Industry Panel Session

DDT-KD Consortium

"What are the Challenges and Needs of Industry?"

Moderator:

Dr. John-Michael Sauer (C-Path)

Panelists:

Dr. Gary Friedman (Pfizer)

Dr. Dennis Andress (AbbVie)

Dr. Irene Nunes (Merck)

Dr. Frank Czerwiec (Otsuka)

Drug Development Tools for Kidney Disease

Industry Panel Introduction

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Dr. Gary Friedman
Pfizer

Economics of Pre- and Post-RRT Therapeutics

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COST of Pre-RRT Treatment

- Medication
- Hospitalization

- Quality of Life

COST of Post-RRT Treatment

- Medication
- Hospitalization
- Dialysis
- Transplantation
- Quality of Life

USRDS and SRTR Data (2013):
Global Imperative for NMEs to Preempt Renal Replacement Therapy

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American Journal of Transplantation

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USRDS and SRTR Data (2013):
Rise of RRT End-Users / Insufficient Reversal of RRT Dependence

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Prevalent counts of reported ESRD:
all patients, U.S. and territories

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Diabetes	138,295	147,417	155,699	163,340	171,200	178,882	187,441	195,834	204,499	213,662	222,867	230,683	239,837
Hypertension	94,861	99,505	104,222	109,229	113,658	117,952	122,352	127,640	133,238	139,900	146,398	152,139	159,049
Glomerulonephritis	77,893	80,606	83,195	85,318	87,861	90,311	92,814	94,992	97,252	99,388	101,527	103,783	106,012
Cystic kidney disease	18,043	18,850	19,653	20,489	21,308	22,333	23,466	24,550	25,792	26,922	27,963	28,888	29,881
Other urologic	8,215	8,540	8,916	9,145	9,334	9,057	8,610	8,263	8,033	7,830	7,708	7,488	7,447
Other cause	33,990	35,619	37,338	38,807	40,469	42,966	45,930	48,486	50,865	53,394	55,962	58,265	59,714
Unknown cause	16,402	17,239	18,030	18,732	19,451	20,471	21,761	22,830	23,646	24,503	25,318	25,797	25,977
Missing disease	3,622	3,799	3,993	4,343	4,565	4,832	5,164	5,319	5,541	5,934	6,446	7,072	8,988
All	391,321	411,575	431,046	449,403	467,846	486,804	507,538	527,914	548,866	571,533	594,189	614,115	636,905
Recovery of renal function	8,169	9,213	10,421	11,703	13,208	14,909	16,696	18,805	20,991	23,539	25,923	28,091	30,854

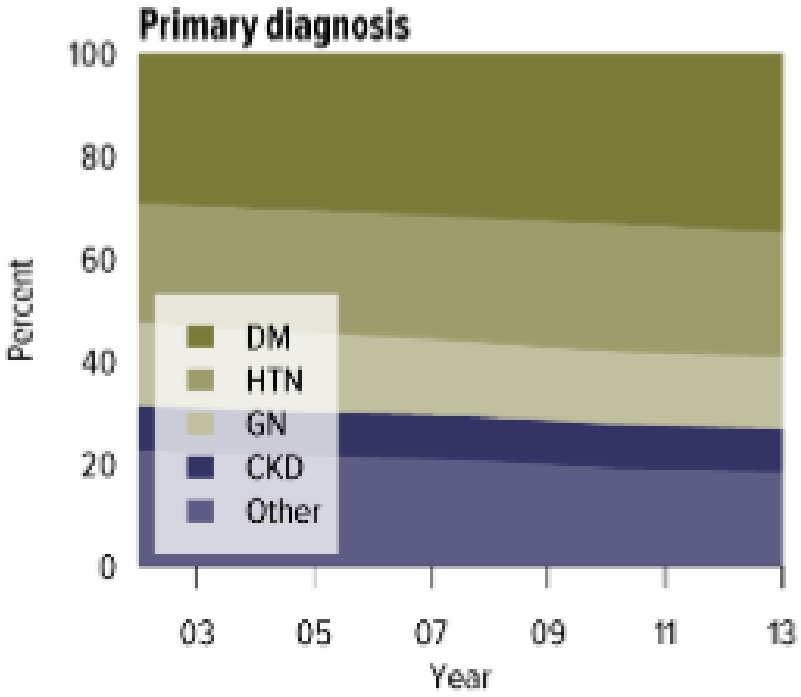
2.3% 2.7% 3.3% 4.2% 4.8%

(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)

