Updates in Cardiology

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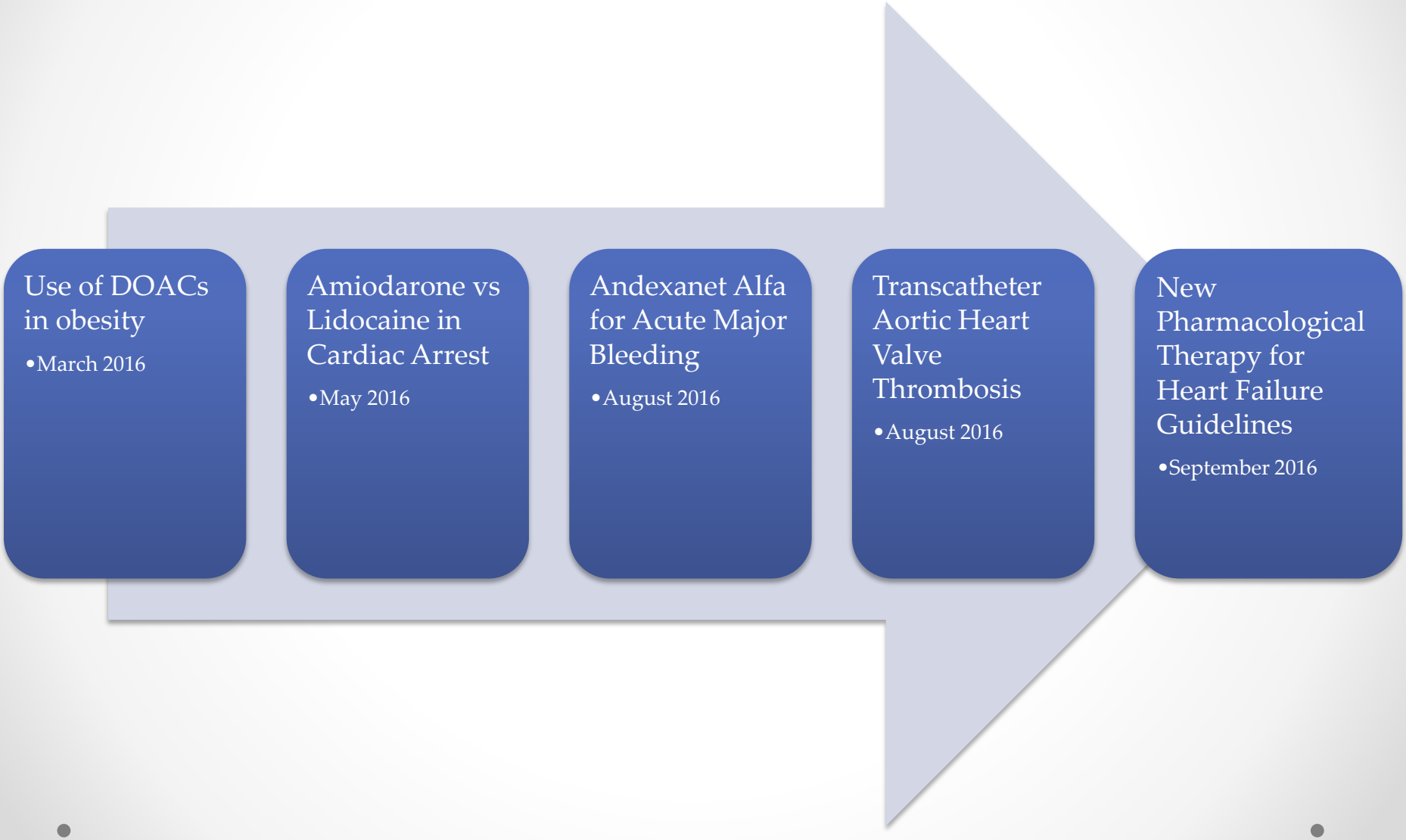
I have no actual or potential conflicts of interest to disclose.

Updates in Cardiology - 2016



Objectives

- Describe outcomes of amiodarone versus lidocaine in out-of-hospital cardiac arrest. ***(How the presented topic impacts patient outcomes)***
- Direct Oral Anticoagulants ***(Recommend therapeutic means to achieve clinical endpoints)***
  - Explain mechanism of andexanet alfa for reversal of Xa inhibitors.
  - Assess limitations of current literature surrounding direct oral anticoagulants in obesity.
- Differentiate between current clinical guideline recommendations for TAVR antiplatelet management, and new concerns for transcatheter aortic valve thrombosis. ***(Review evidence based guidelines and best practices described)***
- New Pharmacological Therapy for Heart Failure
  - Evaluate clinical scenarios where new agents, valsartan/sacubitril and ivabradine, may improve patient outcomes. ***(Identify two clinical endpoints of the presented topic)***

Italicized objective summaries are General NDSHP Drug Therapy Case Series Objectives

Abbreviations

- ACCF/AATS/SCAI/STS
- AF: Atrial fibrillation
- ACC/AHA/AFSA
- ARNI: Angiotensin receptor-neprilysin inhibitor
- BMI: Body Mass Index
- BNP: B-type natriuretic peptide
- CCS: Canadian Cardiovascular Society
- DAPT: Dual Antiplatelet Therapy
- DOACs: Direct Oral Anticoagulants
- ESC/EACTS: European Society of Cardiology/European Association for Cardiothoracic Surgery
- HFrEF: Heart Failure with Reduced Ejection Fraction
- LVEF: Left Ventricular Ejection Fraction
- MACCE: Major Adverse Cardiac and Cerebrovascular events
- NYHA: New York Heart Association
- PK/PD: Pharmacokinetics/Pharmacodynamics
- SAPT: Single antiplatelet therapy
- SAVR: Surgical Aortic Valve Replacement
- SSC of the ISTH: Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis
- STS: Society of Thoracic Surgeons
- TAVI: Transcatheter aortic valve implantation
- TAVR: Transcatheter aortic valve replacement
- VTE: Venous Thromboembolism

