ATRIUM CARDIOLOGY COLLABORATIVE

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Cardiology Mythbusters: Vol 2

Stormi Gale, PharmD, BCPS
Assistant Professor

Kristin Watson, PharmD, BCPS-AQ Cardiology
Associate Professor/Vice Chair for Clinical Services

University of Maryland School of Pharmacy

Objectives

- Discuss the risks and benefits of utilizing intravenous amiodarone for the management of atrial fibrillation.
- Discuss the differences in efficacy between thiazide-type and thiazide diuretics for the management of hypertension.
- Discuss the evidence surrounding the use of anticoagulation in patients with peripheral arterial disease.
- Given a patient with a CHA_2DS_2-VASc score of 0, discuss the appropriateness of therapy for stroke prevention.

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IV VS. PO AMIODARONE: COMPARING BENEFITS

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IV to PO Efficacy

Study Groups	Treatment	Results
72 patients with recent-onset sustained atrial tachyarrhythmia	PO amiodarone 25.7 mg/kg vs. IV amiodarone 3-5 mg/kg bolus then 10-15 mg/kg over 24 h	No difference in conversion to SR between PO and IV (64% vs. 68%, respectively; p=NS)
223 patients with symptomatic atrial fibrillation on digoxin	PO amiodarone 600 mg in 3 divided doses vs. IV amiodarone 5mg/kg over 30 minutes then 1000 mg over 24h	No difference in conversion to SR (p=NS) Longer time to cardioversion with PO (20h vs. 12h; p<0.001)

- Rate-controlling effects of IV amiodarone have been reported as quickly as within 30 minutes of administration

IV, intravenous; PO, oral; SR, sinus rhythm

Eur Heart J. 1994 Oct;15(10):1396-402; Am J Cardiol. 2002;90(9):964-968; Int J Cardiol. 2007;121(3):291-295.

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IV VS. PO AMIODARONE: COMPARING RISKS

Amiodarone Cardiac Toxicities

Acute

- Bradycardia
- Heart Block
- ?Hypotension

Chronic

- Bradycardia
- Heart block
- QTc Prolongation*

*Rarely clinically meaningful

Vasc Health Risk Manag. 2010;6:465-472.

Polysorbate 80

Author	Study Groups	Results
Gough WB et al.	IV amiodarone in ethanol vs. polysorbate 80	80% drop in mean arterial pressure with polysorbate 80, no effect with ethanol group
Munoz A et al.	IV amiodarone 5 mg/kg with or without polysorbate 80	Polysorbate 80 had a significantly greater reduction in blood pressure (23.1 mmHg; p<0.001) compared to control group (8.8 mmHg)

J Cardiovasc Pharmacol. 1982;4(3)375-80;Eur Heart J 1988;9(2):142-8.

Acute Hepatotoxicity with Amiodarone

Author (year)	Case	Result
Rhodes A et al.	72yoM with acute hepatic impairment within 24 hours of IV amiodarone for VT	Resolution of transaminitis after withdrawing IV amio. Treated with PO without further hepatic impairment
Ratz Bravo AE et al.	Cases of elevated transaminases > 100x ULN in 3 post-cardiac surgery patients	Cessation of IV amiodarone resolved transaminitis despite continuation of PO therapy
Lahbabi M et al.	29yoF with transaminitis 24h after IV amiodarone load for AF with RVR	IV formulation changed to PO load, followed by resolution of transaminitis

AF, atrial fibrillation; RVR, rapid ventricular response; ULN, upper limit of normal; VT, ventricular tachycardia

Gut. 1993;34(4):565-66; Crit Care Med. 2005;33(1):128-34; World J Hepatol. 2012;4(6):196-8.

Hepatotoxicity with Polysorbate 80

E-ferol Syndrome

- Seen with IV vitamin E formulation with polysorbate 80
- Causes hepatomegaly, jaundice, renal failure
- Clinical features similar to IV amiodarone

Gut. 1993;34(4):565-66.

