The Most Exciting New Technologies (Excluding Valves) in the Cath Lab and Their Impact on Future

Saibal Kar, MD, FACC, FAHA, FSCAI
Director of Interventional Cardiac Research
Cedars Sinai Heart Institute, Los Angeles, CA
Disclosure Information

Saibal Kar MD, FSCAI

As a faculty member for this program, I disclose the following relationships with industry:

Abbot Vascular, Atritech, St Jude Medical, Circulite, Biotronics: (GRS)
Atritech, Abbot Vascular, St Jude Medical, Gore, Medtronic, GDSSystems: (C)
Introduction

• Lessons have been learned from cardiac surgery
• Combining our successes in Percutaneous Coronary Interventions, and understanding the structure by various imaging techniques, several structural defects of the heart can be treated by an endovascular approach.
Advances in structural heart disease interventions

- Transcatheter valve therapies
- Interventions to prevent cardioembolic stroke
  - Closure of PFO for prevention of cryptogenic stroke
  - Left atrial appendage occlusion in patients with AF
- Renal denervation of HT
- Advances in Heart failure
  - Sensors
  - Parachute device
  - Percutaneous LV assist devices
Advances in structural heart disease interventions

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- Advances in treatment of heart failure
  - Implantable hemodynamic sensors
  - New LA/LV assist devices

- Advances in Imaging
  - Intracardiac echo
  - CT
  - Three dimensional Echocardiography
March 26, 1954 Dr Walter Lillehei performed the first open heart surgical Repair of 13 yr old boy with a ventricular septal defect, using the father for Cross-circulation
History of Cardiac Interventions:

First Human catheterization of the heart

Werner Forssmann self Catheterized himself in 1929

Nobel Laureate 1956
The Birth of Interventional Cardiology

First PTCA in 1977
By Dr Andrea Gruentzig

...This Breakthrough paved the way to the development of field of Interventional Cardiology, and forever altered the role of The Cardiologist in the treatment of coronary artery disease.
Interventional Cardiology Credo

• Anything cardiac surgeons can do open, we can do percutaneously……
Experience with the Edwards Sapien valve in the Pulmonic Position

- Initial Phase I study Compassion study completed
- The Edwards SAPIEN Pulmonic THV can be safely implanted:
  - 92% implant success (33/36)
  - 92.3% survival at 6 months for treated patients; 100.0% survival for implanted patients
- Significant Improvement of symptoms of most patients
- No valve deterioration at one year
Clinical experience with transcatheter pulmonic valve implantation

- Transcatheter Pulmonic Valve Implantation is a safe and effective for the treatment of diseased RV to PA conduits
  - Helps in Restoring function
  - Avoids or postpones the need of redo surgery
- >3000 cases done world wide
- Design modifications are being made for treatment of severe PR/PS without a conduit
Conclusions

- Melody Valve is the only transcatheter valve to be approved in US under HDE for treatment of diseased full circumference RV to PA conduits
- Both Melody and Sapien Valve CE Mark approved
- This technology provides new hope to children with history of congenital heart disease
Percutaneous Repair/replacement of Valves

- Percutaneous Pulmonic valve replacement
- Percutaneous aortic valve replacement
- Percutaneous Mitral Valve Repair
Interventions for prevention of cardioembolic stroke
Interatrial Communications
Patent Foramen Ovale

- Present in 25% of normal persons
- Paradoxical embolism via a PFO
Patent Foramen Ovale and Stroke

• In a general population the presence of PFO is not an independent risk factor for stroke
• Pts with a history of stroke and large PFO and ASA are at sig risk for recurrent events if just on aspirin
• Atrial septal aneurysm without a PFO is not a risk factor for recurrent stroke
Patent Foramen Ovale: Innocent or Guilty

- PFO present 140 pts (24%)
- ASA present 11 (1.9%)
- 6 pts (4.3%) of PFO pts had ASA also

