Testing, Incidence and Outcomes in Kidney Transplant Candidates

Angela Webster angela.webster@sydney.edu.au
CORONARY ARTERY DISEASE IN TRANSPLANT CANDIDATES

• The transplant paradigm: wait listing and waiting
  • What the guidelines say
  • The evidence that underpins the guidelines
• Testing for coronary artery disease in kidney transplant candidates
  • Relative diagnostic performance of non-invasive tests
  • Relative prognostic performance of tests
• Incidence of cardiac events in ESKD and post-transplant
  • New data from Australia and New Zealand
• Mortality from cardiac events in ESKD and post-transplant
  • New data from Australia and New Zealand
• Summary of gaps in evidence and implications
• The CARSK trial
  • Design
  • Progress
Cardiovascular disease is the most common cause of death after kidney transplantation

Adjusted death rates in kidney transplant recipients per 100 patient years

Pilmore et al, Transplantation 2010
Current CAD screening evidence base is not strong

• Current clinical practice recommend two phases of testing:

(1) Before acceptance onto the waiting list
(2) Screening at regular intervals (every 1-2 years) after wait-listing
“Noninvasive stress testing” may be considered in kidney transplantation candidates with no active cardiac conditions based on the presence of multiple CAD risk factors regardless of functional status. Relevant risk factors among transplantation candidates include diabetes mellitus, prior cardiovascular disease, more than 1 year on dialysis, left ventricular hypertrophy, age greater than 60 years, smoking, hypertension, and dyslipidemia. The specific number of risk factors that should be used to prompt testing remains to be determined, but the committee considers 3 or more as reasonable” (Class IIb; Level of Evidence C).
Cardiac surveillance after listing for transplantation

- “The usefulness of periodically screening asymptomatic kidney transplantation candidates for myocardial ischemia while on the transplant waiting list to reduce the risk of MACE is uncertain”

- *(Class IIb; Level of Evidence C).*
Coronary revascularisation in insulin-dependent diabetic patients with chronic renal failure: data from 1992 (!)

26 IDDM randomised to medical therapy vs revascularization. 10/13 medical rx group had a cardiac endpoint versus 2/13 revascularisation group p <0.01.

THE LANCET
Coronary-Artery Revascularization before Elective Major Vascular Surgery


ABSTRACT

Ters, 510 (9 percent) were eligible for the study and were randomly assigned to either coronary-artery revascularization before surgery or no revascularization before surgery. The indications for a vascular operation were expanding abdominal aortic aneurysm or no revascularization before elective major vascular surgery. The primary end point was long-term mortality.

CONCLUSIONS

Coronary-artery revascularization before elective vascular surgery does not significantly alter the long-term outcome. On the basis of these data, a strategy of coronary-artery revascularization before elective vascular surgery among patients with stable cardiac symptoms cannot be recommended.
Perioperative Complications After Vascular Surgery Are Predicted by the Revised Cardiac Risk Index But Are Not Reduced in High-Risk Subsets With Preoperative Revascularization

Santiago Garcia, MD; Thomas B. Moritz, MS; Steven Goldman, MD; Fred Littooy, MD; Gordon Pierpont, MD; Greg C. Larsen, MD; Domenic J. Reda, PhD; Herbert B. Ward, MD, PhD; Edward O. McFalls, MD, PhD

Background—The Revised Cardiac Risk Index (RCRI) is useful for risk stratifying patients before noncardiac operations. Among patients with documented coronary artery disease who undergo vascular surgery, it is unclear whether preoperative revascularization reduces postoperative cardiac complications in high-risk subsets defined by the RCRI.

Methods and Results—The Coronary Artery Revascularization Prophylaxis Trial was a randomized, controlled trial that tested the long-term benefit of a preoperative coronary artery revascularization before elective vascular surgery. Using preoperative baseline characteristics to determine the RCRI, we tested the benefit of preoperative revascularization on death and nonfatal myocardial infarction in patients with multiple risks. Among 462 patients undergoing vascular surgery, there were 72 complications (15.6%) within 30 days post-surgery, including 15 deaths (3.2%) and 57 nonfatal myocardial infarctions (12.3%). The postoperative risk of death and nonfatal myocardial infarction after surgery increased according to the RCRI (odds ratio, 1.73; 95% CI, 1.26 to 2.38; P<0.001), with a rate of 1.6% in patients with no risk that increased to 23.4% in patients with ≥3 risks. Preoperative revascularization had no influence on the incidence of complications in any risk subset (odds ratio, 0.86; 95% CI, 0.50 to 1.49; P=0.60). Among those individuals with ≥2 risks who also demonstrated ischemia on a preoperative stress-imaging test (N=146), the incidence of events was 23% in patients with and without preoperative revascularization (P=0.95).

