

**Dose-finding and tolerability of a new oral platelet glycoprotein IIb/IIIa inhibitor, lotrafiban, in patients with coronary artery and cerebrovascular disease: the APLAUD results**

**Harrington RA, Graffagnino C, Armstrong PW, Joseph D, Card T, Sigmon KN, Granett JR, Chan R, Califf RM, Topol EJ for the Anti-*PL*atelet *U*seful *D*ose (APLAUD) Study Investigators**

**Duke Clinical Research Institute, Durham, NC**



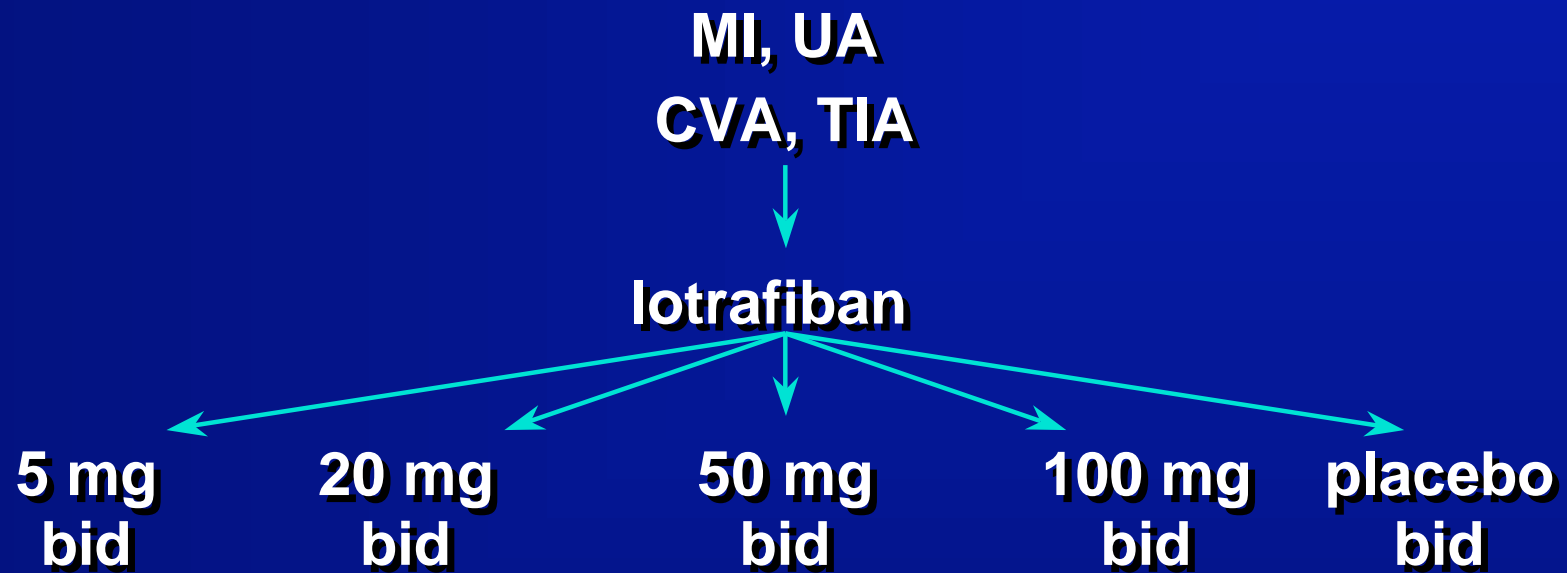
## **APLAUD Trial: Background**

- **Atherosclerosis as a systemic disease**
- **Unstable angina, MI, TIA, CVA**
  - ASA ↓ CV mortality 17%
  - ASA ↓ MI and CVA 33%
- **Aspirin weak antiplatelet agent**
- **Aspirin non-responders and aspirin resistance**
- **Need more effective secondary prevention agents**

## **APLAUD Trial: Objectives**

- **Define safe and tolerable dose(s) of lotrafiban, oral platelet GP IIb/IIIa antagonist**
  - major/minor bleeding
- **Pharmacokinetics/Pharmacodynamics**
  - plasma samples
  - inhibition of platelet aggregation
- **Thrombocytopenia incidence**

# APLAUD: Study Design



- All patients receive aspirin 325 mg qd; 12-weeks' therapy
- Visits: days 3, 7, 10; weeks 2, 3, 4, 6, 8, 12
- Planned enrollment 500 patients

# APLAUD Trial : Bleeding and Tolerability

- **Primary endpoint**
  - combined incidence of major and minor bleeding
- **Tolerability**
  - nurse-administered patient questionnaire
    - assess normal bleeding at baseline
    - at visits compare bleeding to baseline
    - did/does bleeding cause concern or inconvenience?
    - would patient continue taking medication if proven to decrease risk of clinical events (death, MI, CVA, procedures)?

