“Clinical Trials: Hypothesis & Endpoints”

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Clinical Trial: Definitions

• “The application of an **intervention** (treatment) by an investigator, who observes the effect on an **outcome**”
  – Can demonstrate *causality*, as opposed to an observational study

• *Randomisation*: randomly assigning the intervention decreases the influence of **confounding variables**
  – (other differences between the groups, at baseline or during the trial)

• *Blinding*: the administration of the intervention avoids co-intervention bias, and ascertainment bias
  – (effect of knowledge of the treatment assignment on the care and observation of the study subject)
Randomised Trial Design

**THE PRESENT**

- POPULATION
  - SAMPLE
  - RANDOMISATION
  - ACTIVE TREATMENT
    - Disease
    - No Disease
  - PLACEBO
    - Disease
    - No Disease

**THE FUTURE**

Randomized, Blinded Clinical Trial Design

- Hypothesis & Primary Endpoint
- Selection of Participants
- Measurement of Baseline Variables
- Randomisation & Blinding
- Choice of Intervention and Control
- Outcomes
- Analysis
- Other Trial Designs
Hypothesis and Primary Endpoint

• **Phase I studies**: “first in man”. Aimed primarily at establishing tolerated dosing, usually in healthy volunteers, with pharmacokinetic-pharmacodynamic (PK-PD) analysis

• **Phase II studies**: preliminary assessment of efficacy (effects on physiologic endpoints), with additional safety information, in a small sample of the target population

• **Phase III studies**: definitive clinical trials of effectiveness (effects on clinical endpoints, i.e. outcomes) for the proposed indication in the target population, to support drug approval

• **Phase IV studies**: post-approval studies, aimed at new indications, additional safety assessments, or for other purposes
Hypothesis and Primary Endpoint

- **Phase I studies**: question is “what is a safe dose range in man?”. Small sample sizes required.
- **Phase II studies**: question is “does the drug have the desired physiologic effect [efficacy] in the target population?”. Example: study of acute effects of new drug vs placebo on blood pressure (BP) in patients hospitalised with acute decompensated heart failure. Sample size must be sufficient to detect BP differences.
- **Phase III studies**: question is “does the drug alter significant clinical endpoints [effectiveness] in the target population?”. Example: study of clinical effects of new drug vs placebo in patients hospitalised with acute decompensated heart failure. Sample size must be sufficient to detect differences in clinical outcomes (length of hospital stay; rehospitalisation or death within 30 or 90 days)
Randomized, Blinded Clinical Trial Design

- Hypothesis & Primary Endpoint
- Selection of Participants
- Measurement of Baseline Variables
- Randomisation & Blinding
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- Outcomes
- Analysis
- Other Trial Designs
Selection of Participants

• Entry (Inclusion & Exclusion) Criteria:
  – “...to identify an important population for whom a statistically
    significant impact of the intervention on the primary outcome is
    feasible and likely...”
  – Entry Criteria have several aims:
    • Optimise the rate/incidence of the primary outcome
      – Increased by restricting to high-risk subjects
    • Optimise the expected effectiveness of the active treatment
    • Maintain generalisability of the trial findings
      – Diminished by excessive exclusion criteria
    • Optimise the ease of recruitment (minimise barriers)
    • Maximise the likelihood of adherence to protocol and followup

• Sample Size Estimation
  – Requires a reliable estimate of the rate of the primary outcome in
    people who might be included in the trial
Randomized, Blinded Clinical Trial Design

- Selection of Participants
- Measurement of Baseline Variables
- Randomisation & Blinding
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- Outcomes
- Analysis
- Other Trial Designs
Measurement of Baseline Variables

• Tracking Information
• Description of Participants
• Measure Variables that are Risk Factors for the Outcome, Subgroups, Effect Modifiers
• Biobanking
  – Plan collections for ancillary studies: DNA for genomics; RNA for transcriptomics; blood, urine, other samples for proteomics, metabolomics, pharmacokinetics, biomarkers of drug effects- efficacy or toxicity)
• Measure the Outcome Variable (…..at baseline)
Randomized, Blinded Clinical Trial Design

• Selection of Participants
• Measurement of Baseline Variables
• Randomisation & Blinding
• Choice of Intervention and Control
• Outcomes
• Analysis
• Other Trial Designs
Randomisation & Blinding