Conclusions—The risk of death and nonfatal myocardial infarction is accurately predicted by the RCRI in patients undergoing vascular surgery but is not reduced in any high-risk subset of the RCRI with preoperative coronary artery revascularization. (Circ Cardiovasc Qual Outcomes. 2009;2:73-77.)

Key Words: peripheral arterial disease ■ revascularization ■ outcomes
Characteristics of Patients Undergoing Cardiac Catheterization Before Noncardiac Surgery: A Report From the National Cardiovascular Data Registry CathPCI Registry

Joshua Schulman-Marcus, MD; Dmitry N. Feldman, MD; Sunil V. Rao, MD; Abhiram Prasad, MD; Lisa McCoy, MS; Kirk Garratt, MD; Luke K. Kim, MD; Robert M. Minutillo, MD; Shing-Chiu Wong, MD; Anil N. Vora, MD; Harshman S. Singh, MSc, MD; Daniel Wojchyla, MS; Amir Mohseni, MD; Geoffrey Bergman, MD; Rajesh V. Swaminathan, MD

CONCLUSIONS AND RELEVANCE In the largest contemporary US cohort reported to date, most patients undergoing diagnostic coronary catheterization before noncardiac surgery are asymptomatic. The discovery of obstructive coronary artery disease is common, and although randomized clinical trials have found no benefit in outcomes, revascularization is recommended in nearly half of these patients. The overall findings highlight management patterns in this population and the need for greater evidence-based guidelines and practices.
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CONCLUSIONS AND RELEVANCE: In the largest contemporary US cohort reported to date, most patients undergoing diagnostic catheterization before noncardiac surgery are asymptomatic. The discovery of obstructive coronary artery disease is common, and although randomized

Continuing Use of Prophylactic Percutaneous Coronary Intervention in Patients With Stable Coronary Artery Disease Despite Evidence of No Benefit
Déjà Vu All Over Again

David L. Brown, MD; Rita F. Redberg, MD, MSc
Current practice quite variable?

- **Prior to wait listing: CAD screening for (almost) all**
  - Non-invasive CAD screening: exercise test, myocardial perfusion scan or stress echo
  - Coronary angiogram
    - Positive non-invasive test
    - Strong clinical suspicion of IHD: previous AMI, CCF, diabetes and age >50yrs
- **Regular screening whilst on the wait list**
  - Annual for most, second yearly if deemed low risk (age<50, no DM, no PHx)
  - Non-invasive CAD screening: EST, Sestamibi or stress echo
- **Testing as deemed necessary if symptoms develop**
Potential harms from screening?

• May increase morbidity, mortality and cost by:
  • Exposing patients to risk of angiography including loss of residual renal function
  • Delaying access to transplantation and potential missed opportunities for a well matched graft
  • Inconvenience, pain, direct and indirect patient $
  • Psychological impact of asymptomatic disease
  • Cost of tests to healthcare sector
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Comparative accuracy of tests versus angiography for *diagnosis* of coronary artery disease

Original PICO:

- **P**: people being evaluated for kidney transplantation
- **I**: non invasive cardiac testing
- **C**: angiography
- **O**: significant CAD on angio (≥75% stenosis)

Wang et al. *Cochrane Database of Systematic Reviews* 2011, Issue 12 CD008691
for **diagnosis**

**Stress echo** most useful as triage test

<table>
<thead>
<tr>
<th>Test</th>
<th>Pre-test probability of coronary artery disease</th>
<th>Post-test Probability (%) after positive result</th>
<th>Post-test Probability (%) after negative result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine stress echocardiography</td>
<td>Low risk (10-29%)</td>
<td>42-72%</td>
<td>3-10%</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk (30-59%)</td>
<td>73-90%</td>
<td>10-27%</td>
</tr>
<tr>
<td></td>
<td>High risk (60-90%)</td>
<td>91-98%</td>
<td>28-70%</td>
</tr>
<tr>
<td>Myocardial perfusion scintigraphy</td>
<td>Low risk (10-29%)</td>
<td>24-54%</td>
<td>5-15%</td>
</tr>
<tr>
<td></td>
<td>Intermediate risk (30-59%)</td>
<td>55-81%</td>
<td>16-38%</td>
</tr>
<tr>
<td></td>
<td>High risk (60-90%)</td>
<td>81-96%</td>
<td>39-79%</td>
</tr>
</tbody>
</table>
How good are tests at predicting future cardiac events?

