Translating Clinical trials into Daily Practice

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Disclosures

• Steering Committee
  – RELY trial (dabigatran)
  – PALLAS trial (dronedronerone)
  – SAVOR trial (saxagliptin)
  – ARISTOTLE trial (apixaban)

• Consultant
  – Boehringer Ingelheim (Dabigatran)
  – Sanofi-aventis (Dronedarone)
  – Johnson & Johnson / Bayer (Rivaroxaban)
  – BMS / Pfizer (Apixaban)
  – Astra-Zeneca (Ticagrelor)

• Honorarium for CME speaking:
  – Sanofi-aventis / BI / BMS / Pfizer / Bayer / Astra-Zeneca
Antiplatelet therapy in ACS

Stroke prevention in AF

Resistant HT

TAVI for AS in the elderly
Antiplatelet therapy in ACS:

*Cure, Clarity and Plato*
The Progression of Atherosclerosis

Healthy artery  Early stages of atherosclerosis  Inflammatory process  Early atherosclerotic lesions  Vulnerable plaque  Stable plaque

Intravascular ultrasound (IVUS) images compiled by the Cleveland Clinic.
ACS is an Important Manifestation of Atherothrombosis


UA=unstable angina; NSTEMI=non-ST-segment elevation myocardial infarction; PCI=percutaneous coronary intervention
Multiple Complex Coronary Plaques in Patients with Acute MI

The Ruptured Atherosclerotic Plaque

Decreased smooth muscle cells, activated macrophages and inflammatory cells contribute to the weakening of the thin fibrous cap.

Unobstructed lumen

Thrombus formation results activation of platelets and cross-linking by fibrinogen at platelet receptors GP IIb-IIIa

Aggregated platelets

Fibrin

Macrophage

Tissue Factor

Non-ST segment elevation myocardial infarction

ST segment elevation myocardial infarction
The Role of Platelets in Atherothrombosis

- Adhesion
- Aggregation
- Activation
Aspirin in Acute and Prior MI

<table>
<thead>
<tr>
<th>Category</th>
<th>Category of vascular events*</th>
<th>% odds reduction of vascular events*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute MI</td>
<td></td>
<td>30%</td>
</tr>
<tr>
<td>Acute stroke</td>
<td></td>
<td>11%</td>
</tr>
<tr>
<td>Prior MI</td>
<td></td>
<td>25%</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td></td>
<td>22%</td>
</tr>
<tr>
<td>Other high risk</td>
<td></td>
<td>26%</td>
</tr>
<tr>
<td>All trials</td>
<td></td>
<td>22%</td>
</tr>
</tbody>
</table>

*Vascular events = MI, stroke or vascular death

Aspirin in Acute Coronary Syndromes

Unstable Angina

- Placebo: 17.1%
- ASA: 6.5%
- Death or MI: *P<.0001
- Reocclusion: *P=.003

Acute MI

- Placebo: 3.3%
- ASA: 1.9%
- MI: *P=.012
- Death: *P<.001

N= Placebo ASA
- Unstable Angina: 397 399
- Acute MI: 8587 8600

MI, myocardial infarction; ASA, acetylsalicylic acid; RISC, Research on InStability in Coronary artery disease.
Evidence for Clopidogrel + Aspirin in the Management of Non-ST-segment ACS – CURE Methodology

- **Day 0**
  - Clopidogrel 300 mg loading dose + aspirin

- **Day 1**
  - Aspirin 1 tab od

- **12 months**
  - Clopidogrel 75 mg od + aspirin + standard Therapy (n=6259)
  - Aspirin 1 tab od + standard therapy (n=6303)

Patients with non-ST segment elevation ACS within 24 hrs of symptom onset

Standard therapy may have included Heparin, LMWH, GP 11b/11a inhibitors, β-blockers, ACE Inhibitors, LLA, PTCA and CABG

Evidence for Clopidogrel + Aspirin in the Management of Non-ST-segment ACS – Efficacy Results from CURE


Cumulative Events (Myocardial Infarction, Stroke or Cardiovascular Death)

- Placebo* (n = 6,303)
- Clopidogrel* (n = 6,259)

20% relative risk reduction

\( p = 0.00009 \)

*On top of standard therapy (including aspirin)
Evidence for Clopidogrel + Aspirin in the Management of Non-ST segment ACS – Bleeding Episodes Compared to Aspirin

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo* (n = 6,303)</th>
<th>Clopidogrel* (n = 6,259)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding'</td>
<td>2.7%</td>
<td>3.7%</td>
<td>0.001</td>
</tr>
<tr>
<td>• Life-threatening</td>
<td>1.8%</td>
<td>2.2%</td>
<td>NS</td>
</tr>
<tr>
<td>• Other major bleeding</td>
<td>0.9%</td>
<td>1.5%</td>
<td>0.002</td>
</tr>
<tr>
<td>Transfusions of ≥ 2 units of blood'</td>
<td>2.2%</td>
<td>2.8%</td>
<td>0.02</td>
</tr>
<tr>
<td>Minor bleeding'</td>
<td>2.4%</td>
<td>5.1%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Major bleeding by TIMI definition²</td>
<td>1.2%</td>
<td>1.1%</td>
<td>0.70</td>
</tr>
<tr>
<td>Major bleeding by GUSTO definition³</td>
<td>1.1%</td>
<td>1.2%</td>
<td>0.48</td>
</tr>
</tbody>
</table>

*On top of standard therapy (including aspirin)

Evidence for Clopidogrel + Aspirin in the Management of Non-ST segment ACS – Absolute Risk Benefit Analysis from CURE

Primary efficacy (events prevented) and excess in life-threatening bleeding in clopidogrel group compared with placebo group. Difference between the two curves is indication of net benefit of clopidogrel

Clopidogrel Reduced Clinical Events at 30 Days by 20%\textsuperscript{1}

*OR in CV death, MI or recurrent ischaemia leading to urgent revascularisation

“In conclusion, we found that, in patients 75 years of age or younger who have myocardial infarction with ST-segment elevation and who have received fibrinolytic therapy, aspirin and (when appropriate) weight-based heparin, clopidogrel offers an effective, simple, inexpensive, and safe means by which to improve the rate of patency of the infarct-related artery and to reduce the rate of ischaemic complications.”  

