

What's New in Cardiology: Clinic Trials



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Apixaban versus Warfarin in Patients with Atrial Fibrillation *The ARISTOTLE Trial*

Granger CB, et al. NEJM.org, August 28, 2011

Background

- Stroke is the most significant morbidity in patients with atrial fibrillation.
- Warfarin is very effective in reducing strokes but has major limitations and is underused in clinical practice.
- Novel oral anticoagulants have emerged :
 - Dabigatran (Re-LY)
 - Rivaroxaban (ROCKET-AF)
 - Apixaban (ARISTOTLE)
- Apixaban: direct FXa inhibitor, rapid absorption, half life 8-15 hours, multiple elimination pathways (renal 25%), minimal potential for drug interactions.

ARISTOTLE: Objectives

Efficacy:

In patients with atrial fibrillation and at least 1 additional risk factor for stroke, is apixaban noninferior to warfarin at reducing stroke (ischemic and hemorrhagic) or systemic embolism?

Safety:

Compare apixaban and warfarin with respect to incidence of major bleeding

ARISTOTLE: Study Design

Inclusion Criteria: AF plus at least one risk factors:
 • Age \geq 75 years
 • Prior stroke, TIA, or SE
 • HF or LVEF \leq 40%
 • Diabetes mellitus
 • Hypertension

**Randomized
double blind,
double dummy**

n = 18,201
(1034 sites in 39 countries)

Key Exclusion Criteria:
 • Mechanical prosthetic valve
 • Severe renal insufficiency (creatinine $>$ 221 μ mol/L, CrCl $<$ 25 ml/min)
 • Need for ASA + Clopidogrel
 • ASA $>$ 165mg/d

Apixaban 5 mg bid
(2.5 mg bid in selected patients) +
Warfarin placebo

**Warfarin (target INR 2-3) +
Apixaban placebo**

Warfarin/warfarin placebo dose guided by blinded encrypted point-of-care INR testing device

Follow-Up

INR monitoring: monthly. Clinical outcomes/AE: q3mos

Primary outcome: stroke or systemic embolism
Blinded event adjudication

ARISTOTLE: Outcomes

- **Primary Efficacy Outcome:** stroke or systemic embolism
 - Secondary Efficacy: all cause mortality
- **Primary Safety Endpoint:**
 - Major bleeding (ISTH) definition = \downarrow Hgb \geq 20g/L, transfusion of \geq 2 units of blood, in critical site or resulting in death
- **Hierarchical testing:** non-inferiority for primary outcome, superiority comparisons primary outcome, bleeding, mortality
- **Efficacy analysis:** intention-to-treat
- **Bleeding analysis:** on treatment (at least 1 dose of study drug)

ARISTOTLE: Trial Execution

- Enrollment period: December 2006 to April 2010
- Median follow-up of 1.8 years
- Vital status missing for 2.1% of patients (n=380)
- Warfarin mean TTR 62.2% (Rosendall)
- Drug discontinuation:
 - Apixaban 25.3% versus warfarin 27.5% (p=0.001)

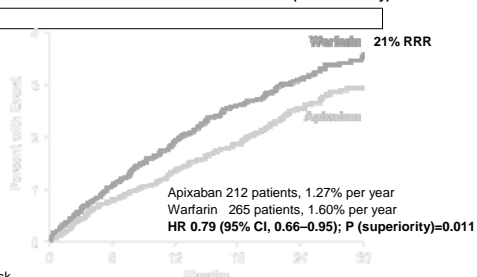
Baseline Characteristics

Characteristic	Apixaban (n=9120)	Warfarin (n=9081)
Age, years, median (IQR)	70 (63, 76)	70 (63, 76)
Women, %	36	35
Warfarin naïve, %	43	43
CHADS score, mean (± SD)	2.1 (±1.1)	2.1 (±1.1)
1 (%)	34	34
2 (%)	36	36
≥ 3 (%)	30	30
Qualifying risk factors, %		
Age ≥75 yrs	31	31
Prior stroke, TIA, or SE	19	20
Heart failure or reduced LV EF	36	35
Diabetes	25	25
Hypertension	87	88
Aspirin	31	31
Clopidogrel	2	2
Amiodarone	11	12

