

# PALLAS

Permanent **A**trial **FibriLL**Ation Outcome **S**tudy using  
Dronedaronone on Top of Standard Therapy

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on behalf of the PALLAS investigators

<http://clinicaltrials.gov> Number: NCT01151137



# 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**

# 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  $\geq$  65 years**

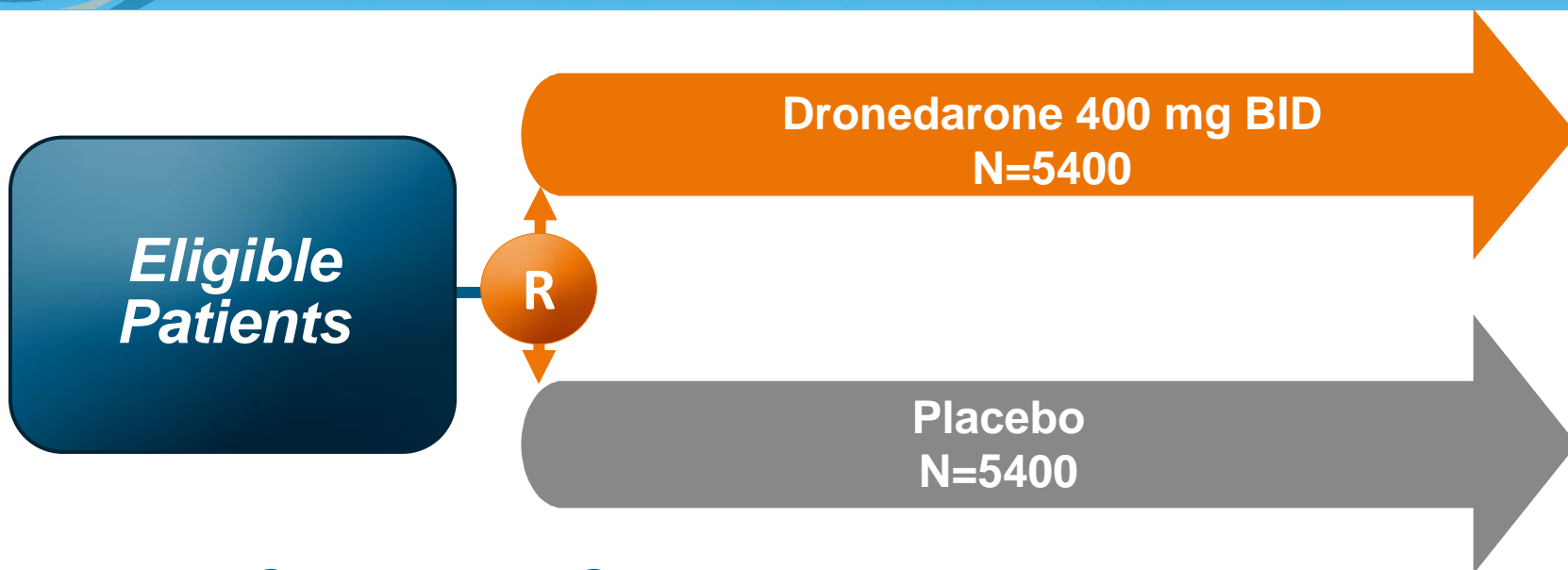
- **Major Risk factor (at least one)**

- History of either coronary artery or peripheral arterial disease
- History of stroke or TIA
- Heart failure hospitalization in past year, or LVEF  $\leq$  40%
- Age  $\geq$  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

