PALLAS

Permanent **A**trial Fibri**LLA**tion Outcome **S**tudy using Dronedarone on Top of Standard Therapy

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on behalf of the PALLAS investigators

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Disclosure

PALLAS was funded by a grant from sanofi-aventis. Data were managed independently of the sponsor at the Population Health Research Institute at McMaster University in Hamilton, Ontario; and the trial was overseen by an international steering committee

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Background

- In paroxysmal and persistent AF, dronedarone reduced AF recurrence; and reduced the combined outcome of cardiovascular hospitalization or death in ATHENA
  - It also reduced cardiovascular death, stroke and arrhythmic death
- Dronedarone has other potentially beneficial effects
  - Heart rate slowing in AF
  - BP lowering
  - Anti-adrenergic effects
  - Anti-ventricular arrhythmia effects
- We hypothesized that dronedarone would reduce major vascular events in permanent AF

PALLAS Patient Inclusion / Exclusion

- **Inclusion criteria**
  - **Permanent AF**
    - Atrial fibrillation or flutter, present for at least 6 months
  - **Age ≥ 65 years**
  - **Major Risk factor (at least one)**
    - History of either coronary artery or peripheral arterial disease
    - History of stroke or TIA
    - Heart failure hospitalization in past year, or LVEF≤ 40%
    - Age ≥ 75 years, with both hypertension and diabetes mellitus
- **Major exclusion criteria**
  - Severe heart failure symptoms (NYHA class IV) or recent unstable NYHA class III
  - Bradycardia < 50 bpm or QTc interval > 500 ms without pacemaker
  - Implantable cardioverter-defibrillator

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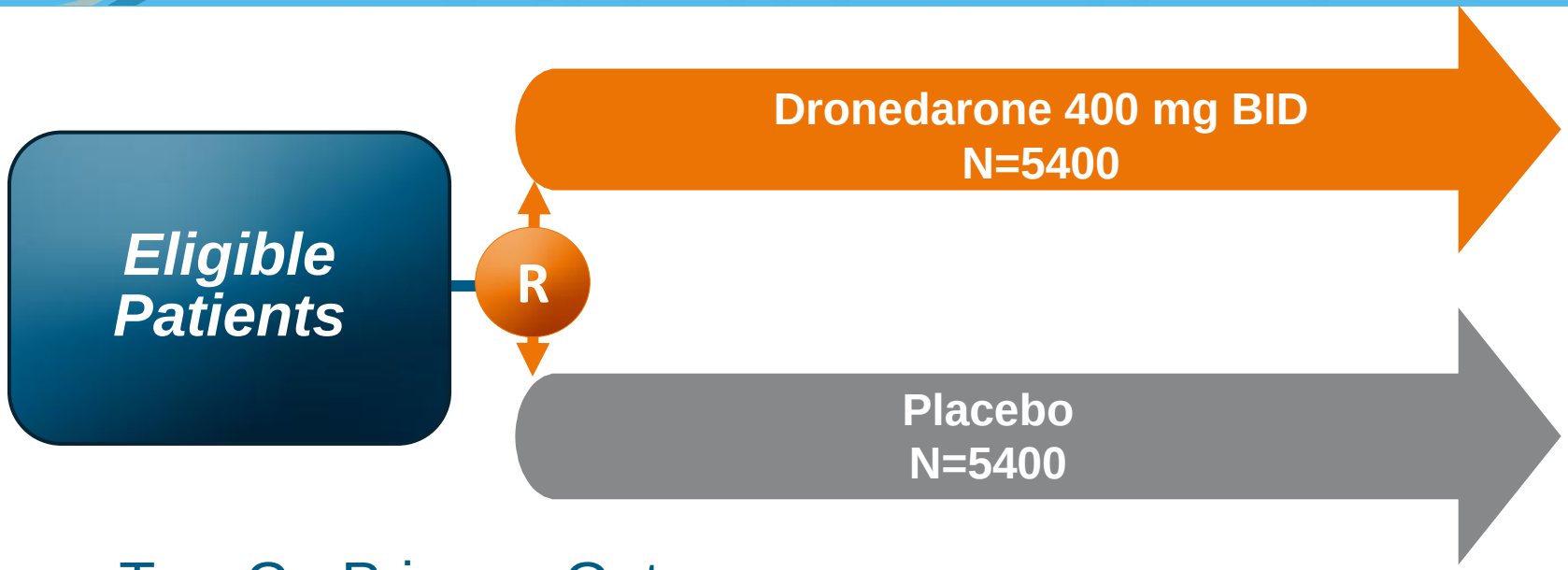
PALLAS Design