Take Home Points

- Amiodarone is highly effective but confusion exists around choosing IV vs. PO therapy
- IV and PO formulations are similar in efficacy
- Polysorbate 80 is the etiology of several acute toxicities associated with IV amiodarone
  - Hypotension and acute liver toxicity

THIAZIDE VS. THIAZIDE – LIKE DIURETICS FOR TREATMENT OF HYPERTENSION

Seventh Joint National Committee	Eighth Joint National Committee	2017 High Blood Pressure Clinical Practice Guideline
• Initial drug choice is thiazide-type diuretic for most • **No preference for specific agent(s)**	• General nonblack population: initial treatment should include a thiazide-type diuretic, CCB, ACEI, or ARB • General black population: initial treatment should include a thiazide-type diuretic or CCB • **No preference for specific agent(s)**	• First-line agents include thiazide diuretics, CCBs, and ACEI or ARBs • Black adults with HTN (without HF or CKD): initial treatment should include a thiazide-type diuretic or CCB • **Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD**

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure, HTN, hypertension

JAMA. 2003;289(19):2560-72; JAMA. 2014;311:507-520; J Am Coll Card. 2017, doi: 10.1016/j.jacc.2017.11.006.

Agents

Thiazide				
Agent	Starting dose (mg)	Typical max dose (mg/d)	Half-life (hrs)	30 d supply (on $4 list*)
Chlorothiazide	125	500	1.5	$7.56 – 20.77 (no)
Hydrochlorothiazide	12.5-25	25	2.5	$2.52 - 12.60 (yes)
Thiazide-like				
Chlorthalidone	12.5	25-50	47	$36.21 - 44.65 (no)
Indapamide	1.25	2.5-5	14	$42.63 – 46.48 (yes)

* Walmart $4 prescriptions; accessed on April 2, 2018
Lexi-Comp, Inc. (Lexi-Drugs®). Lexi-Comp, Inc.; April 2, 2018.

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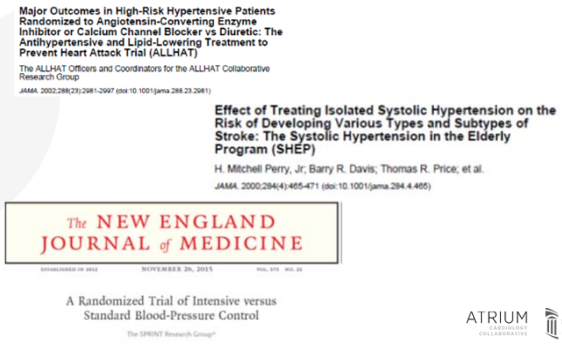
Clinical Trial Data


Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)

The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group

JAMA. 2002;288(23):2981-2997 (doi:10.1001/jama.288.23.2981)

Effect of Treating Isolated Systolic Hypertension on the Risk of Developing Various Types and Subtypes of Stroke: The Systolic Hypertension in the Elderly Program (SHEP)

H. Mitchell Perry, Jr; Barry R. Davis; Thomas R. Price; et al.

JAMA. 2000;284(4):465-471 (doi:10.1001/jama.284.4.465)

The NEW ENGLAND JOURNAL of MEDICINE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

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Hypertension. 2011:57:689-94; Hypertension. 2015;65:1033-40; Hypertension. 2015;65:1041-1046.

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Adverse Effects

- Hydrochlorothiazide associated with increase risk of non-melanoma skin and lip cancer
- Metabolic effects
  - Chlorthalidone associated with higher uric acid levels but NOT risk of gout
  - Hyponatremia and hypokalemia more common with chlorthalidone
  - Metabolic effects of HCTZ and indapamide appear similar

J Intern Med 2017;282:322-31; J Am Acad Dermatol. 2018;78:673-681; J Clin Hypertens. 2014;16:864-8; Hypertension. 2011:57:689-94; Hypertension. 2015;65:1041-1046.

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Reasons for thiazide-like

- Longer half-life duration of action
- Improved blood lowering effect
- Similar adverse effect profile
- Greater reduction in clinical events

- More commonly available in combination products

Reasons for thiazide

PERIPHERAL ARTERIAL DISEASE – IS THERE A NEED FOR ANTICOAGULATION?

Why Consider It?

- Aspirin
- Clopidogrel
- Aspirin + clopidogrel
- Vorapaxar
- Ticagrelor

Lancet. 1996; 348: 1329–39; Lancet. 2009; 373: 1849–60; N Engl J Med. 2006;354:1706-17; Circulation. 2013;127:1522-1529; N Engl J Med. 2017; 376:32-40.