# 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

# 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

# Baseline Characteristics

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

# Physiological Effects of Dronedarone and Medication Discontinuation

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

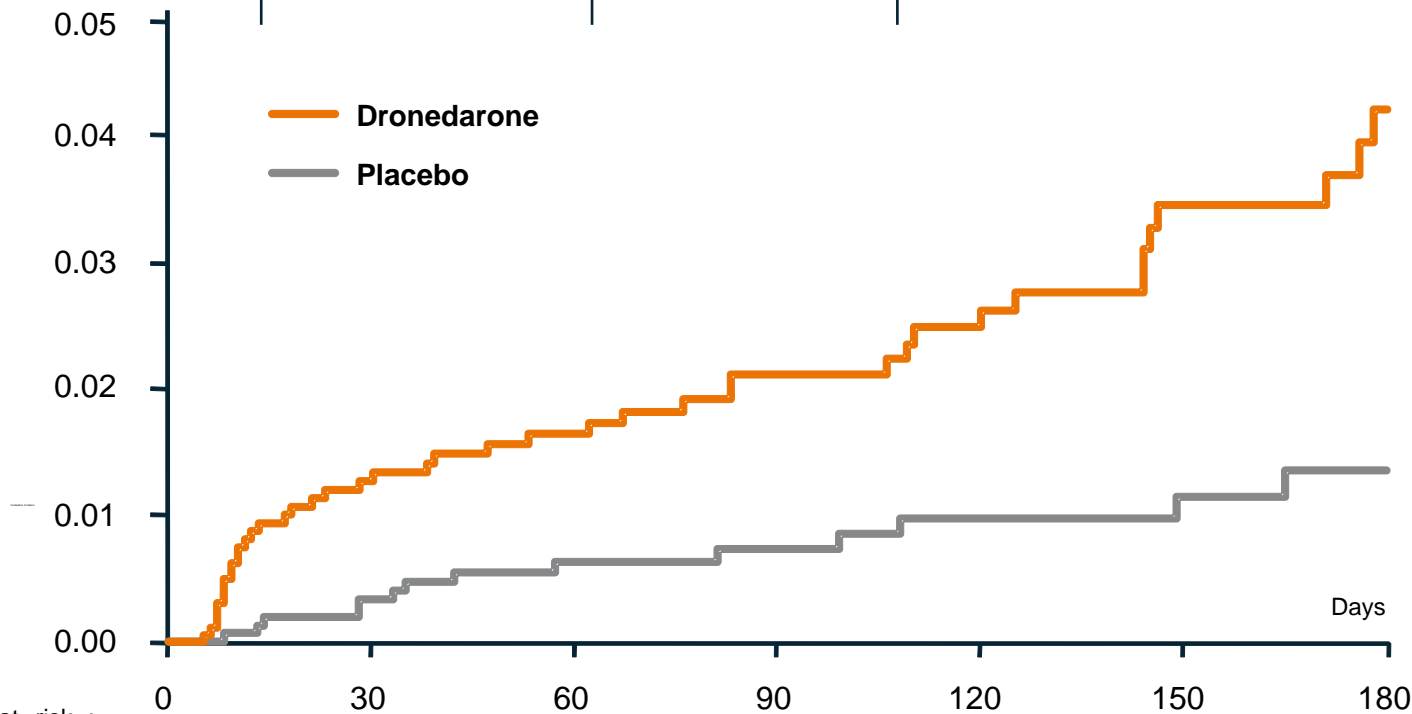
# Stroke, systemic embolism, myocardial infarction or cardiovascular death

First Co-primary Outcome	Dronedarone	Placebo	Dronedarone vs placebo HR and 95% CI
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43 (2.7%)

19 (1.2%)

