RESPECT Trial

Randomized Evaluation of Recurrent Stroke comparing PFO Closure to Established Current Standard of Care Treatment

Steering Committee

John D Carroll, MD, University of Colorado, Denver, CO

Jeffrey L Saver, MD, Geffen School of Medicine at UCLA, Los Angeles, CA

Richard W Smalling, MD, University of Texas Medical School, Memorial Hermann Heart and Vascular Institute, Houston, TX

David E Thaler, MD, Tufts Medical Center, Boston, MA

Sponsor

AGA Medical Corp

Kristine Veltum and Team

Other Committees:

Neurology Executive

DSMB

Clinical Event

Core Labs:

Echocardiography

Baseline Blood Work

Disclosure Statement of Financial Interest

John D. Carroll, MD

Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Grant/Research Support	**AGA Medical**
Consulting Fees/Honoraria	**AGA Medical**

AHA/ASA/ACCF Science Advisory

Percutaneous Device Closure of Patent Foramen Ovale for Secondary Stroke Prevention

A Call for Completion of Randomized Clinical Trials

A Science Advisory From the American Heart Association/American Stroke Association and the American College of Cardiology Foundation

The American Academy of Neurology affirms the value of this science advisory.

Patrick T. O'Gara, MD, FAHA, FACC, Chair; Steven R. Messe, MD, FAHA; E. Murat Tuzcu, MD, FAHA, FACC; Gloria Catha, BA; John C. Ring, MD, FACC

"The optimal therapy for prevention of recurrent stroke or transient ischemic attack in patients with cryptogenic stroke and patent foramen ovale has not been defined…Completion and peer review of ongoing trials are critical steps to establish an evidence base from which clinicians can make *informed decisions regarding the best therapy for individual patients*."

Circulation. 2009.

Clinical Trial Design

- The RESPECT PFO Clinical Trial is a randomized evaluation comparing PFO device closure versus medical therapy.

- Maximum 900 patients (450 per arm)
  - Recent cryptogenic stroke (270 days)
  - 18-60 years of age

- Maximum 75 participating institutions across the U.S. and Canada (60 approved sites)

Randomization Groups

- **Device closure plus medical therapy**
  - AMPLATZER PFO Occluder
  - Clopidogrel for one month
  - Aspirin for six months
    - Discontinuation of the drug is at the discretion of the Investigator.

- **Medical therapy (SOC)**

  <u>Current standard of care: one of the four treatments:</u>

  - Aspirin alone
  - Clopidogrel alone
  - Warfarin alone
  - Aspirin in combination w/ dipyridamole

Study Endpoints

Primary Endpoint:

- Recurrence of a Nonfatal Stroke, Post-randomization Death, or Fatal Ischemic Stroke

Secondary Endpoints:

- Complete closure of the defect demonstrated by TEE and bubble study at 6-month follow-up (device group)
- Absence of TIA

Statistical Design

- **Design is "Event Driven"**
  - **Total number of patients is not considered—only number of endpoint events.**
- **Four stopping rules are derived, which will be implemented based on number of PFO vs. number of SOC events**
- **Success will be declared if a positive stopping rule is reached, that is, a pre-defined stopping rule is obtained and the device is significantly better than SOC**