Warfarin Antiplatelet Vascular Evaluation Trial

	Warfarin + antiplatelet (n = 1080)	Antiplatelet alone (n = 1081)	
MI, stroke, or CV death	12.2%	13.3%	RR 0.92 (95% CI, 0.73 - 1.16; p=0.48)
MI, stroke, severe ischemia of the peripheral/coronary arteries leading to urgent intervention, or CV death	15.9%	17.4%	RR 0.91 (95% CI, 0.74 - 1.12; p=0.37)
Life-threatening bleed	4%	1.2%	RR 3.41 (95% CI, 1.84 - 6.35; p<0.001)

CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; RR, relative risk

N Engl J Med. 2007;357:217-27.

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Cardiovascular OutcoMes for People using Anticoagulation StrategieS

Lower risk of of stroke, MI, or CV death
HR 0.72 (95% CI, 0.57 – 0.90; p=0.0047)

Lower risk of major limb events
HR 0.54 (95% CI, 0.35 – 0.82; p=0.0037)

Increased risk of major bleeding
HR 1.61 (95% CI, 1.12 – 2.31; p=0.0089)

Rivaroxaban 2.5 mg BID + ASA 100 mg/d vs. ASA 100 mg/d

HR, hazard ratio

Lancet. 2018;391:291-29.

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Cardiovascular OutcoMes for People using Anticoagulation StrategieS

Lower risk of major limb events
HR 0.67 (95% CI, 0.45 – 1; p=0.05)

No difference in the risk of stroke, MI, or CV death
HR 0.86 (95% CI, 0.69 – 1.08; p=0.19)

Increased risk of major bleeding
HR 1·68, 95% CI 1·17–2·40; p=0·0043

Rivaroxaban 5 mg BID vs. ASA 100 mg/d

Lancet. 2018;391:291-29.

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What's Next?

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CV Risk Reduction

- Aspirin 81 mg or clopidogrel 75 mg daily
- Statin therapy
- Control blood pressure
- Smoking cessation

2016 AHA/ACC Lower Extremity PAD Guideline:
Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD (Class III Level A)

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Circulation. 2016;CIR.0000000000000470 https://doi.org/10.1161/CIR.0000000000000470

LOW CHA_2DS_2-VASC SCORES: IS ANTITHROMBOTIC THERAPY NECESSARY?

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Case

KJ is a 62 year-old female with a PMH of gastroesophageal reflux disease , osteoarthritis, and hyperlipidemimia. Her current medications include omeprazole 40 mg daily, naproxen 500 mg q12h PRN, and pravastatin 40 mg daily. She presents with a new diagnosis of AF.

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Risk Stratification Systems

C	ongestive heart failure
H	ypertension
A2	ge > 75 years
D	iabetes
S2	troke or TIA

C	ongestive heart failure
H	ypertension
A2	**ge ≥ 75 years**
D	iabetes
S2	troke or TIA
V	**ascular disease**
A	**ge 65 – 74 years**
Sc	**ex category female**

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Chest. 2012;141(2):e531S–e575S; Circulation. January 2014:CIR.0000000000000041; Eur Heart J. 2016;37(38):2893-2962.

Guideline Recommendations for AF Stroke Prevention

Risk Score	ACCP 2012 ($CHADS_2$)	ACC/AHA/HRS 2014 (CHA_2DS_2-VASc)	ESC 2016 (CHA_2DS_2-VASc)
0	No antithrombotic therapy or aspirin	It is reasonable to omit therapy	No antithrombotic therapy
1	OAC (preferred) or DAPT	OAC or no antithrombotic therapy or aspirin	Consider OAC (patient-specific risk)
≥ 2	OAC	OAC	OAC

ACC/AHA/HRS, American College of Cardiology/American Heart Association/Heart Rhythm Society; ACCP, American College of Chest Physicians; ESC, European Society of Cardiology; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant

Chest. 2012;141(2):e531S–e575S; Circulation. January 2014:CIR.0000000000000041. Eur Heart J. 2016;37(38):2893-2962.