Translation of results:

Clopidigrel with aspirin becomes standard therapy after NSTEMI and STEMI for 12 months whether revascularisation or not
Antiplatelet Therapy in Acute Coronary Syndromes

Variability in Inter-Individual Clopidogrel Response

Clopidogrel Response Variability

**Genetic Factors**
- Polymorphisms of CYP
- Polymorphisms of GPIa
- Polymorphisms of P2Y$_{12}$
- Polymorphisms of GPIIIa

**Clinical Factors**
- Failure to prescribe/poor compliance
- Under-dosing
- Poor absorption
- Drug-drug interactions involving CYP3A4
- Acute coronary syndrome
- Diabetes mellitus/insulin resistance
- Elevated body mass index

**Cellular Factors**
- Accelerated platelet turnover
- Reduced CYP3A metabolic activity
- Increased ADP exposure
- Up-regulation of the P2Y$_{12}$ pathway
- Up-regulation of the P2Y$_{1}$ pathway
- Up-regulation of P2Y–independent pathways (collagen, epinephrine, TXA$_2$, thrombin)

Clopidogrel Pharmacogenomics

Biotransformation by CYP3A4, 3A5, 219, 2C9, 1A2
Polymorphic variants

P2Y12 Receptor: H2 haplotype

MDR1 C3435T genotype
CYP2C19 Genetic Variants Influence Clopidogrel Response

2hr inh overall

*\(p=0.0295\)

CYP2C19 genotype

<table>
<thead>
<tr>
<th>2 hr % inhibition</th>
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</thead>
<tbody>
<tr>
<td><em>1</em>1</td>
</tr>
<tr>
<td>*2 or *4 carriers</td>
</tr>
<tr>
<td><em>1</em>17</td>
</tr>
<tr>
<td><em>17</em>17</td>
</tr>
</tbody>
</table>

2hr % inhibition
CYP2C19*2 Allelic Variant and MACE

TIMI Group analysis

- Carriers
  - Primary Efficacy Outcome (%)
  - Days After Randomization
  - Death from cardiovascular causes, myocardial infarction, or stroke
  - \( p = .01 \)
  - 12.1 vs 6.9

- Non-carriers
  - Primary Efficacy Outcome (%)
  - Days After Randomization

- Carriers
  - Death or Radial Stent Thrombosis (%)
  - Days After Randomization
  - 2.6

- Non-carriers
  - Death or Radial Stent Thrombosis (%)
  - Days After Randomization
  - 0.8

Ticagrelor

Not a pro drug

More predictable and potent platelet inhibition

“Reversible” platelet inhibition – wears off more quickly
DISPERSE2 substudy in patients on chronic clopidogrel treatment

Mean ADP-induced platelet aggregation, final extent (% ±SEM)

Note: Substudy included 44 patients
*270 mg dose was the loading dose in the DISPERSE2 study

Storey R et al. Presented at ACC 2006, Atlanta
Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study


Summary

Background Variation in and irreversibility of platelet inhibition with clopidogrel has led to controversy about its optimum dose and timing of administration in patients with acute coronary syndromes. We compared ticagrelor, a more potent reversible P2Y12 inhibitor with clopidogrel in such patients.
PLATO: primary efficacy endpoint:
K-M estimate of time to major CV event
(composite of CV death, MI or stroke)

Cumulative incidence (%)

No. at risk
Ticagrelor  9333  8628  8460  8219  6743  5161  4147
Clopidogrel  9291  8521  8362  8124  6650  5096  4047

Months after randomisation

(HR, 0.84; 95% CI, 0.77-0.92; P<0.001)

K-M, Kaplan-Meier
## Stent thrombosis

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=6,732)</th>
<th>Clopidogrel (n=6,676)</th>
<th>HR for ticagrelor (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stent thrombosis, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>1.0</td>
<td>1.6</td>
<td>0.62 (0.45–0.85)</td>
<td>0.003</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>1.7</td>
<td>2.3</td>
<td>0.72 (0.56–0.93)</td>
<td>0.01</td>
</tr>
<tr>
<td>Possible, probable, or definite</td>
<td>2.2</td>
<td>3.1</td>
<td>0.72 (0.58–0.90)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

*Evaluated in patients with any stent during the study

Time-at-risk is calculated from the date of first stent insertion in the study or date of randomization

* By univariate Cox model

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Cannon CP et al. *Lancet 2010*
Time to non-procedure-related PLATO major bleeding

Completeness of follow-up 99.97% = five patients lost to follow-up

K-M estimated rate (% per year)

HR 1.31 (95% CI 1.08–1.60), p=0.006

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 days</td>
<td>9,235</td>
<td>9,186</td>
</tr>
<tr>
<td>120 days</td>
<td>7,641</td>
<td>7,718</td>
</tr>
<tr>
<td>180 days</td>
<td>7,247</td>
<td>7,371</td>
</tr>
<tr>
<td>240 days</td>
<td>6,979</td>
<td>7,134</td>
</tr>
<tr>
<td>300 days</td>
<td>5,496</td>
<td>5,597</td>
</tr>
<tr>
<td>360 days</td>
<td>4,067</td>
<td>4,147</td>
</tr>
</tbody>
</table>

