Looking Back and Moving Forward:
Therapeutic Hypothermia in Deceased Organ Donors and Recipient Kidney Graft Function

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Agenda

• Looking Back:
  – Overview of Mild Hypothermia Trial
  – Remaining Scientific and Regulatory Questions

• Looking Forward:
  – Donor Management Research Initiative (DMRI)
  – Mild Hypothermia vs. Machine Perfusion RCT
Background

- What is one of the biggest enemy of a successful transplantation?
  - Ischemia/reperfusion
  - What if we cooled the donors prior to removing the organs and putting them “on ice”?
  - Recent trial of targeted temperature management demonstrated significant benefits of mild hypothermia on delayed graft function
Therapeutic Hypothermia in Deceased Organ Donors and Kidney Graft Function:
A Randomized Controlled Trial From The UNOS Region 5 Donor Management Goals Workgroup

• RCT from the Region 5 DMG Workgroup

• All DNDDs with research authorization*

• Targeted temperature management
  • 34-35 C. vs. 36.5-37.5 C

• Primary outcome measure:
  • Kidney Recipient Delayed Graft Function
  • Target: 500 subjects, planned interim analysis
Therapeutic Hypothermia in Deceased Organ Donors and Kidney-Graft Function

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio for Delayed Graft Function (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Hypothermia vs. normothermia</td>
<td>0.62 (0.43–0.92)</td>
<td>0.02</td>
</tr>
<tr>
<td>Organ-procurement organization, A vs. B</td>
<td>0.85 (0.57–1.28)</td>
<td>0.43</td>
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<tr>
<td>Standard-criteria donor vs. expanded-criteria donor</td>
<td>1.21 (0.69–2.13)</td>
<td>0.50</td>
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<tr>
<td>Creatinine level at enrollment, per 1-mg-per-deciliter increase</td>
<td>1.99 (1.42–2.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Donor age, per 1-yr increase</td>
<td>1.04 (1.02–1.05)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney cold-ischemia time, per 1-hr increase</td>
<td>1.03 (1.00–1.05)</td>
<td>0.04</td>
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Mild Hypothermia Trial Summary

• Therapeutic mild hypothermia in the donor leads to a significant decrease in kidney recipient DGF

• Greatest benefit seen in donors with highest risk kidneys

• Mild hypothermia did not affect donor critical care parameters or individual organ transplantation rates
Intervention and Outcome Variables

• Prospective, randomized trial of mild hypothermia (34-35 degrees) in deceased organ donors
  – Temperature management not previously standardized
  – Many donors hypothermic in the operating room

• De-identified recipient graft outcome and demographic data obtained from publicly available information collected for non-research purposes
  – OPTN – UNet and SRTR

• No research was conducted by the transplant programs that accepted organs from donors in our study
Communication and Vetting

- Institutional IRBs*
- HRSA, each OPO Research Oversight Body
- OPO Organ-specific committees
- Donor Hospitals
- UNOS Region 5 – Business Meeting / Research Cmte
- Donor Families
- National UNOS communication
- DonorNet Donor Highlights*
- DSMB
Transplant Center Communication

DONOR HIGHLIGHTS

Criteria may be determined after allocation of abdominal organs is complete. Information as to which arm the donor has been randomized to when the enrollment criteria have been met will be placed here. Please see the attached documents for further information.

This donor is enrolled in HRSA study R380T10586 titled “The effect of therapeutic hypothermia on decreased donor renal graft outcomes – a randomized controlled trial from the Region 5 donor management goals workgroup”. This donor has been randomized to the normothermic arm in which the core temperature is to be maintained at 36.5 – 37.5°C. Please see the attached documents for further information.

HgbA1c – 5.3%
Challenges and Questions

• Non-human subjects research principles not well understood
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METHODS

STUDY DESIGN
The study was evaluated by the institutional review board at the University of California, San Francisco, and was deemed to represent nonhuman subjects research under U.S. federal law, since the patients were deceased. Furthermore, the institutional review board concluded that this study posed minimal risks to the organ recipients and that informed consent would not be required for a recipient to accept an organ from
UCSF IRB Submission Timeline

• Electronic IRB application completed and box checked for “Non-human subjects research”.

• UCSF IRB staff questioned the categorization of “Non-human Subjects Research” and referred this study for a full IRB panel review due to the possibility that the recipients might be considered human subjects of research.
IRB Full Committee Meeting

• Two IRB senior researchers reviewed the study for the IRB full committee meeting.

• Both reviewers carefully considered the recipient of the donor organs and indicated their rationale for their decisions in their written reviews (detailed review on file).

The IRB concluded that this particular study poses minimal risk and imposition to all involved and agreed that neither the donors’ next of kin nor the transplant recipients need to be consented for this research.”

Several other institutional IRBs chose to rely on UCSF IRB
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Challenges and Questions

• Non-human subjects research principles not well understood

• How do we conduct another deceased organ donor intervention trial in the current climate?
  – Letters to the editor – clinicaltrials.gov
  – Public citizen – VA ORO, OHRP, HRSA, DIREP, NEJM
  – The path forward – VA, UCSF, National Academies
Remaining Questions

• If the trial had not been stopped early for efficacy in the “overall DNDD” population, would the benefit in SCDs have been statistically significant?

• What is the role of machine perfusion in the context of mild hypothermia?
Donor Management Research Initiative (DMRI)

• Laura and John Arnold Foundation

• Significant funding over 3 years
  – To produce new evidence-based standards of care by expanding a national, web-based donor management portal and conducting rigorous randomized controlled trials to test donor interventions that maximize the quantity and quality of life-saving organs each donor is able to give.
Donor Management Research Initiative (DMRI)

• Expanding the UNOS DMG Registry Web Portal to all 58 OPOs
  – Two main barriers
    • Finances → total costs for Web Portal covered through 2018
    • Staff manual data entry → EMR data import utility created
  – Myriad possible uses for DMG data
• 2 Randomized Controlled Trials
A Randomized Trial of Mild Hypothermia and Machine Perfusion in Deceased Organ Donors for Protection against Delayed Graft Function in Kidney Transplant Recipients

- Pragmatic Multi-site Randomized Controlled Trial
- “High-risk” DNDDs receive at least one protective measure
- Same methodology as first trial:
  - Full IRB review
  - Donor research authorization
  - Recipient waiver of informed consent for research
  - Every organ offer will be “informed” of donor research status to facilitate communication with recipients/transplant centers
Study Logistics

• Communication / vetting:
  – UCSF IRB
    • Inclusion of recipients as “human research subjects”
    • No more than minimal risk, waiver of informed consent
    • No research occurring at recipient centers
  – UNOS / HRSA / OHRP* administrative reviews
  – OPO advisory boards / organ-specific committees
  – UNOS Region 5 Research Committee*
  – National UNOS communication – public comment
  – Donor Highlights section of all DonorNet offers
  – Bi-annual reporting to all stakeholders
Study Logistics

• Implementation
  – UNOS to serve as study / data coordinating center
  – Local study coordinator / site PI
  – DSMB – interim analyses
  – Pragmatic
  – Rolling addition of new OPOs
Acknowledgements

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• Arnold Foundation
• HRSA
• UNOS
• OHSU
• UCSF