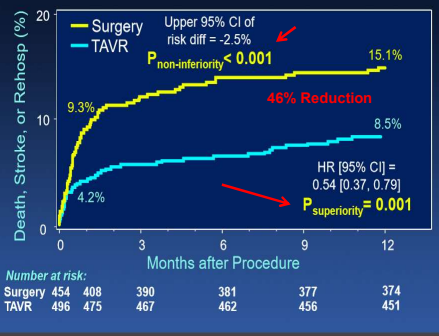
THE PARTNER 3 TRIAL

Primary Endpoint



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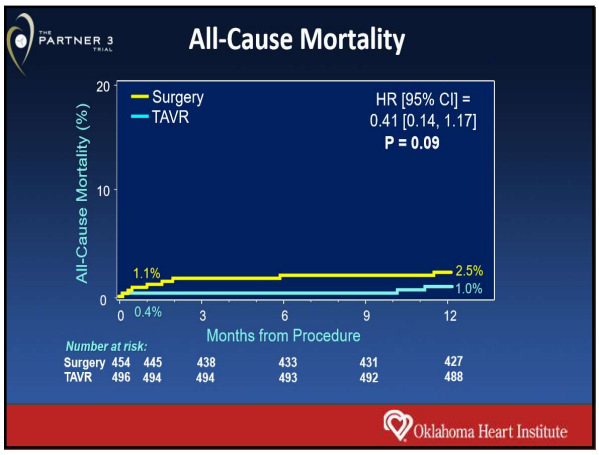
All-Cause Mortality
Surgery
TAVR
HR [95% CI] = 0.41 [0.14, 1.17]
P = 0.09
All-Cause Mortality (%)
1.1%
0.4%
2.5%
1.0%
Months from Procedure
Number at risk:
Surgery 454 445 438 433 431 427
TAVR 496 494 494 493 492 488
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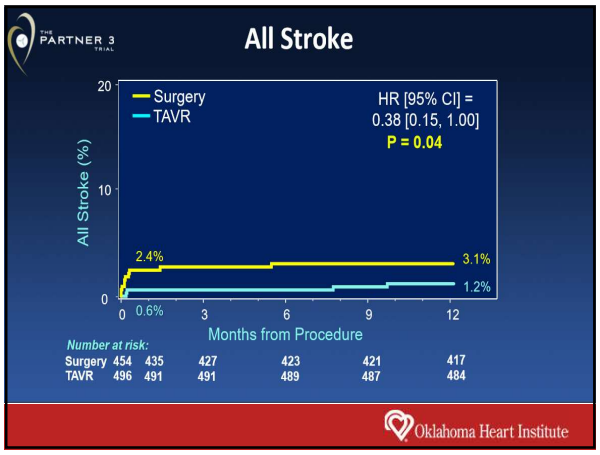
All Stroke
Surgery
TAVR
HR [95% CI] = 0.38 [0.15, 1.00]
P = 0.04
All Stroke (%)
2.4%
0.6%
3.1%
1.2%
Months from Procedure
Number at risk:
Surgery 454 435 427 423 421 417
TAVR 496 491 491 489 487 484
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The PARTNER 3 Trial
The NEW ENGLAND JOURNAL of MEDICINE
Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients
4
1
Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery
3
Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients
2
Transcatheter and Surgical Aortic-Valve Replacement in High-Risk Patients
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The PARTNER 3 Trial
Clinical Implications
Based upon these findings, TAVR, through 1-year, should be considered the preferred therapy in low surgical risk aortic stenosis patients!
PARTNER randomized trials over the past 12 years, clearly indicate that the relative value of TAVR compared with surgery is independent of surgical risk profiles.
The choice of TAVR vs. surgery in aortic stenosis patients should be a shared-decision making process, respecting patient preferences, understanding knowledge gaps (esp. in younger patients), and considering clinical and anatomic factors.
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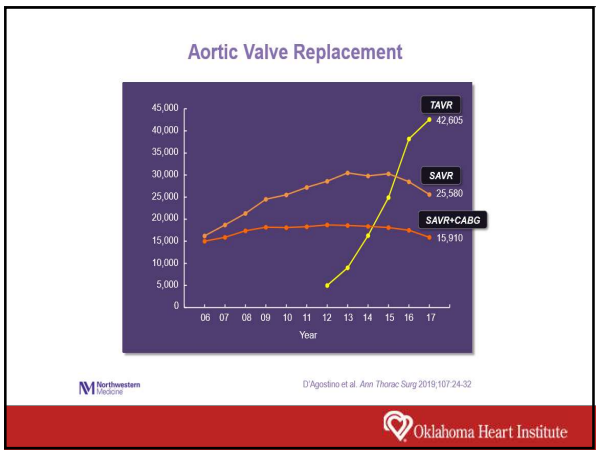
Aortic Valve Replacement
TAVR
42,605
SAVR
25,580
SAVR+CABG
15,910
Year
Northwestern Medicine
D'Agostino et al. Ann Thorac Surg 2019;107:24-32