**Conclusion:** This prospective population based data suggests after correction of age and Co morbidity, PFO is not an independent risk factor for future Cerebrovascular events in a general population

*Meissner et al. J Am Coll Cardiol 2006*
Recurrent Cerebrovascular Events Associated with PFO, Atrial Septal Aneurysm, or Both

- 581 patients with cryptogenic CVA
- ASA 300 mg/day
- 4 year F/U
Optimal Treatment to Prevent strokes in patients with a PFO

- Currently there are no established treatment options
- Options available:
  - Antiplatelet therapy
  - Anticoagulant treatment
  - Surgical Closure
  - Percutaneous Closure
Transcatheter Closure vs Medical Therapy
PFO and Presumed Paradoxical Thromboemboli

10 Transcatheter Closures Studies
1355 Patients

6 Medical Management Studies
895 Patients

Recurrent neuro event @ 1 Yr

0 - 4.9%

3.8% - 12%
ASD/PFO closure Devices

Biotrek Septal Occluder (NMT Medical)

NMT Medical

AGA Medical
Techniques of Closure

PFO Occluder in Clinical Trial

STARFlex™ Septal Occlusion System

NMT Medical, Inc.

PFO occluder (AGA Med)

Helex Septal Occluder (Gore )
Steps For Closure of Patent Foramen Ovale
# Ongoing PFO Stroke Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Respect</th>
<th>Closure I</th>
<th>Reduce</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>900+</td>
<td>909</td>
<td>664</td>
</tr>
<tr>
<td>Device (Company)</td>
<td>Amplatzer (AGA)</td>
<td>StarFlex (NMT)</td>
<td>Helex (Gore)</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Stroke</td>
<td>Stroke or TIA</td>
<td>Stroke or MRI TIA</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>Stroke</td>
<td>Stroke or TIA</td>
<td>Stroke or MRI TIA</td>
</tr>
<tr>
<td>Key Secondary Endpoints</td>
<td>? Migraine</td>
<td>? Migraine</td>
<td>MRI WMLs</td>
</tr>
</tbody>
</table>

**Completed enrollment**

Different Populations, Devices, Endpoints Essential to Building a Body of Evidence
CLOSURE I: Study Flow (Superiority Study)

- Age 18-60yrs
- Documented Cryptogenic Stroke Or TIA
- PFO

910 patients Enrolled between June 2003 and October 2008

Device Group: Starflex Septal Occluder and Aspirin

Control Group: Aspirin and/or Coumadin 2 years

Primary End points
- All case death at 30 days
- 2 year Stroke or TIA
- Neurological death >30 days

Aspirin 2 years Clopidogrel 6 mths

Control Group: Aspirin and/or Coumadin 2 years
## CLOSURE I

**2 Year Primary Endpoint ITT**

<table>
<thead>
<tr>
<th></th>
<th>STARFlex</th>
<th>Medical</th>
<th>Adjusted P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 447</td>
<td>n = 462</td>
<td></td>
</tr>
<tr>
<td><strong>Composite</strong></td>
<td>5.9%</td>
<td>7.7%</td>
<td>0.30</td>
</tr>
<tr>
<td></td>
<td>(n=25)</td>
<td>(n=30)</td>
<td></td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>3.1%</td>
<td>3.4%</td>
<td>0.77</td>
</tr>
<tr>
<td></td>
<td>(n=12)</td>
<td>(n=13)</td>
<td></td>
</tr>
<tr>
<td><strong>TIA</strong></td>
<td>3.3%</td>
<td>4.6%</td>
<td>0.39</td>
</tr>
<tr>
<td></td>
<td>(n=13)</td>
<td>(n=17)</td>
<td></td>
</tr>
</tbody>
</table>

*Adjusted using Cox Proportional Hazard Regression and adjusting for related patient characteristics including: age, atrial septal aneurysm, prior TIA/CVA, smoking, hypertension, hypercholesterolemia*
CLOSURE I: CONCLUSIONS