Amiodarone, Lidocaine, or Placebo for Out-of Hospital Cardiac Arrest

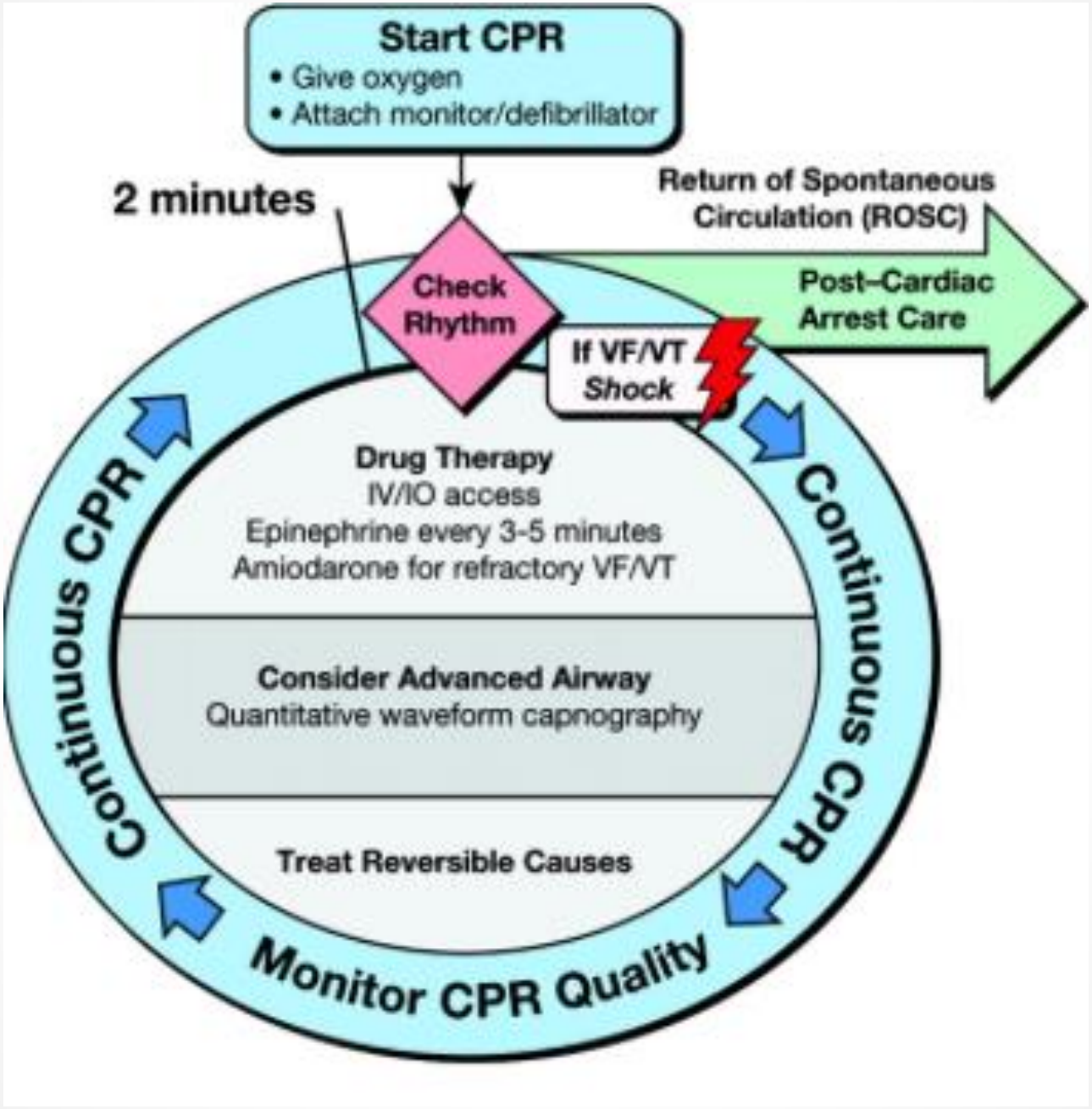
New England Journal of Medicine

May 5, 2016

Out-of-Hospital Cardiac Arrest

- Accounts for 300,000 deaths per year in N. America[1]
  - May have ventricular fibrillation or pulseless electrical activity as the primary rhythm
  - Rate of survival with good neurological function averages 8.5% [1]
- Amiodarone vs placebo,1999 [2]
  - Amiodarone vs placebo was administered after 3 or more shocks were administered
  - Amiodarone group was more likely to survive to hospital admission (44% vs 34%, p=0.03).
- Amiodarone vs lidocaine, 2002 [3]
  - Amiodarone vs lidocaine were administered for refractory ventricular fibrillation after 3 shocks, one dose of epinephrine, and one further shock.
  - Amiodarone vs lidocaine group was more likely to survive to hospital admission (22.8% vs 12%, p=0.009)

1: Mozaffarian, Circulation 2015; 131(4):e29-322.
2:Kudenchuk, N Engl J Med 1999; 341:871-8.
3: Dorian, N Engl J Med 2002;346:884-90.



Link, Circulation 2015;132:Suppl 2:S444-64.

Amiodarone, Lidocaine, or Placebo for Out-of Hospital Cardiac Arrest

- Randomized, double blinded, placebo controlled, pre-hospital trial
- Included 3000 patients with non-traumatic, out-of-hospital cardiac arrest
  - Shock refractory ventricular fibrillation or pulseless ventricular tachycardia
- Amiodarone 300 mg vs lidocaine 120 mg vs normal saline

Kudenchuk, N Engl J Med 2016;374:1711-22.

Outcomes

- No significant differences in primary and secondary outcomes:
  - Survival to discharge and modified Rankin score ≤ 3
  - No significant difference between either treatment vs placebo or amiodarone vs lidocaine
- Exploratory analysis
  - Admitted to hospital
    - Significantly higher rates if received amiodarone or lidocaine vs placebo
    - No differences when amiodarone vs lidocaine

Kudenchuk, N Engl J Med 2016;374:1711-22.

Interpretation and application to practice

- Heterogenicity of treatment effect existed based on if the arrest was witnessed or not
  - If witnessed, amiodarone and lidocaine were associated with higher survival to hospital discharge
- Placebo group more likely to require additional antiarrhythmic, and greater number of shocks
- Estimated survival rates differed less than anticipated, possibly suggesting trial is underpowered to detect a difference

Kudenchuk, N Engl J Med 2016;374:1711-22.

Direct Oral Anticoagulants

Andexanet Alfa for Acute Major Bleeding – August 2016

Use of DOACs in obesity, ISTH recommendations – March 2016

Xa inhibitors

- Approved indications:
  - Stroke prevention in non-valvular atrial fibrillation
    - Rivaroxaban, Apixaban, Edoxaban
  - VTE treatment
    - Rivaroxaban, Apixaban, Edoxaban
  - VTE prevention
    - Rivaroxaban, Apixaban
- Compared with warfarin:
  - DOACs had lower rates of major bleeding in primary atrial fibrillation trials[1]
    - Reduced relative risk of intracranial bleeding
    - Although higher rates of major gastrointestinal bleeding
- Problems exist:
  - No specific antidote for Xa inhibitors
  - Dosing in obesity