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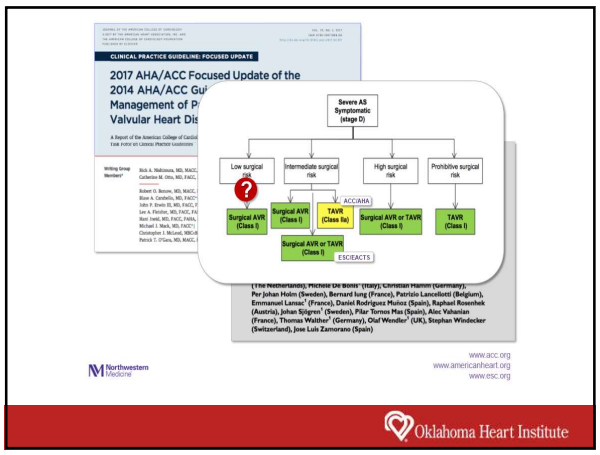
CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE
2017 AHA/ACC Focused Update of the
2014 AHA/ACC Gu
Management of P
Valvular Heart Dis
Severe AS Symptomatic (stage D)
Low surgical risk
Intermediate surgical risk
High surgical risk
Prohibitive surgical risk
ACC/AHA
Surgical AVR (Class I)
Surgical AVR (Class I)
TAVR (Class IIa)
Surgical AVR or TAVR (Class I)
TAVR (Class I)
Surgical AVR or TAVR (Class I)
ESC/EACTS
Northwestern Medicine
www.acc.org
www.americanheart.org
www.esc.org
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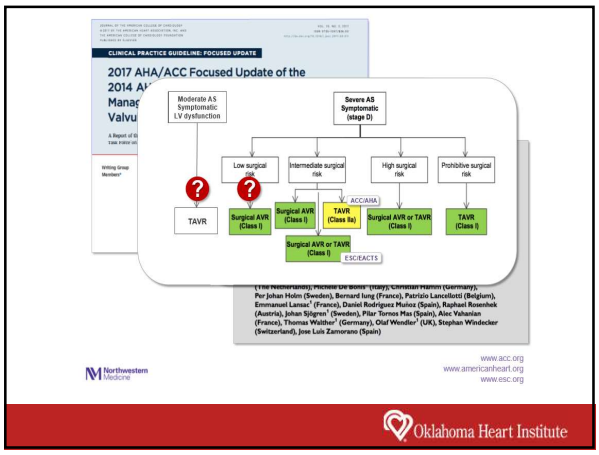
CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE
2017 AHA/ACC Focused Update of the
Moderate AS Symptomatic LV dysfunction
Severe AS Symptomatic (stage D)
Low surgical risk
Intermediate surgical risk
High surgical risk
Prohibitive surgical risk
TAVR
Surgical AVR (Class I)
Surgical AVR (Class I)
TAVR (Class IIa)
Surgical AVR or TAVR (Class I)
TAVR (Class I)
Surgical AVR or TAVR (Class I)
ACC/AHA
ESC/EACTS
www.acc.org
www.americanheart.org
www.esc.org
Northwestern Medicine
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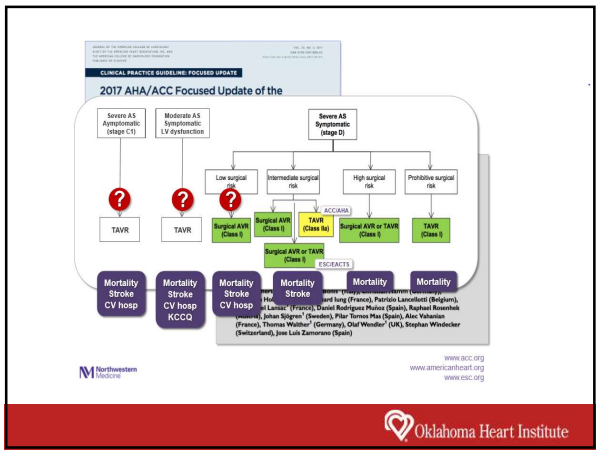
CLINICAL PRACTICE GUIDELINE: FOCUSED UPDATE
2017 AHA/ACC Focused Update of the
Severe AS Asymptomatic (stage C1)
Moderate AS Symptomatic LV dysfunction
Severe AS Symptomatic (stage D)
Low surgical risk
Intermediate surgical risk
High surgical risk
Prohibitive surgical risk
TAVR
TAVR
Surgical AVR (Class I)
Surgical AVR (Class I)
TAVR (Class IIa)
Surgical AVR or TAVR (Class I)
TAVR (Class I)
Surgical AVR or TAVR (Class I)
ACC/AHA
ESC/EACTS
Mortality Stroke CV hosp
Mortality Stroke CV hosp
Mortality Stroke CV hosp KCCQ
Mortality Stroke
Mortality
Mortality
www.acc.org
www.americanheart.org
www.esc.org
Northwestern Medicine
Oklahoma Heart Institute