(P) people being evaluated for kidney transplantation
(I) any cardiac testing
(C) future cardiac events

(MACE defined cardiac death including stroke, MI, arrhythmia, pulmonary oedema)
How good are tests at predicting future cardiac events?

**All cause mortality**
- MPS: 0.07 [0.01, 0.16]
- DSE: 0.12 [0.06, 0.17]
- CA: 0.17 [0.07, 0.26]

**Cardiovascular mortality**
- MPS: 2.23 [1.38, 3.62]
- DSE: 4.24 [1.28, 14.09]
- CA: 3.00 [1.58, 5.78]

**MACE**
- MPS: 3.20 [1.96, 5.21]
- DSE: 4.62 [2.74, 7.79]
- CA: 2.83 [1.82, 4.42]

Relative risk of outcome, after positive test compared with negative test.
How good are tests at predicting future cardiac events?

Percentages of patients developing outcome of interest, stratified by test type and test result

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Test</th>
<th>Percentage of patients with abnormal test results who develop outcome during follow-up (per 100 tested, 95% CI)</th>
<th>Percentage of patients with normal test results who develop outcome during follow-up (per 100 tested, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>MPS studies</td>
<td>28.0 (14.8-41.2)</td>
<td>18.2 (11.5-25.0)</td>
</tr>
<tr>
<td></td>
<td>DSE studies</td>
<td>19.6 (0.08-39.0)</td>
<td>9.4 (0.0-20.6)</td>
</tr>
<tr>
<td></td>
<td>Coronary angiography studies</td>
<td>33.3 (21.8-44.7)</td>
<td>13.4 (7.7-19.0)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>MPS studies</td>
<td>11.2 (5.4-17.0)</td>
<td>4.4 (2.0-6.8)</td>
</tr>
<tr>
<td></td>
<td>DSE studies</td>
<td>16.4 (3.2-29.7)</td>
<td>4.5 (1.4-7.6)</td>
</tr>
<tr>
<td></td>
<td>Coronary angiography studies</td>
<td>24.9 (16.2-33.5)</td>
<td>4.1 (0.3-7.9)</td>
</tr>
<tr>
<td>Major adverse cardiac event</td>
<td>MPS studies</td>
<td>19.0 (12.3-25.6)</td>
<td>3.9 (2.1-5.6)</td>
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<tr>
<td></td>
<td>DSE studies</td>
<td>31.6 (17.7-45.5)</td>
<td>6.3 (4.2-8.4)</td>
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<tr>
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<td>Coronary angiography studies</td>
<td>32.2 (19.6-44.8)</td>
<td>8.5 (4.2-12.3)</td>
</tr>
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CENTRAL ILLUSTRATION: Cardiovascular Outcomes in Hemodialysis: Proportion of Trials Reporting Each Outcome (174 Trials, 26 Outcomes)

KDIGO

### Table 1: RCTs of BMS Versus DES With MACE as an Outcome

<table>
<thead>
<tr>
<th>Reference Year (Ref.)</th>
<th>Composite Event</th>
<th>Cardiac Death</th>
<th>MI</th>
<th>Q-Wave MI</th>
<th>ST</th>
<th>TLB</th>
<th>TVR</th>
<th>CABG (Emergent)</th>
<th>CABG (Stroke)</th>
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</thead>
<tbody>
<tr>
<td>Morice et al. 2002 (11)</td>
<td>RAVEL MACE, P</td>
<td>✓</td>
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<td>✓</td>
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</tr>
<tr>
<td>N Engl J Med</td>
<td>TAXUS-I MACE, P</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<td>Circulation</td>
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<td>Colombo et al. 2003 (13)</td>
<td>Circulation</td>
<td>SIRIUS MACE P &amp; S</td>
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<tr>
<td>Morice et al. 2002 (14)</td>
<td>J Am Coll Cardiol</td>
<td>E-SIRIUS MACE, S</td>
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<tr>
<td>N Engl J Med</td>
<td>SES-SMART MACE and CVA, S</td>
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<td>J Am Coll Cardiol</td>
<td>SCORE MACE, S</td>
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<tr>
<td>Kastratos et al. 2005 (22)</td>
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<td>Circulation</td>
<td>EUTICSTROKE MACE, S</td>
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<td>Circulation</td>
<td>DIABETES MACE, S</td>
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<tr>
<td>Fajadet et al. 2006 (26)</td>
<td>Circulation</td>
<td>ENDEAVOR-II Composite, S</td>
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<td>Suttorp et al. 2006 (27)</td>
<td>Circulation</td>
<td>PRISON-II MACE, S</td>
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<tr>
<td>Tawadros et al. 2006 (28)</td>
<td>Circulation</td>
<td>FUTURE-II MACE, S</td>
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<td>Vermeirssen et al. 2006 (29)</td>
<td>J Am Coll Cardiol</td>
<td>RIBS MACE, S</td>
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<td>✓</td>
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</tr>
</tbody>
</table>