• Alternative explanation unrelated to paradoxical embolism present in 80% of patients with recurrent stroke or TIA
  – cryptogenic stroke and TIA include multiple etiologies
  – in many patients with cryptogenic stroke or TIA a PFO may be coincidental
  – diagnostic criteria for paradoxical embolism are imprecise
  – potential efficacy of PFO device closure in better defined patient subgroups requires further study

• Percutaneous closure with STARFlex® plus medical therapy does not offer any significant benefit over medical therapy alone for the prevention of recurrent stroke or TIA in patients ≤ age 60 presenting with cryptogenic stroke or TIA and a PFO
Conclusions

• The exact role of PFO closure for patients with Cryptogenic stroke and PFO is not well defined

• Randomized trials have been very challenging to enroll
  – Patient and physician bias
  – Availability of off label device

• CLOSURE I trial is the only trial that has completed enrollment
  – Did not reach its primary endpoint
  – Device seems safe and slightly superior to medical treatment
CONCLUSIONS

• In US and Europe, pts with a cryptogenic stroke and a PFO should be encouraged to participate in clinical trial

• In countries where there are no clinical trials
  – Neurologist opinion should be sorted
  – Use your best clinical judgement( common sense)
Atrial Appendage Occluder for Stroke Prophylaxis:
Advances in structural heart disease interventions

- Transcatheter valve therapies
- Interventions to prevent cardioembolic stroke
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  - Percutaneous LV assist devices
Advances in structural heart disease interventions

- Treatment of cardiac defects
- Transcatheter valve replacement
  - Aortic and Pulmonic valve
- Transcatheter Mitral Valve Repair
  - MitraClip
- Transcatheter closure of left atrial appendage
- Advances in imaging
Introduction

• Thrombus arising in the Left atrial appendage is the major cause of stroke in patients with atrial fibrillation (AF)

• Percutaneous closure of the left atrial appendage rather than long term anticoagulant therapy is option to prevent stroke in AF patients

• Recently studies are completed or are ongoing using different devices have supported this hypothesis
Atrial fibrillation (AF) is the commonest arrhythmia
- 1.5 million patients in US

Stroke is an important complication of AF
- 5 fold increased risk in comparison to patients in sinus rhythm

Left atrial appendage is the most important source of thrombus
91% of stroke in AF is caused by blood clots that form in the left atrial appendage (LAA)\(^1\)

Atrial fibrillation and stroke

- Atrial fibrillation (AF) is the commonest arrhythmia
  - 1.5 million patients in US

- Stroke is an important complication of AF
  - 5 fold increased risk in comparison to patients in sinus rhythm

- Left atrial appendage is the most important source of thrombus
Prevention of stroke in AF patients

- Long term intake of blood thinners
  - Warfarin
  - New antithrombotic agents
- Surgical ligation of the left atrial appendage (LAA)
- Percutaneous closure of the LAA
Prevention of stroke in AF patients

- Long term intake of blood thinners
  - Warfarin
  - New antithrombotic agents
- Surgical ligation of the left atrial appendage (LAA)
- Percutaneous closure of the LAA
LAA occlusion Devices

- **Nitinol Frame**
- **Barbs**

**Watchman Device Gen II (Atritech)** §

**Amplatzer Cardiac Plug** §

**WaveCrest Device (Coherex)**#

§ Investigational in US

# Investigational in Europe
WATCHMAN® Left Atrial Appendage Occluder System (Atritech Inc)
Long term blood thinners

There is no free lunch:
If it prevents clots, it will bleed

stroke

• Bleeding risk
• Compliance
• Interaction with other drugs
LAA occlusion Devices (Endovascular approach)

- **Watchman Device Gen II (Atritech)** §
- **Amplatzer Cardiac Plug** §
- **WaveCrest Device (Coherex)**#

- **Nitinol Frame**
- **Barbs**

§ Investigational in US

# Investigational in Europe
LAA occlusion Devices

*Transpericardial approach*

- Lariat Device
  (Sentreheart)
WATCHMAN® Left Atrial Appendage Occluder System (Atritech Inc)