Evolut Low Risk Trial
Primary Results From the Evolut Low Risk Trial
Michael J. Reardon, MD, FACC
Houston Methodist DeBakey Heart & Vascular Institute, Houston, TX
For the Evolut Low Risk Trial Investigators
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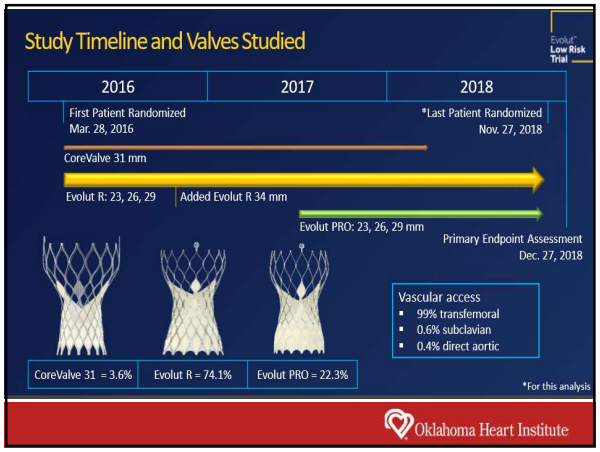
Study Timeline and Valves Studied
Evolut Low Risk Trial
2016
2017
2018
First Patient Randomized
Mar. 28, 2016
*Last Patient Randomized
Nov. 27, 2018
CoreValve 31 mm
Evolut R: 23, 26, 29
Added Evolut R 34 mm
Evolut PRO: 23, 26, 29 mm
Primary Endpoint Assessment
Dec. 27, 2018
Vascular access
99% transfemoral
0.6% subclavian
0.4% direct aortic
CoreValve 31 = 3.6%
Evolut R = 74.1%
Evolut PRO = 22.3%
*For this analysis
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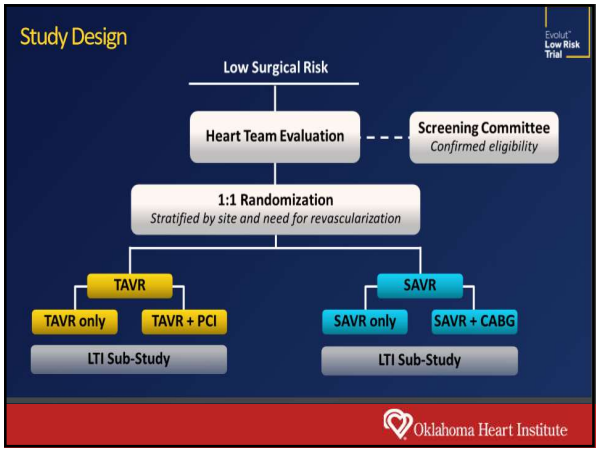
Study Design
Evolut Low Risk Trial
Low Surgical Risk
Heart Team Evaluation
Screening Committee
Confirmed eligibility
1:1 Randomization
Stratified by site and need for revascularization
TAVR
SAVR
TAVR only
TAVR + PCI
SAVR only
SAVR + CABG
LTI Sub-Study
LTI Sub-Study
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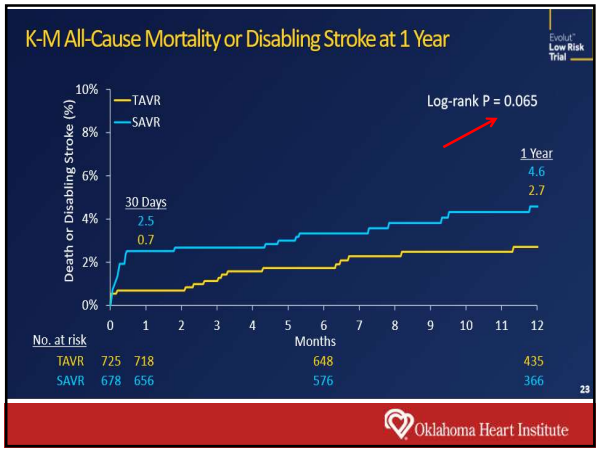
K-M All-Cause Mortality or Disabling Stroke at 1 Year
Evolut Low Risk Trial
Death or Disabling Stroke (%)
10%
8%
6%
4%
2%
0%
TAVR
SAVR
Log-rank P = 0.065
1 Year
4.6
2.7
30 Days
2.5
0.7
0
1
2
3
4
5
6
7
8
9
10
11
12
Months
No. at risk
TAVR 725 718 648 435
SAVR 678 656 576 366
23
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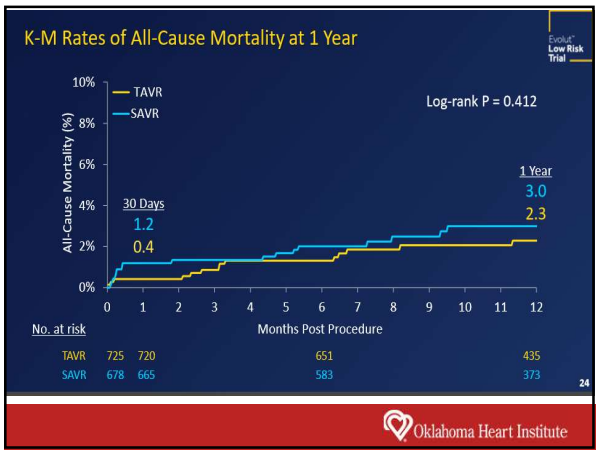