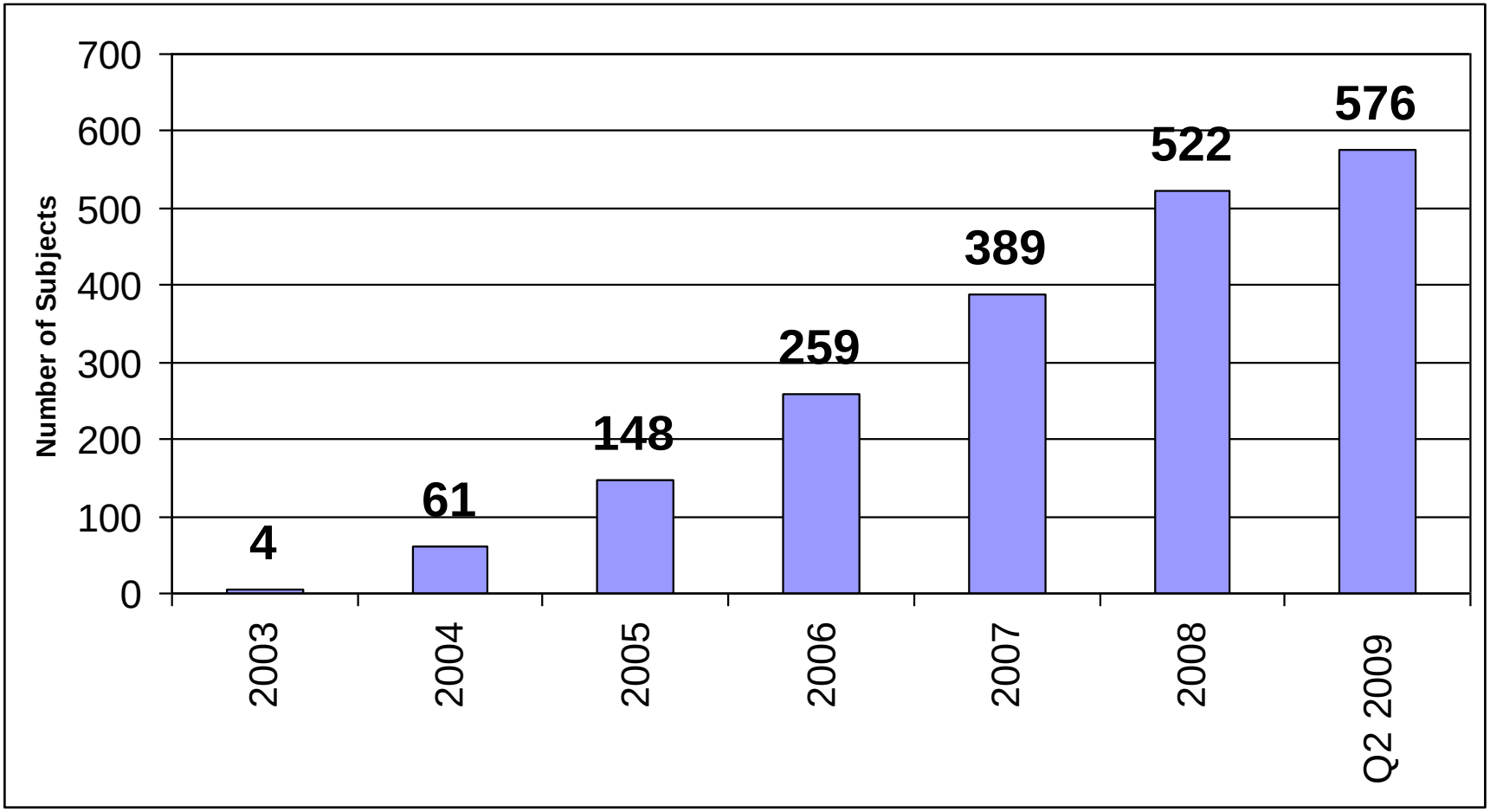
RESPECT

Current Status: 2009

Baseline Characteristics of Enrolled Patients

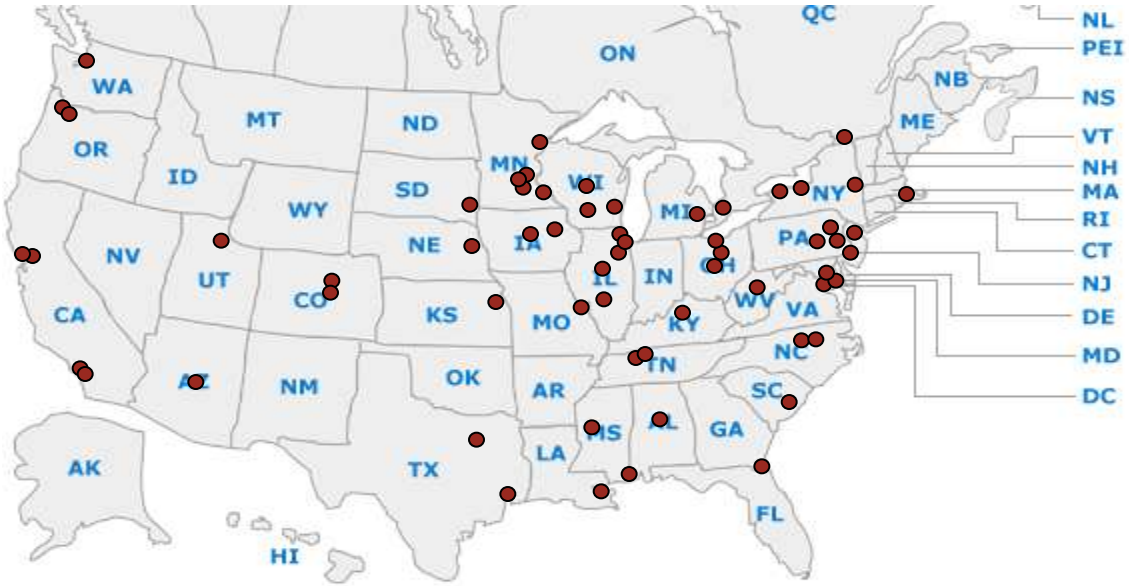
Enrollment by Year

Thru end of second quarter 2009



RESPECT Investigational Sites

All site locations



Top Ten Enrolling Sites

- South Denver Cardiology
- Medical College of Wisconsin
- Tufts Medical Center
- UT Houston/Memorial Herman Hosp
- Univ. of Colorado
- Duke University
- Univ of Washington
- OSF St. Francis Medical Center
- Washington Hospital Center
- Ohio State University

Baseline Data as of June 30, 2009

Number of Subjects: 576

Male: 57.7%

Female: 42.3%

	N	Mean	SD	Range
Age:	575	45.4	9.8	(18, 60)
Days since CVA:	572	89.3	62.2	(1, 265)

Baseline

Medical History

Migraine:	37.4%
Previous TIA:	12.0%
Palpitations:	8.7%
Sinus Bradycardia:	7.4%
CAD:	3.5%
DVT:	3.5%
Sinus Tachycardia:	1.6%
COPD:	1.4%
Previous MI:	1.2%
Peripheral Vascular Disease:	0.9%
Congestive Heart Failure:	0.2%
Unstable Angina:	0.2%

Baseline

Risk Factors

Hypercholesterolemia:	**37.9%**
Family Hx of Ischemic Heart Disease:	**32.9%**
Hypertension:	**31.1%**
Family Hx of Stroke:	**27.1%**
Current Smoker:	**12.9%**
Diabetes:	**7.5%**
Substance Abuse:	**1.2%**

NIH stroke scale scoring system and RESPECT patients *at time of enrollment*:

Scale

- 0= no stroke
- 1-4= minor stroke
- 5-15= moderate stroke
- 15-20= moderate/severe stroke
- 21-42= severe stroke