Sardar, Int J Cardiology, 2015

Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

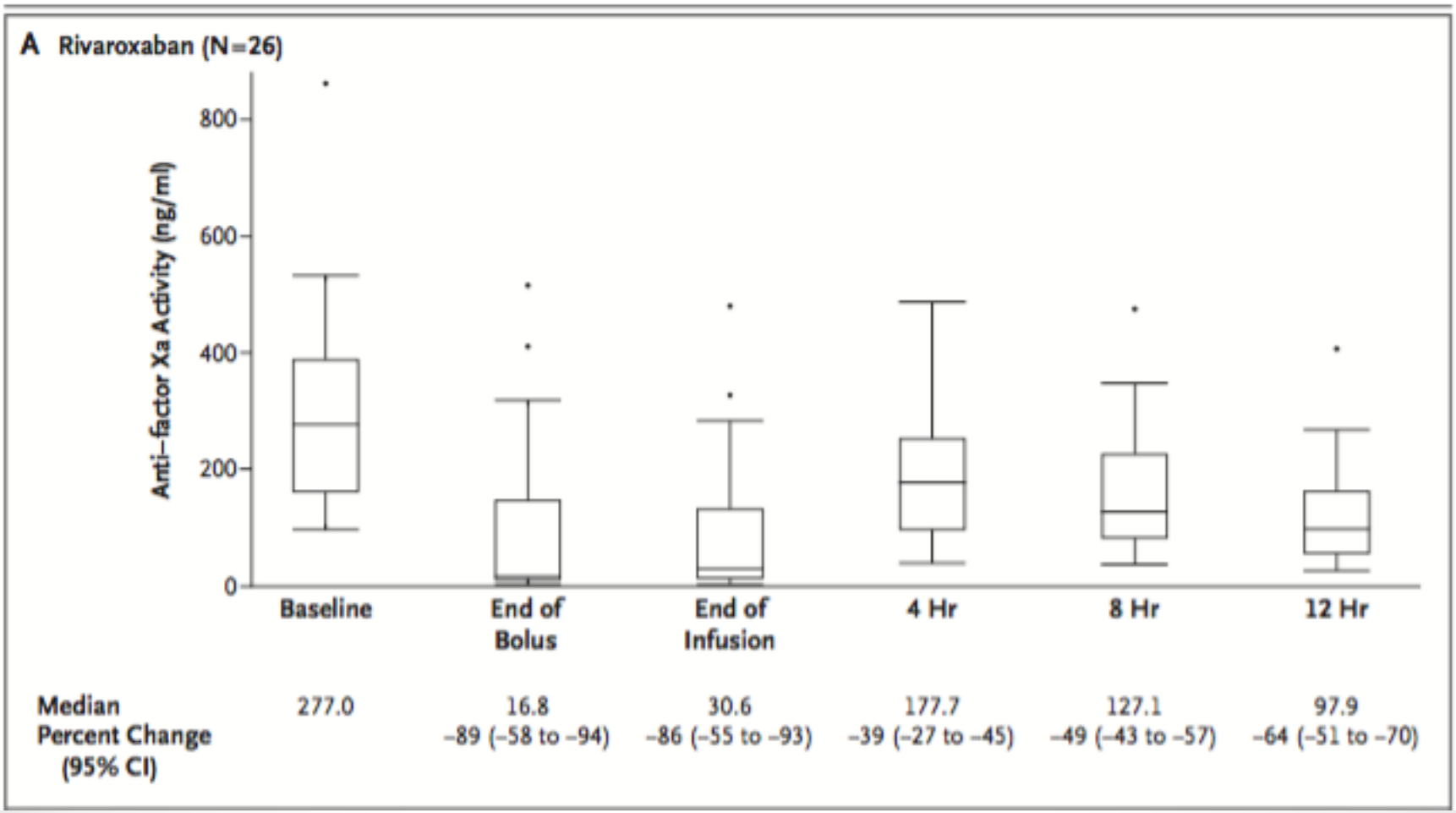
New England Journal of Medicine

August 30, 2016

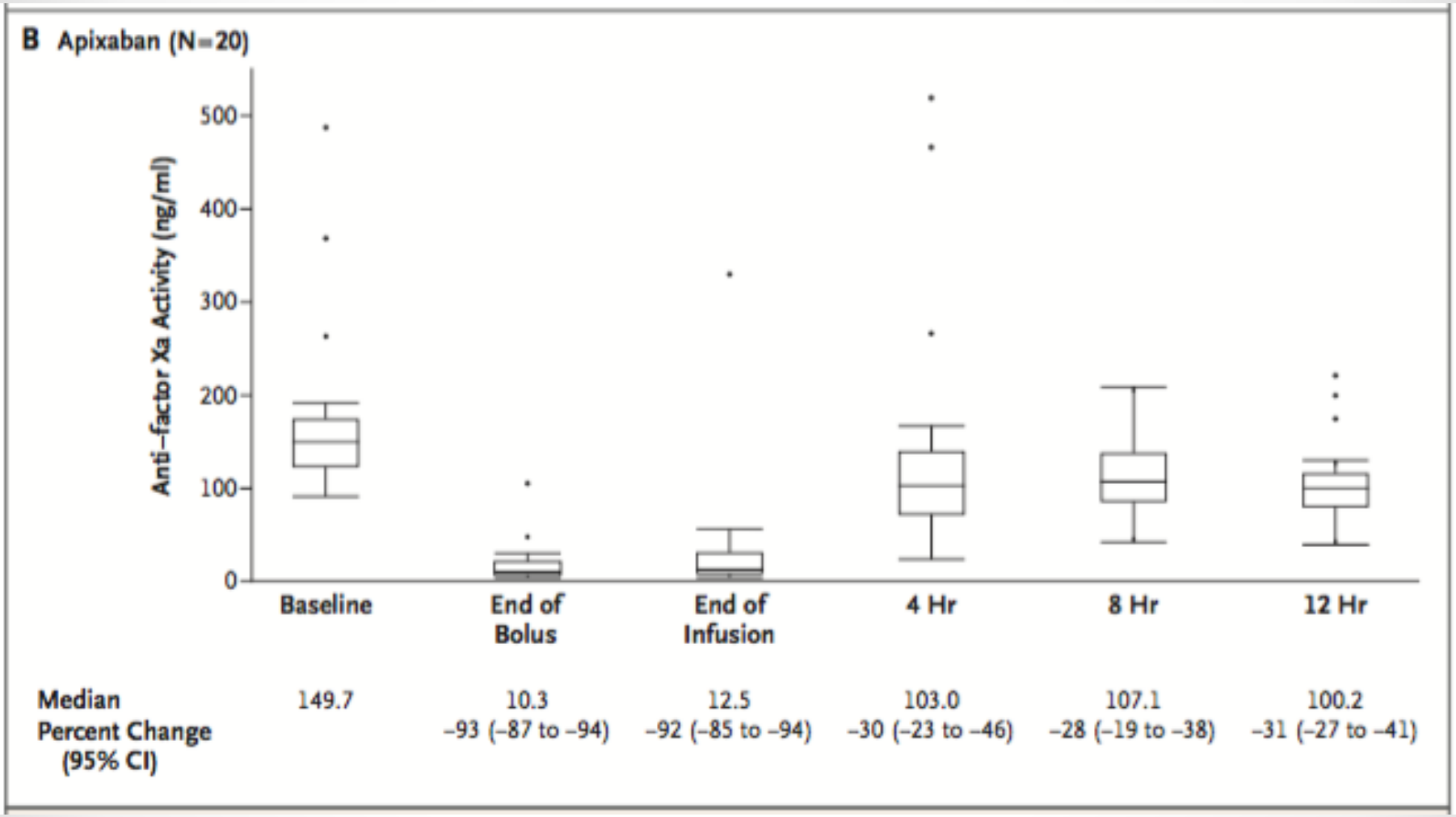
Andexanet Alfa for Acute Major Bleeding Associated with Factor Xa Inhibitors

- Andexanet Alfa
  - Reverses direct and indirect factor Xa inhibitors
  - Recombinant, modified human factor Xa decoy
    - Binds to Factor Xa inhibitors
    - Does not have intrinsic catalytic activity
- ANNEXA-4
  - First study in patients with acute major bleeding
  - Ongoing, multicenter, prospective, open label study
  - Patient population:
    - 67 patients, average age: 77 years
    - Major bleeding
      - Gastrointestinal bleeding: 33 patients
      - Intracranial bleeding: 28 patients
      - Other bleeding: 6 patients

Connolly, N Engl J Med, 2016



Connolly, N Engl J Med, 2016



Connolly, N Engl J Med, 2016

Xa Inhibitors in Obesity

Drug	Trial	Weight categories	Number of obese patients (%)
Dabigatran	RE-COVER I	≥ 100 kg	502/2539 (20)
		BMI ≥ 35	306/2539 (12)
	RE-COVER II	> 100 kg	438/1280 (34.2)
		BMI > 35	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)
Rivaroxaban	EINSTEIN DVT	> 100 kg	245/1731 (14.2)
	EINSTEIN PE	> 100 kg	345/2419 (14.3)
	EINSTEIN EXTENSION	> 100 kg	85/602 (14.1)
	ROCKET-AF	> 90 kg	2035/7131 (28.5)
		BMI > 35	972/7131 (13.6)
Apixaban	AMPLIFY	≥ 100 kg	522/2691 (19.4)
		BMI > 35	349/2691 (13.0)
	ARISTOTLE	None	
Edoxaban	ENGAGE AF TIMI 48	None	
	HOKUSAI VTE	> 100 kg	611/4118 (14.8)

Martin, J of Thrombosis and Haemostasis, 2016

Use of direct oral anticoagulants in obesity: Guidance from SSC of the ISTH

- Recommendations:
  - Standard dosing of DOACs in patients with:
    - BMI ≤ 40 kg/m2
    - Weight ≤ 120 kg
    - For indications including VTE treatment, VTE prevention, and prevention of ischemic stroke in non-valvular atrial fibrillation
  - DOACs should not be used in patients with:
    - BMI > 40 kg/m2 or weight > 120 kg
      - Limited clinical data
      - Available PK/PD suggests decreased drug exposure, lower peak concentrations, and shorter half-lives