Wallentin L et al. NEJM Aug 30, 2009
Translation of results:

Ticagrelor with aspirin becomes standard therapy after NSTEMI and STEMI for 12 months whether revascularisation or not
Anticoagulation for stroke prevention in AF?
Projected number of persons with AF in the U.S. between 2000 and 2050

Assumes no further increase in age-adjusted AF incidence (solid curve) and assumes a continued increase in incidence rate as evident in 1980 to 2000 (dotted curve)

AF Increases Stroke Risk by Nearly 500%

Risk ratio = 4.8
P < 0.001

One Sixth of all Strokes Attributable to AF

Framingham Study

AF prevalence
Strokes attributable to AF

Age Range (years)

Cardiogenic Embolism is the Most Common Cause of Stroke

Figure 3. Age-specific incidence rates for all ischemic stroke subtypes in Adelaide (2009–2010).

Higher Mortality After Stroke, at 30 Days and 1 Year, in AF Patients

Thrombus forms in LA appendage and embolises to brain
How do we prevent stroke related to NVAF?
Warfarin reduces the risk of stroke in patients with AF

Random effects model; Error bars = 95% CI; *P>0.2 for homogeneity; †Relative risk reduction (RRR) for all strokes (ischaemic and haemorrhagic)

Factors Influencing Physician use of Anticoagulation in Atrial Fibrillation

- The decision to use warfarin in NVAF was not driven by the perceived benefit; the perceived risks (Intracerebral Bleeds) strongly affected warfarin use.

- Physician attitudes towards anticipated regret and risk aversion also impacted their treatment recommendations.

- Physicians were more influenced by the risks of anticoagulation than the benefits.

Gross C,........ Ezekowitz et al
Reasons warfarin not used

• **Physician factors:**
  – Perception bleeding risk too high
  – Perception stroke risk is low
  – Patient not suitable for anticoagulation
    • Falls, poor eyesight, poor compliance, inability to be monitored,

• **Patient factors**
  – Rat poison,
  – Doesn’t want blood tests,
  – Dietary and alcohol restrictions
  – Perception of increased bleeding “anecdotes”
  – Perception stroke risk low

Physicians are often more influenced by the risks of anticoagulation rather than the benefits
Patients fear stroke

Even mild stroke is considered as bad as death by some

Moderate stroke is considered as bad as death by many

Major stroke is feared by most

Figure 1. Utilities for mild, moderate, and major stroke in the 70 subjects, ranging from worse than death (<0) to current health (1.0).

Gage et al Arch Intern Med 1996; 156: 1829
Balancing the benefits and risks of anticoagulation

Perspectives of physicians and patients on anticoagulation in AF do differ ........

Devereaux et al BMJ 2001;323:1218
Limitations of VKA therapy

VKA therapy has several limitations that make it difficult to use in practice

Unpredictable response

Narrow therapeutic window (INR range 2-3)

Routine coagulation monitoring

Slow onset/offset of action

Frequent dose adjustments

Numerous food-drug interactions

Numerous drug-drug interactions

Warfarin resistance

Warfarin Issues

- Genes controlling Warfarin action and metabolism identified
  - Genetic variance identified, complicating management

Warfarin Mode of Action & Metabolism

- **Pharmacodynamics**
  Mode of action of warfarin on **VKORC1**

- **Pharmacokinetics**
  Catabolism of warfarin by **CYP2C9**
Narrow therapeutic range with VKA

The anticoagulant effect of vitamin K antagonists are optimized when therapeutic doses are maintained within a very narrow range.

### Time in therapeutic range (*TTR*) of warfarin-treated AF patients in the USA

<table>
<thead>
<tr>
<th>Clinic-based warfarin dosing</th>
<th>TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsa, 2000 (N= 43)</td>
<td>0.60</td>
</tr>
<tr>
<td>Menzin, 2005 (N= 600)</td>
<td>0.62</td>
</tr>
<tr>
<td>Hylek, 2007 (N= 306)</td>
<td>0.58</td>
</tr>
<tr>
<td>Nichol, 2008 (N= 351)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.63</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Community-based warfarin dosing</th>
<th>TTR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Samsa, 2000 (N= 61)</td>
<td>0.47</td>
</tr>
<tr>
<td>Samsa, 2000 (N= 125)</td>
<td>0.36</td>
</tr>
<tr>
<td>McCormick, 2001 (N= 174)</td>
<td>0.51</td>
</tr>
<tr>
<td>Matchar, 2003 (N= 363)</td>
<td>0.56</td>
</tr>
<tr>
<td>Matchar, 2003 (N= 317)</td>
<td>0.49</td>
</tr>
<tr>
<td>Matchar, 2003 (N= 317)</td>
<td>0.52</td>
</tr>
<tr>
<td>Go, 2003 (N= 7445)</td>
<td>0.63</td>
</tr>
<tr>
<td>Shen, 2007 (N= 11,016)</td>
<td>0.55</td>
</tr>
<tr>
<td>Nichol, 2008 (N= 756)</td>
<td>0.42</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Overall effect</strong></td>
<td>0.55</td>
</tr>
</tbody>
</table>

Site of Action of Oral Anticoagulants: VKA

Site of Action of Oral Anticoagulants: NOACs

## Comparison of Features of New Oral Anticoagulants in Advanced Stages of Development

<table>
<thead>
<tr>
<th>Features</th>
<th>Rivaroxaban</th>
<th>Apixaban</th>
<th>Dabigatran Etexilate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>Xa</td>
<td>Xa</td>
<td>IIa</td>
</tr>
<tr>
<td>Molecular Weight</td>
<td>436</td>
<td>460</td>
<td>628</td>
</tr>
<tr>
<td>Prodrug</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bioavailability (%)</td>
<td>80</td>
<td>50</td>
<td>6</td>
</tr>
<tr>
<td>Time to peak (h)</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>9</td>
<td>9-14</td>
<td>12-17</td>
</tr>
<tr>
<td>Renal excretion (%)</td>
<td>65</td>
<td>25</td>
<td>80</td>
</tr>
<tr>
<td>Antidote</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>
Shared properties of the NOAC’s

