My Scientific Journey

The animal laboratory—D.Phil (Oxford)
D.Phil Thesis, Oxford University---Lessons Learned
Ventricular function and Hemodynamics in the Dog
During Anesthesia

Meticulous experimental methodology is the key to good data

- Measuring indices of myocardial contractility is a waste of time
- The failing ventricle cannot deal with an increased afterload
- The fascination of asking questions and analyzing data

To read and write in English and make it all look effortless even when working extremely hard:
Cultivate an air of superiority:
My Scientific Journey

STEMI
Reperfusion injury
Relationship Between Mortality Reduction and Extent of Salvage

**Mortality reduction (%)**

Impact of treatment delay?

**Modifying factors**
- Collaterals
- Ischemic preconditioning
- MVO$_2$
- Stuttering infarction
- Microvascular dysfunction

**Extent of salvage ( % of area at risk) **

**Treatment objectives**
- Time to treatment is critical
- Opening the IRA (PCI > lysis)

Gersh: JAMA, 2005
Pathophysiology of Reperfusion Injury and Microvascular Dysfunction

Large agenda-disappointing results

Heusch and Gersh: EHJ, 2016
**Windows of Opportunity**

- **A** No benefit: *Too early to make a difference*
- **B** Potential benefit: *Difficulties in demonstrating a difference*
- **C** No benefit: *Too late to make a difference*

**Myocardial salvage (%)**

**Time from symptom onset to reperfusion therapy (hour)**

Gersh: JAMA, 2005
My Scientific Journey

Chronic CAD and revascularization

STEMI Reperfusion injury
Benefits and Risks of Revascularization in Stable CAD

“Sicker Patients”
- Location and extent of coronary disease
- Diffuse disease
- Severe symptoms
- LV dysfunction
- Diabetes

Guidelines driven by RCT

Registry driven data
- Comorbidities
- Age
- Frailty

Risk/Benefit
- Procedural risk $\uparrow$
- Long-term benefits $\downarrow$

Revasc > OMT
CABG > PCI
Cumulative Survival With Medical and Surgical Therapy
1491 Patients ≥65 Years Old – CASS Registry

Survival (%)

Adjusted for Preop Risk Factors

Low-Risk Subset
234 Patients (16%)

Medical
Surgical

P=0.7664
Log rank stat=0.088

79%
64%

84%
82%

Gersh: NEJM, 1985
Chronic Stable I.H.D. and the Potential Role of Microvascular Dysfunction
Simple Questions Without Clear Cut Answers

Severity of stenoses and angina
Complex relationships

• Absence of obstructive disease in pts with evidence of ischemia and angina

• Absence of angina in pts with severe coronary atherosclerosis

• High frequency of MVD in pts with ACS without pre-existing angina – ? Preserved microvascular function and collaterals

Continued symptoms and events after coronary revascularization

Progressive epicardial disease

Microvascular dysfunction
AFib
Vascular disease
CHF
OAC
Chronic CAD and revascularization
STEMI Reperfusion injury
My Scientific Journey
AFib as a Vascular Disease
Suggestive Evidence

Obesity
Hypertension
Metabolic syndrome
Sleep apnea

↑ Arterial stiffness
Diastolic dysfunction
↑ LA volume

Diastolic dysfunction
↑ LA volume

Atrial fibrillation

• Neurohormonal factors
  < Ang II
  < CTGF
  < TGFβ1
• Tissue factors
  < MMPs
• Vascular and hemostatic factors
  < PDGF
  < Endothelin-I
• Oxidative stress and inflammation
• Galactin

Cause
Surrogate

Tsang and Gersh: EHJ 2008; JACC 2008; AJC 2008; AJC 2006; JACC 2006; JACC 2003; JACC 2002
Triggers vs Substrate in Pathophysiology of AF

Wyse & Gersh: Circ, 2004

- Paroxysmal?
- Persistent?
- Permanent

Triggers (“lone” AF):
- Genetics?
- ↑ vagal tone

Triggers & diseased substrate:
- Age
- Obesity
- Atherosclerotic risk factors

P vein isolation/ WACA pts

Trials of pharmacologic rhythm vs rate control
Incl. AFFIRM and RACE

AF burden

Modulating factors
My Scientific Journey

Vascular disease
CHF
OAC
AFib

Chronic CAD and revascularization
HCM

STEMI
Reperfusion injury

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HCM – Changing Natural History and the Impact of Referral Bias