Martin, J of Thrombosis and Haemostasis, 2016

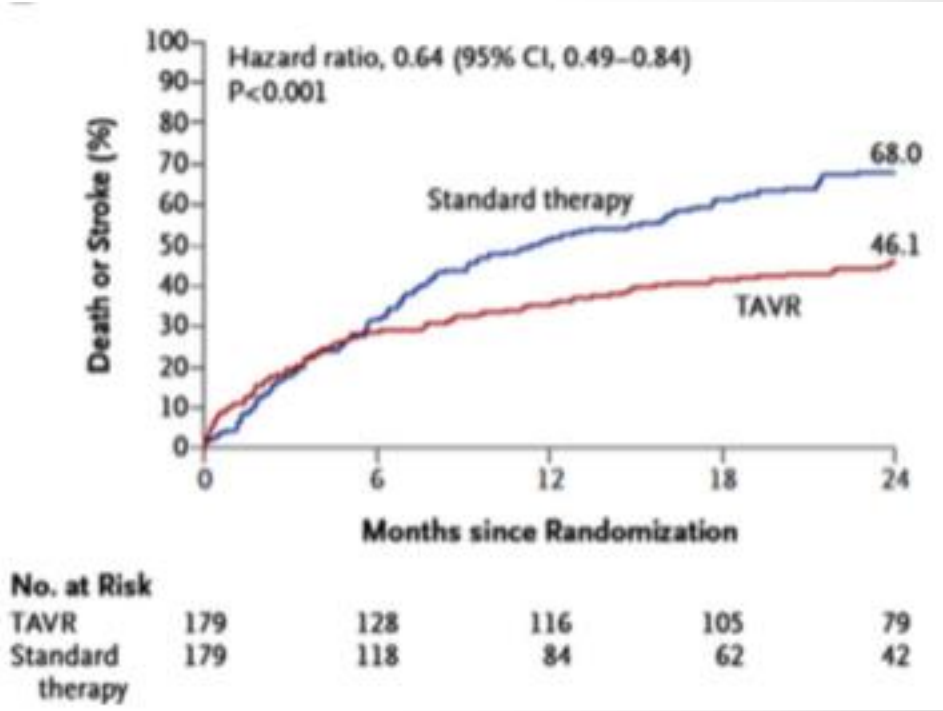
Transcatheter Aortic Valve Replacement

Transcatheter Aortic Heart Valve Thrombosis

Journal of the American College of Cardiology – August 2016

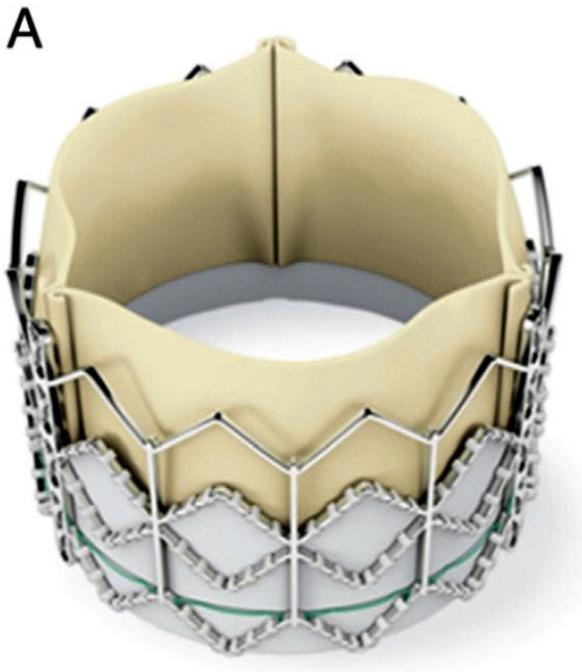
Transcatheter Aortic Valve Replacement

- Treatment technique for patients with severe aortic stenosis, who are not candidates for open-heart surgery
  - TAVR can improve symptoms and extend life
  - Although, rate of stroke higher in TAVR group compared with medical therapy[2]
    - First 30 days: ischemic events 6.7% vs 1.7%, p=0.02
    - Beyond 30 days: hemorrhagic strokes 2.2% vs 0.6%, p=0.16

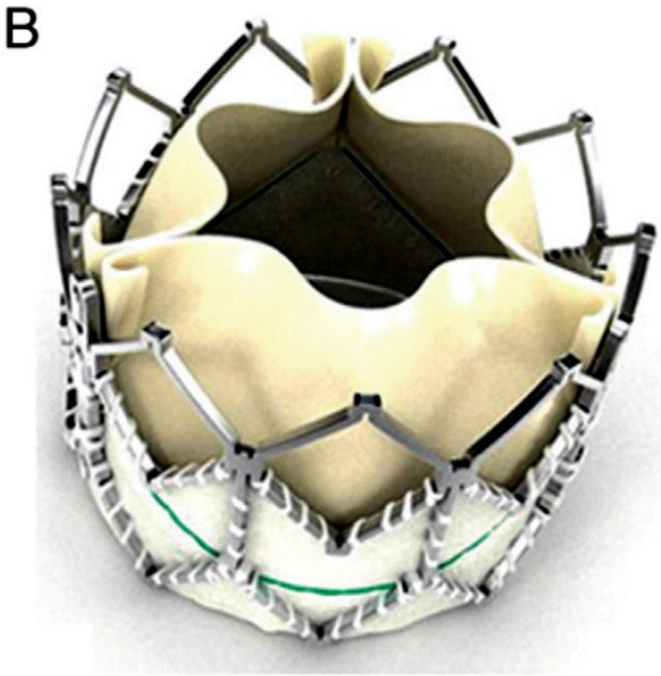


1: Webb, J Am Coll Cardiol 2012;60:483–92.
2: Smith, N Engl J Med, 2011

Available Transcatheter Valves



Edwards SAPIEN



SAPIEN XT

CoreValve

Webb, J Am Coll Cardiol 2012;60:483–92

TAVR Guideline Recommendations

- AHA/ACC Guideline for Management of Patients with Valvular Heart Disease, 2014 [1]
  - TAVR is recommended if patients have (1, B):
    - An indication for aortic valve replacement for aortic stenosis
    - Prohibitive surgical risk
    - Predicted post-TAVR survival > 12 months

1: Nishimura, J Am Coll Cardiol 2014;63:e57–185
2: Whitlock R. CHEST 2012

Antithrombotic Therapy Following TAVR

	AHA/ACC Guidelines, 2014	CCS Position Statement, 2012	ACCF/AATS/SCAI/STS Expert Consensus, 2012	ESC/EACTS Guidelines, 2012
Post-procedural antithrombotic therapy	Aspirin 75-100 mg/day + clopidogrel 75 mg/day for 6 months	Aspirin 80 mg/day + thienopyridine for 1-3 months	Aspirin 81 mg/day + clopidogrel 75 mg/day for 3-6 months	Low-dose aspirin + a thienopyridine early after TAVR
Post-procedural antithrombotic therapy if indication for anticoagulation (AF)	No specifications for AF patients	Avoid triple therapy unless definite indication exists	If warfarin indicated (AF) then no clopidogrel	A combination of VKA and aspirin or thienopyridine is generally used, but should be weighed against increased risk of bleeding
Long-term antithrombotic therapy	Lifelong aspirin 75-100 mg daily (Class IIb; LOE: C)	Low-dose aspirin indefinitely	Aspirin 81 mg/day indefinitely	Low-dose aspirin indefinitely