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Prevalence of Antithrombotic Therapy in Low-Risk Patients

NCDR PINNACLE Registry

Percent of patients with CHA_2DS_2-VASc 0 (n=12,348) on antithrombotic therapy

>60%

NCDR PINNACLE, National Cardiovascular Data Registry Practice Innovation and Clinical Excellence

JAMA Cardiol. 2016;1(1):55-62.

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Annual Stroke Risk

$CHADS_2$	
Score	Adjusted stroke rate (% per year)
0	1.9
1	2.8
2	4
3	5.9
4	8.5
5	12.5
6	18.2

CHA_2DS_2-VASc	
Score	Adjusted stroke rate (% per year)
0	0
1	1.3
2	2.2
3	3.2
4	4
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

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Circulation. January 2014:CIR.0000000000000041.

Net Clinical Benefit of Antithrombotic Therapy

- **Objective:** Determine the NCB of no antithrombotic therapy, aspirin or warfarin in AF patients with none or one stroke risk factor
- **Population:** Danish registry data of patients with nonvalvular AF from 1998 to 2012
  - 49,916 patients with either 0 or 1 stroke risk factor
- **Outcomes:** ischemic stroke, intracranial bleeding, major extracranial bleeding (including gastrointestinal bleeding), MI, death

NCB, net clinical benefit

Thromb Haemost. 2015;114(4):826-834.

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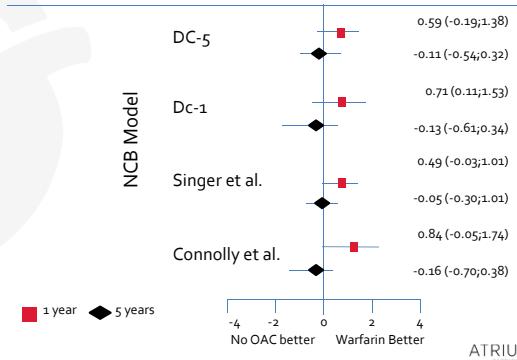
Net Clinical Benefit of Antithrombotic Therapy



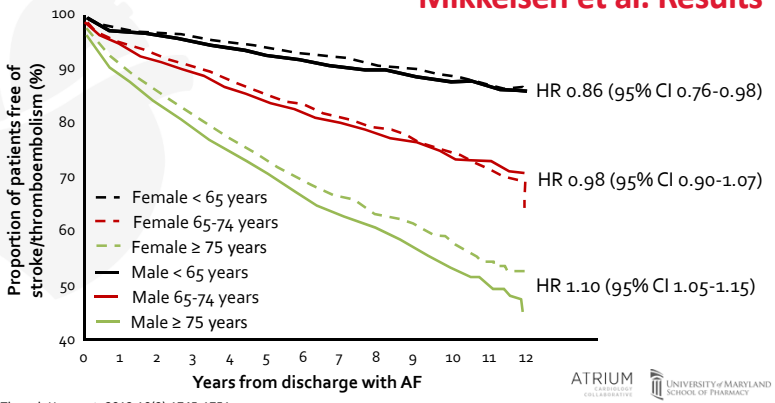
Thromb Haemost. 2015;114(4):826-834.

Female sex as a risk factor: Mikkelsen et al. study

- **Objective:** Determine risk of stroke associated with female sex in patients with nonvalvular AF
- **Population:** Danish registry data of patients with nonvalvular AF from 1997 to 2008
  - Subdivided the population into three age intervals: < 65, 65–74 and ≥ 75 years
- **Outcomes:** stroke rates

Thromb Haemost. 2012;10(9):1745-1751.

Mikkelsen et al. Results



J Thromb Haemost. 2012;10(9):1745-1751.

What about CHA_2DS_2-VASc of 1?

ATRIUM | blog

Treat the Patient, Not the Number: Stroke Prevention in Atrial Fibrillation with Low CHA2DS2-VASc Scores

http://blogs.pharmacy.umaryland.edu/atrium/

Summary

- Utilization of CHA_2DS_2-VASc allows for the identification of patients with AF that are truly at low-risk for stroke
  - Reported rates < 1%
- Data suggests that female sex does not increase the risk for stroke in the absence of other risk factors
  - Low risk = CHA_2DS_2-VASc scores 0 for males, 1 for females
- Patients with low CHA_2DS_2-VASc scores have not shown to benefit from antithrombotic therapy

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