- ✓ **Hemodialysis / Peritoneal Dialysis Annually: $40,000-$80,000 per patient**
- ✓ **To <u>STABILIZE</u> RRT Population ≡ <u>Double</u> the Rate of "Recovery of Renal Function"**
- ✓ **To <u>REDUCE</u> RRT Population ≡ <u>Triple</u> the Rate of "Recovery of Renal Function"**

Prioritization of NME Development Resources

- **Chronic Kidney Disease**
  - Diabetes Mellitus
  - Hypertension
  - GN/NS (SLE, IgAN, MGN, MPGN, FSGS)
  - Cystic Renal Diseases
  - All others (AKI, vascular disease, neoplasia, infection, congenital)
- **Acute Kidney Injury**
  - Reversible
  - Non-reversible



(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)

USRDS and SRTR Data (2013):
Global Imperative for NMEs Prior to Renal Replacement Therapy (RRT)

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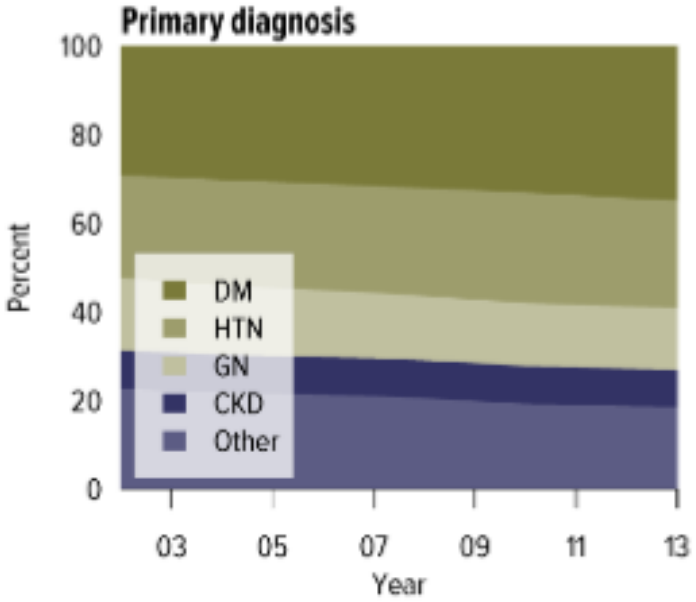
- **Economic impacts**
  - IDDM / NIDDM
    - Intensive insulin management; oral hypoglycemics, weight loss/bariatric surgery
    - Up to 35% progress to require RRT
  - Hypertension
    - oral anti-HTN therapy, daily BP monitoring; <10% progress to require RRT
  - Glomerular diseases—immunosuppression and/or extracorporeal therapies
    - Reversible
    - Non-reversible
  - Cystic Renal Disease co-morbidities
    - Renal cyst infection and/or hemorrhage; Renal cystectomy; Nephrectomy
    - Hepatic cyst formation & hepatic parenchymal loss
  - AKI
    - ICU care
    - <5% require permanent RRT



(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)

USRDS and SRTR Data (2013):

