A Trial of Care for CKD: Can-Prevent

The Canadian Collaborative Group for the Prevention of Renal and Vascular Endpoints Trial (CANPREVENT) New Emerging Team is sponsored by:

CIHR-Institute of Nutrition, Metabolism and Diabetes
CIHR-Institute of Circulatory and Respiratory Health
Heart and Stroke Foundation of Canada
Canadian Diabetes Association
Kidney Foundation of Canada
Merck-Frosst Canada
Amgen Canada Inc.
Ortho-Biotech Canada
Background

- CKD is common
- Increases risk for ESRD and CVD events
- There are evidence based therapies
- They are not optimally applies in routine care
- New models of care need to be tested
CAN-PREVENT

- RCT of care for CKD as a chronic illness
- Nurse coordinated team vs. usual care
- Protocols for evidence-based therapies
- Aim to reduce kidney & CV outcomes
Trial Design

- Randomized
- Multi-centre
- Parallel, 2 group trial
- Usual care v. “Intervention Clinic”
- Blinded assessment of end-points
Inclusion Criteria

- Age 40-75, CrCl 25-60
- Stratum 1: diabetic
- Stratum 2: proteinuria $\geq 1$g/L
- Stratum 3: No DM or proteinuria
Exclusion Criteria

- No consent
- Likely to die < 6 months
- Current malignancy, advanced CVD, transplant
- CKD currently treated by immunotherapy
- ESRD likely in < 6 months
- Current care for CKD or CVD by DM program
- Currently in another interventional trial
- Not able to attend for follow-up
Recruitment

- Used a lab based case finding strategy:
  - Electronic search for those with SCr in range
  - Contact with doctor via lab
  - Doctor refers patients to study
- Mostly (93%) not already referred to nephrology (to minimize contamination)
- 474 randomized and followed - mean 704 days
We Did Find & Follow Patients

Randomized N = 474

Intervention
N = 238
Withdrew N = 12
Lost to follow up N = 12

Control
N = 236
Withdrew N = 15
Lost to follow up N = 8
Intervention

- Nurse co-ordinated
- Protocol guided
- Nephrologist supervised
- Clinic based
- Interventions target CV & kidney disease
- These reflect current state of knowledge
- Modified as evidence emerged
Protocols Include (Tier 1)

- BP and proteinuria control
- RAAS blockade
- Lipid therapy
- Use of ASA
- Beta-blockade post MI & in CHF
Protocols Include (Tier 2)

- Anemia Management
- Mineral and parathyroid management
- Acidosis control
- Diabetes control
- Smoking cessation
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention %</th>
<th>Control %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>31.4</td>
<td>32.9</td>
</tr>
<tr>
<td>Hx MI</td>
<td>16.7</td>
<td>14.3</td>
</tr>
<tr>
<td>Hx CABG</td>
<td>10.7</td>
<td>8.2</td>
</tr>
<tr>
<td>HX PTCA</td>
<td>11.2</td>
<td>8.7</td>
</tr>
<tr>
<td>Hx CHF</td>
<td>5.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Median [IQR]</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>eGFR</td>
<td>42.5 [38-46]</td>
<td>42.3 [37-46]</td>
</tr>
<tr>
<td>24 hr urine protein</td>
<td>0.11 [0.07-0.2]</td>
<td>0.12 [0.08-0.22]</td>
</tr>
<tr>
<td>BP</td>
<td>128/74 [116/66-140/80]</td>
<td>132/74 [120/68-144/81]</td>
</tr>
<tr>
<td>Hba1c in diabetics</td>
<td>7% [6.4-7.9]</td>
<td>7.1 [6.3-7.6]</td>
</tr>
<tr>
<td>LDL</td>
<td>2.6 [2.1-3.3]</td>
<td>2.7 [2.1-3.5]</td>
</tr>
</tbody>
</table>
# Adjudicated Clinical Outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Intervention N (%)</th>
<th>Control N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular death</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Other death</td>
<td>5 (2.1)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Myocardial infarct</td>
<td>5 (2.1)</td>
<td>4 (1.7)</td>
</tr>
<tr>
<td>ACS</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>5 (2.1)</td>
<td>8 (3.4)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (0.4)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Amputation of leg</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Dialysis</td>
<td>2 (0.8)</td>
<td>1 (0.4)</td>
</tr>
<tr>
<td>Doubled SCr</td>
<td>1 (0.4)</td>
<td>4 (1.7)</td>
</tr>
</tbody>
</table>
Time To First Clinical Event

- Exp. Intervention
- Std. care

Probability of survival vs Months since baseline
Rate of Clinical Outcomes

- 48 endpoints
- Two events each in 5 cases
- Three events each in 2 cases
- Annual incidence of events:
  - 5.2% (CI 3.8-6.7%)
Impact on Kidney Function
Blood Pressure Control