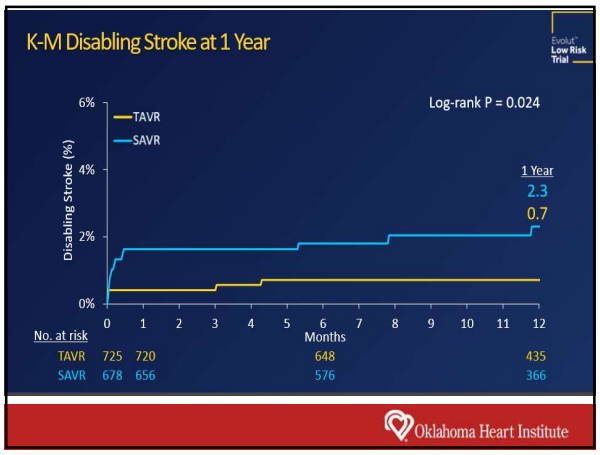

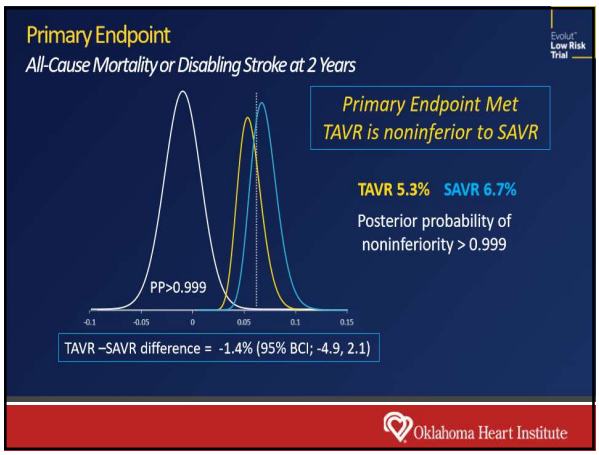

TAVR 2019

- TAVR has been truly transformative
- Surgical AVR has been the standard with proven durability and safety
- TAVR provides treatment options for patients who previously had no options
- TAVR is alternative to SAVR in patients at high and intermediate surgical risk.
- Patients want TAVR

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TAVR 2019 to The Future

- Is SAVR still the standard?
- Should TAVR now be available to low risk patients?
- Will it be difficult to withhold TAVR when patients want it over SAVR?
- Will TAVR have a role in patients with severe Aortic Stenosis but no symptoms?