RESPECT Patients

- N = 570
- NIH Stroke Scale:
  - Mean 0.8
  - SD 1.7
  - Range 0-17

Baseline Neuroanatomic CVA Location

Cortex

Frontal: 26.8%

Parietal: 24.8%

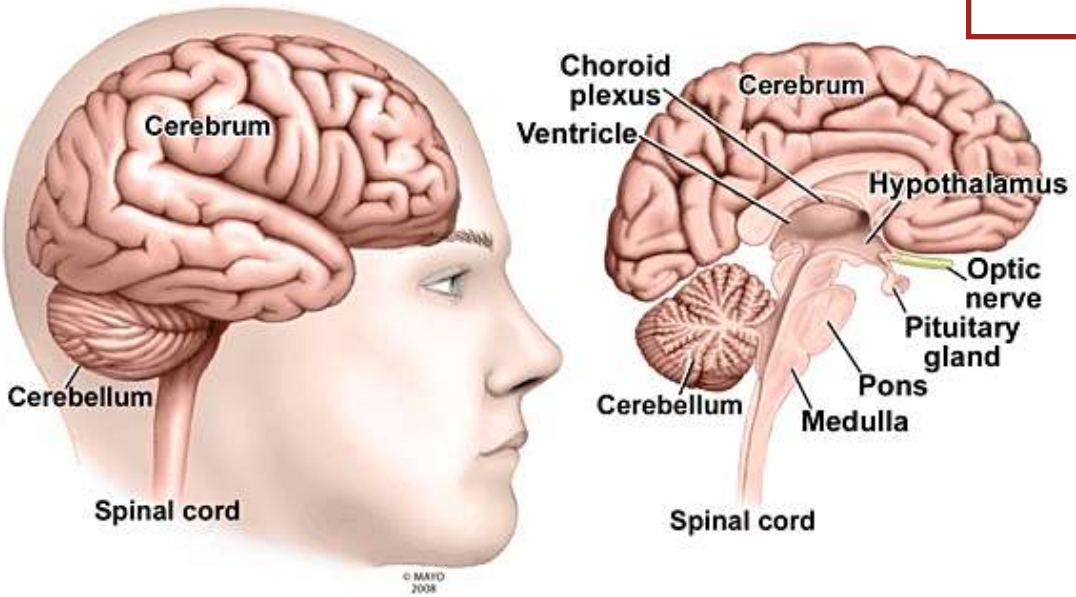
Temporal: 15.7%

Occipital: 14.9%

Centrum Semiovale: 8.6%

Internal Capsule: 5.2%

Basal Ganglia: 10.1%



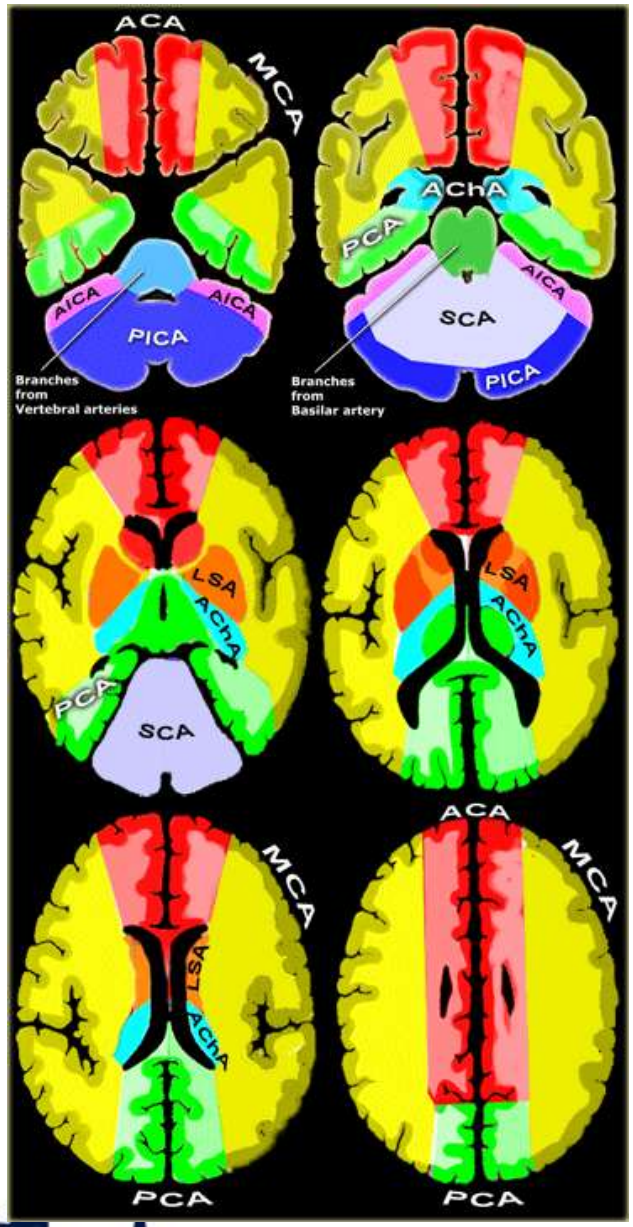
Thalamus: 14.0%

Cerebellum: 15.2%

Brain Stem: 5.6%

Baseline
CVA Vascular Territory

MCA:	**51.8%**
ACA:	**2.6%**
PCA:	**19.9%**
Basilar:	**7.5%**
Vertebral:	**5.4%**
Anterior Choroidal:	**0.7%**
Other:	**6.7%**

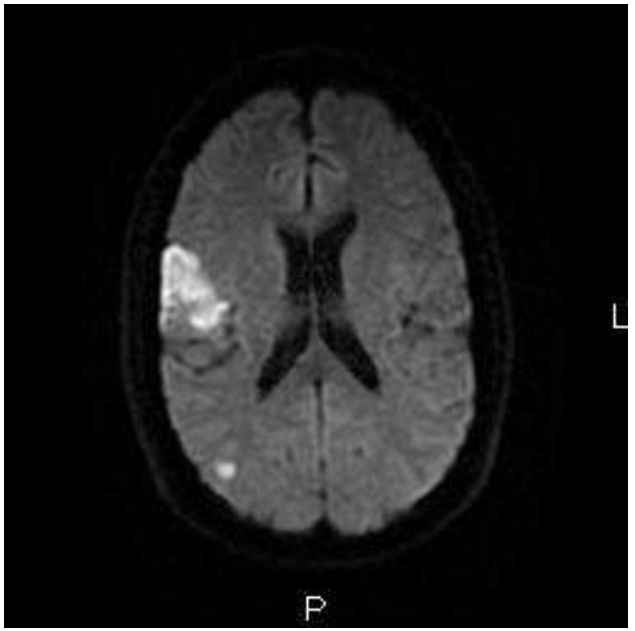


Baseline
Size of Lesion (MRI or CT)

