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Urologic Complications of Diabetes: UroEDIC Our 20-year Journey

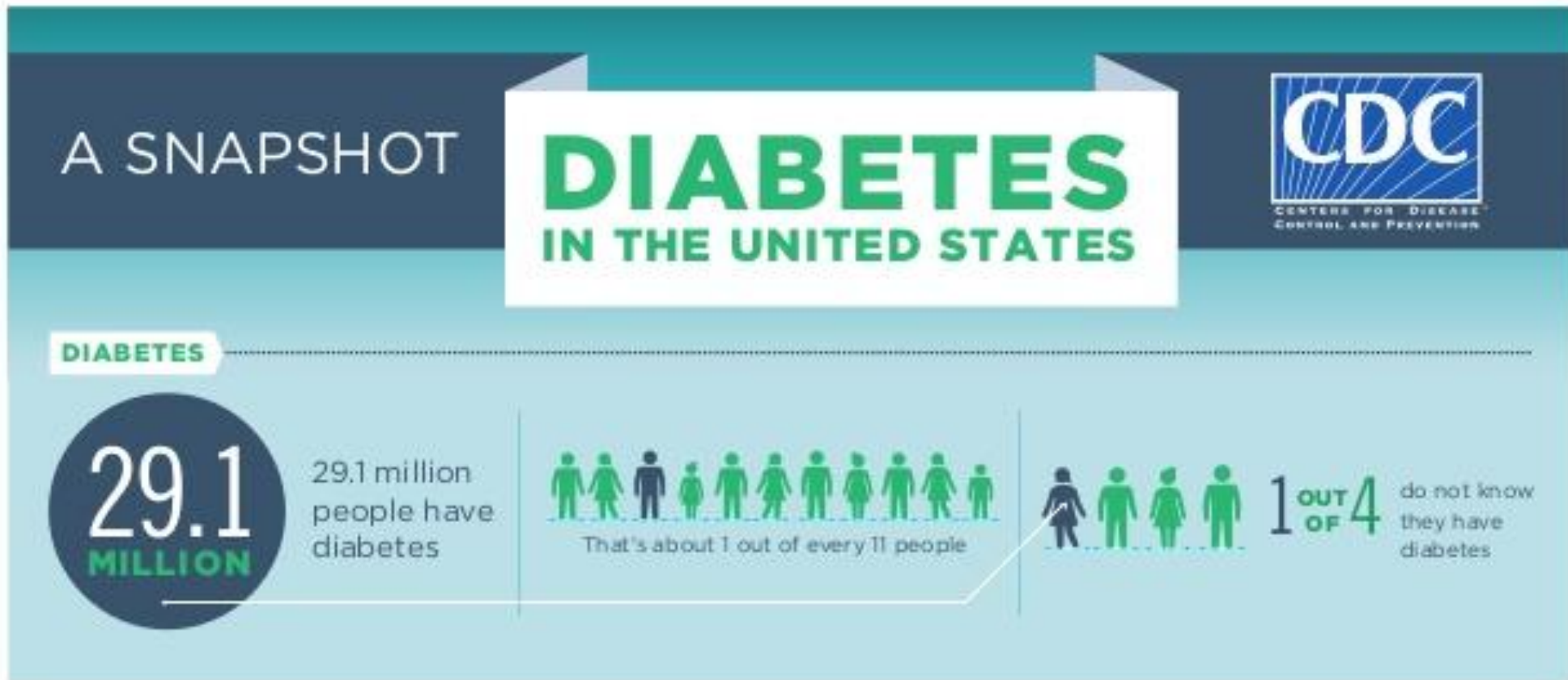


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Diabetes Epidemic



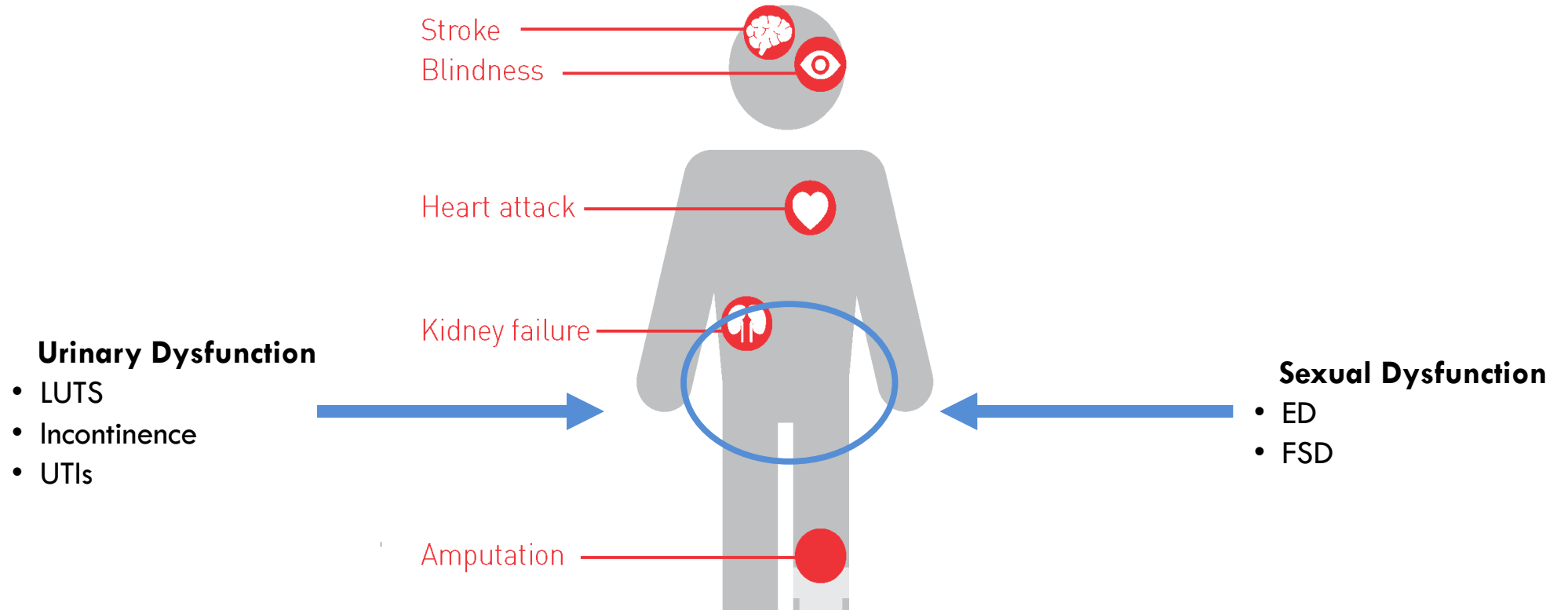
- 95% of diabetes cases in the US are associated with Type 2 diabetes (NIDDM)
- 5% associated with Type 1 DM (IDDM) – 85% living as adults



Diabetes and Urological Disorders

Consequences

Diabetes can lead to complications in many parts of the body and increase the risk of dying prematurely.





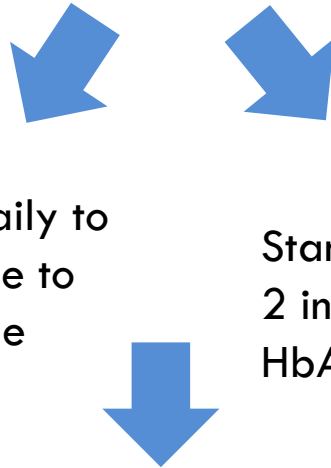
Early Findings: 1965-2000

- Known associations with erectile dysfunction and cystopathy-primarily clinical descriptions
- Comprehensive data in humans is limited (convenience samples, sample size, methodology, gender)
- Animal models offer new mechanistic insight...but...
 - Current clinical paradigms use trial and error treatment of symptoms with no impact on disease progression
 - At the time, no evidence-based intervention or prevention approaches for urologic complications in diabetes



The Diabetes Control and Complications Trial (DCCT)

multicenter, randomized clinical trial to compare ***intensive*** with ***conventional*** diabetes therapy on on early vascular and neurologic complications in T1DM (aged 13-39) (1983-1993)
N=1441



Intensive

At least 3 insulin injections daily to achieve HbA1c levels as close to nondiabetic range as possible (<6.05%)

Conventional

Standard of care in the 1980s: 1 or 2 insulin injections daily to prevent HbA1c levels exceeding 13.5%

Intensive Insulin Therapy Dramatically Reduced Retinopathy, Neuropathy, and Kidney Disease

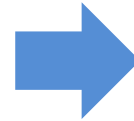


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Epidemiology of Diabetes Interventions and Complications (EDIC) Study

The Diabetes Control and Complications Trial (DCCT)

- Trial suspended and all participants were advised to continue/begin intensive therapy under guidance of their physicians (1983-1993)



Epidemiology of Diabetes Interventions and Complications (EDIC)

Observational (annual) study of the DCCT cohort to examine long term impact of initial randomization and subsequent glycemic control (1994-present) (96% response rate)



Diabetes Control

- Randomization – Metabolic Memory
- Current HbA1c – Glucotoxic effects
- Annual HbA1c – Diabetic complications



