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Hot Topics in Cardiology

Wednesday, December 6, 2017

ACPE Program # 0204-0000-17-278-LO1-P

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Disclosure

All planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

Christina Teeter Doligalski will discuss off label use and/or investigational use of the following drugs/devices: Terbutaline and theophylline

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Prevention of Cardiovascular Disease in Chronic Kidney Disease

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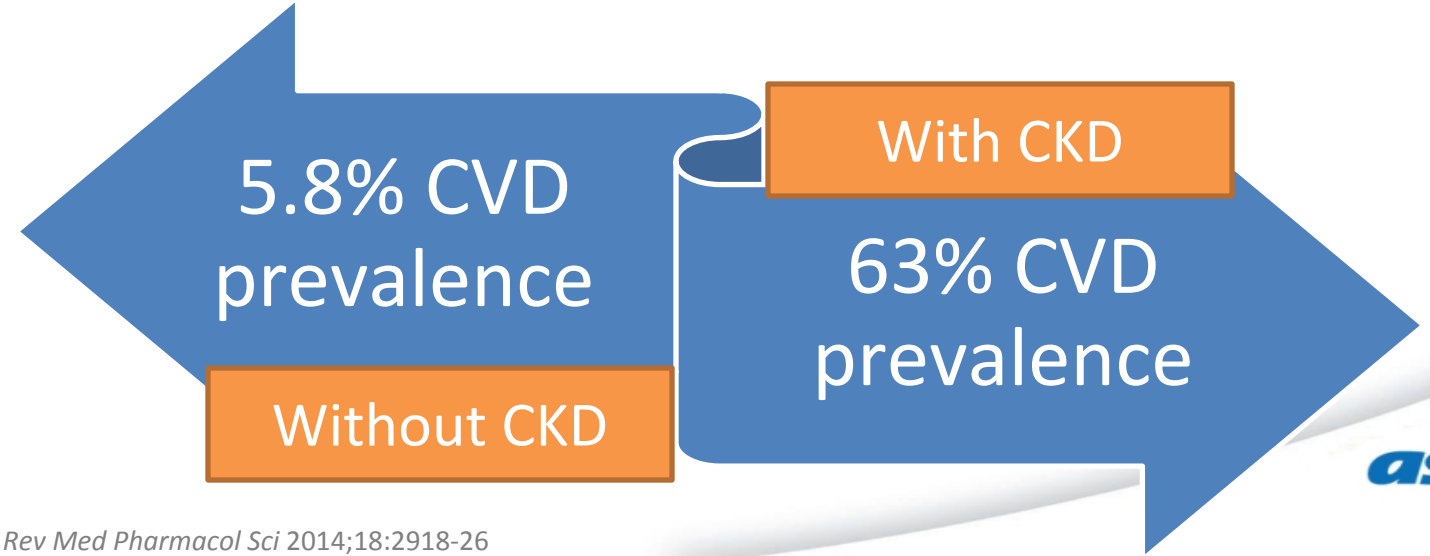
Cardiovascular Disease

- Cardiovascular disease (CVD) closely interrelated with chronic kidney disease (CKD)
- 10-20 fold increased mortality in patients requiring dialysis



Liu M, et al. *Eur Rev Med Pharmacol Sci* 2014;18:2918-26

Cardiovascular Disease

Traditional Risk Factors	Non-Traditional Risk Factors
Advanced age	Anemia
Hypertension	Volume overload
Diabetes mellitus	Proteinuria
Dyslipidemia	Oxidative stress
Metabolic syndrome	Inflammation
	Mineral disorders
	Vascular thickening

Standard clinical interventions may not be effective in CKD

Liu M, et al. *Eur Rev Med Pharmacol Sci* 2014;18:2918-26

Statins in CKD

Study (year)	Patients (n)	Intervention	Outcome
4D (2005)	Dialysis (n=1255)	Atorvastatin 20 mg	No significant effect on composite CV outcome
AURORA (2009)	Dialysis (n=2776)	Rosuvastatin 10 mg	No significant effect on composite CV outcome
SHARP (2011)	CKD, dialysis (n=9270)	Simvastatin 20 mg + ezetimibe 10 mg	22% RRR on composite CV outcome in CKD (95% CI 0.67-0.91) No significant effect in dialysis

RRR = Relative risk reduction

Wanner C, et al. *N Engl J Med* 2005;353:238-48 | Fellstrom BC, et al. *N Engl J Med* 2009;360:1395-1407 | Baigent C, et al. *Lancet* 2011;377:2181-92

Statins in CKD

Adults ≥ 50 years, eGFR <60 mL/min/1.73 m^2 (not on dialysis)

- Initiate statin or statin/ezetimibe

Adults 18-49 years, eGFR <60 mL/min/1.73 m^2 (not on dialysis)

- Initiate statin if CAD, diabetes, prior CVA, or ASCVD risk >10%

Adults that are dialysis-dependent, regardless of age

- Already receiving statin or statin/ezetimibe → may continue therapy
- Recommend not initiating statin or statin/ezetimibe

NKF-KDIGO. *Kidney International Supplements* 2013;3(3):259-305

Statins in CKD

Statin	Recommended dose if eGFR <60 mL/min/1.73 m² (mg)
	20
	80
	Not studied
	2
	40
	10
	(20 if combined with ezetimibe)

More conservative than ACC/AHA guidelines

Considerations to achieve high intensity statin dosing in CKD patients

Sarnak MJ, et al. *Am J Kidney Dis* 2015;65(3):354-66 | NKF-KDIGO. *Kidney International Supplements* 2013;3(3):259-305

CVD Prevention in CKD

Folic acid

Calcimimetic

Vitamin D

Role of Folic acid

Proposed mechanism for CVD prevention

- Increased homocysteine in patients with CKD
- Folic acid plays key role in converting homocysteine to methionine, may also improve endothelial function

Conflicting data - Initial studies of folic acid supplementation (at varying doses) did not show benefit in secondary prevention of recurrent stroke or myocardial infarction

House, A. *Am J Kidney Dis* 2015;66(6):942-44

Role of Folic acid

Trials	Outcomes
Meta-analysis (2011)	• Included 3,886 patients with advanced CKD or ESRD from 7 randomized trials • Folic acid reduced relative risk of CVD by 15% (391/2038 vs. 431/1848, p=0.009)
CSPPT (2013)	• Trial stopped early after clear benefit of folic acid in primary stroke prevention (2.7% vs. 3.4%; p=0.03) • Conducted in provinces in China • Renewed interest for use as primary CV prevention

Qin X, et al. *Clin J Am Soc Nephrol* 2011;6(3):482-8 | Huo Y, et al. *JAMA* 2015;313:1325-35

Role of Calcimimetic

Proposed mechanism for CVD prevention

- Down-regulates parathyroid hormone
- Leads to decreased vascular calcification

Trials	Outcomes with cinacalcet
EVOLVE (2012)	No significant reduction in death or major CV events in patients on dialysis
Meta-analysis (2013)	No improvement in all-cause or CV mortality in patients on dialysis

EVOLVE Trial Investigators. *N Engl J Med* 2012;367:2482-94|Palmer SC, et al. *PLoS Med* 2013;10(4):e1001436

Role of Vitamin D

Proposed mechanism for CVD prevention

- Fibroblast growth factor 23 (FGF-23) is increasingly released from osteocytes as renal function declines
- ↑FGF-23 levels → left ventricular hypertrophy
- Calcitriol believed to provide cardioprotection from FGF-23

Preliminary data in rats suggests that calcitriol inhibits FGF-23 effects on the cardiac myocytes

Leifheit-Nestler M, et al. *Nephrol Dial Transplant* 2017; 32: 1493-1503

Key Takeaways

- Key Takeaway #1
  - High prevalence of CVD in CKD, largely due to non-traditional risk factors where standard interventions may not be effective.
- Key Takeaway #2
  - Initiate statin (± ezetimibe) in patients ≥ 50 years with CKD not on dialysis. Initiation is not recommended in dialysis-dependent patients.
- Key Takeaway #3
  - There is renewed interest in vitamin supplementation for CVD prevention in CKD (folic acid and vitamin D).