Longest linear diameter

Small:	**16.7%**
Intermediate:	**30.3%**
Moderate:	**25.0%**
Large:	**20.2%**
Massive:	**4.2%**
Size Not Reported:	**3.6%**

(Data pending)



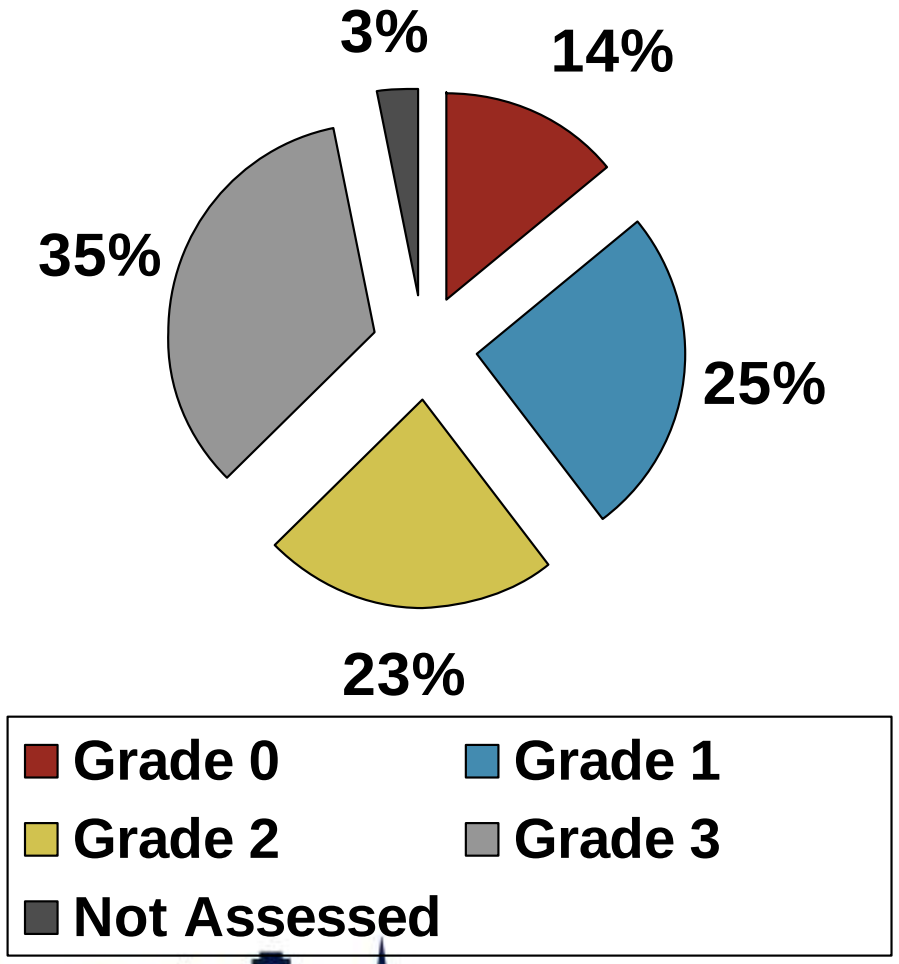
Baseline

PFO Shunt Assessment per TEE with Agitated Saline

Shunt at Rest:	**85.7%**
Shunt at Valsalva:	**97.7%**

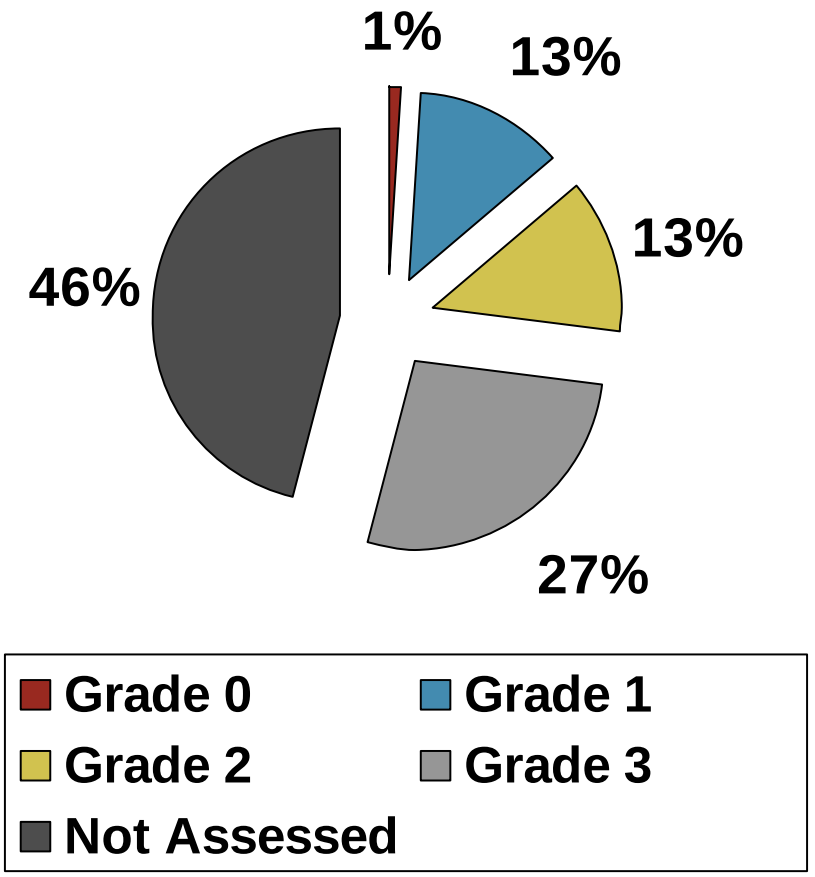
Assessment of Shunting
Resting State

- **Grading: Number of microbubbles in left atrium within 3 beats**
  - **Grade 1: 1-9**
  - **Grade 2: 10-20**
  - **Grade 3: >20**



Assessment of Shunting
Valsalva

- **Grading: Number of microbubbles in left atrium within 3 beats**
  - **Grade 1: 1-9**
  - **Grade 2: 10-20**
  - **Grade 3: >20**



Atrial Septal Aneurysm

Data not core lab adjudicated

ASA Frequency in All Patients

Atrial Septal Aneurysm: 34.8%

No Atrial Septal Aneurysm: 65.2%