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TAVR 2019

- 5 large randomized trials of TAVR versus SAVR. All show non-inferior or superior results for TAVR compared to SAVR.
- Which one would you chose?

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Late Breaking Clinical Trials

Augustus Trial

Anticoagulation strategies in Patients with Atrial Fibrillation who get PTCA/Stenting of a coronary stenosis

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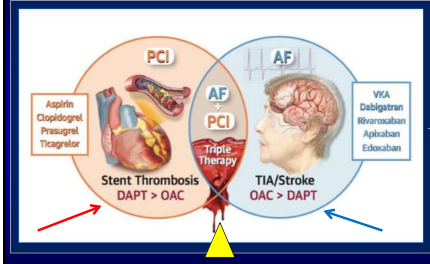
Atrial Fibrillation and PCI: Key Concepts



Stent thrombosis and coronary events

High shear stress platelet-rich thrombi

Antiplatelet therapy

Stroke, TIA and systemic embolism

Low shear stress, less platelet-dependent thrombi

Anticoagulation therapy

Capodanno D, Angiolillo DJ. JACC Cardiovasc Interv. 2017;10:1086-1088

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Trial Design

Duke Clinical Research Institute — Augustus

INCLUSION
- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned $P2Y_{12}$ inhibitor for ≥6 months

Randomize n=4600 patients

EXCLUSION
- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate / severe mitral stenosis)

Apixaban 5 mg BID — Apixaban 2.5 mg BID in selected patients

Open Label

VKA (INR 2–3)

Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

Aspirin — Double Blind — Placebo

Aspirin — Double Blind — Placebo

Primary outcome: ISTH major / CRNM bleeding
Secondary outcome(s): death / hospitalization, death / ischemic events

Lopes RD, et al. Am Heart J. 2018;200:17-23.

ISTH = International Society on Thrombosis & Hemostasis

CRNM = Clinically Relevant Non-major Bleeding

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Major / CRNM Bleeding

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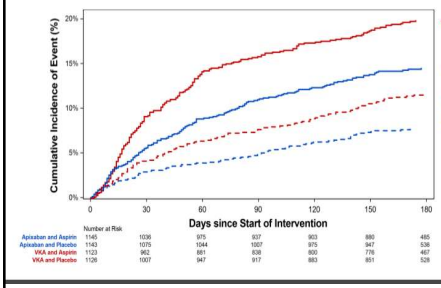
All on Plavix



VKA + Aspirin (18.7%)

Apixaban + Aspirin (13.8%)

VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

Apixaban + Placebo vs. VKA + Aspirin: 11.4% absolute risk reduction (NNT=9)

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Death / Hospitalization

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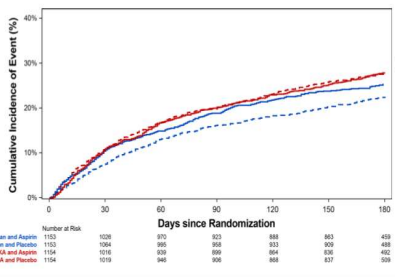
All on $P2Y_{12}$ Inhibitor



VKA + Aspirin (27.5%)
VKA + Placebo (27.3%)
Apixaban + Aspirin (24.9%)
Apixaban + Placebo (22.0%)

Apixaban + Placebo vs. VKA + Aspirin: 5.5% absolute risk reduction (NNT=18)

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Conclusion

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a $P2Y_{12}$ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both

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Clinical Implications

In most patients with atrial fibrillation and a recent acute coronary syndrome or PCI the use of apixaban plus clopidogrel without aspirin should be the preferred antithrombotic regimen whereas regimens that include a VKA plus DAPT should generally be avoided

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LRP – Trial

Lipid Rich Plaque Trial

Predicting the patient at risk of MI from CAD seen at cath.

TCT 2019

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IVUS / InfraRed Spectroscopy

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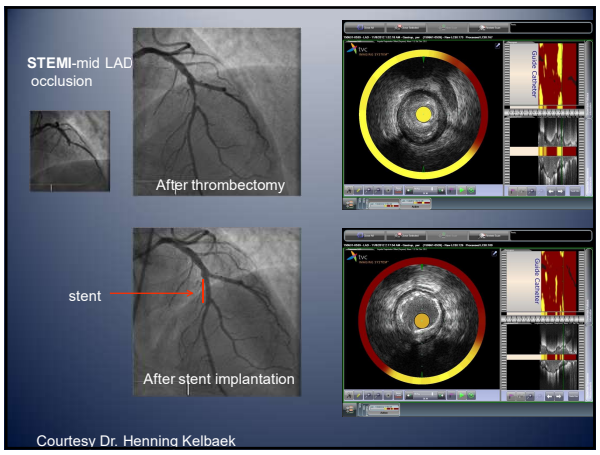