- Randomly assign 2 groups to ≥ 2 interventions
  - Active treatment *versus* Placebo
  - Random assignment should distribute age, sex, other prognostic baseline characteristics evenly

- **Eliminates Confounding by Pre-Randomisation/Baseline Variables**
  - Statistical analysis further accounts for the impact of chance (random error)

- Special Randomisation Techniques:
  - Blocked Randomisation
    - Randomisation is done in “blocks” of predetermined size
    - Aims to ensure that the number or participants is distributed equally among the study groups
  - Stratified Blocked Randomisation
    - Divide the study cohort at baseline into 2 “strata”, with or without an important predictor of outcome
      - to ensure that they are more evenly distributed between the study groups beyond the effects of chance alone
    - Then carry out blocked randomisation within each of these strata
Randomisation & Blinding

• Ideally neither the study subjects nor anyone in contact with them has any knowledge of their study group assignment

• Two Major Benefits of Blinding:
  
  1) Eliminates post-randomisation confounding variables (unintended interventions)
     – “Co-interventions” during followup

  2) Prevents biased assessment of outcome
Randomized, Blinded Clinical Trial Design

- Selection of Participants
- Measurement of Baseline Variables
- Randomisation & Blinding
- Choice of Intervention and Control
- Outcomes
- Analysis
- Other Trial Designs
Choice of Intervention & Control

• Intervention:
  – Balance of efficacy/effectiveness versus safety
    • Choice of maximum tolerated dose for severe or life-threatening illness
    • Choice of lowest effective dose for minor ailments; safety being primary concern
  – Phase of new drug development determines drug regimen

• Control:
  – Placebo: optimal
  – Co-interventions: consider protocolised “standard care”
  – Equivalence trials
Randomized, Blinded Clinical Trial Design

- Selection of Participants
- Measurement of Baseline Variables
- Randomisation & Blinding
- Choice of Intervention and Control
- Outcomes
- Analysis
- Other Trial Designs
Outcomes

- Clinical versus Surrogate outcomes
  - Surrogate markers may be chosen if biologically plausible and proven to be associated with the clinical outcome of interest:
    - Cholesterol or BP and cardiovascular events
    - Bone mineral density and fracture risk
    - *NOT* (suppression of) ventricular arrhythmias and risk of death post-myocardial infarction (Cardiac Arrhythmia Suppression trial, CAST)

- Primary and secondary outcomes
  - Trials are generally designed with adequate sample size to evaluate effects on the primary endpoint alone
  - Effects of secondary endpoints are often hypothesis-generating, rather than conclusive findings

- Adjudication of outcomes
- Adverse effects
Randomized, Blinded Clinical Trial Design

• Selection of Participants
• Measurement of Baseline Variables
• Randomisation & Blinding
• Choice of Intervention and Control
• Outcomes
• Analysis
• Other Trial Designs
Analysis

• Intention-to-treat analysis
  – Effect of cross-overs, dropouts
• Per protocol analysis
• Subgroup analysis
  – Pre-planned
  – Post-hoc
• Clinical Trial Monitoring
  – Interim analysis
  – Stopping rules
    • Safety
    • Futility
Randomized, Blinded Clinical Trial Design

• Selection of Participants
  – Entry Criteria: Inclusion & Exclusion Criteria
  – Sample Size estimation
  – Recruitment barriers
• Measurement of Baseline Variables
• Randomisation
• Choice of Intervention and Control
• Outcomes
• Analysis
• Other Trial Designs: Note: Observational study with added monitoring and samples = European Directive-defined clinical trial
Randomised Trial Design

THE PRESENT

POPULATION

SAMPLE

RANDOMISATION

ACTIVE TREATMENT

PLACEBO

THE FUTURE

Disease | No Disease

Disease | No Disease

Radiocontrast Nephropathy (“RCN”)

- **Definition:** acute decrement in renal function following radiocontrast administration
  - Usually defined as serum creatinine increase of 0.5mg/dl or 25% within 48 (-96) hours of dye
- **3rd commonest cause of hospital-acquired ARF**
- **Usually acute-on-chronic renal failure, superimposed on CKD (not normal renal function)**
- **Typically,** serum creatinine increases within 24-48 hours, reaches peak and plateau in 3-5 days, ± decreases
- Increases morbidity, cost, and mortality
  - Adjusted odds ratio 5.5 for in-hospital mortality (vs no RCN)
Patient-Related Risk Factors for CIN