Primary Outcome

Stroke (ischemic or hemorrhagic) or systemic embolism

P (non-inferiority) < 0.001



No. at Risk

	0	6	12	18	24	30
Apixaban	9120	8726	8440	6051	3464	1754
Warfarin	9081	8620	8301	5972	3405	1768

ARISTOTLE: Efficacy Outcomes

Outcome	Apixaban (N=9120) Event Rate (%/yr)	Warfarin (N=9081) Event Rate (%/yr)	HR (95% CI)	P Value
Stroke or systemic embolism	1.27	1.60	0.79 (0.66, 0.95)	0.011
Stroke	1.19	1.51	0.79 (0.65, 0.95)	0.012
Ischemic or uncertain	0.97	1.05	0.92 (0.74, 1.13)	0.42
Hemorrhagic	0.24	0.47	0.51 (0.35, 0.75)	<0.001
Systemic embolism (SE)	0.09	0.10	0.87 (0.44, 1.75)	0.70
All-cause death	3.52	3.94	0.89 (0.80, 0.998)	0.047
Stroke, SE, or all-cause death	4.49	5.04	0.89 (0.81, 0.98)	0.019
Myocardial infarction	0.53	0.61	0.88 (0.66, 1.17)	0.37

Results consistent in predefined subgroups

ARISTOTLE: Bleeding Outcomes

Outcome	Apixaban (N=9088) Event Rate (%/yr)	Warfarin (N=9052) Event Rate (%/yr)	HR (95% CI)	P Value
Primary safety outcome: ISTH major bleeding	2.13	3.09	0.69 (0.60, 0.80)	<0.001
Intracranial	0.33	0.80	0.42 (0.30, 0.58)	<0.001
Gastrointestinal	0.76	0.86	0.89 (0.70, 1.15)	0.37
Major or clinically relevant non-major bleeding	4.07	6.01	0.68 (0.61, 0.75)	<0.001
Any bleeding	18.1	25.8	0.71 (0.68, 0.75)	<0.001

Subgroup analysis: greater reduction in bleeding in patients who did not have diabetes and those with moderate to severe renal impairment

ARISTOTLE: Implications

Will this change my practice?

- In comparison to warfarin:
 - ↓ stroke and systemic embolism by 21% (p=0.01)
 - ↓ major bleeding by 31% (p<0.001)
 - ↓ mortality by 11% (p=0.047)
 - No difference in rate of myocardial infarction
 - Good tolerability, convenience (no INR monitoring)
- Dabigatran (150mg bid) versus warfarin:
 - greater reduction in rate of ischemic stroke
 - major bleeding similar to warfarin (lower IC bleed, higher GI)
 - mortality – same directional trend
 - myocardial infarction – some uncertainty

ARISTOTLE: Implications

Will my practice change right away?

- Apixaban not approved for any indication in Canada
- Drug cost, cost effectiveness studies
- Longer term safety data
- No antidote to reverse anticoagulant effects

Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms The EMPASIS-HF Trial

Zannad F, McMurray JJV, Krum H, et al. *N Engl J Med* 2011;364:11-21

Background

- Current guidelines for systolic heart failure (HF) with mild symptoms (NYHA class II) include ACEI and beta blockers (mortality and morbidity benefits demonstrated in RCTs).
- Aldosterone antagonist (spironolactone, eplerenone) favourably influence progression of HF.
- Aldosterone antagonists recommended for:
 - Systolic HF, NYHA class III/IV (RALES trial¹ - ↓ mortality & CV hospitalizations)
 - Acute MI with LV systolic dysfunction & HF or diabetes (EPHESUS trial² - ↓ mortality & CV hospitalizations)

