

## My Heart is Dancing .... But Not for Joy! Current Issues in Chronic Therapy of Atrial Fibrillation

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## Disclosure

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- Presenting author has no conflict relationships to disclose

## Objectives

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- To provide participants with a practical update concerning recent trials of **chronic** therapy for atrial fibrillation
  - Role of new antiarrhythmic agent
    - dronedarone
  - Role of dual antiplatelet therapy
    - ASA and clopidogrel
  - Role of new oral anticoagulant
    - dabigatran

## Outline

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- Basics of atrial fibrillation
- Case
- Rate versus rhythm control
  - Role of dronedarone
- Stroke prevention
  - Role of dual antiplatelet therapy
  - Role of dabigatran

## Basics of Atrial Fibrillation

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- Most common sustained cardiac arrhythmia
- AF is an irregularly, irregular supraventricular arrhythmia with atrial rate of 350-450 bpm
  - Cardiovascular
    - Valvular
    - Congenital
    - HTN
    - Cardiomyopathy
    - Atrial hypertrophy
    - LV wall thickness
    - Ischemic / MI
    - Peri/myocarditis
    - Infiltrative heart disease
    - Cardiac tumors/trauma
    - Cardiothoracic surgery
  - Systemic
    - Age
    - Alcohol intox/withdrawal
    - Sympathomimetics
    - Autonomic NS imbalances
    - Electrolyte disturbances
    - Thyrotoxicosis
    - Fever / hypothermia
    - Hypovolemia
    - Diabetes
    - Anemia
    - Pulmonary disease
    - Cerebrovascular disease

## Classification of Atrial Fibrillation

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- First episode
- Paroxysmal
  - AF alternating with NSR, spontaneous reversion
- Persistent
  - AF alternates with NSR but requires treatment to convert to NSR
- Permanent
  - Inability to convert to NSR with therapy

## Outcomes

- Symptoms (may be asymptomatic)
  - Reduced exercise tolerance, weakness, fatigue, dizziness, lightheadedness, palpitations, chest pain, SOB, syncope
- Morbidity
  - ↓ EF, ↓ CO, CHF, hypotension
  - Stroke risk (overall 4.5% per year, but substantial range)
- Mortality
  - Independent risk factor post-stroke, post-MI, CHF

## Goals of Therapy

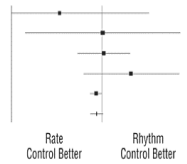
- Control or cure precipitating causes
- Relief of symptoms
  - Control of rapid ventricular rate
  - Conversion of AF to normal sinus rhythm
  - Maintenance of sinus rhythm or reduction in recurrences of AF
- Prevention of thromboembolic complications
- Improvement in quality of life

## Case

- 78 year old male patient presenting with sudden onset SOB and found to be in persistent AF
  - HR 140s and stable BP
- Known CAD, previous MIs and CABG
- Treated hypertension and hyperlipidemia
- EF 45%
- COPD (on home O<sub>2</sub>) and pulmonary fibrosis presumed to be related to industrial exposure
- Creatinine on admission 332 (baseline 160)

## Odds ratios for the end point of all-cause mortality for individual trials and the combined analysis

Trial	Rate	Rhythm	0.1	1	10
HOT CAFE <sup>8</sup>	1/101	3/104			
PIAF <sup>4,13</sup>	2/125	2/127			
RACE <sup>7</sup>	18/256	18/266			
STAF <sup>6</sup>	8/100	4/100			
AFFIRM <sup>5,12</sup>	310/2027	356/2033			
<b>Combined</b>	<b>339/2699</b>	<b>383/2630</b>			
Percentage	13.0	14.6			



OR, 0.87 (95% CI: 0.74-1.02), P = .09

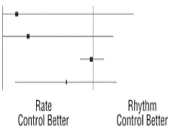
de Denus, S, et al. Arch Intern Med 2005;165:258-262.

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ARCHIVES OF  
INTERNAL MEDICINE

## Odds ratios for the end point of ischemic strokes for individual trials and the combined analysis

Trial	Rate	Rhythm	0.1	1	10
HOT CAFE <sup>8</sup>	0/101	3/104			
STAF <sup>6</sup>	1/100	5/100			
AFFIRM <sup>5,12</sup>	77/2027	80/2033			
<b>Combined</b>	<b>78/2228</b>	<b>88/2237</b>			
Percentage	3.5	3.9			



OR, 0.50 (95% CI: 0.14-1.83), P = .30

de Denus, S, et al. Arch Intern Med 2005;165:258-262.