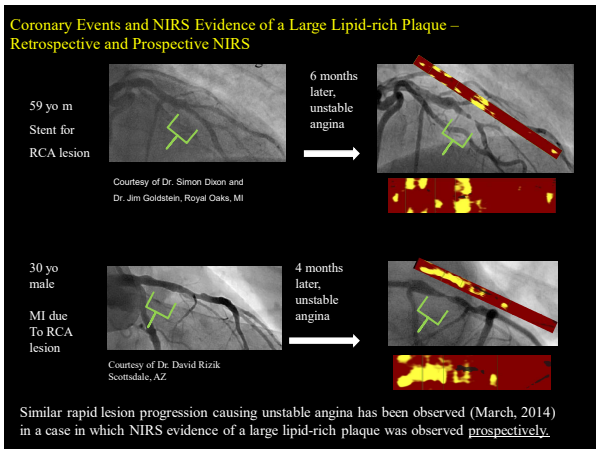

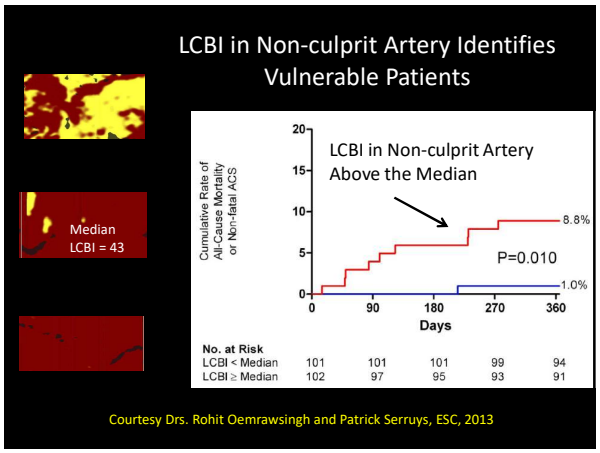

LRP - Trial

- 1271 patients
- 5744 coronary segments analyzed
- Scanned 2.1 vessels/ patient

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LRP – Trial Results

- **For the patient:** A LCBI > 400 resulted in an 87% higher risk of an event in 24 months
- **For the Vulnerable Plaque:** a LCBI > 400 resulted in a 400% greater risk for plaque rupture.

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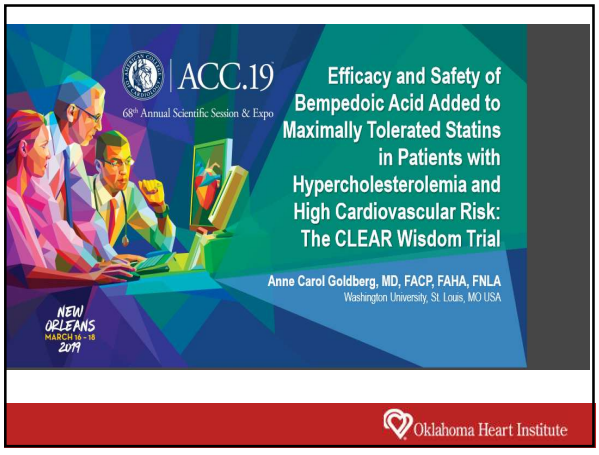

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Background

- Lipid-lowering therapies (statins) have greatly reduced cardiovascular (CV) disease burden[1]
- Many patients at high CV risk have elevated low-density lipoprotein cholesterol (LDL-C), despite statin treatment[2-6]
  - Insufficient response to high-intensity statins
  - Inability to take effective doses of statins due to tolerability issues
- Additional oral options that complement maximally tolerated lipid-lowering therapies are needed for patients unable to achieve adequate LDL-C lowering[7]
- Bempedoic acid is a once-daily oral, first-in-class, small-molecule drug being developed for the treatment of hyperlipidemia

1. Boekholdt SM, et al. *J Am Coll Cardiol*. 2014; 64(5):485-494; 2. deGoma EM, et al. *Circ Cardiovasc Genet*. 2016;9(3):240-249; 3. Gitt AK, et al. *Atherosclerosis*. 2016;256:200-209; 4. Mercan J, et al. *J Manag Care Spec Pharm*. 2017;23(12):1270-1276; 6. Perez de Isla, et al. *J Am Coll Cardiol*. 2016;67(11):1278-1285; 6. Lakey WC, et al. *J Clin Lipidol*. 2016;10:870-879; 7. Grundy SM, et al. *J Am Coll Cardiol*. 2018. doi:10.1016/j.jacc.2018.11.003.