**Legend:**
- **BASSET** = Balanced Outcomes Study Effort; **BMS** = bare metal stent; **CABG** = coronary artery bypass graft surgery; **COST** = cost-effectiveness; **DES** = drug-eluting stent; **E-SIRU** = European SIRU Stenting in Coronary Lesions; **EUTICSTROKE** = EUTIC Study of Circumflex Stenting and Small Metal Stents in Patients With Stable Multivessel Disease; **PRESTIM** = Prospective Randomized Evaluation of Stenting and Stenting in Coronary Lesions; **PRISON-I** = Prospective Randomized Evaluation of Stenting and Stenting in Coronary Lesions; **RIBS** = Randomized Invasive Versus Standard Treatment in Unprotected Sex; **SCORE** = Study to Compare Differences Between Quetelet and QuaDOS-QAD; **SES-STAT** = Semithoracic Stenting; **ST** = stent thrombosis; **TLB** = target lesion revascularization; **TVR** = target vessel revascularization; **w/ = within.
CO-SURF – hospitalisation for cardiac events in people with ESKD

• Data linkage study, NSW hospital admissions 2000-2010

• 10,700 people with ESKD (44,000 years of follow-up)
• 18% had at least 1 cardiac admission
• 2,000 received a transplant
• 11% had at least 1 cardiac admission

• Comparator: general population admissions over same period, adjusted for sex, age, calendar year

<table>
<thead>
<tr>
<th>ICD Code</th>
<th>Diagnosis</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>I20</td>
<td>Angina</td>
<td>37.1</td>
</tr>
<tr>
<td>I21</td>
<td>Acute MI</td>
<td>38.7</td>
</tr>
<tr>
<td>I22</td>
<td>Subsequent MI</td>
<td>0.05</td>
</tr>
<tr>
<td>I23</td>
<td>Complications post acute MI</td>
<td>0.05</td>
</tr>
<tr>
<td>I24</td>
<td>Other acute IHD</td>
<td>0.51</td>
</tr>
<tr>
<td>I25</td>
<td>Chronic IHD</td>
<td>23.6</td>
</tr>
<tr>
<td>I20-I25</td>
<td>AnyIHD</td>
<td>100</td>
</tr>
</tbody>
</table>
Incidence over time since starting dialysis – any cardiac admission
Relative risk of hospitalisation

Angina

Myocardial infarction
Some improvement for men over time, but not women
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Data linkage process
CELESTIAL STUDY

Australian & New Zealand Dialysis and Transplant Registry
(Kidney transplant recipients - 1st transplant 1980–2013)

Australian census data & cause of death general population (1980-2013)

Australian Institute Health & Welfare National Death Index
(fact of death, primary and associated causes)

New Zealand Ministry of Health Mortality Data Collection
(fact of death, primary and additional causes)

New Zealand census data & cause of death general population (1980-2012)

Linked data ICD-10 codes

KDIGO

UNPUBLISHED DATA. NOT FOR FURTHER DISSEMINATION
Results

• 17,628 transplant recipients (n=15,476 in Australia, n=2,152 in NZ)
• 936 cardiac deaths (n=838 in Australia, n=98 in NZ)
  • Ischaemic heart disease n=788 (84% cardiac deaths)
  • Valve disease n=48 (5%)
  • Cardiomyopathy n=44 (5%)
  • Heart failure n=35 (4%)
  • Arrhythmias n=30 (3%)
SMR for any cardiac death by age and gender
Cardiac = IHD, Valvular, Cardiomyopathy, Arrhythmic, Heart failure

UNPUBLISHED DATA. NOT FOR FURTHER DISSEMINATION
Ischaemic heart disease mortality rates and relative risk
Valve disease

KDIGO

UNPUBLISHED DATA. NOT FOR FURTHER DISSEMINATION
Standardised cardiovascular mortality rates over time

UNPUBLISHED DATA. NOT FOR FURTHER DISSEMINATION
Graft failure rates in transplant recipients
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Questions It Would Be Great to Answer

- Should we screen candidates for occult CAD?
- Should we revascularise stenosis in asymptomatic patients?

Published in final edited form as:

Design Considerations and Feasibility for a Clinical Trial to Examine Coronary Screening Before Kidney Transplantation (COST)

Bertram L. Kasiske, MD, FACP, Ajay K. Israni, MD, MS, Jon J. Snyder, PhD, MS, Alexa Camarena, MS, and on behalf of the COST Investigators

1. Would enough transplant programs be willing to participate in the proposed RCT?
2. Would participating centers have enough eligible patients in the proposed RCT?
3. Would enough eligible patients agree to participate in the proposed RCT?