Established
- Pre-existing renal impairment with diabetes
- Pre-existing renal impairment without diabetes
- Dehydration
- CHF
- Multiple myeloma
- Advanced age
- Administration of nephrotoxic drugs

Newly identified
- Hypertension
- Metabolic syndrome

Kidney Disease Outcome Quality Initiative (K/DOQI) Classification of Renal Function

CKD Kidney Function
GFR (mL/min/1.73m²) ≈ CrCl (mL/min)

Stage I
CKD Risk Factors/Damage With Preserved GFR

Stage II
Mild ↓ Kidney Function

Stage III
Moderate ↓ Kidney Function

Stage IV
Severe ↓ Kidney Function

Stage V
Kidney Failure ESRD

130 120 110 100 90 80 70 60 50 40 30 20 15 10 0

CKD, chronic kidney disease; ESRD, end-stage renal disease
Independent Predictors of CIN Following PCI

Average patient = 65 years, 72 kg man

Independent risk factors:
CrCl >> Diabetes >> Contrast Volume

CIN, contrast-induced nephropathy; PCI, percutaneous coronary intervention
CM-induced Medullary Hypoxia

A temporary increase in renal transport work in the thick ascending limb of Henle’s loop (↑ in oxygen consumption)

+  

Constriction of medullary capillaries (↓ medullary oxygen delivery)

MEDULLARY ANGINA

Effects of Fenoldopam on GFR Following Radiocontrast Dye Injection

F=fenoldopam  S=Schering 23390, DA-1 antagonist
* p<0.05 compared with baseline
N=10 volume-depleted dogs total

Study Protocol

Baseline serum/urine electrolytes

Baseline RPF/GFR

Fenoldopam/Placebo Randomization

3 Hr Pre
2 Hr Pre
1 Hr Pre

Contrast Injection
1 Hr Post
2 Hr Post
3 Hr Post
4 Hr Post

Study Drug Initiation

Study Drug Termination

Post Drug RPF/GFR

Pre-hydration 3 hours

Post Catherization RPF/GFR

<table>
<thead>
<tr>
<th></th>
<th>1/2 NS (N=22)</th>
<th>FNP (N=23)</th>
<th>NS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67 y/o</td>
<td>59 y/o</td>
<td>NS</td>
</tr>
<tr>
<td>Male/Female</td>
<td>17 (78%)</td>
<td>17(74%)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetic/Non-diabetic</td>
<td>11 (50.0%)</td>
<td>13 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Serum Cr</td>
<td>2.62+.11 mg/dl</td>
<td>2.61+.18 mg/dl</td>
<td>NS</td>
</tr>
<tr>
<td>Volume Contrast (ml)</td>
<td>96+19</td>
<td>80+15</td>
<td>NS</td>
</tr>
<tr>
<td>Iso Osmo / Low Osmo</td>
<td>21%/ 79%</td>
<td>33%/ 67%</td>
<td>NS</td>
</tr>
<tr>
<td>Non-Ionic</td>
<td>100%</td>
<td>100%</td>
<td>NS</td>
</tr>
<tr>
<td>%PTCA/Cath</td>
<td>72%</td>
<td>60%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Radiocontrast Dyes Reduce RPF: Prophylactic Efficacy of Fenoldopam Mesylate

Pilot Study of Fenoldopam Mesylate in Radiocontrast Nephropathy: Incidence of RCN at 48 Hours

Fenoldopam Mesylate Reduces Peak Serum Cr 72 Hours Post-Contrast

Radiocontrast Nephropathy Correlates with Reduction in RPF and CrCl

CONTRAST Trial: Algorithm

315 patients at 28 U.S. centers

cardiac procedures with calculated CrCl <60 ml/min

Primary endpoint: RCN (SCr increase ≥25%) within 24-96 hrs

Fenoldopam

0.05 µg/kg/min titrated to 0.1 µg/kg/min, starting 1 hr before cath and continuing for 12 hrs after