- Two Co-Primary Outcomes
  1. Stroke, myocardial infarction, systemic embolism or cardiovascular death
  2. Unplanned cardiovascular hospitalization or death
- Planned study enrolment of 10,800 patients
- Two years of recruitment and one final year of follow up
- 844 first co-primary outcome events

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Early Termination of PALLAS

- First patient enrolled on July 19, 2010
- Data monitoring Committee recommended study termination for safety on July 5, 2011
- 3,236 Patients randomized
  - from 489 sites in 37 countries
  - 3.5 months median follow-up

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Baseline Characteristics

	Dronedarone N=1619	Placebo N=1617
Age years mean (SD)	75.0 (5.9)	75.0 (5.9)
Duration of permanent AF > 2 years	1119 (69.1%)	1124 (69.5%)
Coronary artery disease	661 (40.8%)	666 (41.2%)
Peripheral arterial disease	187 (11.6%)	213 (13.2%)
Prior Stroke or TIA	436 (26.9%)	458 (28.3%)
History of heart failure	1139 (70.4%)	1117 (69.1%)
Left ventricular ejection fraction ≤ 40%	345 (21.3%)	335 (20.7%)
Baseline use of a Beta-blocker	1201 (74%)	1201 (74%)
Baseline use of Vitamin K antagonist	1359 (84%)	1363 (84%)

Physiological Effects of Dronedarone and Medication Discontinuation

	Dronedarone N=1619	Placebo N=1617	P-value
Sinus Rhythm at 4 month visit	23 (3.5%)	9 (1.4%)	0.01
Changes between baseline and 1 month			
Heart Rate (Mean) beats/minute	- 7.6	+ 0.1	<0.001
Systolic BP (Mean) mmHg	- 3.5	- 1.7	0.003
QTc Interval (Mean) msec	8	- 2	<0.001
Premature Study Medication Discontinuation N (%)	348 (21%)	178 (11%)	<0.001

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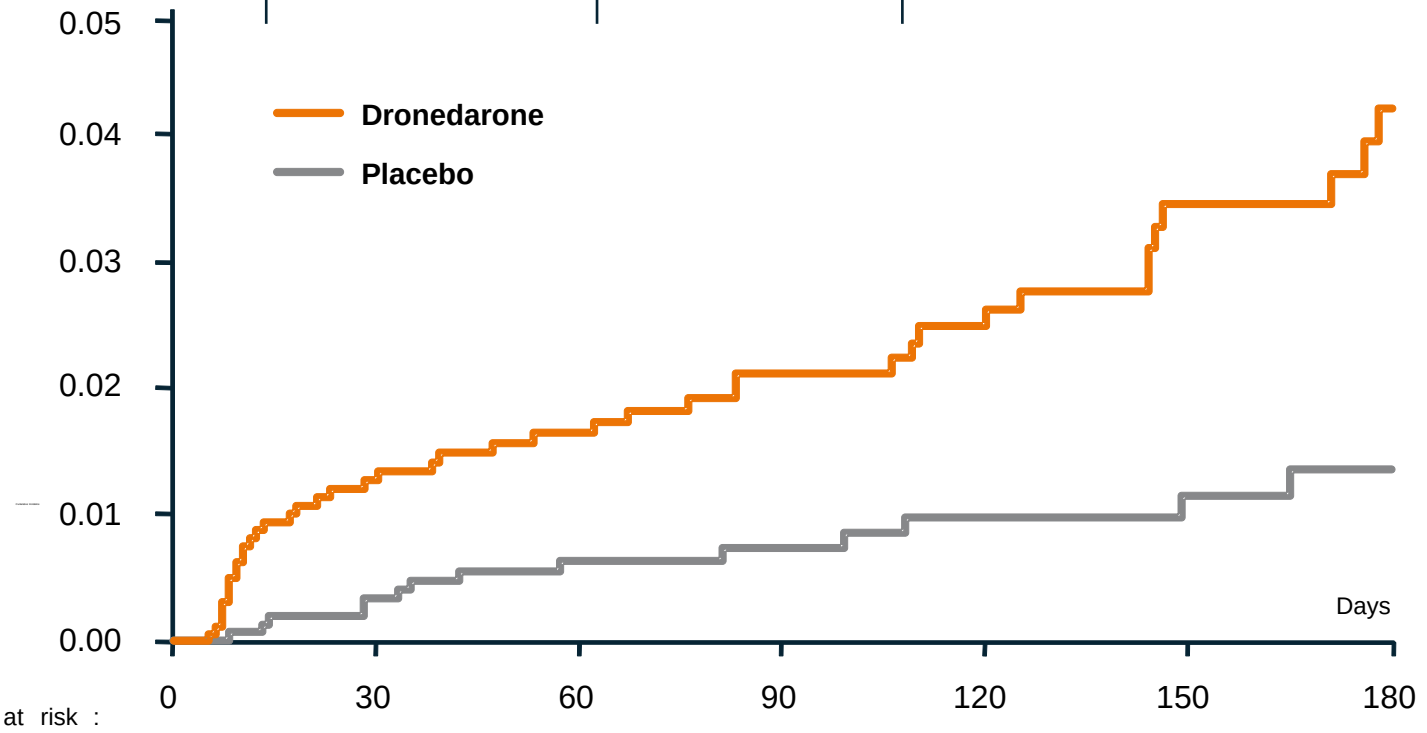
Stroke, systemic embolism, myocardial infarction or cardiovascular death