## **APLAUD Trial: Enrollment By Region**

<b>Total Enrollment</b>	<b>451</b>	
<b>US</b>	<b>317</b>	<b>70.2%</b>
<b>Canada</b>	<b>73</b>	<b>16.1%</b>
<b>Western Europe</b>	<b>61</b>	<b>13.5%</b>
France	4	0.8%
Belgium	22	4.8%
The Netherlands	35	7.7%

## **APLAUD Trial: Reason for Enrollment**

- **Cardiovascular 62.0%**
  - unstable angina 31.0%
  - myocardial infarction 31.0%
- **Cerebrovascular 38.0%**
  - transient ischemic attack 14.0%
  - stroke 24.0%

## APLAUD Trial: Baseline Demographics

n	Lotrafiban 355	Placebo 96
Age	62 (53,72)	63 (56,71)
Female	29.6%	25.3%
Weight	82 (71,93)	81 (70,93)
HTN	66.2%	62.5%
DM	19.2%	19.8%
↑Lipids	63.7%	59.4%
Smoker	19.6%	27.5%

## Early Withdrawal: Treated Patients

n	5 mg 112	20 mg 99	50 mg 104	100 mg* 34	Placebo 95
<b>Withdrawn early</b>	<b>15</b>	<b>14</b>	<b>29</b>	<b>32</b>	<b>20</b>
Major Bleeding	0	1	1	3	1
Minor Bleeding	4	1	9	2	1
↓ Platelet count	0	0	4	1	1
<b>Time to withdrawal (d)</b>	<b>46 (13,63)</b>	<b>33 (13,43)</b>	<b>17 (7,45)</b>	<b>8 (5,9)</b>	<b>49 (18,74)</b>

*\*All active drug withdrawals versus placebo 25.8% vs. 21.1%*



## APLAUD Trial: Bleeding (Treated Patients)

n	5 mg 112	20 mg 99	50 mg 104	100 mg* 34	Placebo 95
Major	0.9%	3.1%	2.9%	12.1%	2.1%
Minor	35.8%	53.6%	61.8%	69.7%	34.7%
Any PRBCs	0%	1.0%	1.0%	11.8%	0%

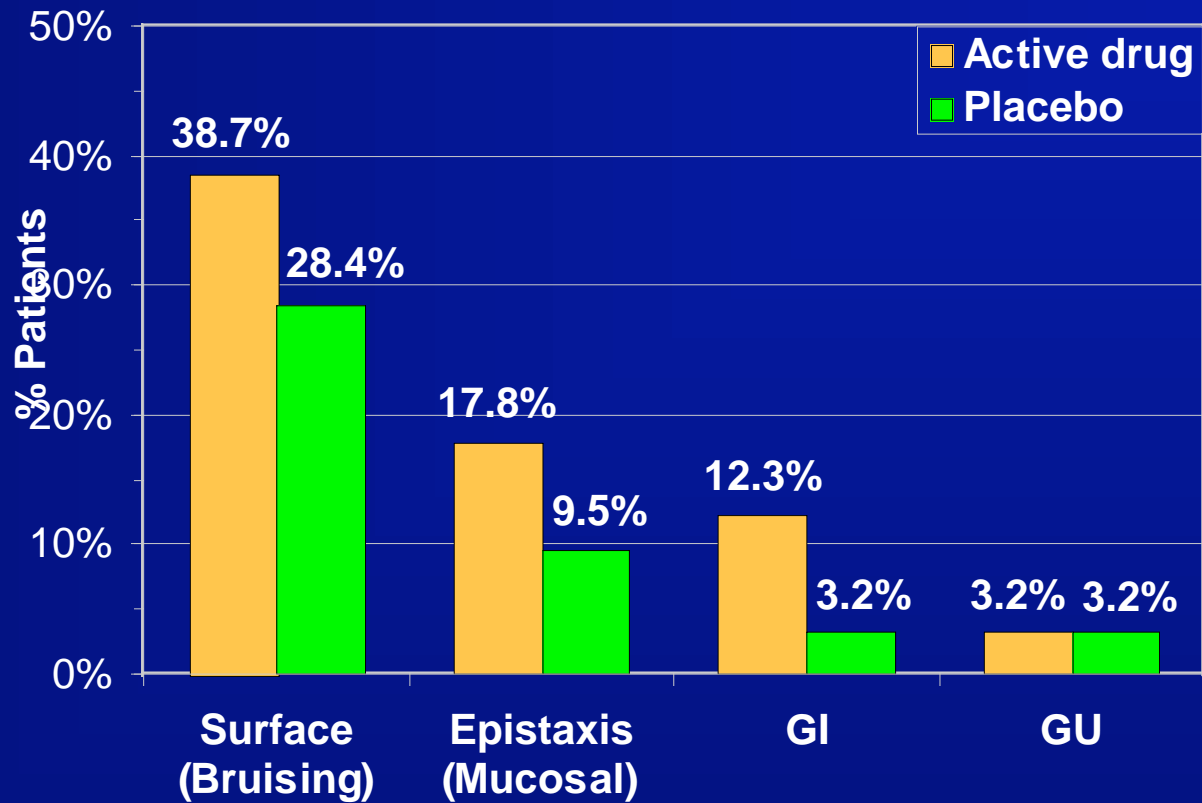
*\*100 mg dose discontinued on DSMB recommendation*