Matching placebo

Hydrate

0.45% NS
1.5 ml/kg/hr X 2-12 hrs

Stratify by diabetes

Randomise

Randomization Flow and Follow-up Process

315 Patients Randomized

157 Assigned to Receive Fenoldopam Mesylate and Received Fenoldopam Mesylate as Assigned
   - 20 Did Not Have Baseline or Follow-up Serum Creatinine Values
   - 4 Did Not Have Complete 30-Day Clinical Follow-up Data
   - 137 Included in Serum Creatinine Analysis (Primary End Point)
   - 153 Included in 1-Month Clinical Event Rate Analysis

158 Assigned to Receive Placebo and Received Placebo as Assigned
   - 12 Did Not Have Baseline or Follow-up Serum Creatinine Values
   - 2 Did Not Have Complete 30-Day Clinical Follow-up Data
   - 146 Included in Serum Creatinine Analysis (Primary End Point)
   - 156 Included in 1-Month Clinical Event Rate Analysis

CONTRAST design

- Hypothesis: fenoldopam prevents radiocontrast nephropathy (RCN)
- Target population: chronic kidney disease (CKD) patients undergoing coronary angiography
- Primary endpoint: \( \text{RCN} = 25\% \) serum creatinine increase within 24-96 hours post-dye
- 268 patients required for 80\% power to detect a decrease in RCN rate from 30\% to 15\%, with 2-sided \( \alpha \) of 0.05 (\( \chi^2 \) test for 2 X 2 tables)
- 300 patients studied to accommodate incomplete data/followup, etc

Table 1: Baseline Characteristics

<table>
<thead>
<tr>
<th>Table 1. Baseline Clinical Features</th>
<th>Fenoldopam Mesylate (n = 157)</th>
<th>Placebo (n = 158)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean (SD) 69.0 (11.1)</td>
<td>70.2 (10.4)</td>
</tr>
<tr>
<td></td>
<td>Range 38.9-93.3</td>
<td>44.3-89.5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>Mean (SD) 83.7 (18.5)</td>
<td>84.5 (16.6)</td>
</tr>
<tr>
<td></td>
<td>Range 49.0-150.0</td>
<td>52.6-144.0</td>
</tr>
<tr>
<td>Male sex, No. (%)</td>
<td>108 (68.8)</td>
<td>100 (63.3)</td>
</tr>
<tr>
<td>Medical history, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>77 (49.0)</td>
<td>76 (48.1)</td>
</tr>
<tr>
<td></td>
<td>Insulin dependent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>45 (28.7)</td>
<td>45 (28.5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>142 (90.4)</td>
<td>128 (81.0)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>121 (77.1)</td>
<td>128 (81.0)</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>83 (52.9)</td>
<td>72 (45.6)</td>
</tr>
<tr>
<td>Prior congestive heart failure</td>
<td>77 (49.0)</td>
<td>73 (46.2)</td>
</tr>
<tr>
<td>Prior coronary bypass surgery</td>
<td>51 (32.5)</td>
<td>54 (34.2)</td>
</tr>
<tr>
<td>Prior percutaneous intervention</td>
<td>60 (38.2)</td>
<td>57 (36.1)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>50 (31.8)</td>
<td>61 (38.6)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>87 (55.4)</td>
<td>86 (54.4)</td>
</tr>
<tr>
<td>Clinical, mean (SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic arterial pressure, mm Hg</td>
<td>139 (21)</td>
<td>145 (22)</td>
</tr>
<tr>
<td>Diastolic arterial pressure, mm Hg</td>
<td>70 (13)</td>
<td>72 (12)</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>68 (13)</td>
<td>69 (12)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>1.82 (0.71)</td>
<td>1.81 (0.83)</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>29.0 (9.8)</td>
<td>29.1 (10.3)</td>
</tr>
</tbody>
</table>

SI conversion factors: To convert serum creatinine to μmol/L, multiply by 88.4; creatinine clearance to mL/s, multiply by 0.0167.
Table 2: Study Drug Administration and Procedural Results