First Co-primary Outcome	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	43 (2.7%)	19 (1.2%)	2.29 (1.34 – 3.94) p=0.002



Number at risk :

Dronedarone	1619	1421	930	353
Placebo	1617	1445	908	377

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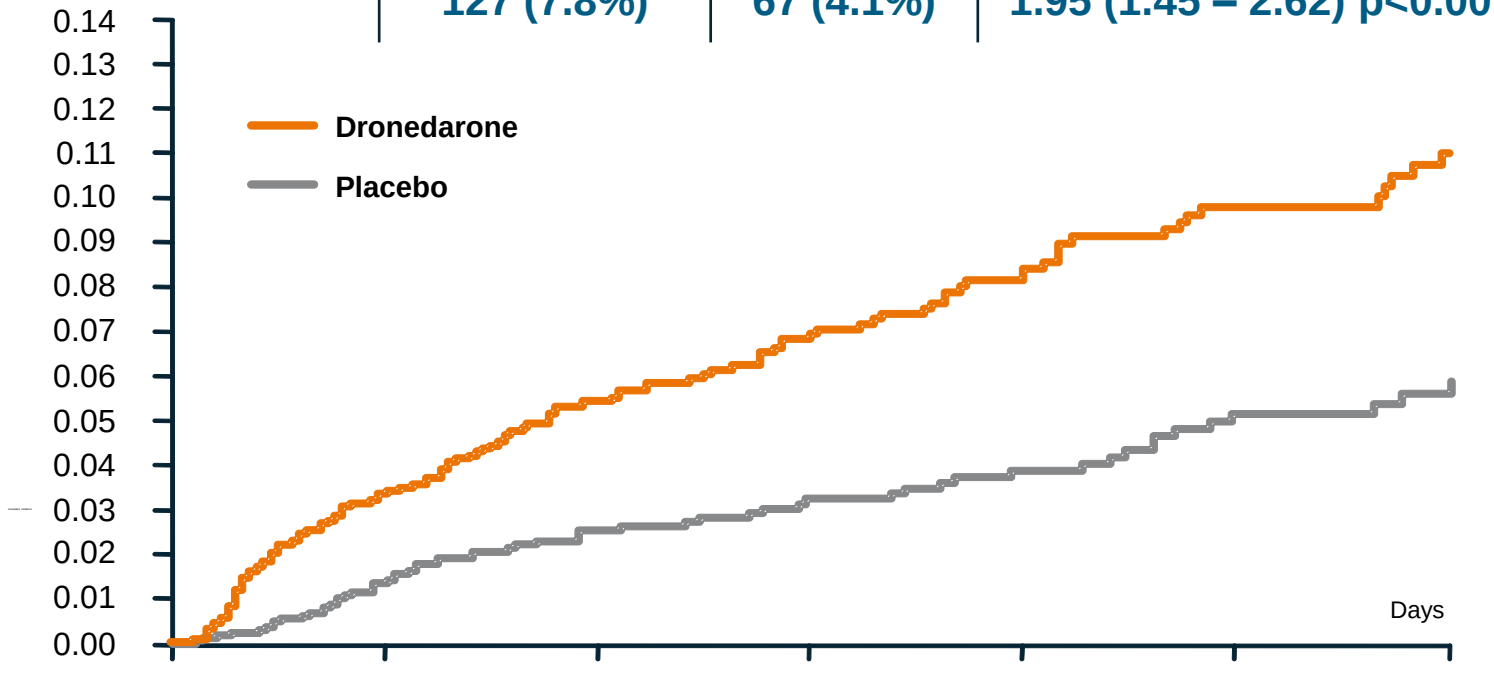
Unplanned cardiovascular hospitalization or death