1. Pitt B, et al. *N Engl J Med* 1999;341:709-17 2. Pitt B, et al. *N Engl J Med* 2003;348:1309-21

EMPHASIS-HF: Objective

To investigate the effects of eplerenone, compared to placebo, on clinical outcomes in patients with systolic HF and mild symptoms (NYHA FC II) treated with recommended evidence-based therapy

EMPHASIS-HF: Study Design

Inclusion Criteria:

- Age > 55 years
- NYHA class II
- LVEF ≤ 30% or EF 30-35% with QRS > 130ms
- ACEI &/or ARB, β-blocker
- CV hosp. within 6 mos.
- If no CV hosp. BNP ≥ 250pg/ml, NT-proBNP ≥ 500 pg/ml (males), ≥ 750 (females)

Randomized

double blind

n = 2737

(278 sites in 29 countries)

Key Exclusion Criteria:

- potassium > 5 mmol/l
- eGFR < 30 ml/min
- NYHA class III or IV
- Acute MI

Placebo

Eplerenone

25 mg daily x 4wk., 50mg daily if K ≤ 5.0. (GFR 30-49 ml/min: 25mg q2d x 4wk, then 25mg daily if K ≤ 5.0)

Follow-Up: q4 months

If K+ ≥ 5.5 mmol/l → dose reduced. If K+ ≥ 6.0 mmol/L → held. Repeat K+ in 72hr, restart drug if K+ ≤ 5.0 mmol/L

Primary outcome: CV death or HF hospitalization

EMPHASIS-HF: Secondary Outcomes

- HF hospitalization or all-cause mortality
- All-cause mortality
- CV mortality
- All-cause hospitalization
- HF hospitalization

Analysis

- Efficacy analysis: intention-to-treat
- Safety analysis: ≥ 1 dose of study drug

EMPHASIS-HF: Trial Execution

- Enrollment period: March 2006 to May 2010
- Trial stopped by DSMB at second interim analysis for benefit
- Median follow-up of 21 months
- Patient lost to follow-up: eplerenone (1.2%), placebo (1.1%)
- Drug discontinuation:
 - eplerenone 16.3%, placebo 16.1%

Baseline Characteristics

Characteristic	Eplerenone (n=1364)	Placebo (n=1373)
Age, years, mean (± SD)	68 (± 7.7)	69 (± 7.6)
Females, %	23	22
LVEF, %, mean (± SD)	26 (± 4.6)	26 (± 4.7)
Ischemic etiology, %	70	68
QRS >130 msec	26	26
Medical history		
HF hospitalization	52	53
Hypertension	67	66
Atrial fibrillation	30	32
Diabetes	34	29
Medication		
Diuretic	84	86
ACEI/ARB/both	94	93
Beta blocker	87	87
Digoxin	27	28
Device therapy ICD	13	13

EMPHASIS-HF: Key Outcomes

Outcome	Eplerenone (N=1364) n(%)	Placebo (N=1373) n(%)	HR (95% CI)	P Value
CV death or HF hospitalization	249 (18)	356 (26)	0.63 (0.54, 0.74)	<0.001
CV death	147 (11)	185 (14)	0.76 (0.61, 0.94)	0.01
HF hospitalization	164 (12)	253 (18)	0.58 (0.47, 0.70)	<0.001
Death from any cause	171 (13)	213 (16)	0.76 (0.62, 0.93)	0.008
Hospitalization for any reason	408 (30)	491 (36)	0.77 (0.67, 0.88)	<0.001

Results consistent in predefined subgroups

EMPHASIS-HF: Key Outcomes

Outcome	Eplerenone (%)	Placebo (%)	P Value
Serum K ⁺ > 5.5 mmol/l	11.8	7.2	<0.001
Serum K ⁺ > 6.0 mmol/l	2.5	1.9	0.29
Hyperkalemia – d/c treatment	1.1	0.9	0.57
Hospitalization for hyperkalemia	0.3	0.2	0.85
Serum K ⁺ < 3.5 mmol/l	7.5	11.0	0.002
Hospitalization for worsening renal failure	0.7	0.6	0.95
Hypotension	3.4	2.7	0.32
Drug d/c due to adverse event	13.8	16.2	0.09

EMPHASIS-HF: Implications

Eplerenone, in addition to recommended therapy, in patients with systolic HF, NYHA FC II, and other high risk features (EF 30-35%, recent HF hospitalization) reduces CV mortality and hospitalizations for HF, as compared to placebo.

