Arterial Revascularization Trial (ART)
Randomized comparison of single versus bilateral internal mammary artery grafting in 3102 patients: Effects on major cardiovascular outcomes after five years of follow up

AHA 2016

David P Taggart MD(Hons),PhD,FRCS,FESC
Professor of Cardiovascular Surgery
University of Oxford, UK

for the Arterial Revascularization Trial Investigators
(No conflicts declared)
Background: What We Already Know

1. Coronary artery bypass grafting (CABG) is highly effective for the symptomatic and/or prognostic management of multi-vessel and left main coronary artery disease (SYNTAX, CORONARY, PRECOMBAT, BEST, EXCEL, NOBLE: 2013-2016)

2. Over 1 million CABG performed worldwide each year; standard operation is CABG x 3 (using 1 internal mammary artery (IMA) and 2 vein grafts)

3. Strong angiographic evidence of increasing failure of vein grafts with time (due to progressive atherosclerosis) that accelerates after 5 years

4. Strong angiographic evidence that internal mammary (thoracic) arteries (IMA) have excellent long term patency rates (> 90% at 20 years)

5. Left IMA (LIMA) is established as the standard of care for grafting the left anterior descending (LAD) coronary artery during CABG

6. Numerous observational studies have estimated a 20% reduction in mortality with bilateral versus single IMA grafts over the long-term

7. Low use of bilateral IMA (<10% in Europe, <5% in USA) due to 3 concerns
   (i) increased technical complexity,
   (ii) potentially increased mortality and morbidity,
   (iii) lack of evidence from RCTs
In current practice of > 1 million CABG per year > 80% of all grafts are SVG

While some contemporary studies show superior vein graft patency the largest current angiographic study (PREVENT IV) show similar patency rates
The right internal thoracic artery: is it underutilized?

James Tatoulis\textsuperscript{a,c}, Brian F. Buxton\textsuperscript{b,c} and John A. Fuller\textsuperscript{b} [2011]

(a) Patency (%)

- LITA–LAD $n = 1965$
- RITA–LAD $n = 149$

LITA: 1273, 626
RITA: 116, 57

Years post-op: 0 1 2 3 4 5 6 7 8 9 10

Patency (%)

98.4% 97.8% 96.5% 94.6%

(b) Patency (%)

- LITA–Cx $n = 292$
- RITA–Cx $n = 436$

LITA: 211, 93
RITA: 291, 138

Years post-op: 0 1 2 3 4 5 6 7 8 9 10

Patency (%)

90.5% 96.4% 96.1% 88.6%

20 years
15,583 patients followed for a mean of >9 years

<10% of CABG in Europe and <5% in USA use BIMA !!!

> 60% in several Asian countries
Randomized comparison of Left IMA (plus vein grafts) versus Bilateral IMA (plus vein grafts) grafting on:

- All-cause mortality at ten years (primary outcome in 2018)
- All-cause mortality at five years (interim outcome)
- Sternal wound complications
- Mortality, myocardial infarction and stroke at five and ten years (secondary outcomes)
Sample Size

• **Estimate**: that at 10 years, bilateral IMA grafting will result in an absolute 5% reduction in mortality (i.e. from 25% to 20%) compared with single IMA grafting

• **Confirm**: with 90% power at the 5% significance level requires 2928 patients

• **Aim**: to enrol >3000 patients (1500 in each arm) over a 2- to 3-year recruitment period
Eligibility

INCLUSION:
✓ Patients with multi-vessel coronary artery disease scheduled for CABG on symptomatic and/or prognostic grounds
✓ Urgent cases for acute coronary syndrome (not evolving MI)
✓ CABG could be performed “on-pump or off-pump”

EXCLUSION:
✗ Patients with evolving myocardial infarction
✗ Patients requiring single graft
✗ Patients requiring concomitant valve surgery
✗ Patients requiring redo CABG
Results

- Enrolment from June 2004 to December 2007
- 28 cardiac surgery centres
- 7 countries (UK, Poland, Australia, Brazil, India, Italy, Austria)
- 3102 patients in total
- 1554 patients randomized to single and 1548 to bilateral IMA
- At 5 years high use of guideline based medical therapy: aspirin (89%), statins (89%), ACE-inhibitor or Angiotensin receptor blockers (73%), beta blockers (75%)

(Much higher than other contemporary PCI vs CABG trials)
**Patient flow**

Total randomized =3102

**Single IMA graft group n=1554**
- 1546 received CABG (99.5%)
  - Single IMA graft n=1494
  - Bilateral IMA graft n=38 [2.4%]
  - Other n=14
  - No surgery n=8
    (death, cancelled surgery, PCI withdrawals)