ACC.19

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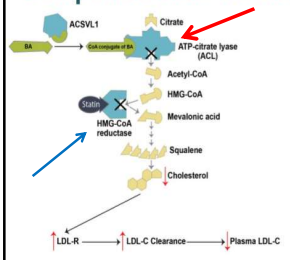
Bempedoic Acid Mechanism of Action



- Bempedoic acid is a prodrug activated in liver by very-long-chain acyl-CoA synthetase-1 (ACSVL1)
- Activated bempedoic acid acts in the same cholesterol synthesis pathway as statins
- Bempedoic acid inhibits ATP-citrate lyase (ACL), an enzyme upstream of HMG-CoA reductase
- Bempedoic acid upregulates LDL receptors and lowers LDL-C
- Activated bempedoic acid is not present in skeletal muscle

For review see: Pinkosky SL, et al. *Nat Commun*. 2016;28;7:13457.
BA, bempedoic acid.

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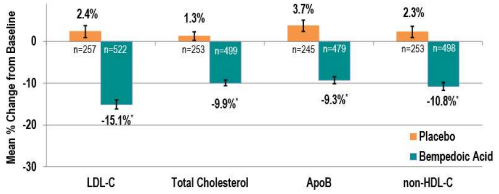
CLEAR Wisdom Efficacy

Percent Change from Baseline to Week 12 in Lipids and Lipoproteins



*P < .001 for all comparisons

Mean = least squares mean (standard error).

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CLEAR Wisdom Summary: Efficacy

- CLEAR Wisdom provides additional evidence that bempedoic acid is efficacious in patients at high CV risk with hypercholesterolemia, despite receiving maximally tolerated statin therapy
  - Bempedoic acid reduced LDL-C at week 12 by 17.4%
  - Reductions in LDL-C were maintained for 52 weeks
  - Bempedoic acid also significantly lowered non–HDL-C, apoB, total cholesterol, and hsCRP

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CLEAR Wisdom Summary: Safety

- Bempedoic acid was safe and well tolerated when given as an adjunct to maximally tolerated statins
  - AE profile of bempedoic acid was generally similar to that of placebo
  - Adjudicated major adverse CV events were 2% lower than placebo with bempedoic acid
  - No worsening of 12-week glycemic measurements in patients with a history of diabetes compared to placebo

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CLEAR Wisdom: Conclusion

- Bempedoic acid may provide an additional therapeutic option to safely lower LDL-C in high CV risk patients with elevated LDL-C treated with maximally tolerated statins and other lipid-modifying therapies

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TRED – HF Trial

- Withdrawal of Pharmacological Heart Failure Therapy in Recovered Dilated Cardiomyopathy: A Randomized Control Trial.

Lancet 2018

AHA 2018

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TRED – HF Trial

- Patients initially with DCM with LV Ej Fx < 40% who achieve LV Ej Fx > 55% for 2 years on GDMT.
- Phased Therapy Withdrawal

AHA 2018

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TRED – HF Trial

- Study stopped very early due to a 44% relapse rate.
- At follow up: 50% remained off meds

AHA 2018

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TRED-HF Trial
Conclusion

- Do not withdraw heart failure meds (Beta-Blockers and Inhibitors of RAAS system) in patients who get normalization of LV systolic function.
- Improvement in LV Ej Fx indicates remission and not cure.

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A Fully Magnetically Levitated Left Ventricular Assist Device

Final Report of the MOMENTUM 3 Trial

Mandeep R. Mehra, MD, Nir Uriel, MD, Joseph C. Cleveland, Jr., MD, Daniel J. Goldstein, MD, National Principal Investigators, on behalf of the MOMENTUM 3 Investigators

MOMENTUM 3

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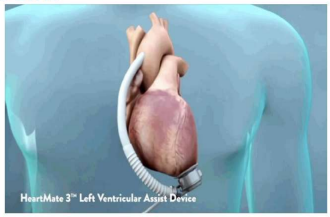
HeartMate 3 LVAS



- **Wide** blood-flow passages to reduce shear stress
- **Frictionless** with absence of mechanical bearings
- **Intrinsic Pulse** designed to reduce stasis and avert thrombosis