*\*\*Trend testing for any bleeding*

*lotrafiban (except 100mg dose) versus placebo,  $p \leq 0.001$*



# APLAUD Trial: Bleeding Sites (Treated Patients)



*\*Includes major and minor bleeding*



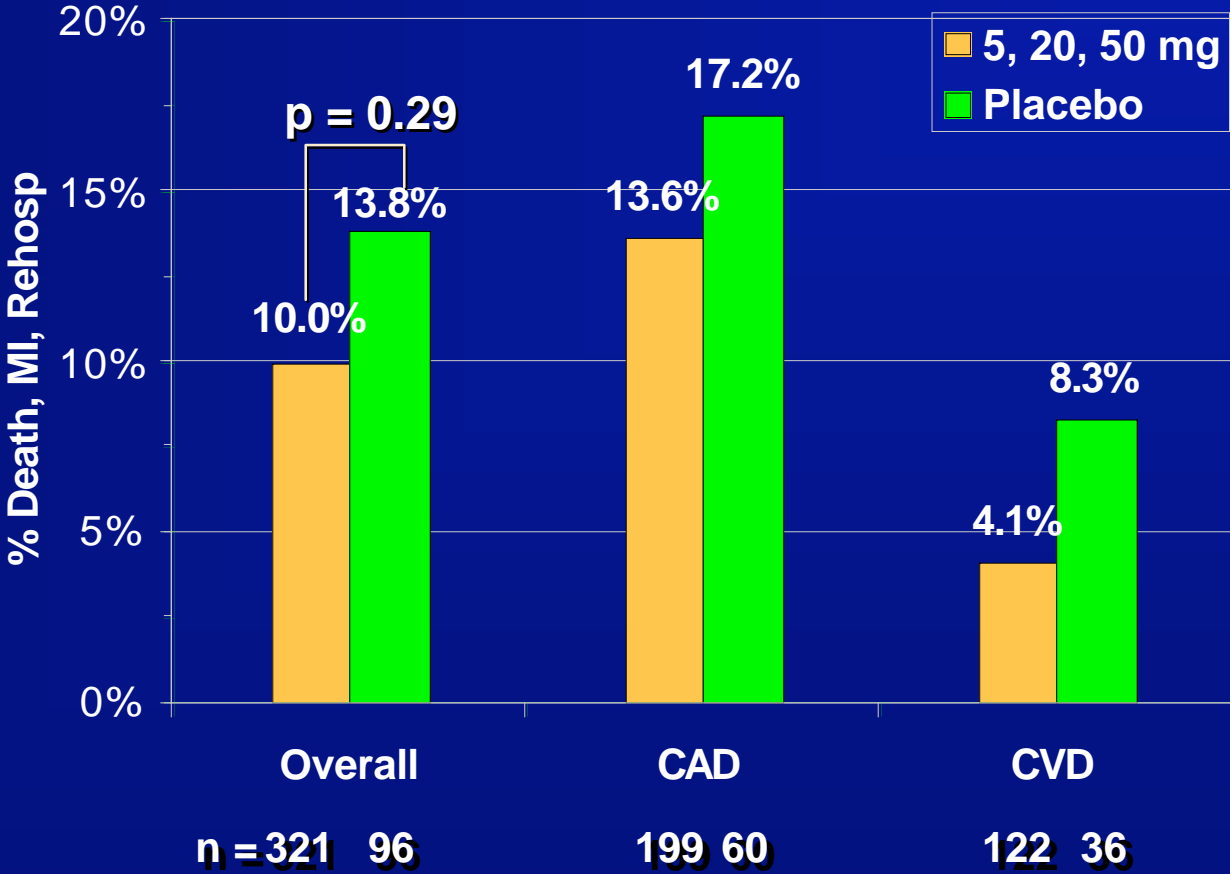
## APLAUD Trial: Thrombocytopenia

	5 mg	20 mg	50 mg	100 mg	Active	Placebo
<b>Platelet count</b>	<b>0/112</b>	<b>0/99</b>	<b>4/102</b>	<b>1/34</b>	<b>5/347</b>	<b>1/95</b>
<b>&lt;100,000/<math>\mu</math>l</b>	<b>(0%)</b>	<b>(0%)</b>	<b>(3.9%)</b>	<b>(2.9%)</b>	<b>(1.4%)</b>	<b>(1.1%)</b>
<b>95% CI</b>	<b>—</b>	<b>—</b>	<b>0.2–7.7%</b>	<b>0–8.6%</b>	<b>0.2–2.7%</b>	<b>0–3.1%</b>