2.29 (1.34 – 3.94) p=0.002



Dronedarone	1619	1421	930	353
Placebo	1617	1445	908	377

# Unplanned cardiovascular hospitalization or death

## Second Co-primary Outcome

**Dronedarone**

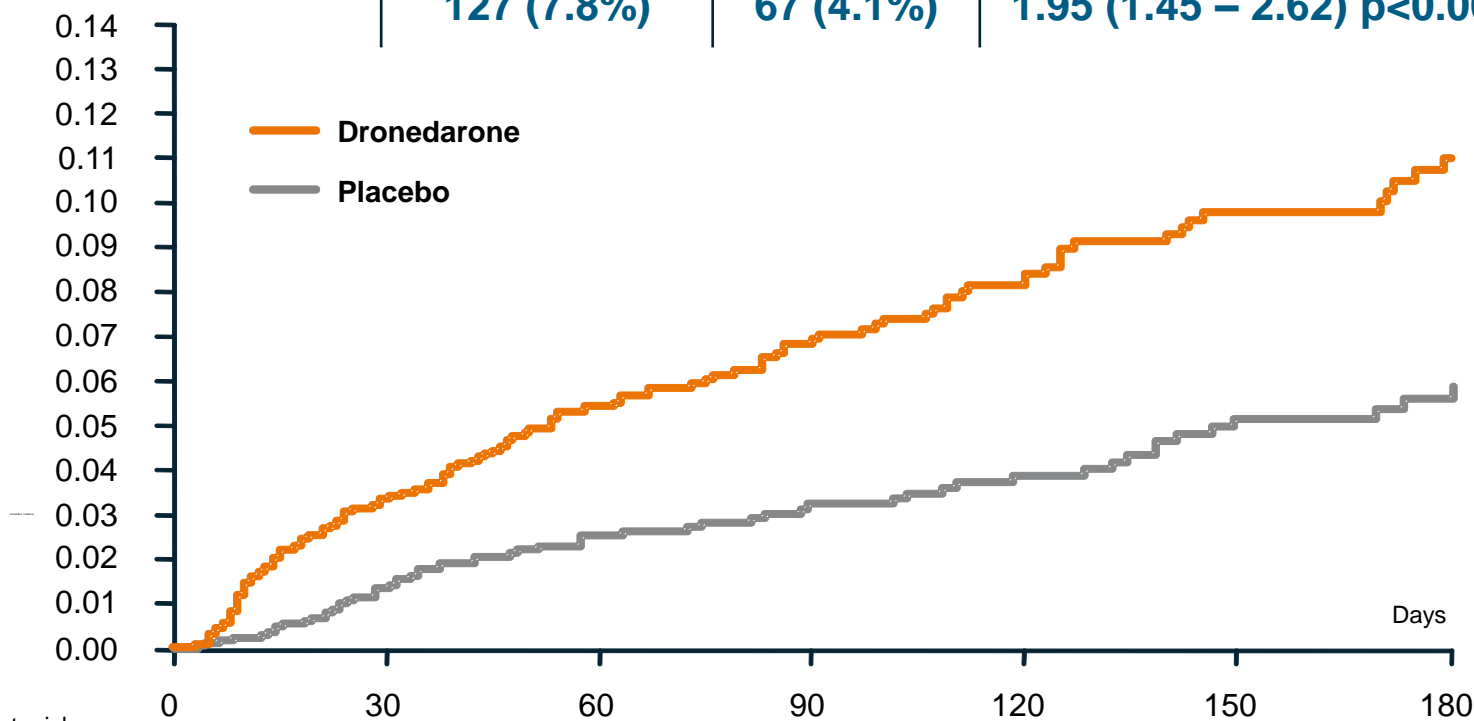
**Placebo**

**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 :

	0	30	60	90	120	150	180
<b>Dronedarone</b>	<b>1619</b>	<b>1389</b>	<b>879</b>	<b>334</b>			
<b>Placebo</b>	<b>1617</b>	<b>1429</b>	<b>882</b>	<b>361</b>			