- Rapid onset & offset of action
- Predictable and consistent anticoagulant effects
- No requirement for routine coagulation monitoring
- Low potential for drug–drug interactions, no drug–food interactions
Trials of novel oral anticoagulants for stroke prevention

<table>
<thead>
<tr>
<th>RE-LY</th>
<th>ROCKET-AF</th>
<th>ARISTOTLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Dabigatran</td>
<td>• Rivaroxaban</td>
<td>• Apixaban</td>
</tr>
<tr>
<td>• ~18 000 pts</td>
<td>• ~14 000 pts</td>
<td>• ~18 000 pts</td>
</tr>
<tr>
<td>• PROBE design</td>
<td>• Double blind</td>
<td>• Double blind</td>
</tr>
<tr>
<td>• Mean CHADS$_2$ 2.1</td>
<td>• Mean CHADS$_2$ 3.5</td>
<td>• Mean CHADS$_2$ 2.1</td>
</tr>
<tr>
<td>• Stroke or systemic embolism</td>
<td>• Stroke or systemic embolism</td>
<td>• Stroke or systemic embolism</td>
</tr>
<tr>
<td>• Major bleeding</td>
<td>• Major and non-major clinically relevant bleeding</td>
<td>• Major bleeding</td>
</tr>
</tbody>
</table>

Primary outcome (stroke or systemic embolism) of recent SPAF trials

Not head to head comparison – For illustrative purposes only

P Value

Dabigatran 110 mg BID  
\[ P = 0.34 \]

Dabigatran 150 mg BID  
\[ P < 0.001 \]

Rivaroxaban 20 mg QD  
\[ P = 0.12 \]

Apixaban 5 mg BID  
\[ P = 0.01 \]
Ischaemic stroke in recent SPAF trials

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose</th>
<th>Comparison</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran</td>
<td>110 mg BID</td>
<td>New Agent Better</td>
<td>0.50 (0.75, 1.00)</td>
<td>P = 0.35</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150 mg BID</td>
<td>New Agent Better</td>
<td>0.50 (0.75, 1.00)</td>
<td>P = 0.03</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>20 mg QD</td>
<td>New Agent Better</td>
<td>0.50 (0.75, 1.00)</td>
<td>P = 0.58</td>
</tr>
<tr>
<td>Apixaban</td>
<td>5 mg BID</td>
<td>New Agent Better</td>
<td>0.50 (0.75, 1.00)</td>
<td>P = 0.42</td>
</tr>
</tbody>
</table>

Not head to head comparison – For illustrative purposes only
Major bleeding in recent SPAF trials

Dabigatran 110 mg BID

Dabigatran 150 mg BID

Rivaroxaban 20 mg QD

Apixaban 5 mg BID

$P$ Value

$P = 0.003$

$P = 0.31$

$P = 0.58$

$P < 0.001$

Not head to head comparison – For illustrative purposes only
Haemorrhagic stroke in recent SPAF trials

- **Dabigatran 110 mg BID**: $P < 0.001$
- **Dabigatran 150 mg BID**: $P < 0.001$
- **Rivaroxaban 20 mg QD**: $P = 0.02$
- **Apixaban 5 mg BID**: $P < 0.001$

Not head to head comparison – For illustrative purposes only

AVERROES Design

- 36 countries, 522 centres

AF and ≥1 risk factor, and demonstrated or expected unsuitable for VKA

- Apixaban 5 mg BID
  - 2.5 mg BID in selected patients

- 5,600 patients

- Double-Blind

- ASA (81-324 mg/d)

Primary Outcome: Stroke or Systemic Embolic Event (SEE)
Major Bleeding

RR = 1.14
95% CI = 0.74-1.75
P = 0.56

Cumulative Risk

No. at Risk
ASA 2791 2744 2572 2152 1570 642 340
Apix 2809 2763 2567 2123 1521 622 357
Permanent Discontinuation of Study Medication

Cumulative Risk

RR = 0.88
95% CI = 0.78-1.00
P = 0.04

No. at Risk

<table>
<thead>
<tr>
<th>Months</th>
<th>ASA</th>
<th>Apix</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2791</td>
<td>2809</td>
</tr>
<tr>
<td>3</td>
<td>2567</td>
<td>2624</td>
</tr>
<tr>
<td>6</td>
<td>2325</td>
<td>2356</td>
</tr>
<tr>
<td>9</td>
<td>1906</td>
<td>1909</td>
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<tr>
<td>12</td>
<td>1365</td>
<td>1328</td>
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<tr>
<td>18</td>
<td>534</td>
<td>521</td>
</tr>
<tr>
<td>21</td>
<td>266</td>
<td>299</td>
</tr>
</tbody>
</table>
Percutaneous LAA Occlusion

The WATCHMAN® Device

From Clinical Trial results to availability of new medication

• TGA approval
  – Efficacy and safety of the new medication

• PBAC approval
  – Is the new medication better than what is currently standard of care?
  – Is it cost effective and represents value for money to Australian public?
Dabigatran: a sorry tale

- RELY study published August 2009, approx. $600 million to conduct
- TGA approval 2010
- PBAC recommendation for funding March 2011
- Pradaxa approved and available NZ, USA, UK, Canada, Brazil and Europe
Dabigatran:

- Government commissions
  - “Review of Anticoagulation in Australia”