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An old Dog with New Tricks: Intravenous Sotalol in Pediatric Arrhythmias

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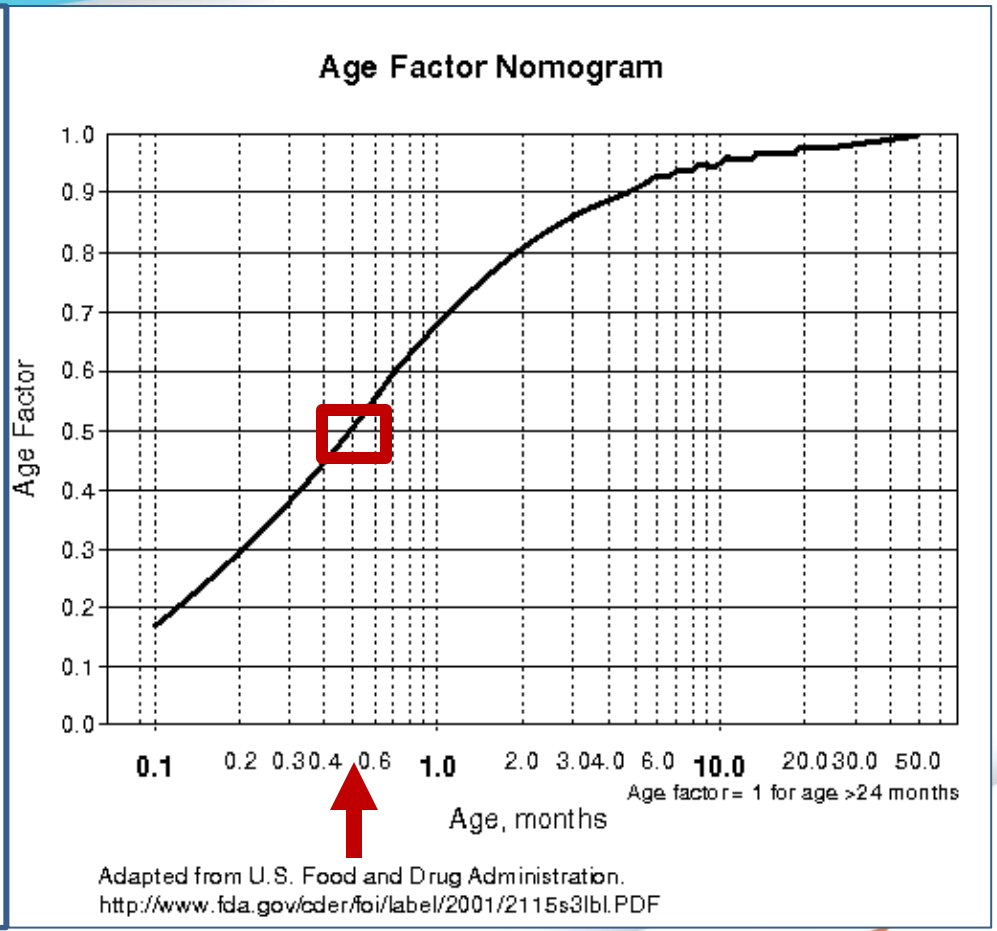
Objective

- Evaluate available literature pertaining to intravenous sotalol in the pediatric population

Manufacturer recommended pediatric dosing

30 mg/m^2/dose every 8 hours X age -related reduction factor for ≤2 years of age

Example
30 mg/m^2/dose X 0.5 = 15 mg/m^2/dose given every 8 hours



Sotalol. Lexicomp. Riverwoods, IL. Available at http://online.lexi.com. Accessed September 24, 2017

Case Report

- Newborn (36 week GA) with fetal SVT ≥50%
- Developed frequent episodes of non-sustained EAT

- IV sotalol dose calculation
  - 30 mg/m^2/dose every 8 hours X 0.17 (age factor)
    - 1 mg Q8H infused over 5 hours
- EKG Monitoring
  - Baseline QTc
  - QTc after each dose

Kim H et al. HeartRhythmCase Rep. 2017; 3:332-335 GA=gestational age; EAT=ectopic atrial tachycardia

Clinical Course

Baseline QTc = 447 msec

Converted with 1st dose

QTc = 480 msec

30 minutes prior to 2nd dose → atrial tachycardia

1.5 mg IV Q8H (45mg/m²/dose) → sinus rhythm

4 IV doses →

2 mg PO Q8H

(60 mg/m²/dose)

Discharged home

No further complications

Case Report

- 16-day-old in SVT, HR 280 bpm
- Vagal/adenosine with transient conversion
- Other failed agents
  - Propranolol 4 mg/kg/day
  - Esmolol 50 mcg/kg/min, up to 150
  - Digoxin load 8 mcg/kg
- IV sotalol dose calculations
  - 30 mg/m^2/dose every 8 hours X 0.5 (age factor) = 3.3 mg Q8H
  - 2 mg/kg/day divided Q8H = 2.4 mg Q8H
  - Initiated 3 mg IV Q8H infused over 5 hours
- EKG Monitoring
  - EKG with QTc at initiation and termination of each dose

Kim H et al. HeartRhythmCase Rep. 2017; 3:332-335 SVT=supraventricular tachycardia

Clinical Course

Baseline QTc = 408 msec

Converted with 1st dose

QTc = 502 msec

Recurrent SVT → 4 mg IV Q8H

(36mg/m^2/dose)

Transitioned to PO after 24 hours

4 mg PO Q8H

Recurrent SVT → stepwise increase to 6 mg PO Q8H

(45 mg/m^2/dose)

Discharged home

No further complications

IV sotalol in pediatrics

Patient characteristics by arrhythmia presentation and conversion success with IV sotalol

Arrhythmias	Mean age (years)	Age range	Number converted	Time to conversion
AVRT	2.5 ± 2.8	22 days to 13.6 years	17/30 (57%)	13.7 ± 13.5 hours
AT**	3.4 ± 3.3	27 days to 11 years	24/36 (67%)	1 ± 0.9 hours
Aflutter*	2.1 ± 3.9	10 days to 10.5 years	4/9 (44%)	11.5 ± 12.2 hours
AF	4.9 ± 7.8	4 months to 14 years	2/3 (67%)	12.5 ± 16.3 hours
VT	3.3 ± 3.1	5 months to 8 years	3/5 (60%)	7.5 ± 10.8 hours
Overall	3 ± 3.4	10 days to 14 years	62/83 (75%)	12 ± 18 hours

AF=atrial fibrillation; Aflutter=atrial flutter; AVRT=atrioventricular reentrant tachycardia; AT=atrial tachycardia; VT=ventricular tachycardia; *$p<0.005$, **$p=0.001$ compared to AVRT

Adapted from: Li X, et al. Am J Cardiol 2017; 119:1366-1370

Loading dose: Weight versus body surface area

Age groups	Loading dose (mg)	Loading dose/BSA (mg/m^2)	Dose per manufacturer recommendations (mg/m^2)
Newborns (n=5)	3.9±0.7	16.3±1.4	17.6±2.5
Infants/toddlers (n=39)	7.6±3	19.5±3	25.5±2.5**
Younger children (n=26)	17.3±5.4	25±2.7	28.5±0**
Older children (n=11)	28±7.6	27.3±3.6	28.5±0
Adolescents (n=2)	55.5±11.2	34.8±6.3	28.5±0

**p<0.001

Adapted from Li X, et al. Pediatr Cardiol. 2017 DOI 10.1007/s00246-017-1683-9

Maintenance Dose: Weight versus body surface area

Age groups	Maintenance dose (mg)	Maintenance dose/BSA (mg/m2)	Dose per manufacturer recommendations (mg/m2)
Newborns (n=5)	18±3	75.1±6.4	52.7±7.6*
Infants/toddlers (n=39)	34.1±13.4	87.9±13.5	76.6±7.4***
Younger children (n=26)	78.3±24.3	112.9±12	85.5±0***
Older children (n=11)	126.2±33.6	123±15.6	85.5±0**
Adolescents (n=2)	250±49.5	156.6±30.2	85.5±0

*p<0.05, **p<0.01, ***p<0.001

Adapted from Li X, et al. Pediatr Cardiol. 2017 DOI 10.1007/s00246-017-1683-9

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Oral sotalol

High-Dose Sotalol Is Safe and Effective in Neonates and Infants With Refractory Supraventricular Tachyarrhythmias

Jarrod D. Knudson · Bryan C. Cannon · Jeffrey J. Kim · Brady S. Moffett

150-200 mg/m^2/day without age factor

Development of a Safe and Effective Pediatric Dosing Regimen for Sotalol Based on Population Pharmacokinetics and Pharmacodynamics in Children With Supraventricular Tachycardia

