PALLAS: Dronedarone in High-Risk Permanent Atrial Fibrillation[1]

Permanent Atrial FibriLLAtion Outcomes Study Using Dronedarone on top of Standard Therapy

BOTTOM LINE

- In a high risk population with *permanent* atrial fibrillation (AF), dronedarone should **NOT** be added on to standard therapy due to ↑ risk of several adverse outcomes such as cardiovascular death, stroke and heart failure (HF). Study was terminated early due to safety concerns.

BACKGROUND

- In ERATO[2] dronedarone ↓ ventricular rate in patients with permanent AF versus placebo.
- A post-hoc analysis of the EURIDIS and ADONIS[3] studies demonstrated that dronedarone ↓ the risk of cardiovascular hospitalization or death in patients with persistent or paroxysmal AF.
- The ANDOMEDA[4] study found that dronedarone↑ mortality in patients hospitalized with symptomatic HF and severe left ventricular systolic dysfunction (was terminated prematurely).
- The ATHENA trial[5,6] found that in patients with AF or atrial flutter, those who were randomly assigned to dronedarone 400mg BID (versus placebo) had lower rates of unplanned hospitalization for cardiovascular causes or death (primary outcome). Dronedarone also ↓ death from cardiovascular causes, stroke & hospitalization for acute coronary syndromes.
- Patients with permanent atrial fibrillation were excluded at the start of ATHENA[5,6], but a post-hoc analysis of patients who developed permanent atrial fibrillation during the trial showed the dronedarone group had a trend towards a↓ in the primary outcome as well as a ↓ in cardiovascular events.
- The PALLAS investigators[1] hypothesized that patients in permanent AF may benefit from dronedarone as this patient population is at high risk of cardiovascular events, similar to patients investigated in ATHENA[5,6]. The investigators also postulated that dronedarone may have benefits beyond its anti-arrhythmic effects such as blood pressure lowering & adrenergic blockade.

TRIAL BACKGROUND[1,7,8,9,10]

DESIGN: Randomized, multi-centre 489 sites in 37 countries worldwide, intention-to-treat, double-blind, placebo-controlled, parallel group trial. Sponsored by Sanofi-Aventis (manufacturer of dronedarone), data analysis by the Population Health Research Institute in Hamilton, Ontario.

INTERVENTION: Dronedarone 400mg PO BID versus placebo

INCLUSION: **permanent AF** documented by ECG ≥6months prior & 14 days before randomization with no plan to restore sinus rhythm, ≥65 years old with ≥1 of the following risk factors: CAD, previous stroke/TIA, symptomatic HF NYHA class II or III & hospital admission in previous year but not last 30 days; LVEF≤40%, PAD *or* the combination of ≥75 years old with HTN and DM.

EXCLUSION: paroxysmal or persistent AF; ICD use; previous AV node ablation; 3rd degree AV block; NYHA class IV or recent, unstable class III; sustained daytime bradycardia of <50 bpm; prolonged QT interval corrected for heart rate of >500 msec or >530 msec for patients with a paced ventricular rhythm; co-administration of QT-prolonging drugs, severe hepatic impairment; any non-cardiovascular disease that could limit survival cancer with metastasis, organ transplantation and immune suppression; dronedarone treatment in prior 3 months; previous clinical trial in last 2 months; patient likely for non-compliance.

POPULATION at baseline (n=3236 over 1 year trial stopped early, target n=10,800): Age 75 ±6 years; ~64% ♂; 69% ≥ 2 year duration of permanent AF, 98% showed AF at baseline (2% atrial flutter), baseline HR 77±16 bpm, Systolic BP 133±17 mmHg, CAD 41%, HF ~66% NYHA class I ~13%, NYHA class II ~45%, NYHA class III ~8%; symptomatic HF ~15%, LVEF ≤40% ~21%, previous stroke/TIA ~27%, PAD ~12%, age 75 years *plus* DM and HTN ~18%, mean $CHADS_2$ score 2.8±1.2, ~88% $CHADS_2$ score ≥2, previous MI ~25%, prior CABG ~13%, pacemaker ~14%, mean corrected QT interval 425 msec ±40, HTN ~85%, DM ~36%. Medications: rate-control medication 88% (β-blocker 74%, verapamil or diltiazem 10%), digoxin ~33%, vitamin K antagonist 84%, dabigatran 2%, diuretics 70%, ACEI 51%, ARB ~25%, statin ~57%.