- PBAC recommends funding 2\textsuperscript{nd} time Aug 2012

- Report released late 2012
  - “if quality of anticoagulation with warfarin could be improved we would not need these new expensive and possibly dangerous drugs”
**Dabigatran:**

- Minister for Health issues press statement expressing concerns about safety of the new drugs, despite FDA, NZ and European regulators publishing data that new agents safer than warfarin if used in right patients

- Instructs TGA and PBAC to review their recommendations

- TGA confirms efficacy and safety of all NOACs and PBAC recommends funding for 3rd time March 2013, as well as for apixaban and rivaroxaban (1\textsuperscript{st} time)
Dabigatran:

- Available in August 2013 ????
  - Authority?
  - Specialist initiation, GP continuation?
  - Only for warfarin failures?
Issues with this Process:

• Ministerial interference with the independent role of the TGA and PBAC

• What is the role of TGA and PBAC if recommendations ignored and new reports are commissioned when Minister doesn't like advice?

• Uncertainty in drug approval process –
  – Expensive - $200-300,000 to submit
  – Slow and non-transparent
Trends of Numbers of Clinical Trials in Australia 1998-2011

TGA website 2012
Costs of Running Clinical Trials in Australia: KPMG report

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>India</td>
<td>$2607</td>
</tr>
<tr>
<td>China</td>
<td>$2981</td>
</tr>
<tr>
<td>Mexico</td>
<td>$3386</td>
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<tr>
<td>Russia</td>
<td>$3550</td>
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<tr>
<td>France</td>
<td>$4488</td>
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<td>Canada</td>
<td>$4980</td>
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<tr>
<td>Brazil</td>
<td>$5622</td>
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<tr>
<td>US</td>
<td>$5650</td>
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<td>Italy</td>
<td>$6045</td>
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<tr>
<td>Germany</td>
<td>$6075</td>
</tr>
<tr>
<td>Australia</td>
<td>$6389</td>
</tr>
<tr>
<td>Japan</td>
<td>$7432</td>
</tr>
</tbody>
</table>

Source: KPMG
CLINICALLY COMPETITIVE:
BOOSTING THE BUSINESS OF
CLINICAL TRIALS IN AUSTRALIA

CLINICAL TRIALS ACTION GROUP REPORT
Antiplatelet therapy in ACS

Stroke prevention in AF

Resistant HT

TAVI for AS in the elderly
World’s #1 Killer: High Blood Pressure and Its Consequences

Number of deaths (000s)

WHO Health Report 2002
CHD deaths due to various risk factors in Australia

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>% of total deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High blood pressure</strong></td>
<td>24</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>21</td>
</tr>
<tr>
<td><strong>High blood cholesterol</strong></td>
<td>20</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>8</td>
</tr>
<tr>
<td>Excess body weight</td>
<td>7</td>
</tr>
</tbody>
</table>

First Choice
ACE inhibitor or angiotensin II receptor antagonist
OR
Calcium channel blocker
OR
Low-dose thiazide diuretic (consider for people aged ≥65 years only)

If target BP not reached
ACE inhibitor or angiotensin II receptor antagonist + calcium channel blocker
OR
ACE inhibitor or angiotensin II receptor antagonist + low-dose thiazide diuretic

If target BP not reached
ACE inhibitor or angiotensin II receptor antagonist + calcium channel blocker + low-dose thiazide diuretic

If target BP not reached
Consider seeking specialist advice
Average Number of Antihypertensive Agents Needed per Patient to Achieve Target BP Goals

Trial/ SBP Achieved

INVEST (136 mm Hg)
CONVINCE (137 mm Hg)
ALLHAT (138 mm Hg)
IDNT (138 mm Hg)
RENAAL (141 mm Hg)
UKPDS (144 mm Hg)
ABCD (132 mm Hg)
MDRD (132 mm Hg)
HOT (138 mm Hg)
AASK (128 mm Hg)

Combination Therapy

Based on the best available evidence, the most effective combination is:

- ACE inhibitor
- Angiotension II receptor antagonist*
- OR
- PLUS
- Calcium channel blocker

*(particular role in the presence of diabetes or lipid abnormalities)*

* ACE inhibitors and angiotensin II receptor antagonists have been shown to be equally efficacious in prevention of combined end points of cardiovascular disease death, myocardial infarction, stroke and heart failure admissions in patients at high risk due to past cardiovascular events.
NHF: Initiating antihypertensive therapy

First Choice
ACE inhibitor or angiotensin II receptor antagonist
OR
Calcium channel blocker
OR
Low-dose thiazide diuretic (consider for people aged ≥65 years only)

If target BP not reached
ACE inhibitor or angiotensin II receptor antagonist + calcium channel blocker
OR
ACE inhibitor or angiotensin II receptor antagonist + low-dose thiazide diuretic

If target BP not reached
ACE inhibitor or angiotensin II receptor antagonist + calcium channel blocker + low-dose thiazide diuretic

If target BP not reached
Consider seeking specialist advice

Where to from here?

- Standard beta-blockers –
  - Be wary of bradycardia with moxonidine

- Verapamil or Diltiazem – if not on dihydropyrididine

  Spironolactone – aldosterone antagonist
  - Hyperkalemia
Where to from here?

- **Alpha Methyl Dopa** – central sympatholytic
- **Prazosin** – alpha blocker
- **Labetolol** (70% alpha, 30% beta blocker)

  - Beware of postural hypotension with all, hemolytic anemia (aldomet) and hepatotoxicity (labetolol)
Where to from here?