- NNT (primary outcome) = 10
- NNT (mortality) = 51

Do current HF guidelines need revision?

EMPHASIS-HF: Implications

- Hyperkalemia in the real world:
 - the “post-RALES” experience
 - “stable” patients may utilize lower doses of loop diuretics
 - Monitor K⁺ (3 days, 1 week and qmonthly x 3)
- Cost
- Is this a class effect?

The influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study

Chronobiology International 2010;27(8):1629-51.

MAPEC Trial

Hermida RC, et al. Chronobiol Int 2010;27:1629-51.

- Background:
 - BP and HR are affected by the body's circadian rhythms. Usually, BP is lowest during sleep, and surges in the am.
 - The circadian rhythm also affects medication PK and PD properties independent of half-life kinetics.
 - Nighttime, or asleep, BP is a better predictor of CV risk than daytime or 24-hour BP.
 - Most MDs and pharmacists continue to advise patients to take once-daily BP medications in the morning.
 - The potential differential effect of HS dosing versus morning dosing **on CV events** has never been evaluated in a RCT.

MAPEC Trial

Hermida RC, et al. Chronobiol Int 2010;27:1629-51.

Question:

- Does bedtime chronotherapy with ≥ 1 antihypertensive medications exert significantly better BP control and CVD risk reduction than conventional dosing (which is all medications ingested upon waking)?

Methods

Hermida RC, et al. Chronobiol Int 2010;27:1629-51.

- Design: PROBE (Prospective, randomized, open-label, blinded endpoint), single-center (Spain)
- Follow-up period:
 - Median 5.6 years (range 0.5-8.6 years)
- Patients:
 - Inclusion: ≥ 18 yo, diurnally active, hypertensive, and referred to Hypertension Clinic
 - Exclusion: pregnancy, secondary hypertension, DMI, hx of drug or EtOH abuse, CVD disorders, diagnosis of AIDS, employment in shift or night work, intolerance to ABPM measurement, inability to communicate and comply with study requirements

Methods

Hermida RC, et al. Chronobiol Int 2010;27:1629-51.

- Intervention:
 - Taking antihypertensives in morning upon awakening (n=1109) or at bedtime (n=1092)
- Outcomes:
 - 1° – death from all causes, MI, angina pectoris, coronary revascularization, heart failure, acute arterial occlusion of lower extremities, rupture of aortic aneurisms, thrombotic occlusion of the retinal artery, hemorrhagic and ischemic stroke, TIA.
- Patient follow-up:
 - 25 patients (2%) lost to follow-up (morning dosing time)
 - 20 patients (2%) lost to follow-up (bedtime dosing time)
 - 1084 and 1072 patients were analyzed respectively

Baseline Characteristics

Hermida RC, et al. Chronobiol Int 2010;27:1629-51.

Variable	Morning	Bedtime	P value
Patients, n	1084	1072	
Duration of hypertension, yrs	6.8 \pm 8.0	6.6 \pm 7.7	.614
Previous cardiovascular events	5.3	5.2	.975
ABPM, Awake SBP mean, mm Hg	134.3 \pm 15.7	134.2 \pm 13.8	.855
ABPM, Asleep SBP mean, mm Hg	122.7 \pm 17.4	122.7 \pm 15.3	<.935
ABPM, Awake DBP mean, mm Hg	81.9 \pm 11.5	82.4 \pm 10.8	.331
ABPM, Asleep DBP mean, mm Hg	70.4 \pm 10.4	71.0 \pm 9.5	.154
Non-dipper, %	55.4	53.0	.252

Main Results

Hermida RC, et al. *Chronobiol Int* 2010;27:1629-51.