Stephanie Läer, MD, PhD,* Jan-Peer Elshoff, PhD,* Bernd Meibohm, PhD, FCP,† Jochen Weil, MD, PhD,‡ Thomas S. Mir, MD,‡ Wenhui Zhang, PhD,† Martin Hulpke-Wette, MD

2 mg/kg/day, titrate to target of 3-6 mg/kg/day

Knudson JD, et al. Pediatr Cardiol 2011; 32:896-903
Laer S, et al. J Am Coll Cardiol 2005; 46:1322-30

Multicenter, prospective registry study

- Newborn through adolescents with or without congenital or acquired heart disease
- Adults with congenital heart disease
- Aims
  - Safety
  - Effective dose
  - Rate of administration
- Outcome
  - Develop consensus dosing and management guidelines

Key Takeaways

- Key Takeaway #1
  - IV sotalol may be considered in pediatric patients with refractory tachyarrhythmias
- Key Takeaway #2
  - Use conservative dosing initially and close monitoring, especially in neonates
- Key Takeaway #3
  - Once arrhythmia under control, transition to oral sotalol with continued monitoring

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Optimizing Antithrombotic Therapy in Atrial Fibrillation Patients Requiring Drug-Eluting Stent Implantation

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Objective

- To identify the most appropriate antithrombotic treatments for use in atrial fibrillation patients requiring drug-eluting stent implantation

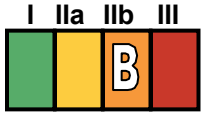
Case

- A 69-year-old white female presented to the ED with intermittent substernal chest pain lasting roughly 30 minutes per episode. Per ECG and biomarkers she was diagnosed with NSTEMI and subsequently transferred to the cath lab.
- PMHx:
  - Hypertension and paroxysmal atrial fibrillation
- Home medications:
  - Toprol XL 50 mg PO daily, warfarin 5 mg PO daily

The patient was loaded with aspirin and ticagrelor and received a Promus (everolimus-eluting) stent within her LAD. Which of the following regimens would this patient most likely be discharged home on from your health-system?

A. Aspirin + ticagrelor + warfarin
B. Aspirin + clopidogrel + warfarin
C. Clopidogrel + warfarin
D. Clopidogrel + DOAC (+/- aspirin)

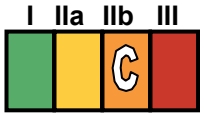
2014 AHA/ACC/HRS Guideline recommendation for AF patients requiring coronary revascularization (PCI or surgical)



- CHA_2DS_2-VASc ≥ 2
  - It may be reasonable to give clopidogrel concurrently with oral anticoagulants
  - No aspirin

January CT, et al. 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. *J Am Coll Cardiol* 2014;64:2246-2280
Dewilde WJ, et al. *Lancet* 2013;381:1107–15.

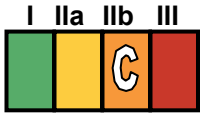
2016 ESC AF Guideline recommendation for AF patients with ACS



- Following ACS with stent implantation in AF with a CHA_2DS_2-VASc ≥ 2
  - Triple therapy with aspirin + clopidogrel + an oral anticoagulant for 1 – 6 months

Kirchor P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS *Eur Heart J.* 2016;37:2893-2962.

2016 ESC AF Guideline recommendation for AF patients with ACS



- Dual therapy with clopidogrel 75 mg/day and an oral anticoagulant may be considered as an alternative to triple therapy in selected patients

Kirchor P, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS *Eur Heart J.* 2016;37:2893-2962.

WOEST

- Study design
  - Open-label, multicenter, randomized controlled trial in Belgium and the Netherlands
- Population
  - 563 patients who required long-term anticoagulation (≥ 1 yr. after study); a severe coronary lesion with indication for PCI
- Treatment Regimen
  - All patients were pretreated with 75 mg clopidogrel x 5 days, a loading dose of 300 mg ≥ 24 h before PCI, or a loading dose of 600 mg ≥ 4 h before PCI
  - All patients received 75 mg clopidogrel daily; triple therapy group received 80-100 mg aspirin daily
    - During PCI warfarin was dosed to a target INR of 2.0 if possible or replaced with LMWH
    - Following PCI warfarin was restarted and dosed to the indicated INR for the comorbidity
- Primary endpoint
  - Occurrence of any bleeding episode during the 12 month follow-up
    - Classified by TIMI, GUSTO, and BARC criteria

Dewilde WJ, et al. *Lancet* 2013;381:1107–15.

WOEST Results

WOEST		
Treatment	Double therapy (n=279)	Triple therapy (n=284)
Any Bleeding event (Primary outcome)	19.4% $p < 0.001$	44.4%
Death, MI, stroke, target-vessel revascularization, or stent thrombosis (Secondary composite)	11.1% $p = 0.025$	17.6%

Dewilde WJ, et al. *Lancet* 2013;381:1107–15.

DAPT + DOAC in AF Trials

Trial	Aspirin	Clopidogrel	Comments
RE-LY	40%	5%	DAPT did not appear to be excluded
ROCKET-AF	36%	unknown	Excluded DAPT and aspirin > 100mg/day
ARISTOTLE	30%	2%	Excluded DAPT and aspirin > 165mg/day
ENGAGE-AF-TIMI 48	29%	2%*	Excluded DAPT

*Listed as thienopyridine, but unclear if prasugrel or clopidogrel

Connolly SJ, et al. *N Engl J Med*. 2009; 361:1139-51.
Tsu LV, Dager WE. *Ann Pharmacother*. 2013; 47:573-7.
Patel MR, et al. *N Engl J Med*. 2011; 365:883-91.
Granger CB, et al. *N Engl J Med*. 2011; 365:981-92.
Giugliano RP, et al. *N Engl J Med*. 2013; 369:2093-2104.

PIONEER AF-PCI

- Study design
  - International, open-label, multicenter, randomized controlled trial
- Population
  - 2124 patients with nonvalvular AF who had undergone PCI with stenting
- Treatment Regimen
  - Group 1: Rivaroxaban 15 mg daily + $P2Y_{12}$ (93.1% C; 1.7% P; 5.2% T)
  - Group 2: Rivaroxaban 2.5 mg BID + DAPT (93.7% C; 1.6% P: 4.8% T)
  - Group 3: Warfarin + DAPT (96.3% C; 0.7% P; 3% T)
    - C = clopidogrel; P = prasugrel; T = ticagrelor
- Primary endpoint
  - Clinically significant bleeding at 1 year

Gibson CM, et al. *N Engl J Med*. 2016;375:2423-2434.

PIONEER AF-PCI

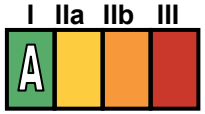
Treatment	Rivaroxaban 15 mg daily + $P2Y_{12}$ for 12 months	Rivaroxaban 2.5 mg BID + DAPT for 1, 6, or 12 months	Warfarin + DAPT for 1, 6, or 12 months
Clinically significant bleeding (1 year)	16.8% p < 0.001	18% p < 0.001 1 month p = 0.20 6 month p < 0.001 12 month p = 0.08	26.7%
MACE	6.5% p = 0.75	5.6% p = 0.76 1 month p = 0.79 6 month p = 0.19 12 month p = 0.10	6.0%
Notable exclusion criteria	History of stroke or TIA; GI bleed within 12 months of randomization; CrCl < 30 mL/min; anemia of unknown cause (Hgb < 10 g/dL); chronic NSAID use (> 4 weeks)		

Clinically significant bleeding - a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction [TIMI] criteria or bleeding requiring medical attention

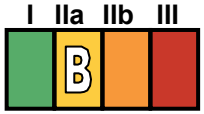
MACE - Major adverse cardiovascular event (composite of death from CV causes, MI or CVA)

Gibson CM, et al. *N Engl J Med*. 2016;375:2423-2434.

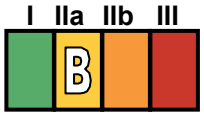
DAPT Duration with anticoagulation



- Administer periprocedural aspirin and clopidogrel to patients undergoing coronary stent implantation.