Renal Replacement Pre-transplantation driven by patients <50 years old

Post-transplant costs driven by co-morbidities in patients <50 years old

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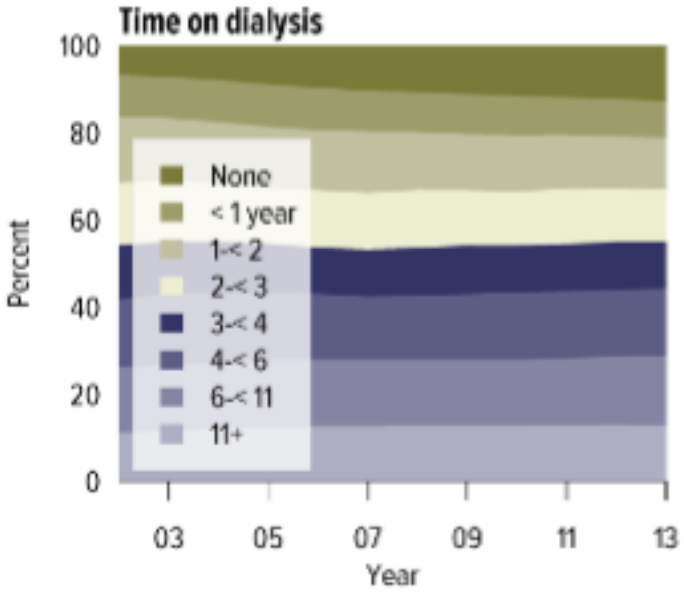

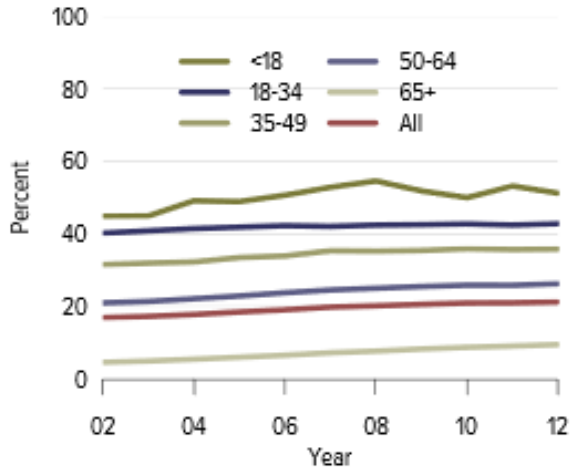

- **Post-Transplant Economic impacts**
  - Organ Rejection
  - IDDM / NIDDM
  - Hypertension
  - Hyperlipidemia
  - Recurrent Disease
  - Cancer
  - Infection

Medication	% 1yr post-tx	Medication	% 2-3yr post-tx
Tacrolimus	51.2	Mycophenolate	65.6
Sulfamethoxazole-Trimethoprim	47.9	Prednisone	64.9
Prednisone	41.6	Hydrocodone	41.3
Valganciclovir	38.7	Amlodipine Besylate	38.1
Hydrocodone	30.1	Metoprolol Tartrate	32.0
Amlodipine Besylate	27.5	Sulfamethoxazole-Trimethoprim	28.4
Oxycodone	27.5	Oxycodone	27.0
Metoprolol Tartrate	27.1	Amoxicillin	26.7
Furosemide	24.0	Furosemide	25.9
Ciprofloxacin	22.2	Omeprazole	24.6
Omeprazole	19.9	Ciprofloxacin	24.5
Amoxicillin	17.7	Azithromycin	23.1
Nystatin	16.2	Lisinopril	22.7
Docusate Sodium	15.2	Simvastatin	21.0

(OPTN/SRTR 2013 Annual Data Report; AmJTransplant, JAN2015, Vol 15, Issue S2; pp 4-13)

Unmet Needs in Kidney Disease:
Disease-specific Outcomes

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DISEASE ENTITIES	CLINICAL & PATIENT REPORTED OUTCOMES
• **AKI**	• Proportion of subjects without further functional loss; Proportion of subjects with reversal of functional loss; Proportion of subjects relegated to RRT
• **Diabetes Mellitus**	• Delay time to renal functional decline by NN% from baseline; PRO/QoL
• **Hypertension**	• % time with adequate BP control vs. baseline; % increase of proteinuria vs. baseline; PRO/QoL
• **Glomerular Diseases** *(FSGS, SLE, IgAN, MGN)*	• Proportion of subjects without further functional loss; proportion of subjects with reversal of functional loss; Proportion of subjects reaching CKD 5; PRO/QoL
• **Cystic Kidney Diseases**	• Renal volume stabilization • Proportion of subjects without further functional loss; proportion of subjects with reversal of functional loss; Proportion of subjects reaching CKD 5 • PRO/QoL