Second Co-primary Outcome	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	127 (7.8%)	67 (4.1%)	1.95 (1.45 – 2.62) p<0.001



Number at risk :

Dronedarone	1619	1389	879	334		
Placebo	1617	1429	882	361		

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Components of the Primary Outcomes

	Dronedarone N=1619	Placebo N=1617	HR 95% CI, p-value
Death	25	13	1.94 [0.99- 3.79] p=0.049
Cardiovascular Death	21	10	2.11 [1.00- 4.49], p=0.046
Arrhythmic Death	13	4	3.26 [1.06- 10.0], p=0.03
Stroke	23	10	2.32 [1.11- 4.88], p=0.02
Myocardial Infarction	3	2	1.54 [0.26- 9.21], p=0.63
Unplanned CV Hospitalization	113	59	1.97 [1.44- 2.70], p<0.001
Heart Failure Hospitalization	43	24	1.81 [1.10-2.99], p=0.02

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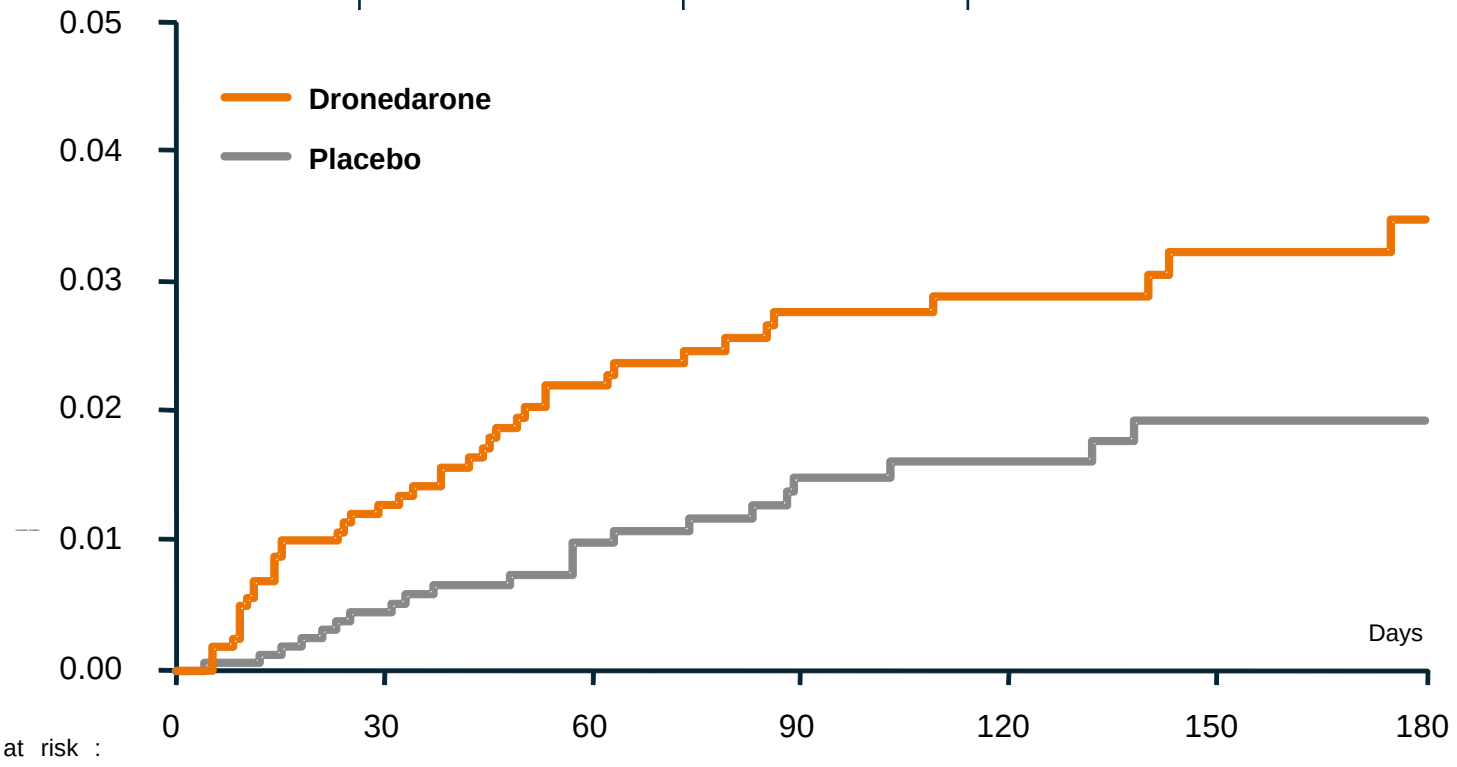
Heart Failure Hospitalization