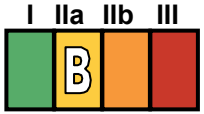
- Triple therapy with aspirin, clopidogrel, and OAC should be considered for 1 month with all stents
  - Consider 6 months with high ischemic risk



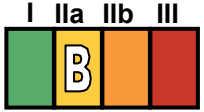
- Dual therapy with clopidogrel and OAC should be considered for 1 month in patients with a high bleeding risk

Valgimigli M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J.* 2017;0:1-48.

DAPT Duration with anticoagulation



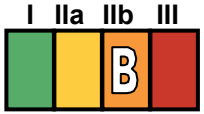
- Consider stopping antiplatelet therapy in patients on OAC at 12 months



- If a DOAC is utilized with aspirin and/or clopidgrel the lowest indicated CVA prevention dose in AF trials should be utilized

Valgimigli M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J.* 2017;0:1-48.

DAPT Duration with anticoagulation



- If rivaroxaban is used in combination with aspirin and/or clopidogrel the suggested dose is 15 mg

- Ticagrelor or prasugrel are not recommended for use as triple therapy with aspirin and OAC

Valgimigli M, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur Heart J.* 2017;0:1-48.

RE-DUAL PCI

- Study design
  - International, open-label, multicenter, randomized controlled trial
- Population
  - 2725 patients with nonvalvular AF who had undergone PCI with stenting
- Treatment Regimen
  - Group 1: Dabigatran 110 mg BID + $P2Y_{12}$ (day 1 = 86.4% C; 12.6% T)
  - Group 2: Dabigatran 150 mg BID + $P2Y_{12}$ (day 1 = 86.9% C; 12.1% T)
  - Group 3: Warfarin + DAPT (day 1 = 90.3% C; 7.8% T)
    - C = clopidogrel; T = ticagrelor
- Primary endpoint
  - ISTH major or clinically relevant nonmajor bleeding (mean follow-up 14 months)

Cannon CP, et al. *N Engl J Med*. 2017;375:2423-2434.

RE-DUAL PCI

Treatment	Dabigatran 110 mg BID + $P2Y_{12}$ for at least 1 yr	Warfarin + DAPT (Aspirin stopped at 1 or 3 months)	Dabigatran 150 mg BID + $P2Y_{12}$ for at least 1 yr	Warfarin + DAPT (Aspirin stopped at 1 or 3 months)
ISTH major or clinically relevant nonmajor bleed	15.4% $p < 0.001$ noninferiority $p < 0.001$ superiority	26.9%	20.2% $p < 0.001$ noninferiority	25.7%
Composite efficacy secondary end point	15.2% $p = 0.30$	13.4%	11.8% $p = 0.44$	12.8%
Notable exclusion criteria	History of stroke or GI bleed within 1 month of randomization; CrCl < 30 mL/min; anemia; treatment with NSAIDs			

ISTH- International Society of Thrombosis and Hemostasis
Composite efficacy end point – Thromboembolic events, death, or unplanned revascularization

Cannon CP, et al. *N Engl J Med*. 2017;375:2423-2434.

RE-DUAL PCI

Treatment	Dual Therapy Groups Combined	Warfarin + DAPT
Composite efficacy secondary end point	13.7% P = 0.005 noninferiority	13.4%

Composite efficacy end point – Thromboembolic events, death, or unplanned revascularization

Cannon CP, et al. *N Engl J Med*. 2017;375:2423-2434.

Ongoing Clinical Trials

- AUGUSTUS
  - 6 month open label trial of apixaban versus warfarin and blinded aspirin versus placebo in AF patients with ACS, or PCI, with stent placement
    - All patients will receive a $P2Y_{12}$ for 6 months
- ENTRUST AF-PCI
  - 12 month open label trial of edoxaban + $P2Y_{12}$ versus warfarin + DAPT in AF patients with ACS, or PCI, with stent placement

Key Takeaways

- Key Takeaway #1
  - In AF patients requiring PCI receiving a DES ticagrelor or prasugrel are not recommended for use as triple therapy with aspirin and an OAC

- Key Takeaway #2
  - If a DOAC is to be given, with aspirin and/or clopidgrel, implementation of the established regimens found in the PIONEER AF-PCI or RE-DUAL PCI trials are recommended in this population at this time

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Propofol: A Safe and Effective Sedative in ECMO?

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Cleveland Clinic
Cleveland, Ohio

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Objective

- Describe the safety and efficacy of propofol in patients utilizing extracorporeal membrane oxygenation (ECMO)

Propofol

- Sedative, hypnotic, amnestic properties via action at several receptors:
  - $GABA_A$
  - Glycine
  - Nicotinic
  - Muscarinic

- Formulated as 10% lipid emulsion

Barr J, et al. Crit Care Med. 2013; 41(1): 263-306.

Choice of Sedative

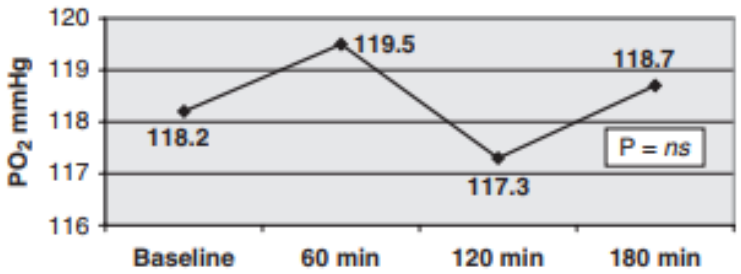
- 2013 SCCM Pain, Agitation and Delirium Guidelines suggest:
  - Sedation strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred over sedation with benzodiazepines (+2B)
- Survey of sedation practices in ECMO found only 35% of responders routinely used propofol
- Others institutions have limited propofol use to as a rescue agent

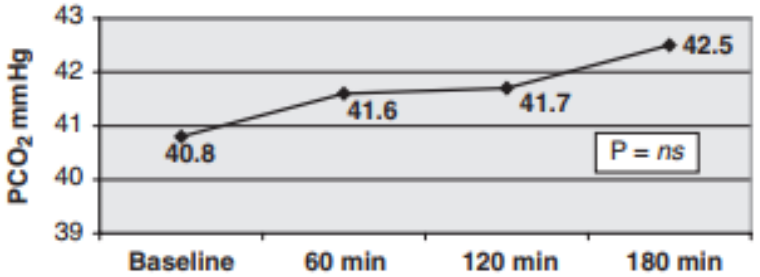
Barr J, et al. Crit Care Med. 2013; 41(1): 263-306.
Buscher H, et al. ASAIO J. 2013; 59(6): 636-641
Shekar K, et al. Anaesth Intensive Care. 2012; 40: 648-655

Propofol and Oxygenators

- Historical concern from cardiopulmonary bypass experience that lipid emulsion will clog/impair gas exchange at oxygenator

- Propofol adsorption will occur with modern oxygenators
  - Gas exchange does not appear to be impaired by propofol adsorption





Rosen DA, et al. J Cardiothorac Anesth. 1990; 4: 332-335.
Hynynen M, et al. Can J Anaesth. 1994; 41(7): 583-588.
Buscher H, et al. ASAIO J. 2013; 59(6): 636-641. Myers GJ, et al. Perfusion. 2009; 24(5): 349-355.

Propofol vs. Non-Propofol in ECMO

Characteristic	Propofol Patients (N = 16)	Non-Propofol Patients (N = 27)	P-Value
Median duration of ECMO (days), n (IQR)	14 (8.5-28)	6.5 (4-12.5)	0.004
Required oxygenator exchange, n (%)	5 (31)	3 (11)	0.10
Total oxygenator exchanges	7	5	N/A
Oxygenator exchanges per ECMO day	0.019	0.017	0.91
Median oxygenator lifespan (days), n (IQR)	9 (7-18)	5 (4-10)	0.02

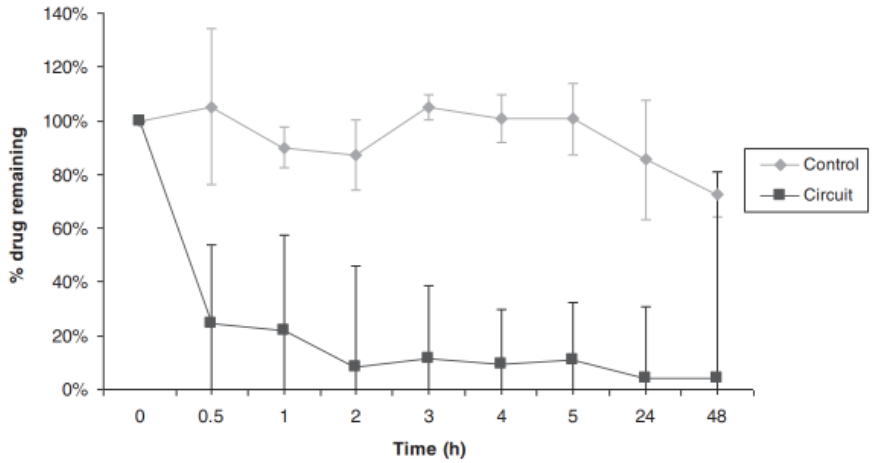
Hohlfelder B, et al. ASAIO J. 2017; 63(2): 179-184.