<table>
<thead>
<tr>
<th>Procedure type</th>
<th>Fenoldopam Mesylate (n = 157)</th>
<th>Placebo (n = 158)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary angiography</td>
<td>155 (98.7)</td>
<td>156 (98.7)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Bypass graft angiography</td>
<td>25 (15.9)</td>
<td>29 (18.4)</td>
<td>.65</td>
</tr>
<tr>
<td>Left ventriculography</td>
<td>50 (31.8)</td>
<td>51 (32.3)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Aortography</td>
<td>14 (6.9)</td>
<td>15 (6.5)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Renal arteriography</td>
<td>18 (11.5)</td>
<td>20 (12.7)</td>
<td>.66</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>54 (34.4)</td>
<td>55 (34.8)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Other procedure</td>
<td>25 (15.9)</td>
<td>30 (19.0)</td>
<td>.55</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Use of contrast</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Contrast amount, mean (SD), mL</td>
<td>153 (107)</td>
<td>162 (110)</td>
<td>.44</td>
</tr>
<tr>
<td>Range, mL</td>
<td>25-600</td>
<td>15-640</td>
<td></td>
</tr>
<tr>
<td>Nonionic contrast</td>
<td>137 (69.5)</td>
<td>140 (69.7)</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study drug administration</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurely discontinued</td>
<td>21 (13.4)</td>
<td>11 (7.0)</td>
<td>.06</td>
</tr>
<tr>
<td>Maximum dose tolerated for entire study</td>
<td>116 (73.9)</td>
<td>139 (89.0)</td>
<td>.002</td>
</tr>
<tr>
<td>Total study drug duration, mean (SD), h</td>
<td>13.0 (4.1)</td>
<td>13.8 (2.7)</td>
<td>.03</td>
</tr>
</tbody>
</table>

*Data presented as No. (%) unless otherwise indicated.
†More than 1 procedure type possible per patient.
Changes in Systolic Blood Pressure, Diastolic Blood Pressure, and Heart Rate During Study Drug Infusions

CONTRAST Trial: Incidence of RCN

Table 3: Primary & Secondary Endpoints

<table>
<thead>
<tr>
<th>Table 3. Primary and Secondary End Points</th>
<th>Fenoldopam Mesylate</th>
<th>Placebo</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Renal function deterioration within 96 hours</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>137</td>
<td>146</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine increase by (\geq 25%), No. (%)</td>
<td>46 (33.6)</td>
<td>44 (30.1)</td>
<td>.61</td>
</tr>
<tr>
<td>2 Consecutive 25% increases in serum creatinine, No. (%)*</td>
<td>20 (20.4)</td>
<td>18 (16.5)</td>
<td>.48</td>
</tr>
<tr>
<td>Serum creatinine increase by (\geq 0.5) mg/dL, No. (%)</td>
<td>39 (28.5)</td>
<td>35 (24.0)</td>
<td>.42</td>
</tr>
<tr>
<td>Maximum serum creatinine change, mean (SD), mg/dL†</td>
<td>0.32 (0.53)</td>
<td>0.26 (0.45)</td>
<td>.85</td>
</tr>
<tr>
<td><strong>Clinical end points, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>153</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>Repeat angiography and/or angioplasty</td>
<td>16 (10.5)</td>
<td>16 (10.3)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Coronary artery bypass graft surgery</td>
<td>15 (9.7)‡</td>
<td>15 (9.6)</td>
<td>&gt; .99</td>
</tr>
<tr>
<td><strong>30-Day adverse events, No. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 (2.0)</td>
<td>6 (3.8)</td>
<td>.50</td>
</tr>
<tr>
<td>Dialysis</td>
<td>4 (2.5)‡</td>
<td>3 (1.9)</td>
<td>.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (3.3)</td>
<td>3 (1.9)</td>
<td>.50</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>27 (17.8)</td>
<td>31 (19.9)</td>
<td>.65</td>
</tr>
<tr>
<td>Composite of death, dialysis, myocardial infarction, or rehospitalization</td>
<td>36 (23.4)‡</td>
<td>36 (23.1)</td>
<td>&gt; .99</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert serum creatinine to \(\mu\)mol/L, multiply by 88.4.
*Denominator = 98 for the fenoldopam group and 109 for the placebo group.
†From baseline value to the peak value within 96 hours after study drug administration.
‡Denominator = 154 (1 patient lost to 30-day follow-up required dialysis and 1 required bypass surgery before hospital discharge).