Variable	Morning	Bedtime	P value
Patients, n	1084	1072	
Primary endpoints, events/1000 patient years (event number in parenthesis)			
Total events	27.8(187)	11.95 (68)	<.001
Total death	4.16 (28)	2.11 (12)	.008
Aortiliac occlusive dx	2.08 (14)	0.53 (3)	.006
Other cause (retinal artery occlusion)	2.08 (14)	1.58 (9)	.25
CVD events (MI, angina, revasc)	11.00 (74)	5.27 (30)	<.001
Cerebrovascular events	3.57 (24)	1.23 (7)	.001
Heart failure	4.91 (33)	1.41 (8)	<.001

Main Results: Clinic BP and AMBP

Hermida RC, et al. *Chronobiol Int* 2010;27:1629-51.

Variable	Morning	Bedtime	P value
Patients, n	1084	1072	
Awake SBP mean, mmHg	124.9±15.1	125.3±12.9	.546
Asleep SBP mean, mmHg	116.1±17.9	110.9±13.9	<.001
Awake DBP mean, mmHg	74.7±10.4	75.9±10.2	.005
Asleep DBP mean, mmHg	65.2±10.4	63.1±9.4	<.001
Non-dipper, %	61.6	34.4	<.001
Controlled ambulatory BP, %	52.8	62.2	<.001
Changes in clinic and ambulatory BP from baseline			
Asleep SBP mean, mmHg	-6.6±12.5	-11.8±13.2	<.001
Asleep DBP mean, mmHg	-5.2±8.3	-7.9±8.5	<.001

Implications

Hermida RC, et al. *Chronobiol Int* 2010;27:1629-51.

- Comments
 - 1st RCT to investigate chronotherapy on CVD event rate
 - Simple intervention with no proven downside except adherence implications
 - Most significant predictors of event-free survival: (1) increase in sleep-time relative BP decline, (2) decrease in asleep BP mean
 - ABPM gives different (lower) BPs compared to clinic
 - Limitations:
 - Single-center study
 - ITT did not include patients without 6-month data
- Bottom line:
 - Dosing at least 1 antihypertensive medication at hs appears to reduce CVD events

Addition of spironolactone in patients with resistant arterial hypertension (ASPIRANT): A randomized, double-blind, placebo-controlled trial

Hypertension 2011;57:1069-75.

ASPIRANT Trial

Václavík J, et al. *Hypertension* 2011;57:1069-75.

- Background:
 - Resistant hypertension, defined as being on 3 or more antihypertensives, including a diuretic, at maximally tolerated doses, affects >10% of all patients with hypertension
 - Spironolactone, an aldosterone antagonist, has been shown to lower BP effectively. A recent Cochrane Review showed decreases of 20 mmHg in sBP and 7 mmHg dBP with spironolactone monotherapy in doses of <50mg daily.
 - Spironolactone has not been studied in a randomized trial for addition to current therapy in patients with resistant hypertension.

ASPIRANT Trial

Václavík J, et al. *Hypertension* 2011;57:1069-75.

Question:

- What blood pressure lowering effect does low-dose spironolactone (25 mg/day) have when added to existing therapy in patients with resistant hypertension?

Methods

Václavík J, et al. *Hypertension* 2011;57:1069-75.

- Design: Prospective, multi-center, randomized, double blind, placebo-controlled, parallel-group trial
- Follow-up period: 8 weeks
- Patients:
 - Inclusion: ≥ 18 yo, with SBP>140 mmHg or DBP>90 mmHg despite being treated with 3 antihypertensives, including a diuretic.
 - Exclusion: severe hypertension (SBP>180 or DBP>110 mmHg) who needed immediate treatment, renal insufficiency with Scr>180 $\mu\text{mol/L}$, hyperkalemia ($K^+>5.4$ mmol/L), pregnant or lactating women

Methods

Václavík J, et al. *Hypertension* 2011;57:1069-75.