Heart Failure Hospitalization	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
	43 (2.7%)	24 (1.5%)	1.81 (1.10 – 2.99) p=0.02



Number at risk :

Dronedarone	1619	1414	912	349
Placebo	1617	1439	896	374

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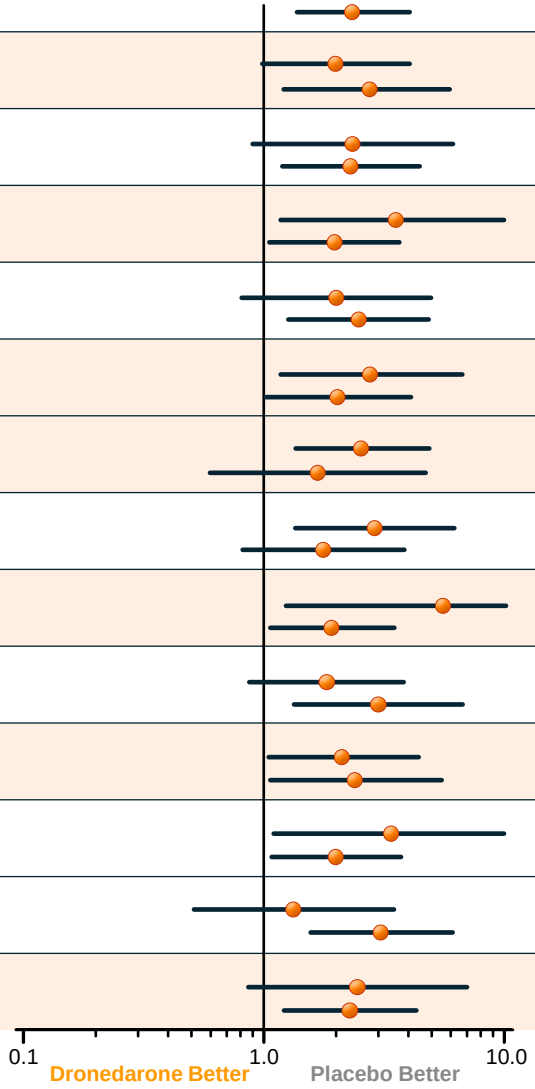
Sub-groups: First Co-primary Outcome