## Table 4: Subgroup Analysis for the Primary Study End Point of Contrast-Induced Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>No./Total (%)</th>
<th>Relative Risk (95% Confidence Interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fenoldopam Mesylate</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>46/137 (33.6)</td>
<td>44/146 (30.1)</td>
<td>1.11 (0.79-1.57)</td>
</tr>
<tr>
<td>Diabetic status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td>23/68 (33.8)</td>
<td>22/73 (30.1)</td>
<td>1.12 (0.69-1.82)</td>
</tr>
<tr>
<td>Diabetes (all)</td>
<td>23/69 (33.3)</td>
<td>22/73 (30.1)</td>
<td>1.11 (0.68-1.79)</td>
</tr>
<tr>
<td>Diabetes (insulin requiring)</td>
<td>13/38 (34.2)</td>
<td>13/42 (31.0)</td>
<td>1.11 (0.59-2.08)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>40/122 (32.6)</td>
<td>37/120 (30.8)</td>
<td>1.06 (0.74-1.54)</td>
</tr>
<tr>
<td>No</td>
<td>6/15 (40.0)</td>
<td>7/25 (26.9)</td>
<td>1.49 (0.41-3.60)</td>
</tr>
<tr>
<td>Baseline serum creatinine value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2.0 mg/dL</td>
<td>40/107 (37.4)</td>
<td>35/106 (32.4)</td>
<td>1.15 (0.60-1.86)</td>
</tr>
<tr>
<td>&gt;2.0 mg/dL</td>
<td>6/30 (20.0)</td>
<td>9/38 (23.7)</td>
<td>0.84 (0.34-2.11)</td>
</tr>
<tr>
<td>N-acetylcysteine use before procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>24/68 (35.3)</td>
<td>21/79 (26.6)</td>
<td>1.33 (0.62-2.16)</td>
</tr>
<tr>
<td>No</td>
<td>22/69 (31.9)</td>
<td>23/67 (34.3)</td>
<td>0.93 (0.58-1.50)</td>
</tr>
<tr>
<td>Contrast amount</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤150 mL</td>
<td>26/64 (41.0)</td>
<td>21/62 (33.8)</td>
<td>1.21 (0.74-1.97)</td>
</tr>
<tr>
<td>&gt;150 mL</td>
<td>20/52 (38.5)</td>
<td>23/62 (37.1)</td>
<td>1.04 (0.65-1.66)</td>
</tr>
<tr>
<td>Precontrast hydration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤475 mL</td>
<td>18/49 (36.7)</td>
<td>12/45 (26.7)</td>
<td>1.36 (0.75-2.53)</td>
</tr>
<tr>
<td>475-950 mL</td>
<td>13/44 (29.5)</td>
<td>14/47 (29.8)</td>
<td>0.99 (0.53-1.87)</td>
</tr>
<tr>
<td>&gt;950 mL</td>
<td>15/44 (34.1)</td>
<td>18/54 (33.3)</td>
<td>1.02 (0.59-1.79)</td>
</tr>
<tr>
<td>Study drug tolerated for 12 h after catheterization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>27/91 (29.7)</td>
<td>31/105 (29.5)</td>
<td>1.00 (0.65-1.55)</td>
</tr>
<tr>
<td>Study drug prematurely discontinued</td>
<td>19/46 (41.3)</td>
<td>13/41 (31.7)</td>
<td>1.30 (0.74-2.29)</td>
</tr>
</tbody>
</table>

SI conversion factor: To convert serum creatinine to μmol/L, multiply by 88.4.