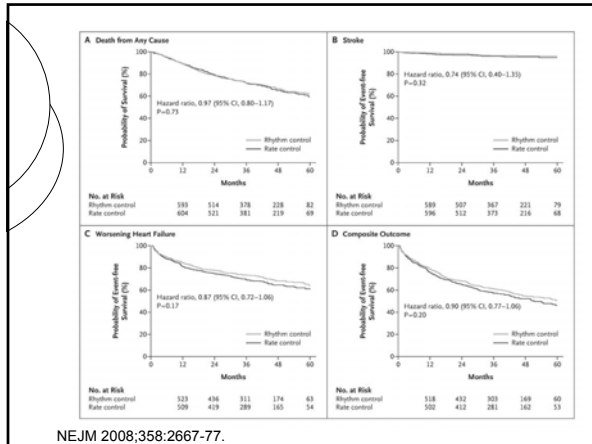
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## AF-CHF

- Prospective, open-label RCT of 1376 patients with LVEF ≤ 35% or NYHA-FC 2 to 4 and a history of AF, hospitalized for HF
- Randomized to rhythm (amiodarone, sotalol, dofetilide) or rate control (titrated doses of beta blockers or digoxin, or both)
- Intention to treat analysis
- Primary endpoint cardiovascular mortality
- All received optimal CHF management and anticoagulation

NEJM 2008;358:2667-77.



### Rate versus Rhythm Control Trials Limitations

- o Patient selection bias
- o Adequacy of rate control in trials
- o Success in achieving / maintaining NSR
- o Safety issues without RCT monitoring
- o Length of follow-up re long-term toxicity
- o **Still question what to do with patients in whom onset of AF is associated with a clear-cut deterioration in clinical status**

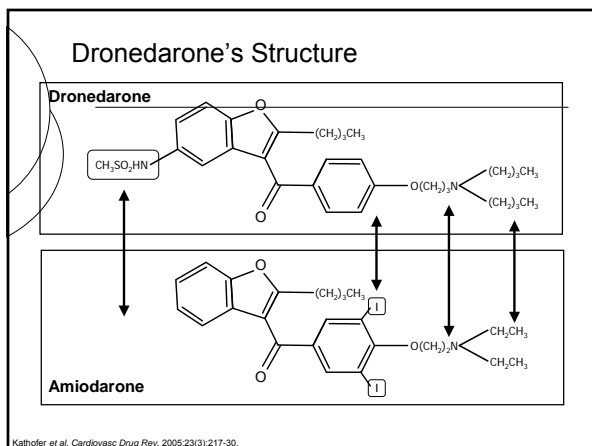
### Case

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### Chronic Antiarrhythmic Therapy

Population	First choice	Alternatives
No co-morbid diseases or HTN (no LVH)	Propafenone Flecainide Sotalol	Amiodarone Dofetilide
CAD or post-MI	Sotalol	Dofetilide
HTN (with LVH)	Amiodarone	Dofetilide
EF <35% or clinical CHF	Amiodarone	Dofetilide

Adapted from: Eur Heart J 2001;22:1852-1923, Can J Cardiol 2005;21(suppl B):19B-25B, JACC 2006;48:e149-246.  
 RSS 2009



### Pharmacological Profile of Dronedarone

- o Absorption
  - ≥70% absorption
  - Food increases bioavailability by 2- to 4-fold
  - First-pass effect results in absolute bioavailability of ~15%
- o Metabolism
  - Extensively metabolized, mainly by CYP3A4
  - Interaction with digoxin / not with warfarin
  - Metabolite SR35021 may contribute to the pharmacologic activity of dronedarone (3-10x less potent)
- o Excretion and Elimination
  - Major route of excretion is in feces (84%)
  - Terminal half-life of dronedarone is 25-30 hours after repeated administration of 400mg BID
  - Steady state reached within 4-8 days

Data on file.