• Rare disease in young people
• Relatively common in older patients in community hospitals

Prognosis

- Young: Frequently fatal
- Middle age: Better than CAD
- Elderly: Similar to population at large in the majority
My Scientific Journey

- AFib
- Vascular disease
- CHF
- OAC
- Chronic CAD and revascularization
- HCM
- STEMI
- Reperfusion injury
- SCD
- Syncope
- Clinical EP
- ©2017 MFMER | 3670502-8
3,496 Patients

Unknown: 18%
Neurally mediated: 36%
Others: 30%
Arrhythmias: 12%
Orthostatic intolerance: 6.1%
CSH: 3.1%
Cerebrovasc. disease: 2.9%
Structural cardio-pulmonary disease: 0.3%

Sorajja: Circ, 2009
The clinical history is the single most important diagnostic aid
Cardiac Cell Repair Therapy is at a Crossroads

“The end of the beginning or the beginning of the end”? – Winston Churchill

Grounds for cautious optimism

- Ongoing basic research on multiple fronts and countries but “lost in clinical translation”
  
  Clinical trial results
  - Safety
  - Modest benefits
  - Trends in the right direction
  - Improved clinical trial design

Concerns

- Benefits – modest
- Neutral trials
- Unrealistic expectations
  - Physicians
  - Public/media
- Overreaction to neutral trial results
- Perceptions in scientific community over extent of stem cell research funding
- Concerns re scientific credibility – justified and unjustified
My Scientific Journey

- Epidemiology of CVD in the developing world
- Stem Cells
- AFib
- Vascular disease
- CHF
- OAC
- Chronic CAD and revascularization
- HCM
- SCD Syncope Clinical EP
- STEMI Reperfusion injury
Global Burden of Cardiovascular Disease – 2010

Total deaths – 52.8 million

- Cardiovascular and circulatory disease: 15.1 million
- Cancer: 8 million
- Communicable, Maternal, Neonatal, Nutritional: 13.2 million
- HIV, TB, Malaria: 4.7 million

Developing (LIMC) Countries

- 80% of worldwide CV deaths
- Occur at a younger age – impact on workforce, productivity and families.
- 2010 – 70% of the elderly living in the developing world

Lopez: Lancet, 2006; Reddy: NEJM, 2004
Lozano: Lancet, 2012
The Potential Epidemic of CVD in Developing Countries

Hostile CV environment

- Diet/lack of exercise
- Tobacco incl second-hand smoke
- Aging society
- HIV survivors- Statins in Primary Prev. ?
- Air pollution
- Rural → urban migration
- Psychosocial/economic stressors
- Culture ← Obesity
  - Traditional healers

Pre-disposing factors

- "The perfect storm"

- Limited national resources
- Lack of infrastructure

Genetic/phenotypic vulnerability? – thrifty gene concept?

- Salt sensitivity
- Insulin resistance
- Lipid/fat metabolism
- Low birth weights

Gersh et al: EHJ, 2010
My Scientific Journey

Clinical trials and registries
Potential
Methodology
Pitfalls

Epidemiology of CVD in the developing world
Stem Cells

AFib
Vascular disease
CHF
OAC

HCM
SCD
Syncope
Clinical EP

STEMI
Reperfusion injury

Chronic CAD and revascularization
Limitations of Randomized Trials and Registry Studies of C. Revascularization

Registry studies
- Selection bias
- Greater relevance to practice at large

Randomized trials
- Entry bias (Inclusion criteria mandate clinical equipoise and eligibility for both forms of therapy)
- Prolonged duration of trials introduces a risk of “obsolescence”

“Things may not be as they seem”
Gersh and Frye: NEJM, 2005
Every Database is Vulnerable to Confounders

Multivariable analysis

Adjust for baseline differences but cannot eliminate these

Can only adjust for known and measured confounders
Placebo Effect

“you have to believe it to see it”
Comparison of Changes in SBP at 6 Months in 3 Trials of Renal Denervation

<table>
<thead>
<tr>
<th>Trial</th>
<th>Denervation</th>
<th>Sham control</th>
<th>Unblinded control</th>
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</thead>
<tbody>
<tr>
<td>SYMPLICITY 1</td>
<td>Denervation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYMPLICITY 2</td>
<td>Denervation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SYMPLICITY 3</td>
<td>Denervation</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean reduction in SBP (mm Hg) (95% CI)

Pocock and Gersh: JACC, 2014
The Natural History of Evolving Therapies

The initial enthusiasm has been tempered and the number of unanswered questions is increasing. Nonetheless the concept remains of interest.