Nitinol Frame

160 µ PET Fabric

Barbs
Device is released
Left atrial appendage (LAA) is the source of thrombus in over 90% of AF patients.
LAA occlusion Devices

- Nitinol Frame
  - Watchman Device Gen II (Atritech)
  - Amplatzer Cardiac Plug

- Barb
  - Watchman Device Gen IV (Atritech)
  - WaveCrest Device (Coherex)

§ Investigational in US
# Investigational in Europe
<table>
<thead>
<tr>
<th>STUDY</th>
<th>PATIENTS</th>
<th>SITES</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot</td>
<td>66</td>
<td>8</td>
<td>• 318 patient years of follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 30 patients with 5+ years of follow-up</td>
</tr>
<tr>
<td>PROTECT AF</td>
<td>800</td>
<td>59</td>
<td>• 1,500 patient years of follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• 27 months average follow-up per patient</td>
</tr>
<tr>
<td>Continued Access Registry (CAP)</td>
<td>566</td>
<td>26</td>
<td>• Significantly improved safety results</td>
</tr>
<tr>
<td>ASAP</td>
<td>150</td>
<td>4</td>
<td>• Treat patients contra-indicated for warfarin</td>
</tr>
<tr>
<td>EVOLVE</td>
<td>69</td>
<td>3</td>
<td>• Evaluate next generation WATCHMAN</td>
</tr>
<tr>
<td>PREVAIL</td>
<td>400</td>
<td>≤50</td>
<td>• Same endpoints as PROTECT AF</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Revised inclusion/exclusion criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Initiate enrollment October 2010</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Enrollment completed in June 2012</td>
</tr>
<tr>
<td>TOTAL</td>
<td>2051</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**PROTECT AF Trial**

**Design**

- **DESIGN**: Prospective randomized, non-inferiority trial of LAA closure versus coumadin in Afib pts for prevention of stroke
- **OBJECTIVE**: Effectiveness and Safety of LAA closure for prevention stroke in comparison to coumadin for afib pts
- **PRIMARY END POINT**: Composite end point of stroke, cardiovascular death or system embolisation
- **PRIMARY SAFETY END POINT**: Device embolization, Bleeding

707 Afib pts with CHADS$_2$ Score ≥ 1 were randomized in 2:1 fashion

463 assigned to closure of the LAA

244 assigned to Warfarin control

408 pts were implanted

1500 pt –year follow up
PROTECT-AF Trial: LAA Closure is effective in stroke prevention

WATCHMAN was non-inferior to warfarin therapy for the prevention of stroke, cardiovascular death, or systemic embolism in patients with nonvalvular AF\(^1\)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>WATCHMAN Rate (Events/Pt-Yrs)</th>
<th>CONTROL (warfarin) Rate (Events/Pt-Yrs)</th>
<th>Relative Risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-To-Treat</td>
<td>3.0 31/1025.7</td>
<td>4.3 24/562.7</td>
<td>0.71</td>
<td>0.44, 1.30*</td>
</tr>
<tr>
<td>Post-Procedure</td>
<td>2.5 25/1015.7</td>
<td>4.3 24/562.7</td>
<td>0.58</td>
<td>0.35, 1.09</td>
</tr>
</tbody>
</table>

Primary Efficacy Endpoint at 1500 Pt-Yrs (ITT population)

Watchman device: clinical summary

• Non inferior to long term blood thinners
• Reduction of bleeding
• Invasive procedure
  ▪ Early safety issues, no late issues
• Safety issues have reduced with experience
Watchman device: status

- Completion of two randomized studies
- Investigational in US
- Enrollment in a continuous access registry
- FDA resubmission in this quarter
- Hopefully FDA will approve the device in late 2013
Left Atrial Appendage Occlusion: Where do we stand