MOMENTUM 3

Bourque K et al. Design Rationale and Preclinical Evaluation of the HeartMate 3 Left Ventricular Assist System for Hemocompatibility. ASAIO J 2016;62(4):375-83

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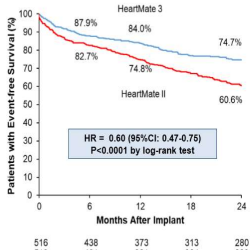
Primary End Point (ITT)

Survival at 2 years free of disabling stroke (>3 mRS) or reoperation to replace or remove a malfunctioning device



HR = 0.60 (95%CI: 0.47-0.75)
P<0.0001 by log-rank test

No. at Risk:					
HeartMate 3	516	438	373	313	280
HeartMate II	512	401	321	264	223

MOMENTUM 3

mRS denotes modified Rankin Score; HR, hazard ratio; CI, confidence interval

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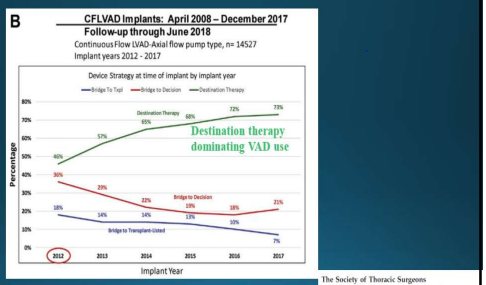
Looking at LVADs for Lifetime Therapy



The Society of Thoracic Surgeons INTERMACS Database Annual Report: Evolving Indications, Outcomes, and Scientific Partnerships

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Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

Results form the DECLARE-TIMI 58 Trial

Eri T. Kato, Michael G. Silverman, Ofri Mosenzon, Thomas A. Zelniker, Avivit Cahn, Remo H.M. Furtado, Julia Kuder, Sabina A. Murphy, Deepak L. Bhatt, Lawrence A. Leiter, Darren K. McGuire, John P.H. Wilding, Marc P. Bonaca, Christian T. Ruff, Akshay S. Desai, Shinya Goto, Peter A. Johansson, Ingrid Gause-Nilsson, Per Johanson, Anna Maria Langkilde, Itamar Raz, Marc S. Sabatine and Stephen D. Wiviott

On behalf of the DECLARE-TIMI 58 Investigators

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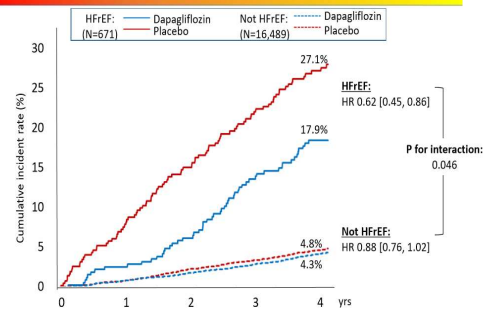
CV Death/HHF by HFrEF vs not HFrEF subgroups



Not HFrEF defined as pts with HF without known reduced EF and pts without hx of HF

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Conclusions

The use of the SGLT2 inhibitor dapagliflozin:

- Is beneficial in reducing HHF in patients with a broad range of LVEF.
- May provide an even greater benefit with lower CV death and mortality in patients with HFrEF.

ACC 2019

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Additional Information

Circulation

Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus

Eri T. Kato, MD, MPH, PhD, Michael G. Silverman, MD, MPH, Ofri Mosenzon, MD, MSc, Thomas A. Zelniker, MD, MSc, Avivit Cahn, MD, Remo H.M. Furtado, MD, PhD, Julia Kuder, MS, Sabina A. Murphy, MPH, Deepak L. Bhatt, MD, MPH, Lawrence A. Leiter, MD, Darren K. McGuire, MD, MHSc, John P.H. Wilding, MD, Marc P. Bonaca, MD, MPH, Christian T. Ruff, MD, MPH, Akshay S. Desai, MD, MPH, Shinya Goto, MD, PhD, Peter A. Johansson, MSc, Ingrid Gause-Nilsson, MD, PhD, Per Johanson, MD, PhD, Anna Maria Langkilde, MD, PhD, Itamar Raz, MD, Marc S. Sabatine, MD, MPH, Stephen D. Wiviott, MD

Article available at www.ahajournals.org

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SGLT2 Inhibitors

- Empagliflozin (Jardiance)
- Dapagliflozin (Farxiga)
- Canagliflozin (Invokana)
- Ertagliflozin (Steglatro)

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