- Excitement/euphoria
- Reality check
- Depression
- Progress
- In perspective
“Twain was convinced that he could only sleep in well-ventilated rooms. Finding himself in a small hotel room with a window that was stuck shut, he tried in vain to fall asleep. Finally unable to bear it any longer, he reached under his bed, picked up a shoe, and heaved it at the window. The ensuing crash relieved him and he quickly fell asleep.

He awoke refreshed, only to find that he had missed the window and shattered a mirror instead.
Composite Endpoints – Potential Pitfalls

**Advantages**
- ↑ statistical power
- ↑ frequency of events

Convenient impact on sample size and costs

**Caveat**
“but a danger of oversimplifying the evidence by putting too much emphasis on the composite”
Pocock: and Gersh JACC, 2015

Summary of Key 1- and 5-Year Findings From the SYNTAX Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>1-year event rates</th>
<th>CABG (n=897)</th>
<th>DES (n=903)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACCE composite</td>
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<td>12.1</td>
<td>17.8</td>
<td>0.002</td>
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<tr>
<td>Death</td>
<td></td>
<td>3.5</td>
<td>4.4</td>
<td>0.37</td>
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<tr>
<td>MI</td>
<td></td>
<td>3.3</td>
<td>4.8</td>
<td>0.11</td>
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<tr>
<td>Stroke</td>
<td></td>
<td>2.2</td>
<td>0.6</td>
<td>0.003</td>
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<tr>
<td>Death/MI/stroke</td>
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<td>7.6</td>
<td>7.5</td>
<td>0.98</td>
</tr>
<tr>
<td>Repeat revascularization</td>
<td></td>
<td>5.9</td>
<td>13.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PCI</td>
<td></td>
<td>4.7</td>
<td>11.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td></td>
<td>1.3</td>
<td>2.8</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Differential Magnitude of Composite Endpoints
Small Studies with Highly Positive Results

Can be misleading

Non-inferiority and inadequate power are two very different entities
### Trials of Magnesium for Acute MI

<table>
<thead>
<tr>
<th>Years</th>
<th>Magnesium better</th>
<th>Placebo better</th>
<th>No.</th>
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<tbody>
<tr>
<td>1980-1990</td>
<td>7 RCTs</td>
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<td>1987-1992</td>
<td>LIMIT 2</td>
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<td>1991-1993</td>
<td>ISIS 4</td>
<td></td>
<td>58,050</td>
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<tr>
<td>1999-2002</td>
<td>MAGIC</td>
<td></td>
<td>6,213</td>
</tr>
</tbody>
</table>

**Odds ratio**

Antman E: Lancet 360:1189, 2002
### Type II Error in a Randomized Trial

<table>
<thead>
<tr>
<th>Status</th>
<th>Percentage</th>
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</thead>
<tbody>
<tr>
<td>Improved</td>
<td>33%</td>
</tr>
<tr>
<td>Unchanged</td>
<td>33%</td>
</tr>
<tr>
<td>Escaped</td>
<td>Monkey no. 3</td>
</tr>
</tbody>
</table>
I HAVE IT ALL FIGURED OUT, MARCIE...

THE WAY I SEE IT THERE SEEM TO BE MORE QUESTIONS THAN THERE ARE ANSWERS

SO?

SO TRY TO BE THE ONE WHO ASKS THE QUESTIONS!
Eminence-Based Medicine

“The more senior the colleague the less importance placed upon anything as mundane as evidence.”

Isaacs: BMJ, 1999
The “sicker” the patient

- Coronary artery symptoms
- LV dysfunction
- Diabetes

The greater the benefit of revascularization vs medical therapy

The greater the benefit of CABG vs PCI-comorbidities?