• Hydrallazine – vasodilator (SLE)

• Minoxidil – vasodilator (oedema)

• Renal Sympathetic Nerve Ablation
The Renal Nerves

...follow the renal artery to the kidney

...primarily within the adventitia
Anatomical Location of Renal Sympathetic Nerves

- Arise from T10-L1
- Follow the renal artery to the kidney
- Primarily lie within the adventitia
Treatment by Renal RF Catheter
Selective Renal Denervation: the ARDIAN® procedure

Focal ablations spaced along vessel

Multiple focal ablations ↑ circumferential coverage
Key Inclusion Criteria

- Office SBP ≥160 mmHg despite 3+ anti-hypertensive medications (including diuretic), or confirmed intolerance to medications
- eGFR (MDRD formula) of ≥ 45 mL/min/1.73m²

Key Exclusion Criteria

- Type I diabetes mellitus
- Hemodynamically significant valvular disease
- Currently taking clonidine, moxonidine, or rilmenidine
- Renovascular abnormalities: significant renal artery stenosis, prior renal stenting or angioplasty, dual renal arteries
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients Undergoing Procedure (N=45)</th>
<th>Patients Anatomically Ineligible for Procedure (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>58 ± 9</td>
<td>51 ± 8</td>
</tr>
<tr>
<td><strong>Gender (% female)</strong></td>
<td>44</td>
<td>20</td>
</tr>
<tr>
<td><strong>Race (% non-Caucasian)</strong></td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Diabetes Mellitus II (%)</strong></td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td><strong>CAD (%)</strong></td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td><strong>Heart Rate (bpm)</strong></td>
<td>72 ± 11</td>
<td>79 ± 9</td>
</tr>
<tr>
<td><strong>eGFR (mL/min/1.73m²)</strong></td>
<td>81 ± 23</td>
<td>95 ± 15</td>
</tr>
<tr>
<td><strong>BP (mmHg)</strong></td>
<td>177/101 ± 20/15</td>
<td>173/98 ± 8/9</td>
</tr>
</tbody>
</table>
## Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patients Undergoing Procedure (N=45)</th>
<th>Patients Anatomically Ineligible for Procedure (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of anti-HTN meds (mean)</td>
<td>4.7 ± 1.5</td>
<td>4.6 ± 0.5</td>
</tr>
<tr>
<td>ACE/ARB (%)</td>
<td>96</td>
<td>80</td>
</tr>
<tr>
<td>Beta-blocker (%)</td>
<td>76</td>
<td>100</td>
</tr>
<tr>
<td>Calcium channel blocker (%)</td>
<td>69</td>
<td>100</td>
</tr>
<tr>
<td>Vasodilator (%)</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Diuretic (%)</td>
<td>96</td>
<td>60</td>
</tr>
</tbody>
</table>
Office BP: All Treated Patients

Change in Blood Pressure (mmHg)

-14 -10
-21 -10
-22 -11
-24 -11
-27 -17

1 month (n=41) 3 months (n=39) 6 months (n=26) 9 months (n=20) 12 months (n=9)

n=45
Renal function

**eGFR (ml/min/1.73m²)**

- Pre-Procedures: 79
- 6-Mths Post Procedure: 83

**Δ eGFR (%)**

- ↓ by ≥ 20%: 4
- No change: 72
- ↑ by ≥ 20%: 24
RDN – Encouraging Results in Controlled setting

### Graph 1: Symplicity HTN-1 BL 176/98 mm Hg

- **Systolic Blood Pressure (SBP):**
  - 3 mo: -21 mmHg
  - 6 mo: -22 mmHg
  - 12 mo: -27 mmHg
  - 24 mo: -29 mmHg
  - 36 mo: -31 mmHg
- **Diastolic Blood Pressure (DBP):**
  - 3 mo: -10 mmHg
  - 6 mo: -10 mmHg
  - 12 mo: -14 mmHg
  - 24 mo: -14 mmHg
  - 36 mo: -16 mmHg

**Time Points:**
- 3 mo
- 6 mo
- 12 mo
- 24 mo
- 36 mo

**Sample Size:**
- 3 mo: 148
- 6 mo: 144
- 12 mo: 132
- 24 mo: 105
- 36 mo: 34

### Graph 2: Symplicity HTN-2 BL 178/97 mm Hg

- **Systolic Blood Pressure (SBP):**
  - 3 mo: -24 mmHg
  - 6 mo: -32 mmHg
  - 12 mo: -28 mmHg
  - 24 mo: -29 mmHg
  - 30 mo: -35 mmHg
- **Diastolic Blood Pressure (DBP):**
  - 3 mo: -8 mmHg
  - 6 mo: -12 mmHg
  - 12 mo: -10 mmHg
  - 24 mo: -10 mmHg
  - 30 mo: -13 mmHg

**Time Points:**
- 3 mo
- 6 mo
- 12 mo
- 24 mo
- 30 mo

**Sample Size:**
- 3 mo: 49
- 6 mo: 49
- 12 mo: 47
- 24 mo: 40
- 30 mo: 37

*P<0.01 for Δ from BL for all time points

Per Protocol, stable anti-HTN drug regimen through 6 months.