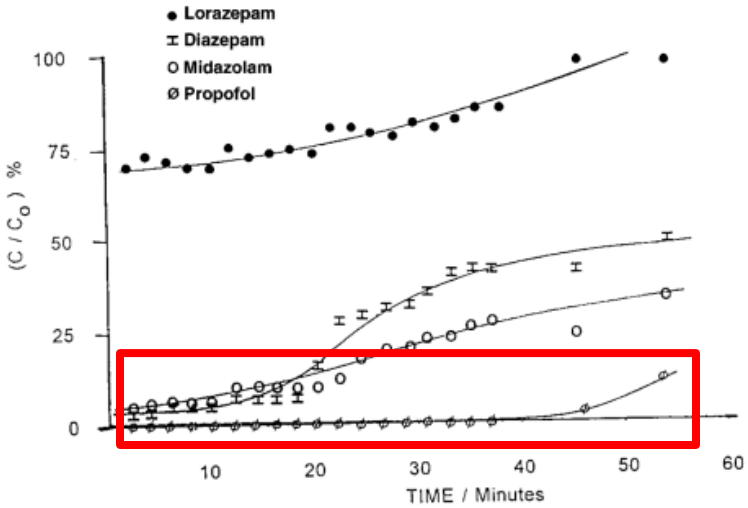
Oxygenator Exchange and Propofol Use in ECMO

Characteristic	Required Exchange (N = 5)	No Exchange (N = 11)	P-Value
ECMO duration (days)*	30 (27-49)	9 (8.5-14.5)	0.09
Propofol duration (days)*	8 (6-10)	2 (1-6)	0.14
Daily propofol dose (mg)*	739 (378-1591)	3196 (1240-4138)	<0.001
Cumulative propofol dose prior to exchange (mg)*	1220 (25-6918)	N/A	N/A
*Median (IQR)			

Hohlfelder B, et al. ASAIO J. 2017; 63(2): 179-184.

Propofol Sequestration in ECMO





- Propofol concentrations significantly lower than expected
  - 89-98% of drug lost in ex vivo circuits

Mulla H, et al. Perfusion. 2000; 15: 21-26.
Lemaitre F, et al. Crit Care. 2015; 19: 40-45.

Real World Experience

- Utilize propofol as first line sedative in ECMO in combination with opioids for pain control/analgosedation

Characteristic	N = 10
Median duration of ECMO (hours), n (IQR)	163 (139 – 244)
Mean weight (kg), n (SD)	84.0 (18.2)
Mean cumulative propofol dose (mg), n (SD)	31,339 (14,761)
Mean propofol administration rate	32.8 mcg/kg/min 2.0 mg/kg/hr

Key Takeaways

- Key Takeaway #1
  - Based on limited data, propofol appears to provide a relatively safe and effective option for sedation in ECMO

- Key Takeaway #2
  - Larger studies needed to describe safety and dosing requirements of propofol in ECMO

Which treatment options have not been shown to have clinical effect on CVD prevention when initiated in dialysis-dependent patients?

A. Statin
B. Cinacalcet
C. Statin + ezetimibe
D. All of the above

What is the manufacturer recommended dose of IV sotalol in pediatric patients?

A. 2 mg/kg/day divided every 8 hours
B. 30 mg/m^2/dose every 8 hours without age factor
C. 30 mg/m2/dose every 8 hours with age factor
D. 150-200 mg/m^2/day divided every 8 hours

Which of the following are potentially appropriate doses of IV sotalol in pediatric patients?

A. 2 mg/kg/day divided every 8 hours
B. 30 mg/m^2/dose every 8 hours with age factor
C. LD 1 mg/kg, followed by 4.5 mg/kg/day continuous infusion
D. All of the above

Which of the following reasons are often cited as reasons that providers avoid propofol use in patients requiring ECMO support?

A. Incompatibility of heparin bound ECMO circuits
B. Risk of clogging/impairing gas exchange at the oxygenator
C. Sequestration of propofol in the ECMO circuit
D. B and C

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Lower Anticoagulation Goals for On -X Aortic Mechanical Valve

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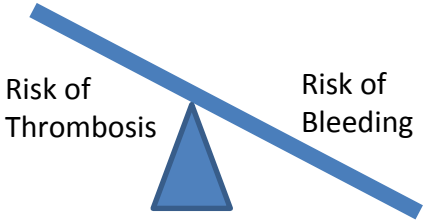
Objective

- Evaluate the available literature supporting and potential limitations of lower anticoagulation goals for the On-X mechanical aortic valve

Speaker has no conflicts of interest to disclose

Thrombogenicity of Mechanical Cardiac Devices



- Mechanical aortic valves are inherently thrombogenic:
  - Non-physiological flow pattern → Blood turbulence and/or stasis
  - Hemolysis / shear stress
  - Device materials → platelet activation
- Thrombogenicity of devices mandates life-long anticoagulation with warfarin
  - Annual risk of bleeding with warfarin 1-2%
  - 60-75% of deaths in patients with mechanical valves are anticoagulation-related
  - Narrow therapeutic window – at risk for bleeding and thromboembolism
  - Quality of life: Frequent lab draws, appointments, dose titrations

Current Guidelines

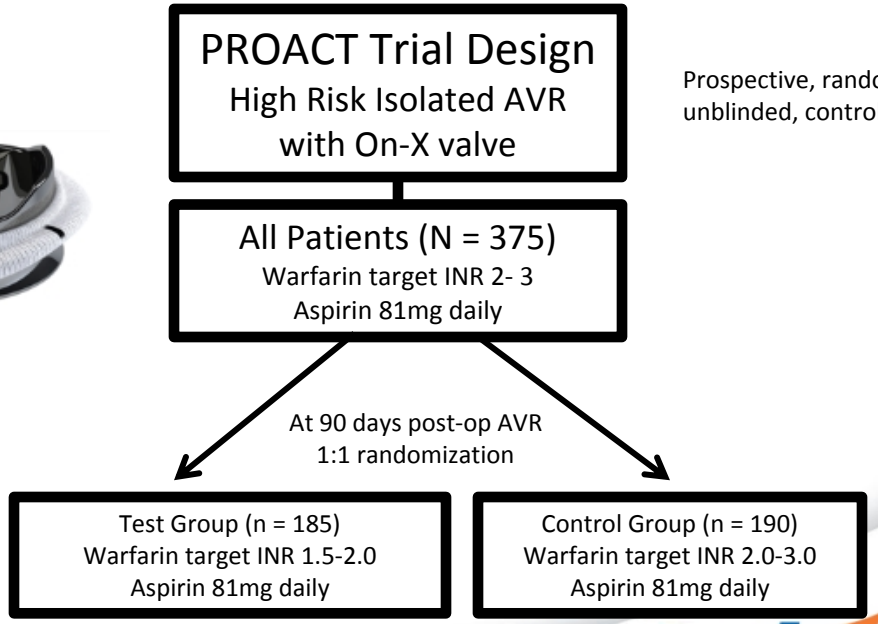
2017 AHA/ACC Focused Update Valvular Heart Disease

Indication (Valve type or RF)	Recommended INR Target
Mechanical leaflet or current-generation single-tilting disc AVR & NO additional RF for TE	2.5
Mechanical AVR and additional RF for TE or an older-generation mechanical AVR (such as ball-in-cage)	3.0
Mechanical On-X AVR and no thromboembolic risk factors	1.5-2.0

Puskas J, et al. J Thorac Cardiovasc Surg 2014;147:1202-11, Yanagawa B, et al. Curr Opin Cardiol 2015;30:140-145, Dasi LP, et al. Clin Exp Pharmacol Physiol. 2009 Feb; 36(2): 225–237, Nishimura RA, et al Circulation. 2017;135:e1159-e1195c

Can Engineering Shift the Thromboembolism "Sweet Spot"?