Lung B, European Heart Journal, 2014

Questions exist…

- Type of valve variations:
  - Sapian Valves[1]
    - PARTNER trial: 6 months of dual antiplatelet therapy
  - CoreValve Study [2]
    - 3 months of dual antiplatelet therapy
- Ussia, 2011[3] – Patients randomized to clopidogrel/ASA or ASA alone
    - No significant differences in major adverse cardiac events at 30 days and 6 months

1: Leon, N Engl J Med, 2010
2: Adams, N Engl J Med, 2014
3: Ussia, Am J Cardiology, 2011

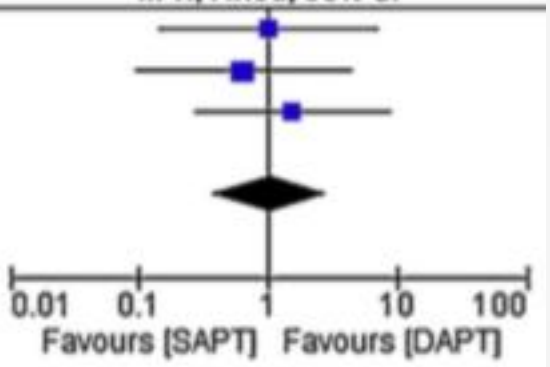
Dual vs Single Antiplatelet Therapy

Stroke (major, minor and TIA)

Study or Subgroup	SAPT Events	SAPT Total	DAPT Events	DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Durand 2014	2	91	2	91	31.2%	1.00 [0.14, 6.95]
Poliacikova 2013	2	91	2	58	38.1%	0.64 [0.09, 4.40]
Ussia 2011	3	39	2	40	30.8%	1.54 [0.27, 8.71]
Total (95% CI)		**221**		**189**	**100.0%**	**1.03 [0.36, 2.96]**
Total events	7		6			

Heterogeneity: $Chi^2 = 0.44$, $df = 2$ ($P = 0.80$); $I^2 = 0\%$

Test for overall effect: $Z = 0.05$ ($P = 0.96$)

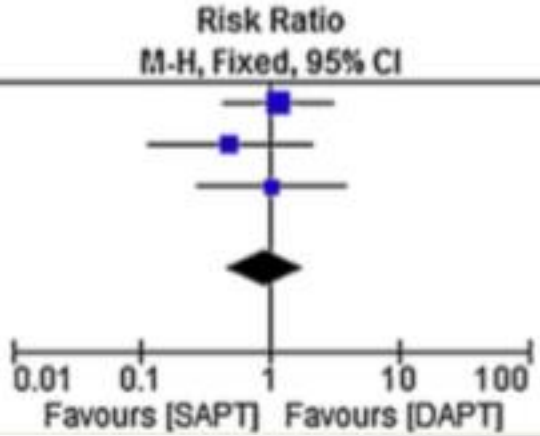


Death

Study or Subgroup	SAPT Events	SAPT Total	DAPT Events	DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Durand 2014	8	91	7	91	44.2%	1.14 [0.43, 3.02]
Poliacikova 2013	3	91	4	58	30.9%	0.48 [0.11, 2.06]
Ussia 2011	4	39	4	40	24.9%	1.03 [0.28, 3.82]
Total (95% CI)		**221**		**189**	**100.0%**	**0.91 [0.46, 1.79]**
Total events	15		15			

Heterogeneity: $Chi^2 = 0.99$, $df = 2$ ($P = 0.61$); $I^2 = 0\%$

Test for overall effect: $Z = 0.28$ ($P = 0.78$)



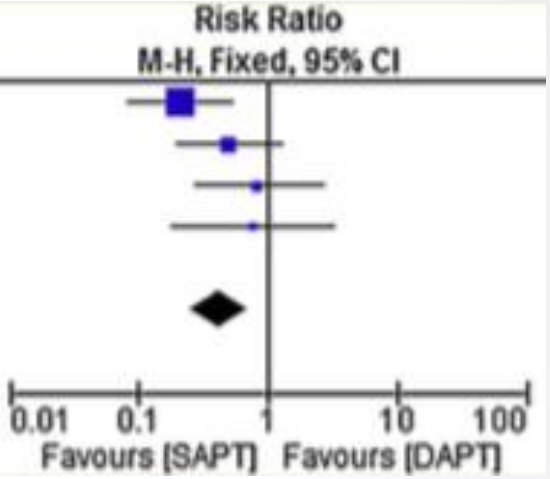
Aryal, Heart, Lung, and Circulation, 2015

Dual vs Single Antiplatelet Therapy

Study or Subgroup	SAPT Events	SAPT Total	DAPT Events	DAPT Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Durand 2014	5	91	24	91	53.4%	0.21 [0.08, 0.52]
Poliacikova 2013	7	91	9	58	24.5%	0.50 [0.20, 1.26]
Stabile 2011	5	60	6	60	13.4%	0.83 [0.27, 2.58]
Ussia 2011	3	39	4	40	8.8%	0.77 [0.18, 3.22]
Total (95% CI)		**281**		**249**	**100.0%**	**0.41 [0.25, 0.69]**
Total events	20		43			

Heterogeneity: $Chi^2 = 4.49$, $df = 3$ ($P = 0.21$); $I^2 = 33\%$

Test for overall effect: $Z = 3.41$ ($P = 0.0006$)



Aryal, Heart, Lung, and Circulation, 2015

Subclinical Leaflet Thrombosis

- Reduced aortic-valve leaflet motion after TAVR[1]
  - 22 of 55 TAVR patients (40%)
    - Reduced leaflet motion less prevalent among patient on anticoagulation compared to dual antiplatelet therapy (0 of 8 patients versus 11 of 20 patients [55%], p=0.01)
- Transcatheter heart valve thrombosis[2]
  - n=405 at 1-3 month follow-up
  - Incidence of valve thrombosis: 7%
    - 18% of these patients with thrombosis formation developed clinical obstructive thrombosis
  - No warfarin post valve implantation was independently associated with an increased risk of valve thrombosis
  - Treatment with warfarin reversed valve thrombosis findings and valve function

1: Makker, N Engl J Med, 2015
2: Hansson, JACC, 2016

TAVR for Intermediate Surgical Risk Patients

- TAVR versus surgical aortic valve replacement[1]
  - Intermediate risk:
    - STS risk score of 4-8%
    - STS < 4% if conditions not represented in the risk calculation existed
  - Composite endpoint of death and disabling stroke at 2 years
    - Non significant differences – non-inferiority trial
- FDA granted approval for subsequent study in low risk populations
  - Currently enrolling
  - STS risk score < 4%

1: Leon, N Eng J Med, 2016

TAVR for Low Risk Patients?

- Italian OBERVANT registry, 2016[1]
  - Outcomes at 3 years

	SAVR (n=355)	TAVR (n=355)	p value
Survival	83.4%	72.0%	0.0015
Freedom from MACCE	80.9%	67.3%	< 0.001

- Widening TAVR patient population intensifies urgency to:
  - Define patient characteristics favorable for SAVR vs TAVR
  - Solidify antiplatelet/anticoagulant therapeutic goals
  - Determine clinical significance of subclinical leaflet thrombosis