- No statistically significant differences in baseline characteristics between the two study groups

RESULTS

Follow-up: median 3.5 months

NOTE: TRIAL ESTIMATED ENROLLMENT OF 10,800 PATIENTS OVER 2 YEARS FOR POWER 90% BUT WAS STOPPED EARLY (AFTER ~1YEAR) WITH 3236 PATIENTS DUE TO SAFETY CONCERNS

CLINICAL ENDPOINTS	DRONEDARONE 400MG BID (n=1619)	PLACEBO (n=1617)	HR (95% CI)	P-VALUE	ARI/NNH (MEDIAN 3.5 MONTHS FOLLOW-UP)	HARM RATE/100 PT YEARS	COMMENTS
COPRIMARY ENDPOINTS:							
First Coprimary Endpoint: composite of stroke, MI, systemic embolism or death from CV causes	2.66% (n=43)	1.18% (n=19)	2.29 (1.34-3.94)	0.002	1.48% / 68	**22**	**First Coprimary Endpoint:** assumed an event rate of 4.5% in control group at 1 year for statistical analysis **Secondary Endpoints:** Ischemic stroke, systemic embolism, MI or UA, and MI alone were NS between groups **Subgroup analysis** - showed that the 2nd coprimary outcome occurred more often in DM patients (p=0.03) - risk with dronedarone for both primary outcomes & for hospitalization was seen regardless of LVEF or NYHA classification - heart failure alone was NS in terms of contribution to death between groups *NOTE: In the trial results, death from any cause was reported as significant (p=0.049) but when values are calculated, p=0.05 and confidence interval crosses 1 indicating non-significance
First Coprimary Endpoint: unplanned hospitalization for a CV cause or death	7.84% (n=127)	4.14% (n=67)	1.95 (1.45-2.62)	<0.001	3.7% / 27	**8**	
SECONDARY ENDPOINTS							
Death from CV causes (arrhythmia, heart failure, stroke, vascular events)	1.3% (n=21)	0.6% (n=10)	2.11 (1-4.49)	0.046	0.68% / 147	48	
Death from arrhythmia	0.8% (n=13)	0.2% (n=4)	3.26 (1.06-10)	0.03	0.56% / 167	59	
Death from any cause	1.5% (n=25)	0.8% (n=13)	1.94 (0.99-3.79)	0.05*	NS	---	
Any Stroke	1.4% (n=23)	0.6% (n=10)	2.32 (1.11-4.88)	0.02	0.8% / 125	40	
Unplanned hospitalization for CV causes	7% (n=113)	3.6% (n=59)	1.97 (1.44-2.7)	<0.001	3.33% / 30	9	
Hospitalization for HF	2.7% (n=43)	1.5% (n=24)	1.81 (1.1-2.99)	0.02	1.17% / 85	27	
HF episode or hospitalization	7.1% (n=115)	3.4% (n=55)	2.16 (1.57-2.98)	<0.001	3.7% / 27	8	

Dronedarone had a positive effect on surrogate outcomes but ↑ detrimental endpoints versus placebo

Sinus rhythm: at baseline, no patients in either group were in sinus rhythm. At 4-month follow-up, 3.7% in dronedarone group and 1.4% in placebo group were in sinus rhythm (p=0.01)

Mean Heart Rate (bpm±SD): at baseline, dronedarone 77±16, placebo 78±16. At 1-month follow-up, dronedarone ↓ by 7.6±14.5 and placebo ↑ by 0.1±14 (p=0.001)

Systolic blood pressure (mmHg±SD): At baseline, dronedarone 133±17 and placebo 133±17. At 1-month follow-up, dronedarone ↓ by **3.5±16.1** and placebo ↓ by **1.7±16.1** (p=0.003).

- **NOTE:** for digoxin patients, mean serum digoxin levels on day 7 were HIGHER in the dronedarone group (1.2±0.8 ng/mL versus 0.9±0.6 ng/mL; **p<0.001**)
- **NOTE:** mean time in therapeutic INR 2.0-3.0 was lower in dronedarone group (55.6%) & 58.6% in the placebo group (**p=0.02**)