- Good overall
- Intervention v Control SBP
  - 129 v 133 @ baseline
  - 124 v 130 @ 12 mos, p<0.01
  - 123 v 128 @ 24 mos, p=NS

95% CI for the difference -1.1 to -8.5 mmHg for marginal mean in GLM adjusting for baseline
<table>
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<tr>
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<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>% SBP &gt; 140 @ baseline</td>
<td>25.8</td>
<td>34.5</td>
</tr>
<tr>
<td>In which # BP meds @ baseline</td>
<td>Av 2.4</td>
<td>Av 2.3</td>
</tr>
<tr>
<td>In which # BP meds @ 12 mo</td>
<td>Av 2.9</td>
<td>Av 2.5</td>
</tr>
<tr>
<td>% BP &gt;140 @ 12 mo</td>
<td>15.6</td>
<td>26.1</td>
</tr>
</tbody>
</table>
% on RAAS Blockers

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (DM)</td>
<td>88</td>
<td>91</td>
</tr>
<tr>
<td>Baseline (all)</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>12 months all</td>
<td>75</td>
<td>66*</td>
</tr>
<tr>
<td>24 months all</td>
<td>78</td>
<td>66*</td>
</tr>
</tbody>
</table>

* p<0.05
Mean LDL Levels

<table>
<thead>
<tr>
<th></th>
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<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>2.75</td>
<td>2.82</td>
</tr>
<tr>
<td>12 months</td>
<td>2.56</td>
<td>2.65</td>
</tr>
<tr>
<td>24 months</td>
<td>2.34</td>
<td>2.41</td>
</tr>
</tbody>
</table>

P<0.0001 for time, NS between groups
Impact on Lipid Management

- % on statin among those with baseline LDL > 2.5 mmol/L

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</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>39</td>
<td>35</td>
</tr>
<tr>
<td>12 mos</td>
<td>65</td>
<td>42*</td>
</tr>
<tr>
<td>24 mos</td>
<td>84</td>
<td>51*</td>
</tr>
</tbody>
</table>

P<0.001 between groups
Other Impacts

- ESA use in 1-5 of each group at any time
- Tsat < 0.2 treated in 35% v. 14%
- No difference in hemoglobins
- No difference in phosphate, calcium or PTH levels (≈ 90% of upper normal)
- No difference in phosphate binders (used in 2-5% cases during trial)
### What The Intervenors Did Not Do

<table>
<thead>
<tr>
<th></th>
<th>Intervention Grp by 12 months</th>
<th>Controls by 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Hba1c in diabetics</td>
<td>-0.49%</td>
<td>-0.52%</td>
</tr>
<tr>
<td>Mean Hgb if &lt; 110 at baseline</td>
<td>110 (3 on ESA)</td>
<td>108 (0 on ESA)</td>
</tr>
</tbody>
</table>
What The Intervenors Did Not Do

- Refer more to dietitians (23% v. 25% in the first 12 months)
- Involve diabetes nurse educators (16% v. 18% in the first 12 months)
Cost-effectiveness

- We monitored all health care resources used
- We measured quality of life by EQ5D
- We constructed a cost-utility analysis
  
  $\text{Diff in }$ $\text{QALYs}$

$\text{Diff in QALYs}$
## Costs – 2 year study patients

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease related costs</td>
<td>$4,631</td>
<td>$5,741</td>
</tr>
<tr>
<td>(mean)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All costs</td>
<td>$11,739</td>
<td>$14,180</td>
</tr>
<tr>
<td>(mean)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cost Difference was significant

- Trend to higher up front costs in the intervention group (clinic time etc)
- More than offset by less hospitalization and indirect costs in the intervention group
Difference in Utility (EQ-5D)

Intervention started lower and rose. Area under curve greater for Intervention over 2 years - implies better quality of life.
Overall Cost-Utility

Incremental Costs

Incremental QALYs

Lower $, better QALYs

With Intervention in this quadrant
Conclusions

- The largely unreferred population had a low risk of renal progression, but some CV risk
- Trial was too small to detect effect on clinical outcomes
- No impact on QoL
- Intervenors did address BP, RAAS blockade, lipids and iron
- Need for and use of ESAs was low
- Need and use of phosphate binders was low
- Diabetes impact equal to controls
Conclusions 2

- There is potential for the model of care to impact clinical outcomes beyond usual care.
- It was feasible to apply the intervention, but the impact on surrogate outcomes was not consistent.
- Intervention was cost-effective.
- The trial did not really test impact on those at risk for kidney disease progression.
- Further studies may be justified.
There are people out there with CKD who may need care aimed at reducing CV risk, but the nature of the care should be within the competence of many physicians.

Nephrologists are likely to have little specific to offer in many of these cases.
Thanks

- Questions?
- Comments?
- Criticism?