Industry Drivers to Address Unmet Needs in Kidney Disease

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Biomarker Goals—Industry Needs:
Balance Benefit/Risk: Efficacy/Safety Assessments

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SAFETY

- Current PSTC and SAFE-T outputs may provide sufficient starting point.
- Accumulation of data from consortia members and academia may further flesh out/refine utility
- Timely safety decisions to meet “Early Development” needs

EFFICACY

- Serum creatinine, Alb/Cr ratio, eGFR shift tables have been “industry standard”
- Limited success moving NMEs forward to date
- Resources dedication to AKI and CKD NME development programs more likely with “more proximal” biomarkers of efficacy demonstration

Renal Biomarkers: Understanding the Issues

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Dr. Frank Czerwiec
Vice President, Global Clinical Development
Otsuka Pharmaceutical

Using Biomarkers for CKD Treatments: Issues

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- Kidney-specific issues:
  - Discrete and complex filtration units
  - Limited repair/regeneration (inflammation/scarring)
  - Damage control through redundancy (delays detection)
- Efficacy biomarker (surrogate endpoint) issues:
  - Complicated validation prolonged by need for multiple therapies
  - Dissociated effects on biomarker and on outcome (especially for early markers)
  - Confounding off-target effects
- Treatment issues:
  - Early treatments (e.g., HbA1c control) take many years to detect renal outcomes (UKPDS-9 years for SCr Doubling, DCCT/EDIC-26.5 years for persistent CKD-3)
  - Few treatments improve renal outcomes in late disease (e.g., ACEi or ARB)
- Harmonization issues:
  - Understanding the relationship of biomarkers and accepted outcomes
  - Harmonized use of biomarkers

“Many people who receive a serious medical diagnosis dream about heading off on a global adventure.”

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Yukari Iwatani Kane and her husband Patrick Kane on a gorilla trek in the Virungas in Rwanda in November 2014. *PHOTO: YUKARI IWATANI KANE WSJ 2015 SEP 21*

“Dr. Riordan said he didn’t see any reason to stop me from going because I wasn’t actively sick.”

eGFR = 11 mL/min/1.73m^2

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Unanticipated "Off-target" Effects can Dissociate Biomarkers from Later Disease Outcomes

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- Everolimus is often used as an anti-rejection agent for transplantation
- Early evidence suggest it is less nephrotoxic than calcinurin inhibitors in CKD-1
- **Recent evidence in oncology suggests it is associated with AKI in CKD 2-4**
- Off-target effects may explain everolimus' "dissociation" of eGFR and TKV in ADPKD:
  "Unexpectedly, a significant reduction in the TKV (P = 0.02) coincided with a significant worsening of renal function and a drop in estimated GFR (P = 0.004) after 1 year of treatment with everolimus … Among male patients with ADPKD who had an estimated GFR of less than 60 ml per minute, those in the everolimus group had a significantly more rapid decline in the estimated GFR than did those in the placebo group. This was not seen among male patients with an estimated GFR of 60 ml per minute or more … " G. Walz 2011 NEJM Letter