- On-X mechanical heart valves were designed for lower thrombogenicity
  - Smooth pivots, pure carbon surface, 90 degree leaflets, flared inlet, longer orifice
- FDA approved for lower INR goals for high-risk aortic valves
  - INR target 1.5-2.0 for aortic valves
  - 65% fewer bleeds with no increase in thromboembolism rates



Puskas J, et al. J Thorac Cardiovasc Surg 2014;147:1202-11, Chan V, et al. J Thorac Cardiovasc Surg 2010;140:1053-8, Chambers JB, et al. J Thorac Cardiovasc Surg 2013;145:420-4, Yanagawa B, et al. Curr Opin Cardiol 2015;30:140-145, http://www.cryolife.com/products/on-x-heart-valves/reduced-anticoagulation/ accessed 9/2017

Results of the High-Risk AVR Arm of the PROACT Trial

	Test Group (pt-yr = 766.2)		Control Group (pt-yr = 878.6)		
Event	Patients (n)	Rate (%/pt-yr)	Patients (n)	Rate (%/pt-yr)	p-value
Major Bleeding	12	1.57	34	3.87	0.007
Minor Bleeding	9	1.17	35	3.98	0.001
Total Bleeding	21	2.74	69	7.85	<0.001
Ischemic Stroke	6	0.78	7	0.80	0.975
All TE	21	2.74	15	1.71	0.161
Thrombosis	2	0.26	2	0.23	0.891
Major Event	35	4.57	51	5.8	0.275
Primary Endpoint	44	5.74	86	9.79	0.004

TE = thromboembolism, major event = major bleeding, all TE and valve thrombosis, Primary Endpoint = all bleeding, all TE and valve thrombosis

Puskas J, et al. J Thorac Cardiovasc Surg 2014;147:1202-11, Chan V, et al. J Thorac Cardiovasc Surg 2010;140:1053-8, Chambers JB, et al. J Thorac Cardiovasc Surg 2013;145:420-4, Yanagawa B, et al. Curr Opin Cardiol 2015;30:140-145, http://www.cryolife.com/products/on-x-heart-valves/reduced-anticoagulation/ accessed 9/2017

Lessons from the Past

- Heartmate II Left Ventricular Assist Device (LVAD)
  - Thought to have lower intrinsic thrombogenicity
  - Lowered anticoagulation goals
  - Less than 5 years later, unexpected increase in pump thrombosis
    - Unexpected Abrupt Increase in Left Ventricular Assist Device Thrombosis NEJM 2013
  - Anticoagulation goals subsequently increased

- Study Population
  - Patients with HeartMate II LVAD
  - 837 patients at 3 institutions (895 devices)
  - Implanted from 2004 through mid-2013

Event	Prior to March 2011	March 2011 to January 2013
Confirmed pump thrombosis at 3 months post implantation	2.2% (95% CI, 1.5-3.4)	8.4% (95% CI, 5.0-13.9)
Median Time from implantation to thrombosis	18.6 months (95% CI, 0.5-52.7)	2.7 months (95% CI, 0.0-18.6)

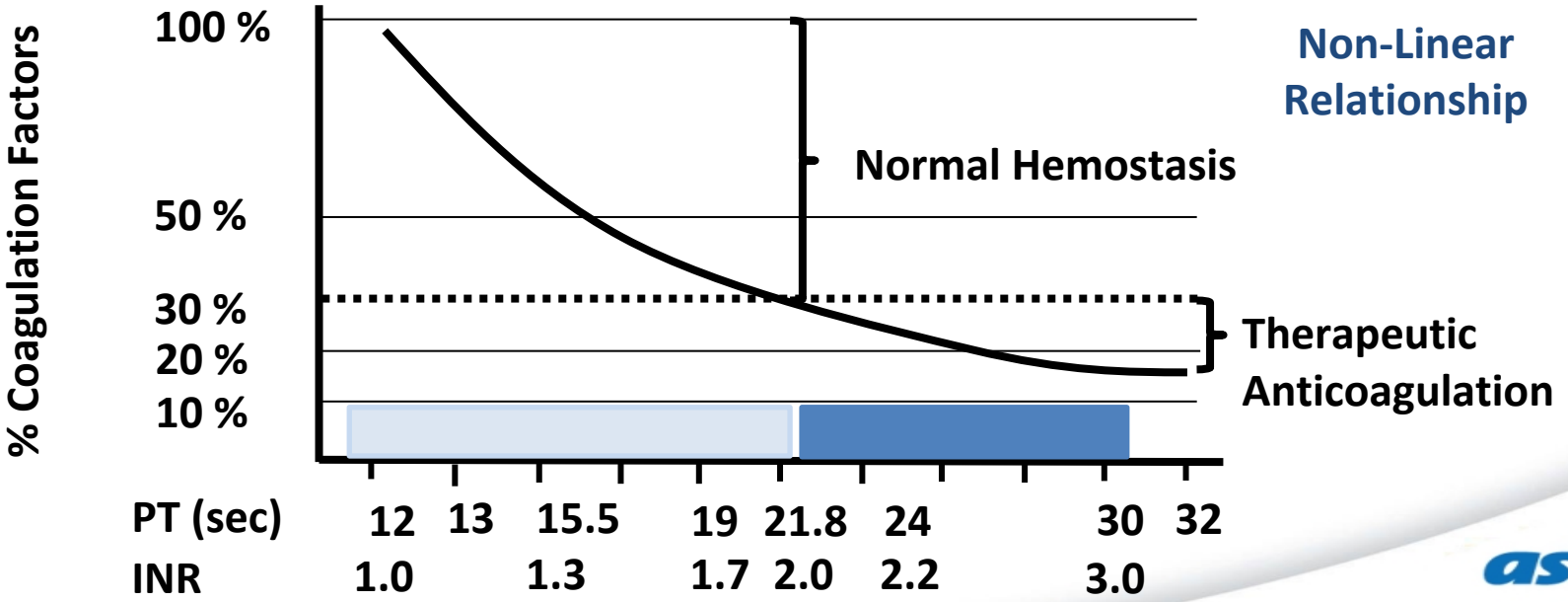
Slaughter MS, et al. J Heart Lung Transplant 2010;29:S1-S39, Starling RC, et al. N Engl J Med 2013; 370(1):33-40, Eikelboom JW, et al

Lessons from the Past

- Could we see a similar rebound effect with mechanical heart valves with lower anticoagulation targets?
  - Should that concern keep us from pushing anticoagulation targets as low as possible to find the “sweet spot”?
- Does this apply to non-warfarin anticoagulants?
  - Results of the RE-ALIGN trial and Dabigatran in LVADs pilot trial
  - Dabigatran failed in both populations

Eikelboom JW, et al. N Engl J Med 2013;369:1206-1214, Andreas MM, et al. Circ Heart Fail. 2017;10:e003709

Relationship Between INR and Clotting Factors



Dzik WS. Transfusion. 2012 May;52 Suppl 1:45S-55S

Future Strategies

- Engineering
  - Continuous improvement in design to match physiologic blood flow with thromboresistant materials
- Alternative anticoagulant strategies
  - Targeting intrinsic pathway factors XI and XII
  - Targets beyond the coagulation cascade (e.g. mast cells)
- Anticoagulants with Antiplatelet(s) or low-dose dual anticoagulants
  - Using low-dose warfarin in combination with a direct-acting oral anticoagulant

Connors JM. Circ Heart Fail 2016;9:e003166, Ponomaryov T, et al. Circulation Res 2017;DOI:CIRCRESAHA.117.311185

Key Takeaway

- After the standard anticoagulation therapy for mechanical AVR for the first 90 days post-operatively:
  - A strategy of reduced anticoagulation (warfarin targeting an INR of 1.5 -2.0 in combination with aspirin 81mg daily) after mechanical aortic valve replacement with the On-X valve appears safe and effective based on interim and 5-year results of the PROACT Trial (single RCT)
  - But long-term data and vigilant monitoring is required to ensure we do not see increased thrombotic event rates

References

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Key Takeaway

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Isoproterenol, Theophylline, Terbutaline, Oh My! Post-transplant Sinus Node Dysfunction