### Dronedarone and Renal Function

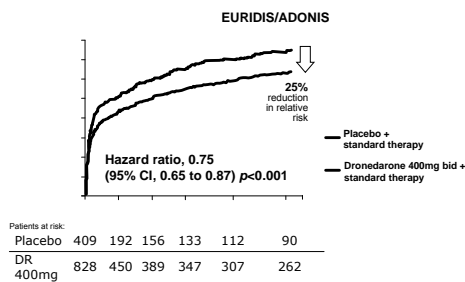
- o Reduction in calculated creatinine clearance by ~18%
- o No evidence of effect on measured glomerular filtration rate
- o Specific partial inhibition of tubular organic cation transporters

### EURIDIS and ADONIS

- o Two identical, PC, DB parallel group trials examining the efficacy of dronedarone 400mg BID for maintaining sinus rhythm (n=1237)
- o Excluded patients in NYFC III or IV HF – only 17% CHF
- o Time to first documented recurrence of AF – scheduled ECG plus transtelephonic ECG monitor with symptoms x 1 yr

NEJM 2007;357:987-99.

### Combined Analysis for First AF Recurrence



Singh BN, et al. N Engl J Med. 2007;357:987-99.

### EURIDIS and ADONIS

- o At 12 months, dronedarone reduced proportion of patients with:
  - Any AF recurrence NNT = 9 (6-17)
  - Symptomatic AF recurrence NNT = 24 (10-71)
- o Elevation of serum creatinine NNH = 46 (30-100)
- o Trial too small and duration too short for incidence of long-term adverse effects

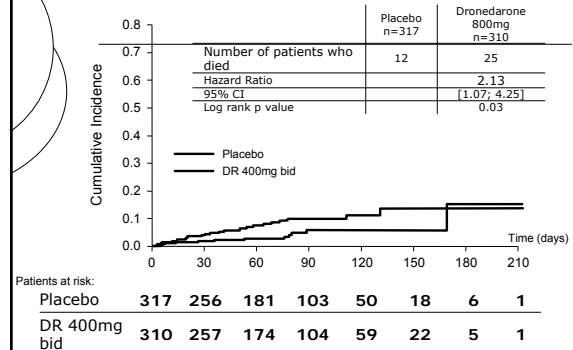
NEJM 2007;357:987-99

### ANDROMEDA

- o **NOT** an AF/AFI trial
- o DB, PC, RCT of dronedarone 400mg BID in patients hospitalized with new or worsening HF (n=627)
- o Primary outcome death from any cause or hospitalization for worsening HF
- o Prematurely terminated in early 2003 with additional 6 months of f/u

NEJM 2008;358:2678-87.

### Cumulative Incidence of All-cause Mortality



Kaber L, et al. N Engl J Med. 2008;358:2678-87.

## Heart Failure

- Contraindication – severe congestive heart failure (stage NYHA IV) and other unstable hemodynamic conditions
- It should be used with caution in patients with moderate CHF (stage NYHA III) and only if the benefits are deemed to outweigh the risks involved

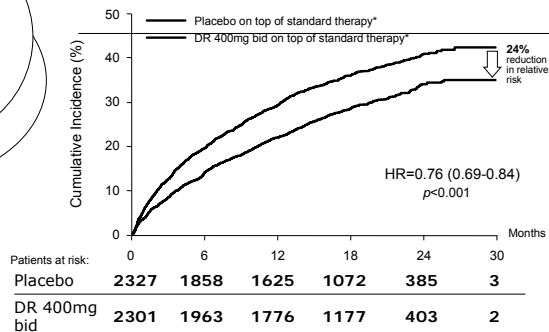
Product monograph 2009.

## ATHENA

- R, DB, PC trial of dronedarone 400mg BID in 4628 patients with paroxysmal or persistent AF (hx of HF ~20%)
- Composite outcome of first hospitalization for CV event or death
- Hospitalization / death NNT 14

NEJM 2009;360:668-78.

## Risk of CV Hospitalization or Death



\*Standard therapy may have included rate control agents (beta blockers, and/or Ca-antagonist and/or digoxin) and/or anti-thrombotic therapy (V, K antagonists and/or aspirin and other antiplatelets therapy) and/or other cardiovascular agents such as ACEIs/ARBs and statins.  
Mean follow-up 21 ±5 months.  
Hohnloser SH et al. N Engl J Med 2009;360:668-78.