Charateristics	N	HR [95% CI]	P value[b]
Overall		2.29 [1.34;3.94]	
Age			0.61
<75	1562	2.01 [0.98;4.15]	
≥75	1674	2.71 [1.20;6.12]	
Duration of perm. AF			0.99
6 months to 2 years	988	2.32 [0.89;6.03]	
>2 years	2243	2.27 [1.18;4.37]	
Baseline LVEF			0.41
LVEF≤40%	680	3.45 [1.14;10.50]	
LVEF>40%	2556	1.98 [1.06;3.70]	
NYHA			0.72
No class II/III	1490	2.00 [0.81;4.97]	
Class II/III	1746	2.48 [1.26;4.86]	
CHADS			0.57
CHADS ≤2	1326	2.76 [1.16;6.57]	
CHADS >2	1908	2.02 [1.01;4.03]	
Stroke or TIA history			0.49
N	2342	2.57 [1.36;4.87]	
Y	894	1.68 [0.60;4.73]	
Coronary artery disease			0.38
N	1908	2.90 [1.35;6.22]	
Y	1327	1.77 [0.82;3.84]	
Baseline HR			0.20
HR <65 bpm	644	5.43 [1.22;24.26]	
HR ≥65 bpm	2591	1.91 [1.05;3.44]	
Baseline SBP			0.61
SBP <130 mmHg	1468	2.03 [0.95;4.33]	
SBP ≥130 mmHg	1708	2.69 [1.19;6.07]	
Digoxin			0.82
N	2166	2.15 [1.05;4.41]	
Y	1070	2.42 [1.07;5.50]	
Beta blocking agents			0.41
N	834	3.38 [1.10;10.36]	
Y	2402	2.01 [1.08;3.73]	
Vitamin K antagonist or Dabigatran			0.12
N	447	1.34 [0.51;3.48]	
Y	2789	3.10 [1.57;6.12]	
Regions			0.93
North America/Western Europe	1512	2.42 [0.85;6.86]	
Other regions	1724	2.27 [1.21;4.27]	



Adverse Events and Laboratory Abnormalities

High Level Term (preferred term)	Dronedarone N=1614	Placebo N=1609	p-value
Any Adverse Event	49.4%	37.3%	<0.001
Adverse Event; medication discontinuation	13.1%	5.0%	<0.001
Any Serious Adverse Event	7.0%	4.8%	0.008
Asthenic conditions (asthenia, fatigue)	5.5%	2.9%	<0.001
Diarrhea	6.3%	2.4%	<0.001
Gastrointestinal or abdominal pain	2.0%	0.9%	0.009
Nausea and vomiting symptoms (nausea)	4.7%	1.7%	<0.001
Breathing abnormalities (dyspnea)	4.6%	2.2%	<0.001
Edema (peripheral edema)	3.7%	1.8%	<0.001
Neurological signs and symptoms (dizziness)	4.7%	2.4%	<0.001
Rate and rhythm disorders (bradycardia)	4.2%	1.2%	<0.001
Renal failure and impairment	2.2%	0.7%	0.001
Alanine aminotransferase >3 times ULN	1.5%	0.4%	0.05

PALLAS Conclusions

- In patients with permanent AF and major risk factors for vascular events, dronedarone increased both PALLAS primary outcomes
- This was due to increases in death, heart failure and stroke
- There was an increased rate of discontinuation of dronedarone due to adverse events
- Dronedarone should not be used in this patient population

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PALLAS: Study Committees

- Steering Committee
  - Stuart J. Connolly (Chairman), Stefan H. Hohnloser, (Co- Principal Investigator), A. John Camm (Operations Committee), Jonathan Halperin (Operations Committee)
  - Marco Alings, John Amerena, Dan Atar, Álvaro Avezum, Per Blomström, Martin Borggrefe, Andrzej Budaj, Shih-Ann Chen, Chi Keong Ching, Patrick Commerford, Antonio Dans, Jean-Marc Davy, Etienne Delacrétaz, Giuseppe Di Pasquale, Rafael Diaz, Paul Dorian, Gregory Flaker, Sergey Golitsyn, Antonio Gonzalez-Hermosillo, Christopher Granger, Hein Heidbüchel, Josef Kautzner, June Soo Kim, Fernando Lanas, Basil Lewis, Jose L. Merino, Jan Murin, Calambur Narasimhan, Ernesto Paolasso, Alexander Parkhomenko, Nicholas S. Peters, Kui-Hian Sim, Martin Stiles, Supachai Tanomsup, Lauri Toivonen, János Tomcsányi, Christian Torp-Pedersen, Hung-Fat Tse, Panos Vardas, Dragos Vinereanu, Denis Xavier, Jun Zhu, Jun-Ren Zhu
- Adjudication Committee
  - Campbell Joyner (Chairman), Jeff Healey and Christian Torp-Pedersen
- Data Monitoring Committee
  - D. George Wyse (chairman), Marc Pfeffer, Stuart Pocock, John Cairns, Hein Wellens,

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ORIGINAL ARTICLE

Dronedarone in High-Risk Permanent Atrial Fibrillation

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