Rosato, Circ Cardiovasc Interv, 2016

New Pharmacological Therapy for Heart Failure: ACC/AHA/AFSA Focused update

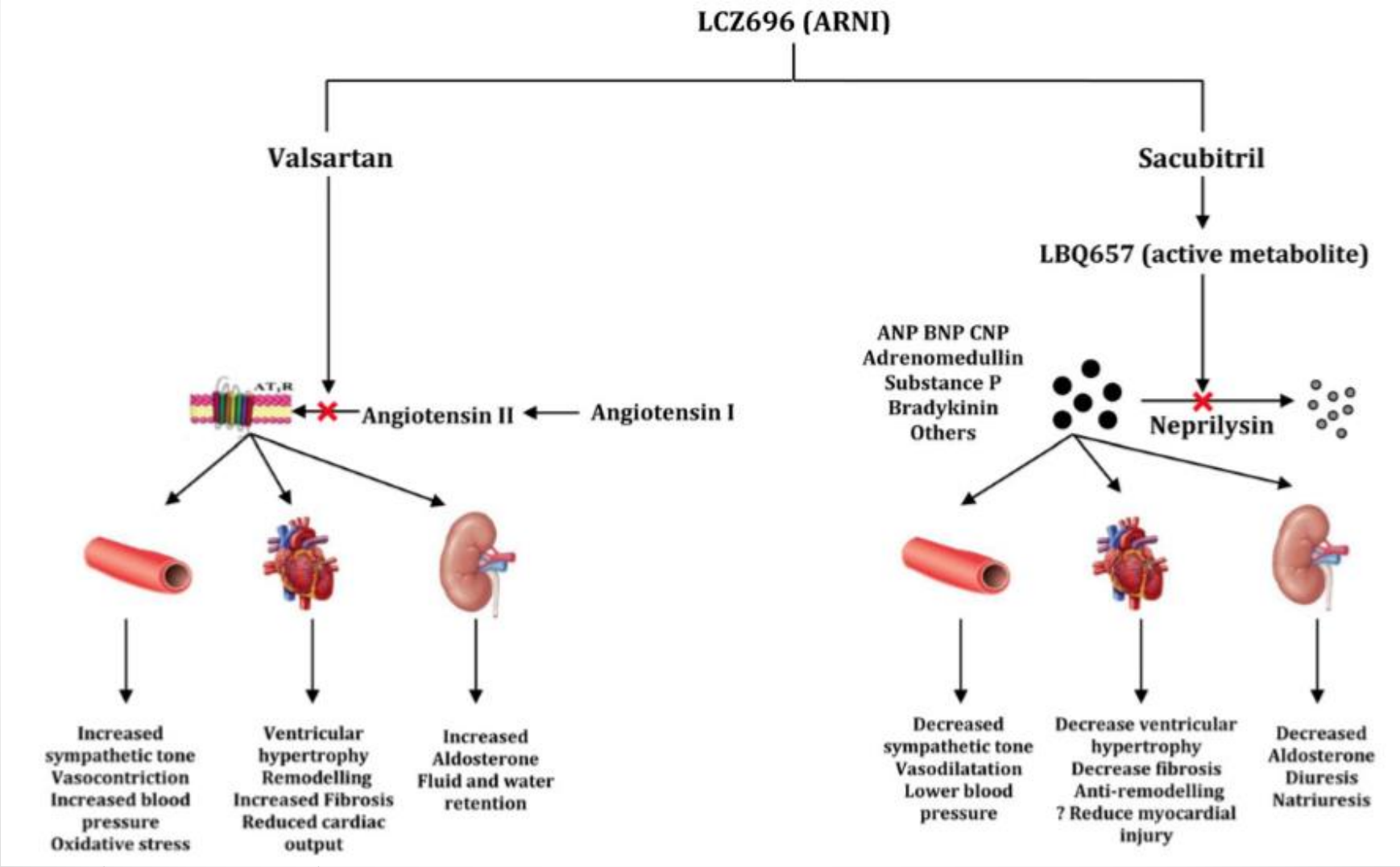
American Journal of Cardiology
September 2016

New Pharmacological Therapy for Heart Failure: ACC/AHA/AFSA Focused update

- Angiotensin receptor-neprilysin inhibitor (ARNI)
  - Valsartan/Sacubitril
- Sinoatrial node modulator
  - Ivabradine

Yancy, *Circulation*. 2016

Angiotensin receptor-neprilysin inhibitor



Bavisha, *European Heart Journal*, 2015

Sacubitril/valsartan (Entresto®) Dosing

- Dosing:
  - Staring dose:
    - In patients taking > 10 mg/day enalapril or > 160 mg/day of valsartan or equivalent dose of another ACE inhibitor or ARB
      - Sacubitril 49 mg/valsartan 51 mg twice daily.
  - Escalating doses:
    - Double the dose after 2-4 weeks to the target of sacubitril 97 mg/valsartan 103 mg twice daily
  - Reduced dose:
    - Initiating at sacubitril 24 mg/valsartan 26 mg BID can be considered if:
      - Previously not taking or low dose ACE/ARB therapy
      - Severe renal impairment (eGFR < 30 ml/min/1.73m2)
      - Moderate hepatic impairment

Uptodate, Entresto

Sacubitril/valsartan (Entresto®) Dosing

- Concomitant use of ACE inhibitor is contraindicated
  - 36 hour washout period is required before initiating sacubitril/valsartan
- Dosing considerations:
  - Difference in bioavailability between valsartan salt formulations
    - Valsartan (Entresto) 103 mg = valsartan (Diovan) 160 mg
  - Dosing in clinical trials was based on total of both components
    - 200 mg = 97/103 mg

Uptodate, Entresto

Guideline Recommendations

- Patients with symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.[1] (I, BR)
- ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.[1,2,3] (III Harm)
  - Oral neprilysin inhibitors in combination with ACE inhibitors can result in angioedema
- ARNI should not be administered to patients with a history of angioedema.[1] (III Harm)

1: Yancy, *Circulation*. 2016
2: Packer, *Circulation*, 2002
3: Kostis, *Am J Hypertension*, 2004

Angiotensin-Neprilysin Inhibition vs Enalapril in Heart Failure

- Double-blinded, randomized trial
  - Included single-blind screening phase with each drug prior to randomization to ensure an acceptable side effect profile
  - n=8399
- Patients included:
  - Symptomatic patients with HFrEF (NYHA class II, III, or IV)
  - EF of 40% or less
    - Changed to 35% by amended protocol mid study
  - BNP >150 pg/ml OR BNP >100 pg/ml if patient had been hospitalized for HF in previous 12 months
  - Patients taking any dose of ACE inhibitor or ARB were considered
    - Were required to tolerate a stable dose of beta-blocker and ACEi/ARB equivalent to at least of enalapril 10 mg daily for at least 4 weeks prior