## Treatment Emergent Adverse Events

	Dronedarone	Placebo	NNH
Any	72.0	69.3	37
Bradycard	3.5	1.2	43
QT prolong	1.7	0.6	91
GI events	26.2	22.0	24
Skin	10.3	7.6	37
↑ Cr	4.7	1.3	29
Respiratory	14.5	14.6	NS
Endocrine	1.1	1.1	NS

NEJM 2009;360:668-78.

## DIONYSOS

- DB RCT comparing dronedarone (400mg BID) and amiodarone (600mg/d x 28 d then 200mg OD) for the maintenance of sinus rhythm in AF
- AF>72 h and investigator required CV and antiarrhythmic therapy and receiving anticoagulation
- Recurrence of AF or premature study drug discontinuation for intolerance or lack of efficacy

NEJM 2009;360(18):1811-13; clinicaltrials.gov.

## DIONYSOS

- 504 patients followed for 7 months
- AF recurrence or premature drug DC for intolerance or lack of efficacy
  - D 73.9% vs A 55.3% (p<0.001) NNT=6
- AF after DC cardioversion
  - D 36.5% vs A 24.3%
- Premature drug discontinuation
  - D 26 pts vs A 34 pts
- No pulmonary or liver toxicity observed

NEJM 2009;360(18):1811-13; clinicaltrials.gov; sanofi-aventis.com

## DIONYSOS

Safety Endpt	Dronedarone	Amiodarone
Combined	83	107
Thyroid	2	15
Neurological	3	17
Drug DC	13	28
GI	32	13
Bradycardia	8	22
QTc prolong	27	52
Torsades	0	0

NEJM 2009;360(18):1811-13, sanofi-aventis.com.

## Dronedarone - Synopsis

- Reduction in hospitalization or death compared to placebo
- Not as efficacious as amiodarone for prevention of recurrence of AF
- Other than GI effects, APPEARS to be better tolerated than amiodarone in a trial population
- Trial duration likely too short to assess risks of all adverse effects

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## CHADS<sub>2</sub>

- Recent CHF
- History of Hypertension
- Age > 75 years
- Diabetes
- Previous Stroke or TIAs

## CHADS<sub>2</sub> Stroke Risk Strata

CHADS <sub>2</sub> score	Stroke Rate/Yr	95% CI
0	1.9	1.2 – 3.0
1	2.8	2.0 – 3.8
2	4.0	3.1 – 5.1
3	5.9	4.6 – 7.3
4	8.5	6.3 – 11.1
5	12.5	8.2 – 17.5
6	18.2	10.5 – 27.4

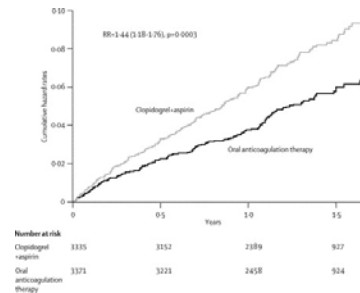
JAMA 2001;285:2864-70.

## ACTIVE W

- Randomized non-inferiority trial of oral anticoagulation vs ASA and clopidogrel in 6708 pts with AF and stroke risk factors
- Eligible /willing to take oral anticoagulation
- Open treatment with blinded adjudication
- Primary outcome – first occurrence of stroke, non-CNS systemic embolism, MI or vascular death
- Stopped early for benefit of oral anticoagulation

Lancet 2006;367:1903-12.

## ACTIVE W – Primary Outcome



Lancet 2006;367:1903-12.

## ACTIVE W - Hemorrhage

	C plus ASA (% per yr)	Oral Anticoag (% per yr)	RR
Major	2.42	2.21	1.10 (0.83-1.45)
Severe	1.70	1.57	1.09 (0.78-1.52)
Fatal	0.17	0.26	0.64 (0.25-1.66)
Minor	13.58	11.45	1.23 (1.09-1.39)
Total	15.40	13.21	1.21 (1.08-1.35)

Lancet 2006;367:1903-12.