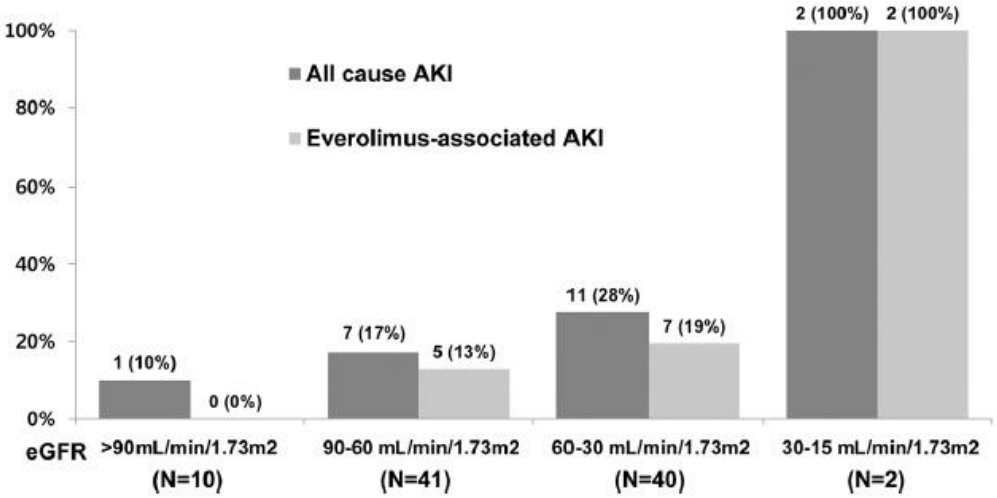

Figure 2 Incidence of AKI according to baseline eGFR categories in the RCC group. The incidence of all-cause AKI and everolimus-associated AKI increased progressively with decreasing eGFR ($P = 0.029$ and $P = 0.004$ for trend, respectively).

