Time to Reduce Mortality in End-Stage Renal Disease (TiME)

A Large, Pragmatic Cluster Randomized Trial in Maintenance Hemodialysis

Laura M. Dember, M.D.
on behalf of the TiME Trial Study Group

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TiME Trial Team

Academic Investigators

Laura Dember – U Penn
Alfred Cheung – U Utah
John Daugirdas – U Illinois
Tom Greene – U Utah
Czaba Kovesdy – U Tenn
Dana Miskulin – Tufts
Ravi Thadhani – MGH
Wolfgang Winkelmayer - Stanford

Dialysis Provider Organizations

Steven Brunelli – DaVita
Amy Young – DaVita
Mary Burgess - DaVita
Eduardo Lacson, Jr – Fresenius
Christina Kahn – Fresenius
Leland Brown - Fresenius

Penn CRCU / CCEB

J. Richard Landis
Harold Feldman
Peter Yang
Susan Ellenberg
Denise Cifelli
Rosemary Madigan
Steve Durborow

Outline

- Dialysis care in the United States
- Dialysis as a learning health system
- Rationale and design of the TiME Trial
- Efficiencies and challenges for implementing a pragmatic trial within large dialysis organizations
- Relevance of the dialysis setting to pragmatic trials in other health care delivery systems

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Health Care Settings in the HCS Research Collaboratory

- Academic medical centers
- Health plans
- For-profit hospital chain
- Safety net community health centers
- Large for-profit dialysis organizations (LDOs)

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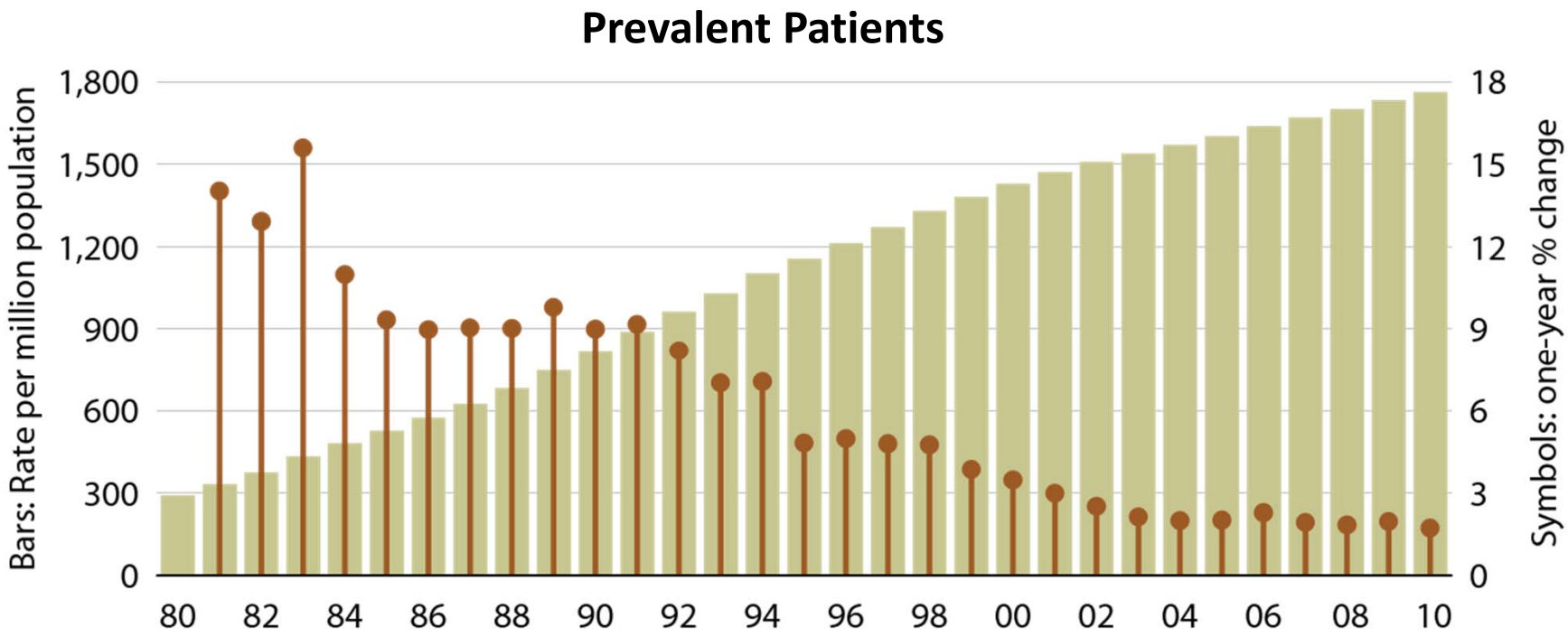
End-Stage Renal Disease in the U.S.