## ACTIVE A

- DB, PC RCT comparing clopidogrel 75mg daily to placebo in patients receiving ASA (75 to 100mg daily)
- AF – persistent or intermittent plus risk factors for stroke
- Pts at increased risk of stroke who were “unsuitable” for oral anticoagulation

NEJM 2009;360:electronic

## ACTIVE A

- 7554 patients; CHADS<sub>2</sub> = 2
- <1% lost to follow-up
- Median duration 3.6 years
- Rates of discontinuation:
  - 16.3% clopidogrel and 15.2% placebo – 1yr
  - 39.4% clopidogrel and 37.1% placebo – 4yr
- Primary outcome – any major vascular event

NEJM 2009;360:electronic

## ACTIVE A - Efficacy

	Combo (%/y)	ASA (%/y)	NNT / RR
Primary	6.8	7.6	125
Any stroke	2.4	3.3	111
Ischemic stroke	1.9	2.8	111
Nondisabling	0.9	1.2	333
Disabling	1.6	2.1	200
MI	0.7	0.9	0.78 (0.59-1.03)

NEJM 2009;360:electronic

## ACTIVE A - Safety

	Combo (%/yr)	ASA (%/yr)	NNH
Major bld	2.0	1.3	143
Severe bld	1.5	1.0	200
Minor bld	3.5	1.4	48
Any bleed	9.7	5.7	25
GI bleed	1.1	0.5	167

NEJM 2009;360:electronic

## Balancing the Risk: What about bleeding?

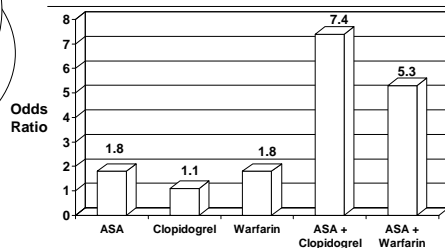
ACTIVE A (NEJM 2009)	ASA	ASA + Clopidogrel	P
Stroke - N (%/year)	408 (3.3)	296 (2.4)	<0.001
Major Bleed - N (%/year)	162 (1.3)	251 (2.0)	<0.001
ICH - N (%/year)	29 (0.2)	54 (0.4)	0.006
GI - N (%/year)	68 (0.5)	132 (1.1)	<0.001

Warfarin - Meta (Arch Intern Med 1994)	Placebo	ASA	Warfarin	Placebo or ASA
Major Bleed (%/year)	1.0	1.0	1.3	
ICH (%/year)	-----	-----	0.3	0.1

Observational Study	INR Target	ICH	Major Bleed
Van der Meer et al (1993)	2.8-4.8	0.6%/year	2.0%/year
Palareti et al (1996)	2.0-4.5	0.5%/year	0.9%/year
Go et al (2003)	2.0-3.0	0.5%/year	1.0%/year

Tammy Bungard 2009.

## Risk of UGIB with Antithrombotic Therapies



- Population-based, case-control study
- 1443 cases of serious UGIB; 57,720 controls
- Minimum of 90 days use of agent
- 8.8% died within 30 days of index event

BMJ 2006, doi:10.1136/bmj.38947.697558.AE

## Dual Antiplatelet Therapy - Synopsis

- Dual antiplatelet therapy is not as efficacious as warfarin
- Dual antiplatelet therapy appears to be more efficacious than ASA alone
- Dual antiplatelet therapy carries a bleed risk similar to that of warfarin

## Dabigatran Etexilate

- Competitive, reversible, direct thrombin inhibitor
- Prodrug – rapidly converted to dabigatran by esterase-catalysed hydrolysis in plasma/liver
- 6.5% bioavailability
  - Tartaric acid
  - Original packaging to protect from moisture
- Drug interactions
  - P-glycoprotein inhibitors (quinidine, amiodarone, verapamil, clarithromycin) increase exposure; inducers (rifampin, St John's wort) decrease exposure
  - Not effected by cytochrome P450 system

Br J Clin Pharmacol 2007; Clin Pharmacokinet 2008

## Dabigatran Etexilate

- Cmax 0.5 to 2 hours
- Food delays peak by 2 hours but no difference in AUC
- t<sub>1/2</sub> 11 – 17 hours
- 80% renal elimination (contraindicated in CrCL < 30 mL/min)
- No unexpected accumulation with multiple doses
- Predictable pharmacokinetics