At five years
- 129 died
- 62 lost to follow-up [4%]
  (mean 3 years follow-up)
- 9 withdrew
- Known to be alive n=1349

**Bilateral IMA graft group n= 1548**
- 1531 received CABG (98.9%)
  - Bilateral IMA graft n=1294
  - Single IMA graft n=215 [14%]
  - Other n=22
  - No surgery n=16
    (death, cancelled surgery, PCI withdrawals)

At five years
- 133 Died
- 71 lost to follow up [4.6%]
  (mean 3 years follow-up)
- 5 withdrew
- Known to be alive n= 1330
## Baseline Characteristics Well Matched

<table>
<thead>
<tr>
<th></th>
<th>Single graft (n=1554)</th>
<th>Bilateral graft (n=1548)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>86%</td>
<td>85%</td>
</tr>
<tr>
<td>Age mean (SD) years</td>
<td>64 (9)</td>
<td>64 (9)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>14 %</td>
<td>15 %</td>
</tr>
<tr>
<td>Systolic BP mean (SD) [mmHg]</td>
<td>132 (19)</td>
<td>132 (18)</td>
</tr>
<tr>
<td>Body Mass index mean (SD)</td>
<td>28 (4)</td>
<td>28 (4)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>92 %</td>
<td>92 %</td>
</tr>
<tr>
<td>South Asian</td>
<td>5 %</td>
<td>5 %</td>
</tr>
<tr>
<td>Insulin dependent diabetes</td>
<td>5 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Non insulin dependent diabetes</td>
<td>18 %</td>
<td>18 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>78 %</td>
<td>77 %</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>93 %</td>
<td>94 %</td>
</tr>
<tr>
<td>Peripheral arterial disease</td>
<td>8 %</td>
<td>7 %</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>3 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>44 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>16 %</td>
<td>16 %</td>
</tr>
<tr>
<td>NYHA class 1 and 2</td>
<td>79%</td>
<td>78%</td>
</tr>
<tr>
<td>CCS class 1-3</td>
<td>84%</td>
<td>84%</td>
</tr>
</tbody>
</table>
## Surgical Details, Post-operative Care and Length of Stay

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Single graft (n=1546)</th>
<th>Bilateral graft (n=1531)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Details of operation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>On pump</td>
<td>60 %</td>
<td>58 %</td>
</tr>
<tr>
<td>Off pump</td>
<td>40 %</td>
<td>42 %</td>
</tr>
<tr>
<td>Conversion to bypass</td>
<td>2 %</td>
<td>2 %</td>
</tr>
<tr>
<td><strong>CABG duration minutes mean (SD)</strong></td>
<td>199 (58)</td>
<td>222 (61)</td>
</tr>
<tr>
<td>Number of grafts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>18 %</td>
<td>18 %</td>
</tr>
<tr>
<td>3</td>
<td>49 %</td>
<td>50 %</td>
</tr>
<tr>
<td>4+</td>
<td>33 %</td>
<td>31 %</td>
</tr>
<tr>
<td>Cell saver</td>
<td>32 %</td>
<td>31 %</td>
</tr>
<tr>
<td>Aprotinin during surgery</td>
<td>24 %</td>
<td>24 %</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>12 %</td>
<td>12 %</td>
</tr>
<tr>
<td>Return to operating theatre</td>
<td>4 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Intra-aortic balloon pump use</td>
<td>4 %</td>
<td>4 %</td>
</tr>
<tr>
<td>Renal support therapy</td>
<td>4 %</td>
<td>6 %</td>
</tr>
<tr>
<td>Hospital stay Mean days (SD)</td>
<td>8 (8)</td>
<td>8 (7)</td>
</tr>
</tbody>
</table>
Randomized trial to compare bilateral vs. single internal mammary coronary artery bypass grafting: 1-year results of the Arterial Revascularisation Trial (ART)

David P. Taggart\textsuperscript{1*}, Douglas G. Altman\textsuperscript{2}, Alastair M. Gray\textsuperscript{3}, Belinda Lees\textsuperscript{4,5}, Fiona Nugara\textsuperscript{4}, Ly-Mee Yu\textsuperscript{2}, Helen Campbell\textsuperscript{3} and Marcus Flather\textsuperscript{4,5}, on behalf of the ART Investigators

- 3102 patients randomized to single or bilateral IMA grafts
- \textbf{primary outcome is 10 year survival (available 2018)}
- 67 surgeons, 28 centres, seven countries
- 30 day mortality 1.2\%, 1 \textit{yr} mortality 2.4\%
- 1 year incidence of stroke, MI, repeat revasc all < 2\%
- \times Sternal wound reconstruction: 0.6\% SIMA vs 1.9\% BIMA (NNH = 78)
All Cause Mortality at 5 years