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Meet AW

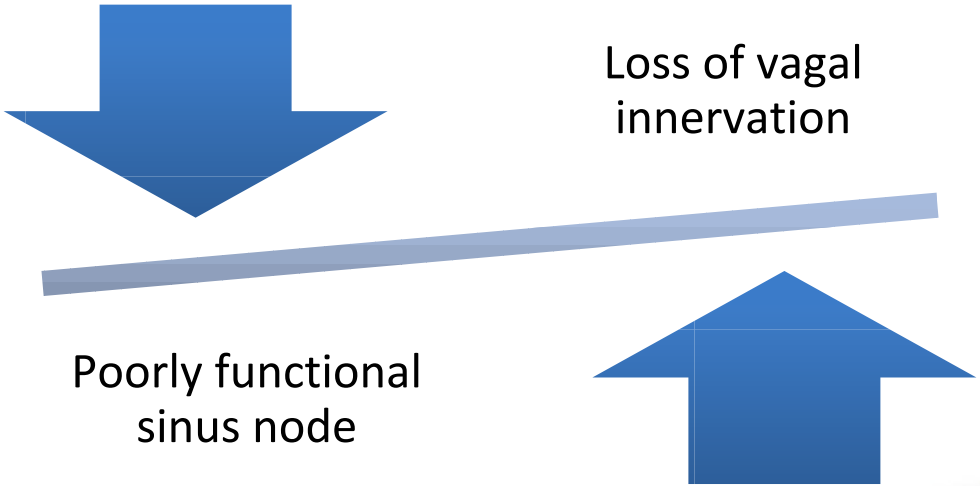
- AW is a 60 year old female with ischemic cardiomyopathy and recurrent VT on amiodarone 400mg daily, now POD2 from orthotopic heart transplant
- HR 100 secondary to epicardial pacing wires
- Underlying heart rate 60 bpm
  - CI and BP drop when pacing turned off

Meet AW

What is the best therapy to recommend for AW's low heart rate?

A. Theophylline 200mg PO BID
B. Terbutaline 5mg PO TID
C. Isoproterenol 1mcg/min IV
D. Continue pacing only

Heart Transplant and Heart Rate



Sinus Node Dysfunction (SND)

- Remember equation for cardiac output? CO = HR x SV
- Incidence of SND: up to 40% of heart transplant recipients
- Risk factors
  - Surgical approach (bicaval > biatrial)
  - Ischemic time
  - Pre-operative amiodarone

Sinus Node Dysfunction Management

- Goal Heart Rate: 90-110 bpm
- Maintained for 3 – 4 weeks post-transplant or until systolic and diastolic dysfunction resolve

Therapy for SND

Non-Pharmacologic

- Temporary epicardial pacing
- Permanent pacemaker

Pharmacologic

- Isoproternol
- Theophylline
- Terbutaline
- Albuterol

Isoproterenol (Isuprel®)

- Non-selective direct β agonist
- Chronotrope, inotrope, vasodilator
- Dose: 2 – 20 mcg/min
  - Can be titrated to HR of 90 – 110 bpm
  - Tachycardia usually dose-limiting effect
- Renal elimination (50-80%)
- T1/2: 3 – 7 hours
- Comparable to atrial pacing + dobutamine
- **Recent acquisition cost increases**

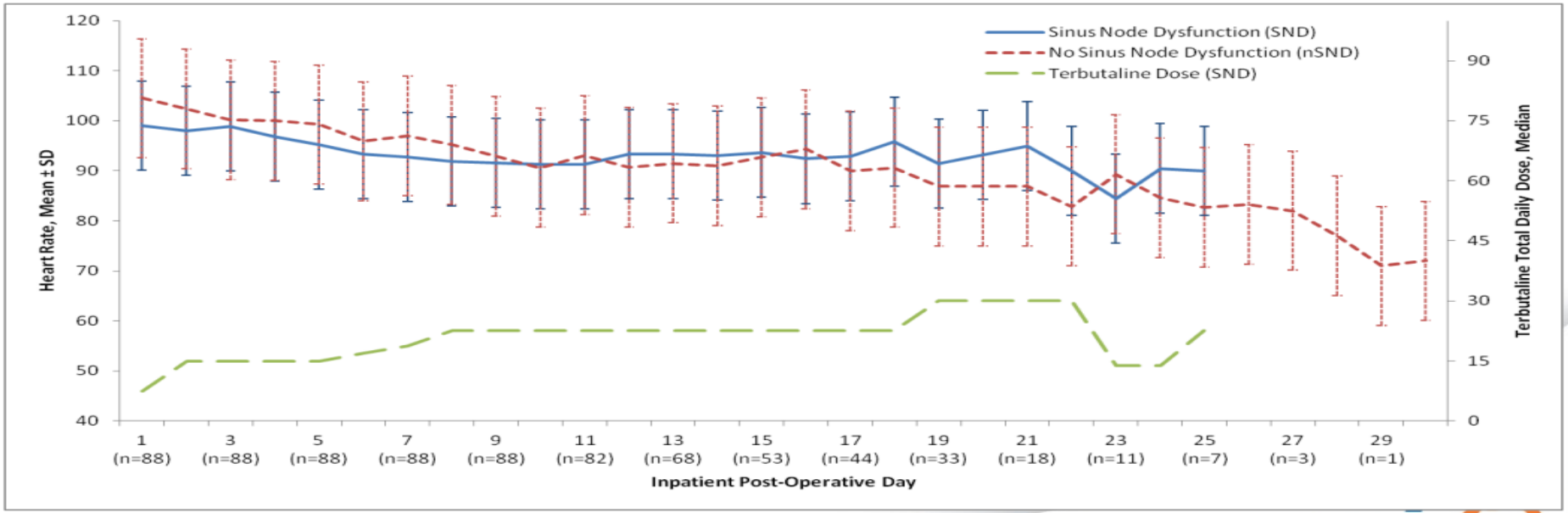
Terbutaline (Brethine®)

- Oral direct β-agonist
- Onset of action: 30 – 40 minutes
- Dose range (anecdotal): 2.5 mg – 10 mg
- Phase II hepatic metabolism
- $t_{1/2}$ = 3.4 hours
  - Dosing 2 – 3 times a day
- Adverse Effects
  - CNS: nervousness, restlessness, trembling
  - Cardiovascular: palpitations, arrhythmias

Terbutaline Evidence

- 40/42 (95%) with SND: isoproterenol → PO terbutaline
- 2/42 (5%) with SND: isoproterenol → PO theophylline

No permanent pacemakers implanted



J Heart Lung Transplant. 2014:33(4) S115

Theophylline

- Direct myocardial stimulation and increased release of natural catecholamines
- Onset of action: 1 – 2 hours
- $T_{1/2}$: 6 – 12 hours
- TDM needed?

Theophylline Evidence

Study	Sample Size	Theophylline Dose	Outcomes	Notes
Redmond 1993	15 treated compared to 112 historical controls	150mg PO BID → increased PRN to maintain HR >90 No concentrations reported	93.3% maintained HR >90 16.1% vs. 2.6% required permanent pacing	No AE reported
Bertolet 1996	18 treated compared to 29 without SND	IV theophylline changed to mean 474mg/day Mean concentration 15.7mg/dL	HR increased from 62 bpm to 89 bpm after therapy, no difference compared to non-SND patients	1/15 severe nausea

J Heart Lung Transplant. 1993 Jan-Feb;12(1 Pt 1):133-8
J Am Coll Cardiol 1996;28:396-9

Summary of Agents

Agent	Cardiac contractility	Peripheral vasodilation	Chronotropic effect	Arrhythmia risk
Isoproterenol	++++	+++	++++	++++
Terbutaline	+/-	+	+/++	+
Theophylline	+/-	-	+/++	+

Back to AW

What is the best pharmacologic therapy to recommend for AW's low heart rate?