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001

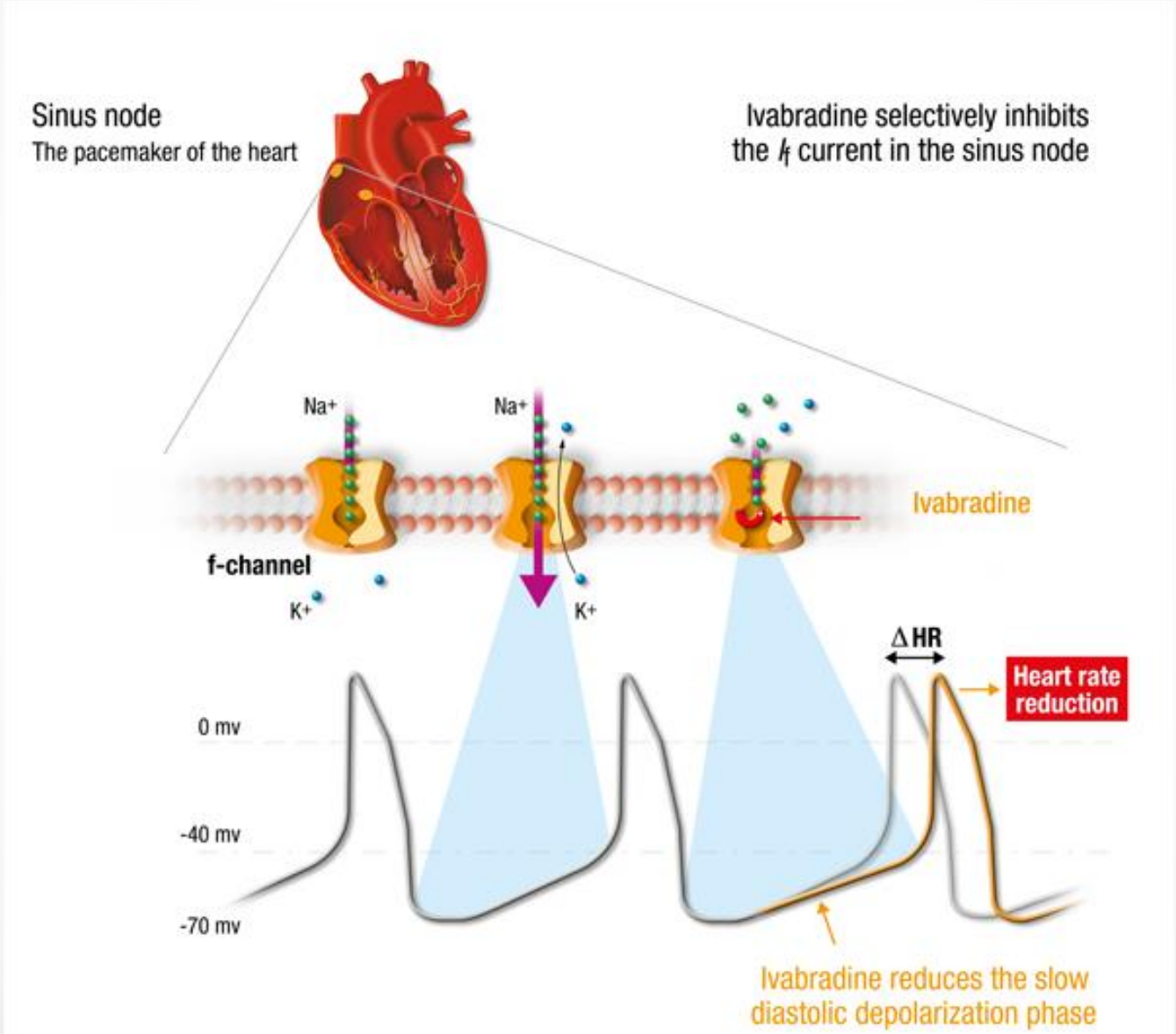
McMurray, N Engl J Med, 2014

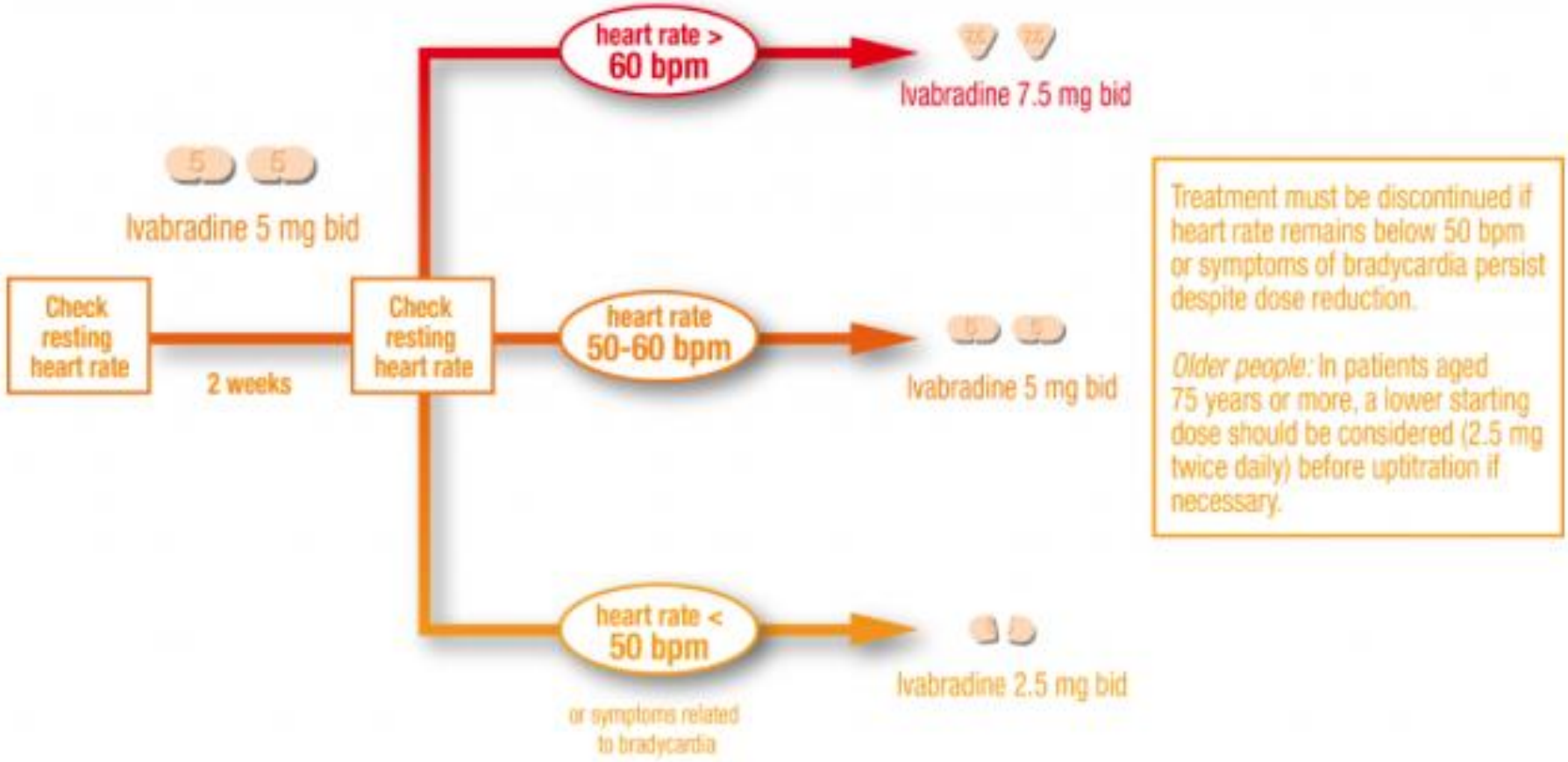
Angiotensin-Neprilysin Inhibition vs Enalapril in Heart Failure

- Limitations:
  - "Drug run in" study design is controversial
    - 2079 patients excluded during this 4 week period
  - Amended study protocol with modifications to inclusion criteria
    - EF inclusion changed from 40% to 35%
  - Enalapril was dosed up to 10 mg BID vs heart failure goal dose of valsartan
    - Some of efficacy of new treatment related to more significant blood pressure reduction in treatment group?

McMurray, N Engl J Med, 2014
Ferrari, Intern Emerg Med, 2015

Ivabradine Mechanism




heart rate > 60 bpm
Ivabradine 7.5 mg bid
Ivabradine 5 mg bid
Check resting heart rate
2 weeks
Check resting heart rate
heart rate 50-60 bpm
Ivabradine 5 mg bid
heart rate < 50 bpm
or symptoms related to bradycardia
Ivabradine 2.5 mg bid
Treatment must be discontinued if heart rate remains below 50 bpm or symptoms of bradycardia persist despite dose reduction.
Older people: In patients aged 75 years or more, a lower starting dose should be considered (2.5 mg twice daily) before uptitration if necessary.