We assumed that the proposed RCT would randomly allocate patients referred for kidney or simultaneous kidney and pancreas transplant to follow either the current standard of practice for CAD screening at the center, or to follow the 2007 ACC/AHA guidelines for perioperative management of non-cardiac surgery.
CARSK — Canadian Australasian Randomised trial of Screening Kidney Transplant recipients for coronary artery disease

Aims and hypotheses

• screening for wait list entry, no cardiac screening tests is non-inferior (ie no worse) versus the current standard care which is screening all asymptomatic wait-listed patients for coronary artery disease (CAD) at regular intervals

• Compare the benefits and costs of screening and subsequent treatment, at wait list entry only versus regular CAD screening from a health system perspective.
**CARSK Study Design**

**diagram**

Recruitment period: 2-3 years
- Aus: 900
- NZ: 200
- Canada: 2206

Follow up: 6 monthly phone call/study visit (alternating)

Study duration: 5 years
Study population

• Participants identified from site waiting lists, and approached when attending routine wait list review appointments

• Inclusion:
  • Adults
  • currently being assessed for or active on the kidney transplant waiting list
  • expected to require further screening for CAD prior to transplantation (by current standard of care);
  • Able to give consent
  • Anticipated to undergo transplantation more than 12 months from date of enrolment
Exclusion criteria

• Exclusions:
  • signs or symptoms suggestive of uncontrolled cardiac disease such as unstable coronary syndromes, decompensated heart failure, uncontrolled arrhythmia, and severe valvular heart disease
  • patients who “on-hold” for transplantation due to a medical problem
  • patients with other solid organ transplants
  • multi-organ transplant candidates (e.g. kidney-pancreas)
  • planned living donor/ PKE transplant
Outcome measures

- **Primary efficacy endpoint**: major adverse cardiac event (MACE): any of cardiovascular death, myocardial infarction, emergency revascularisation, hospitalisation with unstable angina.

- **Primary safety endpoint**: the above MACE endpoint plus complications from cardiac diagnosis or treatment including major bleeding requiring transfusions or hospitalizations, vascular intervention subsequent to cardiac interventions, stroke and all-cause death.

- **Secondary endpoints**: death, cardiovascular death, procedure-related death, myocardial infarction, emergency revascularisation, stroke, hospitalisation with unstable angina, hospitalisation with heart failure, hospitalisation with arrhythmia, major bleeding, health-related quality of life (QoL), time off list (including number of temporary suspension and duration of each suspension), cost-effectiveness, incidence of permanent removal from list for cardiac causes; incidence of transplantation and cancellation of transplant due to CAD.
Testing procedures - pragmatic

• Non-invasive cardiac screening test:
  • exercise stress test, myocardial perfusion scintigraphy, dobutamine stress echo

• The management of abnormal screening test:
  • performance of coronary angiography + revascularisation as usual

• clinical symptoms of CAD, regardless of randomised allocation:
  • evaluated and treated according to the standard of care at the local transplant centre
Economic evaluation

• cost-effectiveness and cost-utility analysis

• cost per MACE avoided; the cost per life year gained; and the cost per quality adjusted life year (QALY) gained of no screening compared to usual screening.

• 6-12 monthly quality of life surveys
  • EQ-5D-5L
  • KDQOL – 36

• Patient diaries for hospitalisations

• Linkage to administrative datasets – hospitalisation, medication, procedures
Barriers and facilitators to CARSK success?

- Equipoise?
  - Nephrologists
  - Cardiologists

- Contamination?
  - Testing outside/ in rooms

- Patients

- Transplantation rates increasing; effect of eligibility

- Sub-studies
  - Biomarker collection

- Diagnostic accuracy
  - Prognostic accuracy

- Qualitative work

- Ancillary analysis

- Building on CARSK
CARSK TEAM

- **Australia**
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- **New Zealand**
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- **Canada**
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- **Funding**
  - NHMRC Australia
  - National Heart Foundation NZ
  - CIHR

- **Clinical events committee**
  - Chair Charles Herzog

- **DSMB**
  - Andreas Laupacis - Chair
  - Andrew Day-Statistician/Queens
  - Brenda Hemmelgarn – Nephrologist Calgary
  - Matthew Jose - Nephrologist Tasmania
  - Anushka Patel - Cardiologist Sydney
  - Independent Statistician – Stephanie Clark
Thanks for listening