S.H. Ha 2014 BMC Cancer

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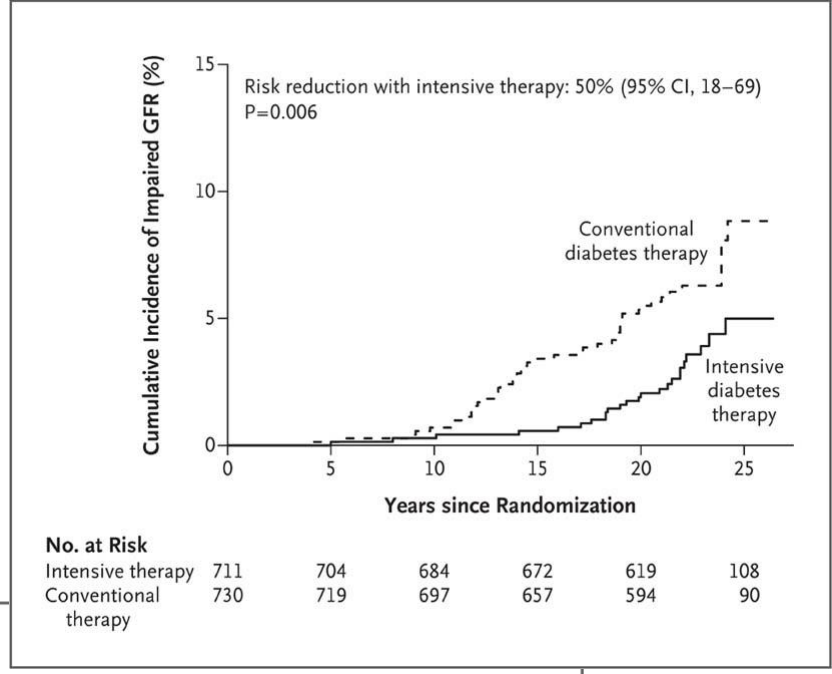
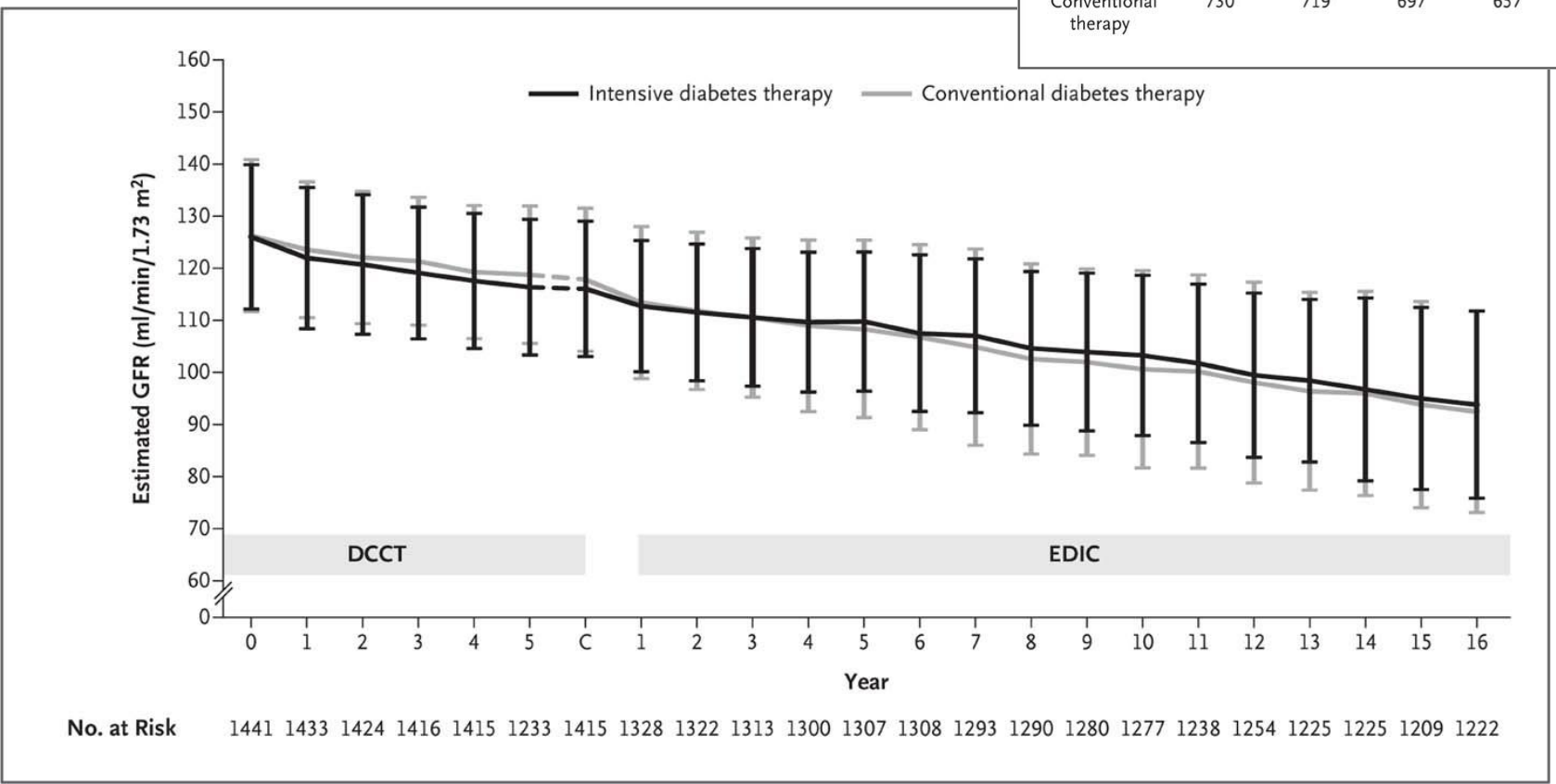
DCCT-EDIC Trials: Nephropathy Results over 20 Years

I.H. de Boer, et al., 2011 NEJM





Relationship of Outcomes and Biomarkers: Understanding Clinical Interpretability

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- **RENAAL** Trial[1]: (N=1513, age 31-70 yrs, NIDDM, mean SCr=1.9 mg/dL, losartan vs. placebo)
  - **↓16% Dbl SCr/ESRD/Death**