ASA Excursion Direction

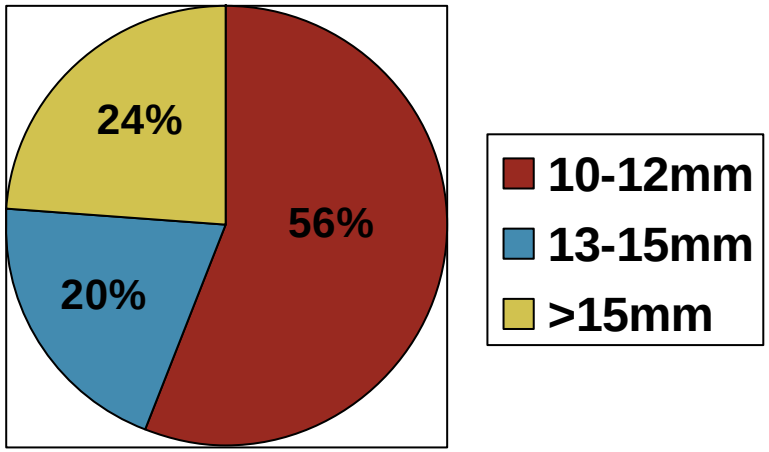
RA 8%

LA 32%

Both 60%

ASA Size

% of All ASA



Randomization

Randomization

Device:	**291 (50.5%)**
Medical Mgmt:	**285 (49.5%)**

Stratification

Aspirin alone:	**240 (42.1%)**
Coumadin alone:	**167 (29.3%)**
Clopidogrel alone:	**57 (10.0%)**
Aspirin w/ dipyridamole:	**106 (18.6%)**

Conclusions

- **RESPECT continues to enroll at a reasonable pace.**
- **A substantial number of patients have been enrolled to date.**
  - **Represent a spectrum of patients in terms of CVA and PFO characteristics.**
    - **Substantial number with “high risk” PFO characteristics**
      - **Baseline right to left shunting (85.7%) and atrial septal aneurysm (34.8%).**
  - **A relatively “pure” population free of confounding clinical comorbidities.**
- **RESPECT will end when a stopping point is achieved.**