- **LAA occlusion investigational in US, clinical available in Europe**

- **Percutaneous Closure of LAA is an effective alternative to long term anticoagulation**
  - Early safety but no long term issues

- **Ongoing studies and more clinical experience**
  - Confirm the hypothesis
  - Improve safety
Advances in structural heart disease interventions

- Transcatheter valve therapies
- Interventions to prevent cardioembolic stroke
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- Advances in Heart failure
  - Sensors
  - Parachute device
  - Percutaneous LV assist devices
Interventional treatment for HT

• Catheter based renal denervation
  – Radiofrequency
  – Ultrasound

• Devices
  – Every company seems to have a device
  – (Medtronic, Boston Scientific, St Jude Medical, Johnson & Johnson)
Renal denervation for HT

- > 2000 cases performed Worldwide
- Approved in Europe, Australia and some countries in Asia
- Investigational in US
- Pivotal study in US
  - Refractory HT
  - Randomized 1:1 to medical therapy alone versus RF ablation and medical therapy
Renal denervation for HT
Advances in structural heart disease interventions

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Approaches for heart failure

- Implantable heart monitor devices
- Percutaneous treatment of functional MR
- New LV/RV assist devices
  - Percutaneous approaches for assist devices
>90% of HF hospitalizations have symptomatic pulmonary congestion.

The proximate cause of pulmonary congestion is sustained Left atrial pressure (LAP) and/or Pulmonary Capillary wedge pressure (PCW) elevation (> 25 mmHg).

Most episodes due to fluid overload and effectively respond to diuretics and venodilators.

Earlier treatment of ADHF may prevent or shorten hospitalization.
Rationale for Heart failure monitoring devices

LAP/PCW guided HF therapy will control of pressure excursions and prevent ADHF episodes.

Technology Challenge

Develop a permanently implantable stable pressure sensor that is directly linked with a physician-directed, patient self-management paradigm.
Intra-Cardiac pressure monitoring Devices

- RV sensor
- Left Atrial Sensor
- Implantable Communications Module (ICM) (St Jude Medical)

HeartPOD® ICM (St Jude Medical)
Pressure sensors deployed in Pulmonary Artery

CardioMEMS

Remon ImPressure™
HeartPOD® Stand-alone HF Management System
(Model LAP1068)

Implantable Sensor Lead (ISL)

Proximal Anchor

Distal Anchor

Sensor Diameter ~ 3 mm

Measures
• LAP
• IEGM
• Core Temp

Implantable Communications Module (ICM)
HeartPOD® Stand-alone HF Management System
Superior placement

Patient FDT-011
Patient Advisor Module - PAM®
CardioMEMS
Radiofrequency based wireless sensor

Small stable transducer
NO batteries
No leads
Sensor Does Not Impact Blood Flow

Flow around sensor

Sensor in Distal PA
Role of Intracardiac monitoring of pressures

- Changes in filling pressures precede the onset of acute decompensated heart failure

- Intra-cardiac and intra-pulmonary artery implantable pressure sensors are reliable and safe

- Preliminary data suggest that HF therapy tailored to the filling pressures may reduce HF reduced morbidity

- Large scale clinical trials testing this hypothesis are currently enrolling patients
Approaches for heart failure

- Implantable heart monitor devices
- Percutaneous treatment of functional MR
- New LV/RV assist devices
  - Percutaneous approaches for assist devices
CircuLite Endovascular System in Development

- Cannula transseptally deployed in LA
- Outflow Graft attached to Subclavian Artery
Conclusions

• Percutaneous Treatment of selected patients with structural heart defects is safe and feasible.

• Percutaneous approach may associated with lower morbidity than surgery.

• Improvements in technology will further improve the scope of percutaneous approaches.
Conclusions

• A very thorough understanding of the physiology and imaging of the heart by Echo, CT, MRI is essential.

• A team approach involving the Imaging cardiologist, interventional cardiology, and Surgeons are required to make this field a success.
- Yesterday was an experience
- Today is an opportunity
- Tomorrow is just an imagination