Symplicity HTN-2: 2 week compliance check prior to randomization and primary endpoint.
# SYMPLECTICITY RDN Global Clinical Program

## Enrollment Complete / In Follow Up

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Duration</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symplicity HTN-1</td>
<td>Series of non-randomized pilot studies (n=153)</td>
<td>3 yr</td>
<td>Europe</td>
</tr>
<tr>
<td>Symplicity HTN-2</td>
<td>1:1 Randomization Symplicity Catheter System vs control (n=106)</td>
<td>2 yr</td>
<td>Europe</td>
</tr>
</tbody>
</table>

~5900 Subjects

## Planning / Enrolling

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Sites</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symplicity HTN-3</td>
<td>Randomized Controlled Trial (2:1), (530 randomized)</td>
<td>328</td>
<td>USA</td>
</tr>
<tr>
<td>SYMPLECTICITY-HF</td>
<td>Feasibility Study, 40 subjects</td>
<td></td>
<td>UK, Europe</td>
</tr>
<tr>
<td>Global SYMPLECTICITY Registry</td>
<td>Prospective, non-interventional Registry, “5,000 subjects”</td>
<td></td>
<td>Asia, Europe</td>
</tr>
<tr>
<td>SYMPLECTICITY HTN-Japan</td>
<td>Randomized Controlled Trial (1:1) n=100</td>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td>SYMPLECTICITY HTN-4</td>
<td>Randomized Controlled Trial</td>
<td></td>
<td>USA, Japan</td>
</tr>
<tr>
<td>Symplicity HTN-India</td>
<td>Single-arm Study</td>
<td></td>
<td>India</td>
</tr>
</tbody>
</table>
Global SYMPLICITY Registry

Consecutive patients treated in real world population ~ 5000 patients

- GREAT Registry N=1000
- Korea Registry* N=102
- South Africa Registry* N=400
- Canada and Mexico*
- Rest of GSR N~3500

~ 200 sites International
Min. 10% randomly assigned to 100% monitoring
30% monitoring to date

Follow-up schedule
- 3mo
- 6mo
- 12mo
- 2yr
- 3yr
- 4yr
- 5yr

*: limited to resistant hypertension only
Baseline Patient Characteristics N=617

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60 ± 13</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>63%</td>
</tr>
<tr>
<td>Race (% caucasian)</td>
<td>87.5%</td>
</tr>
<tr>
<td>BMI</td>
<td>30 ± 5.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Co-Morbidities</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus II</td>
<td>38%</td>
</tr>
<tr>
<td>History of Cardiac Disease (%)</td>
<td>49%</td>
</tr>
<tr>
<td>eGFR (ml/min/1.73 m²) n=578</td>
<td>80 ± 53.1</td>
</tr>
<tr>
<td>eGFR &gt; 45 ml/min/1.73 m²</td>
<td>96%</td>
</tr>
<tr>
<td>Serum Creatinine (mg/dl) n=227</td>
<td>1.2 ± 1.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood Pressure</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BP (mm Hg)</td>
<td>164/89 ± 23/16</td>
</tr>
<tr>
<td>Number of classes anti-HTN meds (mean)</td>
<td>4.35 ± 1.34</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic (%)</td>
<td>77%</td>
</tr>
<tr>
<td>Aldosterone blocker (%)</td>
<td>19%</td>
</tr>
<tr>
<td>ACE (%)</td>
<td>33%</td>
</tr>
<tr>
<td>ARB (%)</td>
<td>67%</td>
</tr>
<tr>
<td>Beta-Blocker (%)</td>
<td>79%</td>
</tr>
<tr>
<td>Calcium Channel Blocker (%)</td>
<td>74%</td>
</tr>
<tr>
<td>Alpha adrenergic Blocker (%)</td>
<td>34%</td>
</tr>
<tr>
<td>Vasodilator (%)</td>
<td>14%</td>
</tr>
<tr>
<td>Direct Renin Inhibitor (%)</td>
<td>9%</td>
</tr>
</tbody>
</table>
Change in Office BP According to Baseline Measurement

- **3 Months**
  - SBP: -13, -17, -28
  - DBP: -6, -8, -9
- **6 Months**
  - SBP: -15, -18, -16
  - DBP: -8, -9, -30 (≥ 180 mm Hg, 6 mo)

* ≥ 150 mm Hg in Type II Diabetes

**P < 0.001 for all values compared to baseline except:**
- p = 0.0002 (SBP ≥ 180 mm Hg, 6 mo)
- p = 0.0008 (DBP ≥ 180 mm Hg, 6 mo)
Change in ABPM According to Baseline Measurement

3 Months

-8
-10
-13

-22

≥ 140
n=104

≥ 160/150*
≥ 180
n=76
n=10

6 Months

-11
-11

-13
-19

≥ 140
n=34

≥ 160/150*
≥ 180
n=30
n=5

* ≥ 150 mm Hg in Type II Diabetes
Conclusions

- Preliminary data demonstrates excellent procedural and clinical safety profile of renal denervation in a real world population
- Majority of patients treated resemble current consensus statements
- Early look at clinical data shows RDN has a significant reduction in both Office and Ambulatory BP compared to baseline
- Enrolment and analyses continue to meet goal of establishing procedure safety and efficacy of the Symplicity Flex™ catheter
Antiplatelet therapy in ACS

Stroke prevention in AF

Resistant HT

TAVI for AS in the elderly
Natural History of Aortic Stenosis (AS)

- 740 pts with severe AS
- AVA $\leq 0.8$ cm$^2$
- 451 had non surgical treatment
- Mean age: 75 ± 13 yrs
- LVEF $\leq 40\%$: 33%
- CHF: 42%

Mortality (%)

- 1 year: 38%
- 5 years follow-up: 68%
- 10 years: 82%

ACC/AHA recommendations for AVR

- **Class I**
  - Symptomatic severe AS
  - Asymptomatic severe AS undergoing CABG
  - Severe AS undergoing surgery of the aorta or other valves
  - Severe AS and LV dysfunction (EF<50%)

- **Class IIa**
  - Moderate AS and patients undergoing CABG

J Am Coll Cardiol 2008;52:e1-e142
Operative Mortality for AVR

- AVR in octogenarians
  - 220 pts
  - Op mortality 13% if AVR
  - Op mortality 24% if AVR + CABG
  - Morbidity 60%
  - Survival 85%, 80%, 73% (1,3,5 yrs)

- Benefits of AVR in octogenarians
  - 81% no/mild disability for daily activities
  - 93% feel less disabled
  - 93% reassured to have access to treatment despite their age

<table>
<thead>
<tr>
<th></th>
<th>STS2001 (%)</th>
<th>UKCSR 1999-2001 (%)</th>
<th>EHS 2001 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>3.7</td>
<td>3.1</td>
<td>2.7</td>
</tr>
<tr>
<td>AVR + CABG</td>
<td>6.3</td>
<td>7</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Many patients are not surgically treated!