- 600,000 prevalent patients
  - Hemodialysis: 390,000 (65%)
  - Peritoneal dialysis: 30,000 (5%)
  - Functioning allograft: 180,000 (30%)
- 117,000 incident patients per year
  - 91% are treated with hemodialysis as initial renal replacement modality
  - 17,000 kidney transplants / year

Growth of the ESRD Program



USRDS Annual Data Report 2012

TIME

ESRD Healthcare Utilization

- Entitlement program of 1972 ensures Medicare coverage for ESRD regardless of age
- Medicare spending for ESRD patient care (total costs) is $47.5 billion / year
- ESRD costs are disproportionate: 7.5% of Medicare expenditures for 1.3% of beneficiaries

Dialysis-Dependent ESRD

- Life-long dependence on dialysis unless transplanted
- High comorbidity burden and poor quality of life
- Exceedingly high mortality
  - 21% in first year
  - 50% at 3 years

Delivery of In-Center Dialysis Care

Dialysis facilities can be:

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- Free-standing or hospital-based

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Dialysis Provider Organizations

- Dialysis Providers
  - Large dialysis organizations (LDOs): 4160 units
  - Small dialysis organizations: 500 units
  - Hospital-based or independent: 1600 units
- TiME Trial LDOs
  - DaVita 1850 units
  - Fresenius Medical Care 2100 units

} 280,000 pts

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Dialysis Facility is the Principal Source of Health Care for Many Patients with ESRD

- Patients have frequent contact with multi-disciplinary team members
- Dialysis facilities perform/provide laboratory studies, blood pressure measurements, QOL assessments, vaccinations, nutritional supplements, pharmacy services
- Burdensome for patients to go elsewhere for care
- Primary care providers often relinquish care to nephrologists and dialysis unit personnel

Nespor SL ASAIO 1992; Holley JL AJKD 1993; Bender FH AJKD 1996;
Zimmerman DL, NDT 2003; Shah N, Int Urol Nephrol 2005; Nissenson AR AJKD 2012.

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Dialysis is Already a Learning Health System

- United States Renal Data System (USRDS)
- Dialysis Outcomes and Practice Patterns Study (DOPPS)
- Dialysis provider organization data
- Quality improvement initiatives

But very little data from randomized clinical trials!

Strippoli GFM et al J Am Soc Nephrol 2004

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Many Unanswered Questions in Dialysis about Fundamental Aspects of Care

- Duration of hemodialysis sessions?
- Dialysis solution potassium concentration?
- Blood pressure target?
- Phosphorus target?
- Hemoglobin target?
- Preventive health care?
- Anticoagulation for atrial fibrillation?

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Determination of "Adequate" Hemodialysis

- Focus has been on clearance of small solutes (urea)
- Session duration decreased markedly with the development about 20 years ago of more efficient dialyzers that provide "adequate" urea clearance in 3-4 hours rather than 5-6 hours.
- But small solute clearance is not the full story
  - Fluid removal
  - Hemodynamic stability
  - Removal of sequestered solutes

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Observational Studies of Time

Reference	Source	Longer Treatment Time
Tentori et al NDT 2012	DOPPS	Lower mortality
Flythe et al Kidney Int 2012	Fresenius Medical Care	Lower mortality
Ramirez et al CJASN 2012	CMS ESRD CPM Project	Higher mortality (not statistically significant)
Brunelli et al Kidney Int 2010	Fresenius Medical Care	Lower mortality
Saran et al Kidney Int 2006	DOPPS	Lower mortality
Marshall et al Kidney Int 2006	ANZDTA	Lower mortality

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TiME Trial Hypothesis

Thrice weekly hemodialysis with session durations of at least 4.25 hours improves outcomes compared with usual care.