# Components of the Primary Outcomes

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

# Heart Failure Hospitalization

Heart Failure Hospitalization

Dronedarone

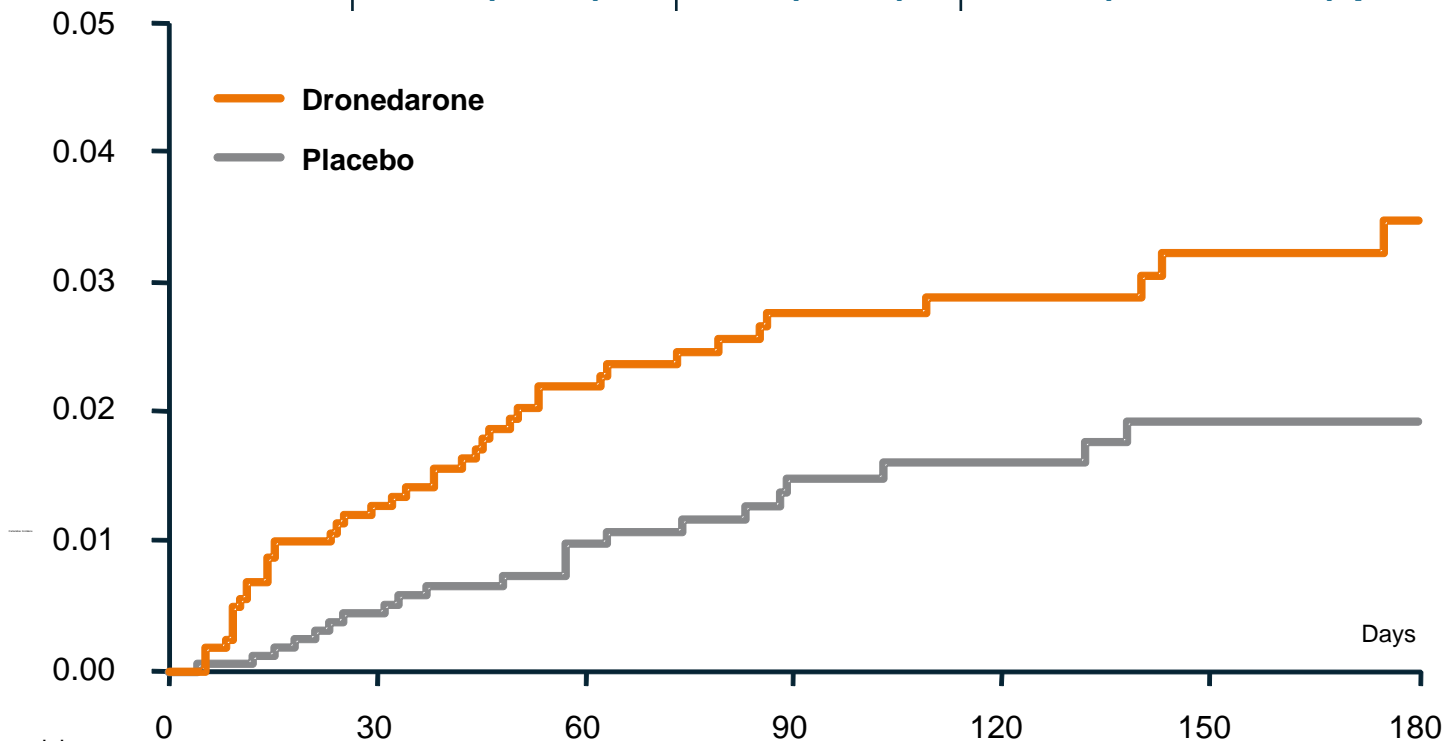
Placebo

Dronedarone vs placebo  
HR and 95% CI

43 (2.7%)

24 (1.5%)

1.81 (1.10 – 2.99) p=0.02



Dronedarone

1619

1414

912

349

Placebo

1617

1439

896

374

# Sub-groups: First Co-primary Outcome

Charateristics	N	HR [95% CI]	Hazard Ration (95% CI)	P value <sup>b</sup>
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]		

0.1 1.0 10.0  
Dronedaron Better Placebo Better

# Adverse Events and Laboratory Abnormalities

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

# 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

# PALLAS: Study Committees

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- Campbell Joyner (Chairman), Jeff Healey and Christian Torp-Pedersen

## ● Data Monitoring Committee

- D. George Wyse (chairman), Marc Pfeffer, Stuart Pocock, John Cairns, Hein Wellens,

ORIGINAL ARTICLE

# Dronedarone in High-Risk Permanent Atrial Fibrillation

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for the PALLAS Investigators\*