Ivabradine (Corlanor®)

- Unique side effects:
  - 14.5% of patients experience luminous phenomena
    - Brightness in a fully maintained visual field
    - Due to blockage of the Ih ion channels in the retina
    - Symptoms are mild and reversible, resulted in discontinuation of about 1% of patients in clinical trials
- Contraindications:
  - Acute decompensated heart failure
  - Sick sinus syndrome, sinoatrial block, or 3rd degree AV block unless a functioning pacemaker is in place
  - Severe hepatic impairment
- Drug interactions:
  - 3A4 inducers and inhibitors

Uptodate, Corlanor

Sinoatrial node modulator: Ivabradine

- Guideline recommendation (COR IIa, LOE B-R): can be beneficial to reduce HF hospitalization for patients with:
  - Symptomatic (NYHA class II-III) stable chronic HFrEF (LVEF <35%)
  - And receiving a beta blocker at maximum tolerated dose
  - And in sinus rhythm with a heart rate of 70 bpm or greater at rest

Yancy, *Circulation*. 2016

Ivabradine and outcomes in chronic HF (SHIFT)

- Randomized, double-blind, placebo-controlled trial
  - N=6558, 677 centers in 37 countries
- Inclusion:
  - Sinus rhythm with resting HR > 70 bpm
  - Stable, symptomatic chronic heart failure, with a hospitalization for HF within previous 12 months AND left ventricular EF < 35%
  - Required to be at optimum and stable background medication treatment for at least 4 weeks

	Ivabradine (n=3241)	Placebo (n=3264)	p value
Primary endpoint			
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	<0.0001
Mortality endpoints			
All-cause mortality	503 (16%)	552 (17%)	0.092
Cardiovascular mortality	449 (14%)	491 (15%)	0.128
Other endpoints			
Hospital admission for worsening HF	514 (16%)	672 (21%)	<0.0001

Swedberg, Lancet, 2010

Ivabradine and outcomes in chronic HF (SHIFT)

- Limitations:
  - Number of patients on goal beta-blocker therapy
    - Patients on goal therapy: 23%
    - Patients receiving 50% or more of target dose: 49%
  - Subgroup analysis: benefit of ivabradine diminished in patients with lower baseline heart rates (<77 beats per minute)

Swedberg, Lancet, 2010

Heart Failure Guideline Conclusions

- Sacubitril/valsartan
  - Patients tolerating an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality
  - Recognizing flaws in clinical trial
    - Amended protocol
  - Cost associated with new medication may be limiting factor
- Ivabradine
  - May be beneficial to reduce hospitalizations
    - Patients should be optimized on beta-blocker first

Assessment Question #1:

JD is a 62 year old male, who was admitted to your intensive care unit with hemodynamic instability and right heart strain on ECHO. He was diagnosed with a pulmonary embolism and has been on a heparin infusion with therapeutic aPTTs for the past 48 hours. Providers are asking for your opinion on long term anticoagulation:

- Scr: 0.9
- Weight: 135 kg

A: Apixaban 10 mg BID for the first 7 days, followed by 5 mg BID. No clinical differences have been seen in obese patients, no matter how extreme of weight.

B: Apixaban 10 mg TID: dose should be increased given weight, and shortened half life in extreme obesity

C: Given extreme weight, ISTH guidelines would suggest warfarin in patients > 120 kg.

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Assessment Question #2:

BG is 65 year old female with systolic heart failure (EF = 30%). She has been started on lisinopril 10 mg daily and metoprolol succinate 50 mg daily. She is tolerating these medications well, and is coming into your clinic for a check up, and to optimize her medication therapy.

- BP: 109/60 mmHg
- HR: 67 bpm
- Renal function: stable at baseline SCr of 0.9

To optimize BG's medication regimen, you decide to:

A: Continue to increase lisinopril and metoprolol to goal

B: Add ivabradine to further lower HR, which has morbidity benefits in preventing hospital admissions.

C: Discontinue lisinopril, as blood pressure is getting low. Optimize metoprolol dose for better heart rate and blood pressure control.

D: Optimize dose of lisinopril as blood pressure allows in the future. Increase dose of metoprolol. Ivabradine should not be started until metoprolol optimized and if HR still > 70 bpm.

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References

- Abdul-Jawad Altisent O, et al. Warfarin and antiplatelet Therapy vs Warfarin Alone for Treating Patients With Atrial Fibrillation Undergoing transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv 2016; 9:1706-17
- Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
- Amat-Santos IJ, Rodés-Cabau J, Urena M, et al. Incidence, Predictive Factors, and Prognostic Value of New-Onset Atrial Fibrillation Following Transcatheter Aortic Valve Implantation. J Am Coll Cardiol 2012;59:178-88
- Aryal M, et al. Dual Versus Single Antiplatelet Therapy in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Metaanalysis. Heart, Lung, and Circulation 2015:24: 185-192
- Bavishi C, Messerli F, Kadkosh B, Ruilope L, Kario K. Role of neprilysin inhibitor combinations in hypertension: insights from hypertension and heart failure trials. European Heart Journal. 2015
- Connolly S, et al. Adexanet Alfa for Major Bleeding Associated with Factor Xa Ihibitors. N Engl J Med 2016; 375:1131-1141
- Dorian P, Cass D, Schwartz B, Cooper R, Gelaznikas R, Barr A. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. N Engl J Med 2002;346:884-90.
- Ferrari L, Sada S. Efficacy of angiotensin-neprilysin inhibition versus enalapril in patients with heart failure with a reduced ejection fraction. Intern Emerg Med 2015; 10:369-371
- Hansson N, et al. Transcatheter Aortic Heart Valve Thrombosis: Incidence, Predisposing Factors, ad Clinical Implications. JACC. 2016
- Kostis JB, Packer M, Black HR, et al. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial. Am J Hypertens. 2004;17: 103–11.
- Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. N Engl J Med 1999; 341:871-8.
- Kudenchuk PJ, Brown SP, Daya M, et al. Amiodarone, lidocaine, or placebo in out-of-hospital cardiac arrest. N Engl J Med 2016;374:1711-22.
- Leon M, et al. Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients who Cannot Undergo Surgery. N Engl J Med. 2010; 363:1597-1607
- Leon M, et al. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016; 374:1609-1620
- Link MS, Berkow LC, Kudenchuk PJ, et al. Adult advanced cardiovascular life support: 2015 American Heart Association Guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 2015;132:Suppl 2:S444-64.
- Lung B, et al. The optimal management of anti-thrombotic therapy after valve replacement: certainties and uncertainties. European Heart Journal. 2014; 35: 2942-2949

- Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015-24.
- Martin K, etal. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J of Thrombosis and Haemostatis. 2016; 14: 1308-1313
- McMurray JJV, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.
- Mok M, Urena M, Nombela-Franco L, et al. Clinical and prognostic implications of existing and new-onset atrial fibrillation in patients undergoing transcatheter aortic valve implantation. J Thromb Thrombolysis 2013;35:450–5.
- Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics — 2015 update: a report from the American Heart Association. Circulation 2015; 131(4):e29-322.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM III, Thomas JD. 2014 AHA/ ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.
- Packer M, Califf RM, Konstam MA, et al. Comparison of omapatrilat and enalapril in patients with chronic heart failure: the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE). Circulation. 2002;106:920–6.
- Rosato S, Santini F, Barbanti M, et al. Transcatheter aortic valve implantation compared with surgical aortic valve replacement in low-risk patients. *Circ Cardiovasc Interv*. 2016;9:e003326.
- Smith CR, Leon MB, Mack MJ, et al.; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
- Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet. 2010;376: 875–85.
- Ussia GP, Scarabelli M, Mulè M, et al. Dual antiplate- let therapy versus aspirin alone in patients undergoing transcatheter aortic valve implantation. Am J Cardiol 2011;108:1772-6.
- Webb J, et al. Current Status of Transcatheter Aortic Valve Replacement. J of the Am Coll of Cardiology. 2012; 60: 483-92
- *Whitlock R, et al.* Antithrombotic and Thrombolytic Therapy for Valvular Disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *CHEST 2012; 141(2)(Suppl):e576S–e600S*
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos G, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2016 ACC/AHA/HFSA focused update on new pharmacological therapy for heart failure: an update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation.* 2016;134