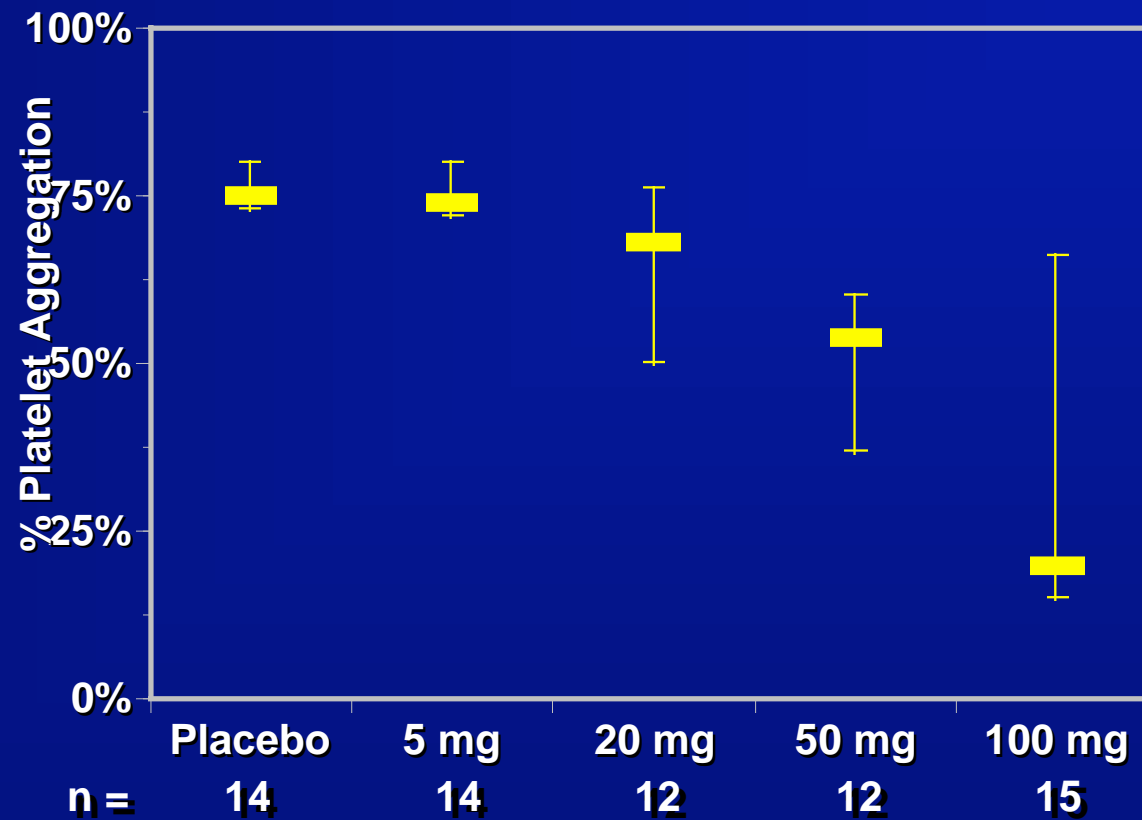
## Efficacy Events

n	5 mg 112	20 mg 99	50 mg 104	100 mg* 34	Placebo 95
<b>Death</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1.0%</b>
<b>MI</b>	<b>0.9%</b>	<b>0</b>	<b>0.9%</b>	<b>5.9%</b>	<b>1.1%</b>
<b>PTCA</b>	<b>4.3%</b>	<b>2.0%</b>	<b>1.9%</b>	<b>0</b>	<b>8.4%</b>
<b>CABG</b>	<b>0</b>	<b>3.1%</b>	<b>0.9%</b>	<b>0</b>	<b>0</b>
<b>CVA</b>	<b>0.9%</b>	<b>1.0%</b>	<b>0</b>	<b>0</b>	<b>1.1%</b>
<b>CEA</b>	<b>0.9%</b>	<b>2.0%</b>	<b>0.9%</b>	<b>0</b>	<b>1.1%</b>

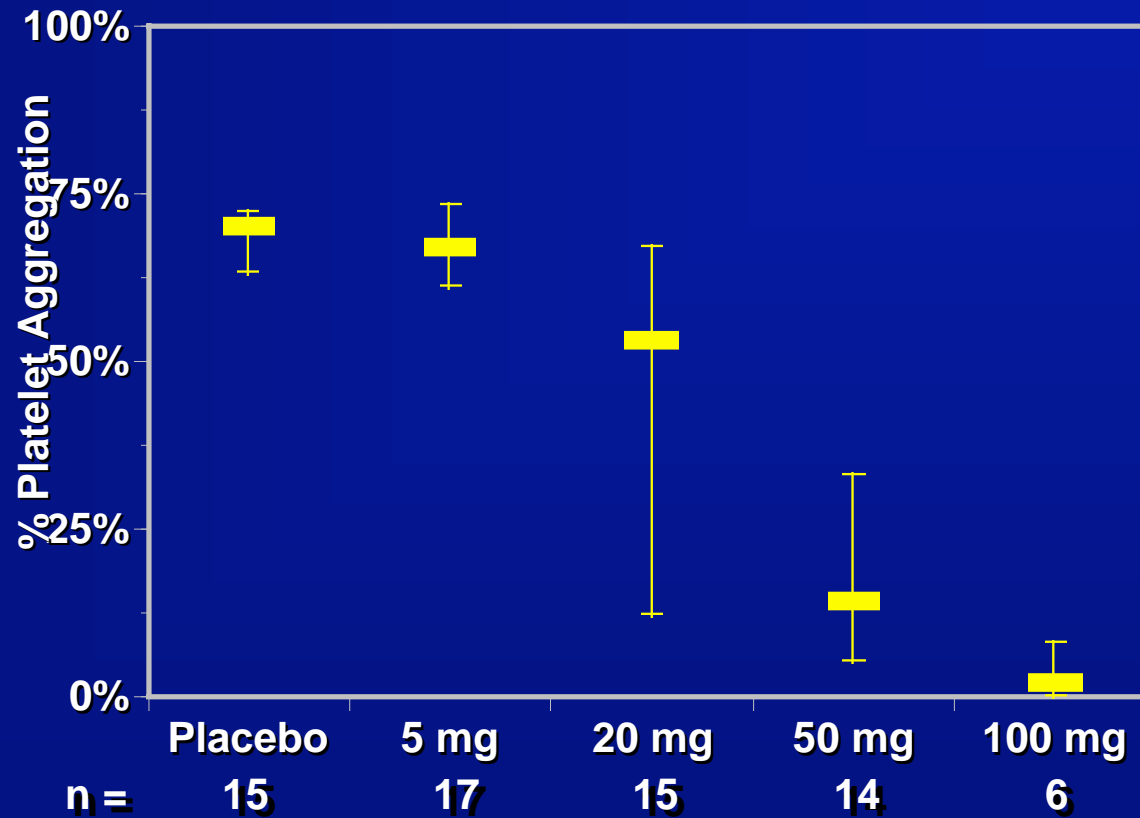
# Composite Efficacy Events : CAD vs. CVD Patients



## Platelet Aggregation: 2 Week Visit (Pre-dose)



# Platelet Aggregation: 2 Week Visit (Minimum Post-dose)



## **APLAUD Trial: Summary**

- **Efficient trial organization → rapid enrollment**
- **Good collaboration: cardiology and neurology**
- **5 mg: similar placebo**
- **100 mg: unacceptable**
- **Dose-dependent bleeding risk**
- **Thrombocytopenia within expected range**
- **Pharmacodynamics delineated**
  - Effects of age/creat clearance
- **Basis for large, definitive Phase III RCT**