Br J Clin Pharmacol 2007; Clin Pharmacokinet 2008

## RE-LY Trial

- Randomized non-inferiority trial comparing two blinded fixed doses of dabigatran (110mg BID or 150mg BID) with open-label warfarin in patients with AF at increased risk of stroke
- Excluded patients with CrCL <30
- Primary outcome stroke or systemic embolism – blinded adjudication
- Primary safety outcome major hemorrhage

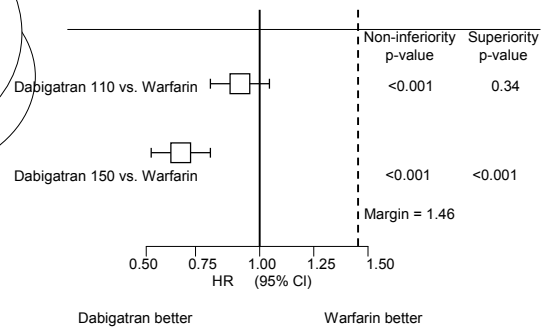
NEJM 2009;361.

## RE-LY – Baseline Characteristics

- LFTs monthly for first year, then decreased once 6000 patients evidence
- Median follow-up 2 years
- Warfarin mean TTR 64% (Rosendaal)
- Mean age 71 years
- 64% male
- Half received long-term therapy with vitamin K antagonists
- Mean CHADS2 score of 2.1

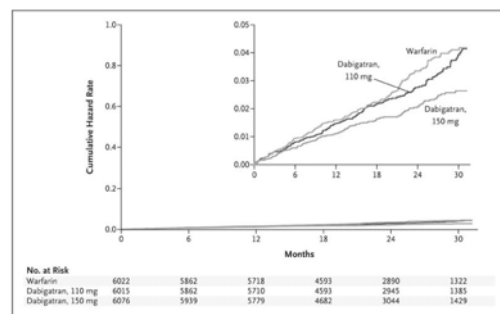
NEJM 2009;361.

## RE-LY: Stroke or Systemic Embolism



Tammy Bungard 2009.

## RE-LY



NEJM 2009;361.

## Net Clinical Benefit

stroke, systemic embolism, pulmonary embolism, myocardial infarction, major bleeding & death

D 110	D 150	W	Dab 110 vs Warf		Dab 150 vs Warf		Dab 150 vs Dab 110	
Annual Rate (%/year)			RR	P	RR	P	RR	P
			95%CI		95%CI		95%CI	
7.09	6.91	7.64	0.92	0.10	0.91	0.04	0.98	0.66
			0.84-1.02		0.82-1.00		0.89-1.08	

Pick your benefit –

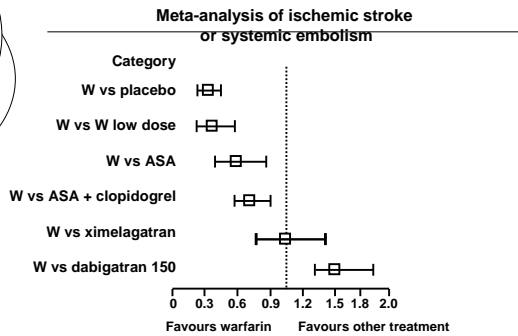
Dabigatran 110 mg BID vs warfarin – reduced major bleeding with similar efficacy  
 Dabigatran 150 mg BID vs warfarin – reduced stroke with similar major bleeding

Tammy Bungard 2009.

## Unanswered Questions?

- Clinical relevance of drug interactions
- Use in patients with previous GIB, PUD or dyspepsia
- Clarification surrounding risk of MI
  - Warfarin and coronary ischemic events
  - Timing of MIs
  - Concomitant use of ASA
  - History of CAD

## Warfarin: Study Summary



Tammy Bungard 2009.

Cammi J.: Oral presentation at ESC on Aug 30th 2009.

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## Summary

- For patients requiring antiarrhythmic therapy for maintenance of NSR, dronedarone appears to offer less efficacy than amiodarone, perhaps with fewer ADRs
- Dual antiplatelet therapy is more efficacious than ASA alone but carries a bleed risk that may be similar to warfarin
- Dependent upon dosing, dabigatran compared to warfarin reduced major bleeding with similar efficacy or reduced stroke with similar major bleeding