### Subgroup Analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Fenoldopam</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>33.6%</td>
<td>30.1%</td>
<td>0.61</td>
</tr>
<tr>
<td>No diabetes</td>
<td>33.8%</td>
<td>30.1%</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes - all</td>
<td>33.3%</td>
<td>30.1%</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes – insulin dependent</td>
<td>34.2%</td>
<td>31.0%</td>
<td>0.81</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32.8%</td>
<td>30.8%</td>
<td>0.78</td>
</tr>
<tr>
<td>No hypertension</td>
<td>40.6%</td>
<td>26.9%</td>
<td>0.49</td>
</tr>
<tr>
<td>Baseline SCr ≤2.0 mg/dl</td>
<td>37.4%</td>
<td>32.4%</td>
<td>0.48</td>
</tr>
<tr>
<td>Baseline SCr &gt;2.0 mg/dl</td>
<td>20.0%</td>
<td>23.7%</td>
<td>0.78</td>
</tr>
<tr>
<td>N-acetylcysteine pre</td>
<td>35.3%</td>
<td>26.6%</td>
<td>0.28</td>
</tr>
<tr>
<td>No N-acetylcysteine pre</td>
<td>31.9%</td>
<td>34.3%</td>
<td>0.86</td>
</tr>
<tr>
<td>Contrast amount ≤ 150 cc</td>
<td>31.0%</td>
<td>25.6%</td>
<td>0.49</td>
</tr>
<tr>
<td>Contrast amount &gt;150 cc</td>
<td>38.5%</td>
<td>37.1%</td>
<td>0.99</td>
</tr>
<tr>
<td>Pre-contrast hydration ≤475 cc</td>
<td>36.7%</td>
<td>26.7%</td>
<td>0.37</td>
</tr>
<tr>
<td>Pre-contrast hydration 475 – 950 cc</td>
<td>29.5%</td>
<td>29.8%</td>
<td>0.99</td>
</tr>
<tr>
<td>Pre-contrast hydration &gt;950 cc</td>
<td>34.1%</td>
<td>33.3%</td>
<td>0.99</td>
</tr>
<tr>
<td>Study drug tolerated for 12 hrs post cath</td>
<td>29.7%</td>
<td>29.5%</td>
<td>0.99</td>
</tr>
<tr>
<td>Study drug prematurely discontinued</td>
<td>41.3%</td>
<td>31.7%</td>
<td>0.38</td>
</tr>
</tbody>
</table>
Prevention of CIN With NaHCO$_3$: A Randomized Controlled Trial

- **Objective:** To determine whether IV infusion of isotonic NaHCO$_3$ solution is superior to 0.9% saline in the prevention of CIN
- **Design:** Prospective randomized controlled trial of 119 patients undergoing a nonemergent exposure to iodinated contrast
- **Methods:** Patients received 154 mEq/L NaHCO$_3$ or 0.9% saline as bolus of 3 mL/kg/h for 1 h before contrast followed by 1 mL/kg/h for 6 h postprocedure
- **Contrast agent:** Iopamidol (796 mOsm/L)
- **Entry criteria:** SCr >1.1 mg/dL
- **Exclusion:** Patients receiving dopamine, FNP, NAC, or mannitol
- **Primary endpoint:** Rise in SCr by 25% at 48 h

CIN, contrast-induced nephropathy; FNP, fenoldopam; NAC, N-acetylcysteine
Incidence of CIN Reduced in Patients Hydrated With NaHCO₃

CIN, contrast-induced nephropathy
Prevention of CIN With NaHCO$_3$: A Randomized Controlled Trial

$P=0.02$

$-0.1\%$

$+8.5\%$

CIN, contrast-induced nephropathy
Prevention of Contrast - Induced Nephropathy With Sodium Bicarbonate

Study Termination:

Midway through accumulation of patients, study halted because of “ethical concern about continuing to expose the control group to the substantially higher risk of contrast nephropathy.”

## Prevention of Contrast - Induced Nephropathy With Sodium Bicarbonate

### Results:

<table>
<thead>
<tr>
<th></th>
<th>NaCl</th>
<th>Bicarbonate</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of nephropathy</td>
<td>13.6 % (8)</td>
<td>1.7 % (1)</td>
<td>11.9 % (CI = 2.9 – 21.2)</td>
</tr>
</tbody>
</table>

(P = 0.02)

Prevention of Contrast - Induced Nephropathy With Sodium Bicarbonate

Registry Phase:

- 191 patients with baseline Cr = 1.7mg/dl
- Mean change in Cr = 0 %
- CIN in 3 of 191 patients. (1.6%)

Adequate Hydration

IV fluids

0.9% NaCl or 150 mEq NaHCO₃ in 1 L 5% dextrose-water IV @ 1 mL/kg/h
6-12 hours preprocedure & continue for 12-24 hours postprocedure

Summary

• Hypothesis and Primary Endpoint Selection choices vary according to trial Phase
• Phase II trials of efficacy for interventions commonly use surrogate endpoints (BP, cholesterol, glycosylated Hb)
• Phase III trials of effectiveness for interventions should use clinical endpoints, such as survival, decreased morbidity, hospitalisation, QOL, or composites
• Phase IV trials may examine efficacy, effectiveness, safety, QOL, or other endpoints, and should be designed accordingly