- **IDNT** Trial[2]: (N=1715, 30-70 ($\bar{x}$=59) yrs, NIDDM, SCr 1.0♀,1.2♂-3.0 mg/dL, $\bar{x}$=1.67, irbesartan vs. placebo)
  - **↓23% Dbl SCr/ESRD/Death**

- **AASK** Trial[3,4]: (N=1094, 18-70 ($\bar{x}$=54) years, HTN, eGFR 20-65 mL/min/1.73m^2, $\bar{x}$= 46, ramipril vs. amlodipine)
  - **↓38% Dbl SCr/ESRD/Death**

[1] Brenner BM, NEJM 2001, [2] Lewis EJ, NEJM 2001. [3] Wright JT, JAMA 2002, [4] Agodoa LY, JAMA 2001

Relationship of Outcomes and Biomarkers: Understanding Clinical Interpretability

DDT-KD Consortium

- **RENAAL** Trial[1]: (N=1513, age 31-70 yrs, NIDDM, mean SCr=1.9 mg/dL, losartan vs. placebo)
  - **↓16% Dbl SCr/ESRD/Death → 0.8 mL/min/1.73m^2/year difference**

    15% reduction in eGFR decline (4.4 vs. 5.2 mL/min/1.73m^2/year)

- **IDNT** Trial[2]: (N=1715, 30-70 ($\bar{x}$=59) yrs, NIDDM, SCr 1.0♀,1.2♂-3.0 mg/dL, $\bar{x}$=1.67, irbesartan vs. placebo)
  - **↓23% Dbl SCr/ESRD/Death → 1.0 mL/min/1.73m^2/year difference**

    15% reduction in Creatinine clearance decline (5.5 vs. 6.5 mL/min/1.73m^2/year)

- **AASK** Trial[3,4]: (N=1094, 18-70 ($\bar{x}$=54) years, HTN, eGFR 20-65 mL/min/1.73m^2, $\bar{x}$= 46, ramipril vs. amlodipine)
  - **↓38% Dbl SCr/ESRD/Death → 1.16 mL/min/1.73m^2/year difference**

    36% reduction in eGFR decline (chronic slope = 2.07 vs. 3.22 mL/min/1.73m^2/year)

[1] Brenner BM, NEJM 2001, [2] Lewis EJ, NEJM 2001. [3] Wright JT, JAMA 2002, [4] Agodoa LY, JAMA 2001

Harmonizing Approaches to Efficacy Biomarkers

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- 2014 EU Guideline for products to prevent/slow progression of CRI

  "Recommendations are given regarding assessment methods to be used in relation to selected endpoints, strategy and design of clinical trials, criteria for the choice of comparator, study duration, factors confounding the interpretation of study results, specific aspects to be considered for paediatric and elderly patients, and for safety assessment, focusing on overlapping safety signals **and encouraging broader exploration of more sensitive tools, namely biomarkers**."

- 1998 FDA Evidence for Effectiveness Guidance:

  "A **pharmacologic effect that is accepted as a validated surrogate endpoint can support ordinary approval** (e.g., blood pressure effects, cholesterol lowering effects) and a **pharmacologic effect that is considered reasonably likely to predict clinical benefit can support accelerated approval** under the conditions described in 21 CFR 314 Subpart H and 21 CFR 601 Subpart E (e.g., CD4 count and viral load effects to support effectiveness of anti-viral drugs for HIV infection). … the approval of beta-interferon (Betaseron) for prevention of exacerbations in multiple sclerosis was based on a single multicenter study, at least partly because there were both **a decreased rate of exacerbations and a decrease in MRI-demonstrated disease activity** — two entirely different, but logically related, endpoints."

- 2012 Everolimus in Tuberous Sclerosis Complex renal angiomyolipoma

  Approved for "adults with renal angiomyolipoma and tuberous sclerosis complex (TSC), not requiring immediate surgery. The effectiveness of AFINITOR in the treatment of renal angiomyolipoma is **based on an analysis of durable objective responses in patients treated for a median of 8.3 months. Further follow-up of patients is required to determine long-term outcomes**."