CABG MORTALITY @ 5 YEARS in SYNTAX 9%; BEST 12%; NOBLE 9%; CORONARY 14%

All cause mortality (%)

Time from randomization (years)

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Single IMA</th>
<th>Bilateral IMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>5 years</td>
<td>5 years</td>
</tr>
<tr>
<td></td>
<td>1554</td>
<td>1548</td>
</tr>
<tr>
<td></td>
<td>1502</td>
<td>1496</td>
</tr>
<tr>
<td></td>
<td>1467</td>
<td>1468</td>
</tr>
<tr>
<td></td>
<td>1435</td>
<td>1425</td>
</tr>
<tr>
<td></td>
<td>1389</td>
<td>1370</td>
</tr>
<tr>
<td></td>
<td>1332</td>
<td>1321</td>
</tr>
</tbody>
</table>

Single IMA: 8.4%
Bilateral IMA: 8.7%
HR: 1.04 (0.81-1.32) p = 0.77

CABG MORTALITY @ 5 YEARS in SYNTAX 9%; BEST 12%; NOBLE 9%; CORONARY 14%
Death, Myocardial Infarction or Stroke at 5 years

Death / myocardial infarction / stroke (%)

Time from randomization (years)

Number at risk

Single IMA: 12.7%
Bilateral IMA: 12.2%
HR: 0.96 (0.79, 1.17) p=0.69

Arterial Revascularisation Trial
## Clinical Outcomes and Adverse Events

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Single graft (n=1554)</th>
<th>Bilateral graft (n=1548)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY: MORTALITY</td>
<td>130 (8.4%)</td>
<td>134 (8.7%)</td>
<td>1.04 (0.81, 1.32)</td>
<td>0.77</td>
</tr>
<tr>
<td>Composite – Death, myocardial infarction, stroke</td>
<td>198 (12.7%)</td>
<td>189 (12.2%)</td>
<td>0.96 (0.79, 1.17)</td>
<td>0.69</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>54 (3.5%)</td>
<td>52 (3.4%)</td>
<td>0.97 (0.66, 1.41)</td>
<td>0.86</td>
</tr>
<tr>
<td>Stroke</td>
<td>49 (3.2%)</td>
<td>38 (2.5%)</td>
<td>0.78 (0.51, 1.19)</td>
<td>0.24</td>
</tr>
<tr>
<td>ADVERSE EVENTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major Bleed</td>
<td>41 (2.6%)</td>
<td>48 (3.1%)</td>
<td>1.18 (0.78, 1.77)</td>
<td>0.44</td>
</tr>
<tr>
<td>Repeat Revascularisation</td>
<td>103 (6.6%)</td>
<td>101 (6.5%)</td>
<td>0.98 (0.76, 1.28)</td>
<td>0.91</td>
</tr>
<tr>
<td>Sternal wound complication</td>
<td>29 (1.9%)</td>
<td>54 (3.5%)</td>
<td>1.87 (1.20, 2.92)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sternal wound reconstruction</td>
<td>10 (0.6%)</td>
<td>29 (1.9%)</td>
<td>2.91 (1.42, 5.95)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Summary: Five Year Analysis of the ART

- Excellent 5 year outcomes for CABG in both groups
- Confirmation of safety of bilateral IMA grafts over medium term
- No significant differences in all cause mortality or composite of mortality, myocardial infarction or stroke
- No significant differences in major bleeds, need for repeat revascularization, angina status and quality-of-life measures (angina and QoL data not shown)
- Early excess of sternal wound reconstruction with bilateral IMA (1.9% vs 0.6%) mainly in Diabetes Mellitus with high BMI
- Differential non-adherence to randomization (4% SIMA to BIMA vs 14% BIMA to SIMA): ? Surgeon experience with BIMA
- Primary outcome is 10 year survival (available in 2018)
- Acknowledgements
Acknowledgements

- Presented on behalf of all investigators and patients participating in ART
- Trial Steering Committee: Peter Sleight, Doug Altman, Keith Channon, John Dark, Barbara Farrell, Marcus Flather, Alastair Gray, John Pepper, Rod Stables, David Taggart, Geza Vermez, Jeremy Pearson, Mark Pitman, Belinda Lees
- Data Monitoring Committee: Salim Yusuf, Stuart Pocock, Desmond Julian, Tom Treasure
- Funded by UK Medical Research Council, British Heart Foundation, National Institute of Health Research Efficacy and Mechanism Evaluation, sponsored by University of Oxford
- Design, conduct and analysis conducted independently of funding agencies and sponsor