A. Theophylline 200mg PO BID
B. Terbutaline 5mg PO TID
C. Isoproterenol 1mcg/min IV
D. Continue pacing only

Key Takeaways

- Key Takeaway #1
  - Sinus node dysfunction is a common post-transplant complication
- Key Takeaway #2
  - Isoproterenol is an optimal pharmacologic therapy for sinus node dysfunction, however cost and IV route only make its widespread use challenging
- Key Takeaway #3
  - Oral agents such as theophylline and terbutaline are reasonable oral alternatives to isoproterenol

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To Do or Not to Do?
DOAC Dosing in Obesity

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Background

- Obesity is both common and costly
  - 1 in 3 adults you take care of will be obese
  - Estimated annual medical cost of obesity was $147 billion in 2008
- Significant pharmacokinetic changes have been observed in obese patients

JAMA. 2014;311(8):806-814 | J Clin Pharm Ther. 2014, 39, 584–608
http://www.who.int/mediacentre/factsheets/fs311/en/
http://www.cdc.gov/obesity/data/adult.html

Categories of Weight

Classification	Body Mass Index (BMI, kg/m^2)
Underweight	< 18.5
Normal	18.5-24.9
Overweight	25-29.9
Obese	≥ 30
Obese Class I	30-34.9
Obese Class II (Severely Obese)	35-39.9
Obese Class III (Morbidly Obese)	≥ 40

http://apps.who.int/bmi/index.jsp?introPage=intro_3.html
https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm

(DOACs)

DIRECT-ACTING ORAL ANTICOAGULANTS

DOAC Overview

Medication	Absorption	Distribution	Metabolism	Excretion
Dabigatran	3-7%	Vd: 50-70 L 35% PPB	Hepatic	Urine (80%)
Rivaroxaban	10 mg: 80-100% 20mg: 66%	Vd: 50 L 92-95% PPB	Hepatic	Urine (66%) and feces
Apixaban	50%	Vd: 21 L 87% PPB	Hepatic	Urine (27%) and feces
Edoxaban	62%	Vd: 107 L 55% PPB	Hepatic	Urine (50%) and feces

PPB: plasma protein bound

LexiComp | Dabigatran Package Insert | Rivaroxaban Package Insert | Apixaban Package Insert | Edoxaban Package Insert

Dabigatran

Trial	Weight Categories	Number of Obese Patients
RE-COVER	≥ 100 kg BMI ≥ 35 kg/m^2	502/2539 (20%) 306/2539 (12%)
RE-COVER II	≥ 100 kg BMI ≥ 35 kg/m^2	438/1280 (34.2%) 302/1280 (23.6)
RE-LY	≥ 100 kg	3099/18,113 (17.1%)
RE-MEDY	≥ 100 kg	299/1430 (20.9%)
RE-SONATE	≥ 100 kg	122/681 (17.9%)

J Thromb Haemost 2016; 14: 1308–13

Dabigatran

Author (year)	Breur (2013)	Rafferty (2013)
Design	Case report	Case report
Sample size	48 YOM, BMI 44.7 kg/m^2, taking dabigatran 150 mg BID	69 YOF, BMI 48.3 kg/m^2, taking dabigatran 150 mg BID
Results	Ischemic stroke occurred while on therapy; peak plasma level on day 4 below therapeutic threshold	PE occurred while on therapy, patient switched to enoxaparin and warfarin
Safety	Not addressed	Not addressed
Conclusions	Fixed-dose regimen of dabigatran may be ineffective in patients with severe obesity	Patient had several factors that could contribute to decreased dabigatran exposure, including obesity

N Engl J Med 2013; 368: 2440-2. | Ann Pharmacother 2013;47:e20.

PE: pulmonary embolism

Dabigatran

Author (year)	Safouris (2014)
Design	Case report
Sample size	67 YOM, BMI 39.6 kg/m^2, taking dabigatran 150 mg BID
Results	Dabigatran levels never reached IQR for therapeutic Cmax, most of the time was below IQR for therapeutic Cmin; Patient changed to rivaroxaban and had therapeutic levels
Safety	Not addressed
Conclusions	Obese, non-diabetic patients may not be appropriate candidates for fixed-dose dabigatran; consider monitoring levels if used in patients > 100 kg

IQR: interquartile range

J Neurol Sci 2014; 346: 366-7.

Rivaroxaban

Trial	Weight Categories	Number of Obese Patients
ROCKET-AF	≥ 90 kg BMI ≥ 35 kg/m^2	2035/7131 (28.5%) 972/7131 (13.6%)
EINSTEIN DVT	≥ 100 kg	245/1731 (14.2%)
EINSTEIN PE	≥ 100 kg	345/2419 (14.3%)
EINSTEIN EXTENSION	≥ 100 kg	85/602 (14.1%)

J Thromb Haemost 2016; 14: 1308–13

Rivaroxaban

Author (year)	Kubitza (2007)	Mahlmann (2013)
Design	Randomized, single-dose, placebo-controlled, parallel-group PK study	Case report
Sample size	16 weighing ≤ 50 kg 16 weighing 70-80 kg 16 weighing > 120 kg	27 YOF, s/p gastric bypass surgery, 145 kg
Results	C_{max}, AUC, $t_{1/2}$, and Factor Xa activity inhibition similar between > 120 kg and 70-80 kg	Peak values of rivaroxaban were in the expected range
Safety	No bleeding events reported	Not reported
Conclusions	Rivaroxaban is unlikely to require dose adjustment for body weight	Standard doses of rivaroxaban resulted in therapeutic drug levels

J Clin Pharmacol 2007; 47: 218-26 | J Thromb Thrombolysis (2013) 36:533–535

Apixaban

Trial	Weight Categories	Number of Obese Patients
AMPLIFY	≥ 100 kg BMI > 35 kg/m^2	522/2691 (19.4%) 349/2691 (13.0%)
ARISTOTLE	BMI ≥ 30 kg/m^2	7159/17,913 (40%)

J Thromb Haemost 2016; 14: 1308–13

Apixaban

Author (year)	Upreti (2013)
Design	Open-label, single-dose, parallel group PK study
Sample size	18 weighing ≤ 50 kg 18 weighing 65-85 kg 19 weighing ≥ 120 kg
Results	Cmax 31% lower, AUC 23% lower in high weight group Anti-factor Xa activity was linear with plasma concentrations
Safety	No bleeding events reported
Conclusions	The change in exposure based on body weight is unlikely to require dose adjustment

Br J Clin Pharmacol. 2013 Dec;76(6):908-16.

Edoxaban

Trial	Weight Categories	Number of Obese Patients
ENGAGE AF	Not assessed	Not provided
HOKUSAI VTE	> 100 kg	611/4118 (14.8%)

J Thromb Haemost 2016; 14: 1308–13

Edoxaban

- No studies examining the effects of body weight on the pharmacokinetics of edoxaban have been published to date

J Thromb Haemost 2016; 14: 1308–13

DOACs

Weighing in…

- ISTH Guidelines:
  - Suggest that DOACs not be used in patients with a BMI > 40 kg/m^2 or weight > 120 kg due to limited clinical data
  - Available PK/PD data suggests decreased drug exposures, reduced peak concentrations, and shorter half-lives as weight increases

ISTH = International Society on Thrombosis and Hameostasis

J Thromb Haemost 2016; 14: 1308–13

DOACs

Weighing in…

- ISTH Guidelines:
  - If DOACs are used in these patients, suggest monitoring of drug-specific levels
  - If level is subtherapeutic, suggest changing to a vitamin K antagonist rather than dose-adjusting DOAC

ISTH = International Society on Thrombosis and Hameostasis

J Thromb Haemost 2016; 14: 1308–13

Summary

- Total body weight should be used in patient assessment

Anticoagulant	Recommendation in Obesity
Dabigatran	Avoid; consider monitoring levels
Rivar	ng levels
Apix	ng levels
Edoxaban	Lack of data precludes recommendation

Always consider patient's clinical picture

Key Takeaways

- Key Takeaway #1
  - Data on use of DOACs in obesity is limited
- Key Takeaway #2
  - Consider avoiding DOACs in patients with a BMI > 40 kg/m^2, particularly dabigatran and edoxaban
- Key Takeaway #3
  - If using DOACs in patients with a BMI > 40 kg/m^2, consider drug-specific monitoring

Self Assessment Question

Results from the PROACT Trial of On-X mechanical heart valves suggest the following regarding anticoagulation due to lower intrinsic thrombogenicity:

A. Anticoagulation is not required for On-X valves in the aortic position
B. Reduced anticoagulation with warfarin targeting an INR of 1.5-2.0 is sufficient for On-X valves in the aortic position
C. Reduced anticoagulation with warfarin targeting an INR of 1.5-2.0 is sufficient for On-X valves in the aortic or mitral positions
D. Anticoagulation with a direct acting oral anticoagulant should replace warfarin for On-X valves

Which DOACs are most suitable for use in obese patients based on the limited available data?

A. Dabigatran and apixaban
B. Rivaroxaban and apixaban
C. Apixaban and edoxaban
D. Rivaroxaban and edoxaban

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