Severe AS* - Percent of Patients Treated

- Charlson 2006: 60% untreated, 40% surgically treated
- Pellikka 2005: 30% untreated, 70% surgically treated
- Lung 2004: 32% untreated, 68% surgically treated
- Bouma 1999: 41% untreated, 59% surgically treated

*AS: Aortic Stenosis

References:
- J Heart Valve Dis 2006;15:312-321
- Circulation 2005
- European Heart Journal 2003;24:1231-1243
- Heart 1999;82:143-148
1993: Andersen

- First description of valve sutured in stent
- Animal model
- Encountered 2 major limitations
  - Removal of the native valve
  - Obstruction of coronary ostia
Transcatheter Aortic Valve Implantation (TAVI)

- Placement of a prosthetic valve mounted inside stent/frame in the aortic valve position via a transarterial (retrograde) or transapical (antegrade) approach.

CoreValve Revalving system

Edwards SAPIEN valve
CoreValve
Patient Evaluation

- **Multidisciplinary approach**
  - Cardiac Surgery
  - Cardiology

- **Valvular Heart Disease Clinic**
  - Patients are seen simultaneously by surgeons and cardiologists to assess:
    - Operative candidacy
    - Symptom severity
    - Frailty
    - Patient interest
    - Is aortic valve replacement going to improve their quality of life?
PARTNER Study Design

Symptomatic Severe Aortic Stenosis

ASSESSMENT: High-Risk AVR Candidate
3,105 Total Patients Screened

Total = 1,057 patients
2 Parallel Trials: Individually Powered

n = 699
High-Risk

ASSESSMENT: Transfemoral Access

High-Risk TF
High-Risk TA

1:1 Randomization
1:1 Randomization

TF TAVR VS AVR
TA TAVR VS AVR

Primary Endpoint: All-Cause Mortality (1 yr) (Non-inferiority)

n = 358
Inoperable

ASSESSMENT: Transfemoral Access

1:1 Randomization

TF TAVR n = 179 VS Standard Therapy n = 179

Primary Endpoint: All-Cause Mortality Over Length of Trial (Superiority)
All Cause Mortality (ITT) Crossover Patients Followed

All Cause Mortality (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Standard Rx</th>
<th>TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>179</td>
<td>179</td>
</tr>
<tr>
<td>6</td>
<td>138</td>
<td>121</td>
</tr>
<tr>
<td>12</td>
<td>124</td>
<td>85</td>
</tr>
<tr>
<td>18</td>
<td>110</td>
<td>67</td>
</tr>
<tr>
<td>24</td>
<td>83</td>
<td>51</td>
</tr>
</tbody>
</table>

**Numbers at Risk**

- **TAVR**: 179, 138, 124, 110, 83
- **Standard Rx**: 179, 121, 85, 67, 51

**HR [95% CI]** = 0.57 [0.44, 0.75]

p (log rank) < 0.0001

Δ at 1 yr = 20.0%
NNT = 5.0 pts

Δ at 2 yr = 24.3%
NNT = 4.1 pts
NYHA Class Over Time
Survivors

Treatment Visit

Baseline

1 Year

2 Year

TAVR

Standard Rx

p = 0.61

p < 0.0001

p < 0.0001

Percent

100%

80%

60%

40%

20%

0%

92.2%

23.7%

16.9%

93.9%

60.8%

57.5%

NYHA Class

IV

III

II

I

Survivors

119
All Strokes (%)

Note: Percents are of patients in the trial (n/179).

<table>
<thead>
<tr>
<th></th>
<th>≤ 30 Days</th>
<th>31 Days – 2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Stroke</strong></td>
<td>p = 0.010</td>
<td>P = 0.319</td>
</tr>
<tr>
<td>Ischemic Stroke</td>
<td>p = 0.017</td>
<td>p = 0.437</td>
</tr>
<tr>
<td>Hemorrhagic Stroke</td>
<td>p = 0.316</td>
<td>p = 0.160</td>
</tr>
</tbody>
</table>
Mortality or Stroke (ITT)

HR [95% CI] = 0.64 [0.49, 0.84]

p (log rank) = 0.0009

∆ at 1 yr = 16.1%
NNT = 6.2 pts

∆ at 2 yr = 21.9%
NNT = 4.6 pts

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>Standard Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td>179</td>
<td>118</td>
</tr>
<tr>
<td></td>
<td>128</td>
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</tr>
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<td>116</td>
<td>62</td>
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<td>105</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>
Staged or Combined PCI With TAVR

30-day mortality in published studies (43,57,60,61) including patients undergoing staged or combined percutaneous coronary intervention (PCI) with transcatheter aortic valve replacement (TAVR).
Unanswered Questions

- What is the in vivo durability?

- Which institutions should be qualified to perform TAVI if it is marketed?

- Should younger patients receive a surgical bioprosthesis in order to avoid long term use of oral anticoagulation, planning that they may receive a TAVI for prosthesis degeneration?

- Will there be a use of catheter valve implantation in lower risk population?
My Predictions:

Ticagrelor will replace clopidogrel as the 2\textsuperscript{nd} antiplatelet agent in ACS

NOAC’s will replace warfarin for stroke prevention in NVAF

RSNA will become a standard Rx for HT

TAVI will become routine Rx for severe AS in the elderly