TABLE 2: ADVERSE EVENTS AND LAB ABNORMALITIES

EVENT	DRONEDARONE (n=1614)	PLACEBO (n=1609)	P-VALUE	NNH	COMMENTS
Any adverse event	49.4% (n=797)	37.3% (n=600)	<0.001	8	Dronedarone produced **significantly** more adverse outcomes than placebo & more patients prematurely discontinued dronedarone than placebo (21% vs 11% respectively) Most common adverse events were diarrhea, asthenic conditions, nausea and vomiting, dizziness, dyspnea and bradycardia. Consistent with other clinical studies, dronedarone ↑ liver function tests At 1 month, QT prolongation was ↑ with dronedarone (dronedarone 8±40 msec versus placebo 2±39 msec, p=0.0001)
Any serious adverse event	7% (n=113)	4.8% (n=77)	0.008	45	
Any adverse event leading to treatment discontinuation	13.1% (n=212)	5% (n=80)	<0.001	12	
Any reported liver function abnormality	3.8% (n=61)	1.7% (n=28)	<0.001	49	
Asthenic conditions (asthenia, fatigue)	5.5% (n=89)	2.9% (n=46)	<0.001	38	
Breathing abnormalities (dyspnea)	4.6% (n=75)	2.2% (n=36)	<0.001	42	
Diarrhea	6.3% (n=101)	2.4% (n=38)	<0.001	26	
QT prolongation	2% (n=33)	1% (n=16)	0.02	95	
Edema (peripheral)	3.7% (n=60)	1.8% (n=29)	<0.001	52	
GI or abdominal pain	2% (n=33)	0.9% (n=15)	0.009	90	
↑ creatinine	3% (n=49)	0.7% (n=11)	<0.001	43	
Lower respiratory or lung infection	2.5% (n=40)	2.6% (n=42)	NS	NS	
Nausea or vomiting	4.7% (n=76)	1.7% (n=28)	<0.001	34	
Neurologic signs/symptoms (dizziness)	4.7% (n=76)	2.4% (n=39)	<0.001	44	
Rate and rhythm disorders (bradycardia)	4.2% (n=67)	1.2% (n=19)	<0.001	34	
Renal failure or impairment	2.2% (n=35)	0.7% (n=12)	<0.001	70	
Upper respiratory tract infection	2.1% (n=34)	2.2% (n=35)	NS	NS	
Alanine aminotransferase >3x ULN	1.5% (n=23)	0.6% (n=9)	0.013	116	
Alanine aminotransferase >3x ULN AND bilirubin >2x ULN	<0.1% (n=1)	0	NA	NA	

KAPLAN-MEIER CURVES FOR PRIMARY AND SECONDARY OUCOMES[1]

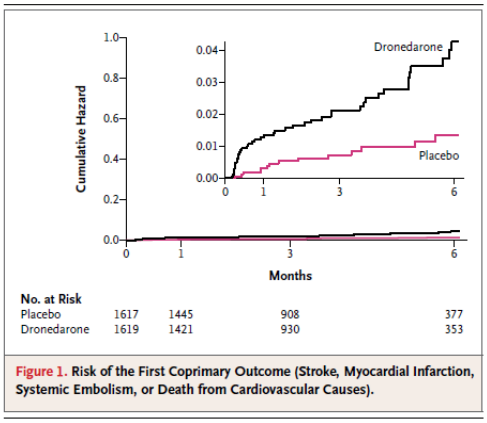

Figure 1. Risk of the First Coprimary Outcome (Stroke, Myocardial Infarction, Systemic Embolism, or Death from Cardiovascular Causes).

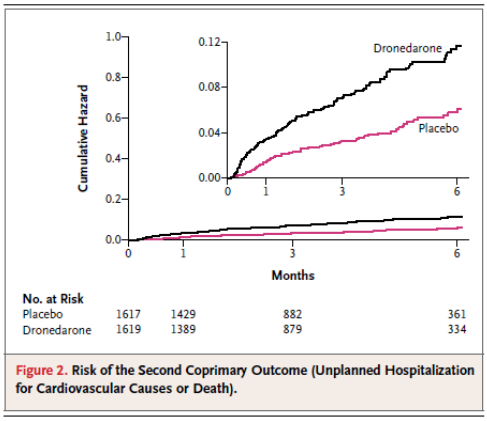

Figure 2. Risk of the Second Coprimary Outcome (Unplanned Hospitalization for Cardiovascular Causes or Death).