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TiME Trial Design

- Cluster Randomization by dialysis facility
- Intervention

  Facility adopts approach of recommending minimum dialysis session duration of 4.25 hours for patients new to dialysis
- Usual Care

  No trial-driven facility approach for dialysis session length
- Patient Eligibility

  All patients initiating treatment with maintenance hemodialysis at participating facilities
- Outcomes:

  Mortality, hospitalization rate, HRQOL

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Primary Treatment Analysis Population

- Comprised of subset for which separation in session duration between treatment groups is likely
  - Exclude large patients (V >42.5L)
- Expect 63% of participants to be in primary treatment analysis population

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Sample Size

- 402 facilities, 6437 patients (4023 primary analysis population)
- Average cluster size: 16 (10 in primary analysis population)
- Power 80% for HR 0.85
- Assumptions
  - Mortality rate 18% per year
  - Intra-class correlation 0.03
  - 5% loss to f/u per year

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Data Acquisition

- Clinical and administrative data are transmitted electronically from individual facilities and centralized laboratory to LDO data warehouses
- De-identified data elements are transmitted from LDO data warehouses to Penn DCC

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Pragmatic Features

- All patients starting dialysis are eligible
- Intervention is delivered by clinical providers
- Outcomes:
  - ascertained from routine clinical data
  - derived from data elements common to all sites
- Adherence to intervention at the patient level will be promoted using systems already in use
- Highly centralized implementation approach
- Testing effectiveness rather than efficacy

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Dialysis Environment for Pragmatic Trials

- Dialysis organizations have the features of large, highly structured businesses

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Dialysis Environment for Pragmatic Trials

- Dialysis organizations have the features of large, highly structured businesses
  - Multiple administrative levels, regional divisions, and governance levels
  - Operate under business rules and conventions
  - Operate in a highly regulated environment which necessitates a level of uniformity and rigidity

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Dialysis Environment for Pragmatic Trials

- But at the dialysis facility level there is always some degree of variability in practices and conventions
  - Small team of care providers
  - Local culture and “neighborhood flavor”

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We are accommodating and leveraging aspects of both the centralized business structure and the local operations

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Example: Facility Selection

Facility Eligibility

1. Willingness to adopt minimum session duration approach
2. Current median treatment time ≤3.5 hours
3. Capacity to increase times (14 – 18 patients)

Both centralized systems and local activities will be used to determine facility eligibility

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Example: Facility Selection

- Central level:
  - Screen for facilities with treatment time ≤ 3.5 hours
  - Use centrally-developed tools for determining operational capacity for increased time
- Local level:
  - Supplement centralized assessment of operational capacity with local determination
  - Willingness to participate is a local decision and implementing the intervention requires formal approval by facility's governing body

Example: Adherence to Intervention

- Central level:
  - Use provider organization's electronic system to "label" patients as trial participants
  - Use centralized data systems for monitoring prescribed and delivered treatment times by participating facilities
- Local level:
  - Use direct communication and trouble shooting with individual facilities

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Relevance of Dialysis Setting to Other Health Care Settings for Pragmatic Trials

- Model for trials involving:
  - Patients with large burden of illness and complex disorders
  - Interventions implemented at the health care delivery site
  - Large number of centers, broad geographic distribution
  - Research alliances between academic institutions and business organizations

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Relevance of Dialysis Setting to Other Health Care Settings for Pragmatic Trials

- Other “chains”
  - Nursing homes
  - Rehabilitation facilities
  - Chemotherapy centers
  - Free-standing surgical centers
  - Pharmacies
  - IVF centers

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