- Intervention:
 - Spironolactone 25 mg qam (n=55) or placebo (n=56)
- Outcomes:
 - 1° – fall of average daytime systolic and diastolic blood pressure on ABPM between spironolactone and placebo
 - 2° – fall of average 24-hour systolic and diastolic BP and a difference in the fall of office BP between spironolactone and placebo
 - 2° – changes in serum levels of sodium, potassium, Scr and body weight
 - 2° – evaluate response to spironolactone treatment based on baseline aldosterone level and baseline aldosterone/renin ratio (ARR)

Baseline Characteristics

Characteristic	Spironolactone (n=55)	Placebo (n=56)
Age, years, mean (\pm SD)	61.4 (\pm 9.6)	60.1 (\pm 9.4)
Females, %	32.7	42.9
BMI	32.3 (\pm 5.1)	32.3 (\pm 5.3)
Mean baseline BP		
Office SBP, mmHg	154.9 (\pm 10.4)	154.9 (\pm 10.4)
Office DBP, mmHg	92.6 (\pm 10.7)	90.6 (\pm 10.9)
ABPM SBP, mmHg	144.7 (\pm 14.8)	144.7 (\pm 16.2)
ABPM DBP, mmHg	83.6 (\pm 11.1)	80.9 (\pm 10.4)
Baseline serum labs		
Aldo to renin ratio (ARR)	15.2	32.3
Aldosterone, pmol/L	261 (64; 824)	338 (94; 1193)
Mean number antihypertensives	4 (3; 6)	4(3; 6)

Main Results

Václavík J, et al. *Hypertension* 2011;57:1069-75.

Trial was stopped after first interim analysis secondary to benefit in spironolactone arm.

Variable	Spironolactone	Placebo	P-value
Patients, n	55	56	
Systolic BP			
AMBP daytime, mmHg	-9.3 (\pm 12.6)	-3.9 (\pm 12.1)	0.024
AMBP nighttime, mmHg	-11.2 (\pm 17.6)	-2.6 (\pm 17.7)	0.011
Diastolic BP			
AMBP daytime, mmHg	-4.2 (\pm 8.0)	-3.2 (\pm 8.2)	0.358
AMBP nighttime, mmHg	-5.6 (\pm 10.5)	-2.6 (\pm 11.0)	0.079
Serum K ⁺ , mmol/L	0.3 (-0.5; 1.5)	0.0 (-0.8; 0.6)	<0.001
Serum creatinine, $\mu\text{mol/L}$	7 (-11; 22)	0 (-11; 18)	<0.001
Microalbuminuria, mg/day	-4.4 (-257; 11.0)	0.0 (-87; 98.0)	0.023

Main Results: Mean BP Differences in Relation to Baseline Labs

Václavík J, et al. *Hypertension* 2011;57:1069-75.

Baseline Parameter	First Tertile	Second Tertile	Third Tertile	P
Serum Aldosterone,	≤ 205	205-341	>341	
Systolic BP	-13	-9.0	-8.0	.615
Diastolic BP	-3.0	-6.0	-2.1	.524
ARR	≤ 7	7-45	>45	
Systolic BP	-4	-13	-15	.019
Diastolic BP	0.0	-5.0	-7.0	.049

Frequency of Adverse Effects leading to Drug Discontinuation
 *N=2 in spironolactone group, n=1 in placebo group

Implications

Václavík J, et al. *Hypertension* 2011;57:1069-75.

- Comments
 - 1st RCT to investigate spironolactone in resistant hypertension patients.
 - Low usage of this agent for resistant HTN.
 - Pharmacists need to be aware that spironolactone has a dose-response hyperkalemic effect. This needs to be monitored at baseline and with dose increases.
 - Those with elevated Scr need to be watched diligently. This trial excluded patients with a Scr >180 $\mu\text{mol/L}$.
- Bottom line:
 - Spironolactone in doses of 25 mg/day is effective in lowering SBP in resistant hypertension patients.
 - The impact on CV events has not been reported.



Questions?