STRENGTHS, LIMITATIONS, & UNCERTAINTIES[8,9,10]

STRENGTHS:
- ♦ first Phase III RCT to assess dronedarone use in *permanent* AF with measured CV morbidity/mortality outcomes

LIMITATIONS:
- ♦ trial stopped early due to safety concerns; did not reach desired enrolment, statistical power not met, p values questionable
- ♦ short duration of follow-up median 3.5 months ♦ patients were older mean 75 years compared to similar studies mean ~65 years
- ♦ high CV risk group ?higher than other studies, large proportion (~66%) with HF NYHA class I to III

UNCERTAINITIES:
- ♦ perhaps patients with well-established permanent AF>6months are at ↑ risk of adverse events than patients with paroxysmal or intermittent AF & should be treated differently results of ATHENA should NOT have been extrapolated to this patient population
- ♦ 1/3 of patients were on digoxin, 7-day serum concentrations were statistically significantly higher in the dronedarone group dronedarone can cause a 2.5x ↑ in digoxin concentrations potentially resulting in significant toxicity[8] which may have contributed to death from arrhythmia or death from CV causes
- ♦ dronedarone may have ↑ incidence of stroke due to interaction with vitamin K antagonists mean time in therapeutic INR lower in dronedarone group ♦ no comment on allocation concealment
- ♦ no comment on safety analysis & cut-off parameters to stop trial why was the trial stopped at 1 yr & not before this point if safety was a concern?

♂=male **ACE-I**=angiotensin converting enzyme inhibitor **AF**=atrial fibrillation **ARB**=angiotensin receptor blocker **ARI** = absolute risk increase **AV**= atrioventricular **BB** or **β-blocker**=beta blocker **BP** = blood pressure **bpm**=beats per minute **CABG** = coronary artery bypass graph **CAD**=coronary artery disease **$CHADS_2$**= risk score to estimate stroke risk **CHF**=congestive heart failure **CI**=confidence interval **CV**=cardiovascular **DM** = diabetes mellitus **ECG** = electrocardiogram **GI** = gastrointestinal **HF**=heart failure **HR**=hazard ratio & heart rate **HTN**=hypertension **ICD** = implanted cardiac defibrillator **INR**=international normalized ratio **ITT**=intention to treat **LVEF** = left ventricular ejection fraction **MI**= myocardial infarction, **msec** = milliseconds **NA** = not applicable **NNH**=number needed to harm **NS**=non-significant **NYHA**=New York Heart Association **PAD** = peripheral artery disease **RCT**=randomized controlled trial **SD**=standard deviation **TIA** = transient ischemic attack **UA** = unstable angina **ULN** = upper limit of normal

REFERENCES:

[1] Connolly SJ, Camm AJ, Halperin JL et al; **PALLAS Investigators.** Dronedarone in High-Risk Permanent Atrial Fibrillation. N Engl J Med. 2011Dec 15;365:2268-76

[2] Davy JM, Herold M, Hoglund C et al; **ERATO Investigators**. Dronedarone for the control of ventricular rate in permanent atrial fibrillation: the efficacy and safety of dronedarone for the control of ventricular rate during atrial fibrillation (ERATO) study. Am Heart J 2008;156:527.e1-9

[3] Singh BN, Connolly SJ, Crijns HJJ, et al. **EURIDIS and ADONIS Investigators**. Dronedarone for maintenance of sinus rhythm in atrial fibrillation or flutter. N Engl J Med 2007;357:987-99

[4] Kober L, Torp-Pederson C, McMurray JJV et al. **ANDROMEDA Investigators.** Increased mortality after dronedarone therapy for severe heart failure. N Engl J Med 2008;358:2678-87.

[5] Hohnloser SH, Crijns HJJ, van Eickels M, et al. **ATHENA Investigators** . Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med 2009;360:668-78

[6] Hohnloser SH, Crijns HJJ, van Eickels M, et al. Dronedarone in patients with congestive heart failure: insights from ATHENA. Eur Heart J 2010;31:1717-21

[7] Suplementary Appendix. Supplement to: Connolly SJ, Camm AJ, Halperin JL, et al. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med 2011;365:2268-76

[8] Doggrell SA and Hancox J. PALLAS: limiting indications for dronedarone treatment of atrial fibrillation? Expert Opin. Pharmacother. 2012. 13(6):867-871

[9] De Ferrari GM and Dusi V. Drug safety evaluation of dronedarone in atrial fibrillation. Expert Opin. Drug Saf. 2012;11(6):1023-1045

[10] Naccarelli GV, Wolbrette DL, Levin V et al. Safety and Efficacy of Dronedarone in the Treatment of Atrial Fibrillation/Flutter. Clinical Medicine Insights: Cardiology 2011:5 103–119