UroEDIC

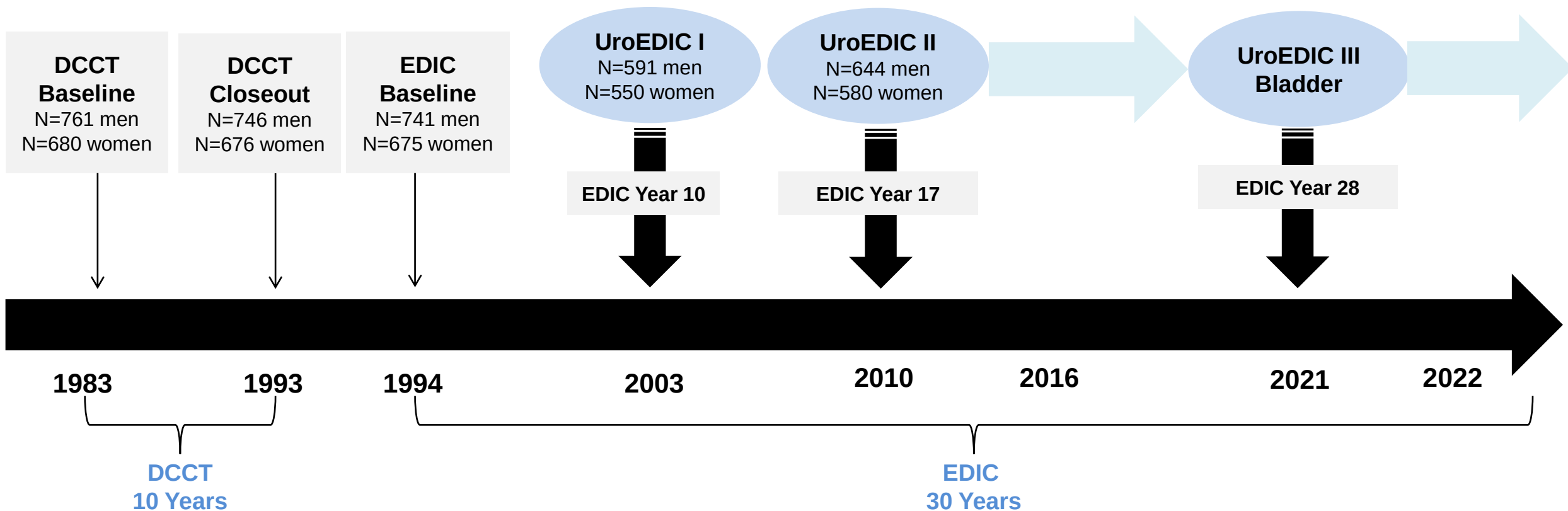
2003, 2010-current

Ancillary study to examine urologic disease



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DCCT, EDIC, UroEDIC Timeline



UROEDIC I Baseline (EDIC Year 10)

- Understand the Burden of Urologic Complications in T1DM

UROEDIC II Follow-up (EDIC Years 17-current)

- Incidence, Progression, Risk factors
- Effects of hormonal status and prostate growth
- Quality of Life

UROEDIC III Bladder (EDIC Year 10)

- Longitudinal Phenotyping
- Full Spectrum of Bladder Dsfxn
- Mechanistic Studies RNAseq



Validated & Standardized Protocols:

- **BPH/LUTS:** AUASI, BII, BPH-QOL
- **UI/OAB:** NHANES UI, Sandvik Severity, Bother, Interference, ICIQ-OAB
- **UTI:** NHANES UTI Battery
- **KSD:** NHANES UTI Battery
- **Sexual Function:** IIEF, FSFI, Sexual Function QOL
- **Quality of Life:** EQ-5D, DQOL, SF-36, SCL-90R
- **Serum Measures:** Total and Free Testosterone, PSA, AMH
- **Bladder Retention Measures:** Post Void Residual Urine
- **Urine Measures:** RNA seq



Urological Disorders at Baseline UroEDIC (2003)

	Respondents	Prevalence
	N (%)	%
Women	508	
LUTS	506 (99)	22
FSD	297 (58)	42
UI	493 (97)	31
Men	551	
LUTS	550 (99)	24
ED	525 (95)	45
Low desire	506 (92)	40

- Mean age at time of these assessments <40 years
- Definitions based on moderate to severe ED and UI



Glycemic control and Erectile Dysfunction

Table 1. Multivariable logistic regression model of the difference between DCCT intensive vs conventional glycemic therapy in the prevalence of ED

	OR (95% CI)	p Value (likelihood ratio chi-square test)
DCCT intervention (intensive vs conventional glycemic therapy)*		
Primary prevention cohort	1.24 (0.68, 2.28)	0.49
Secondary intervention cohort	0.33 (0.18, 0.60)	<0.001
HbA1c at eligibility (per HbA1c%)	1.36 (1.19, 1.56)	<0.001
Diabetes duration (per mo)	1.00 (0.99, 1.01)	0.87
Age (per yr)	1.13 (1.09, 1.17)	<0.001

- HbA1c at trial baseline associated with 36% increased odds of ED onset 20 years later
- Early glycemic control important for future risk of ED - **“Metabolic memory”**

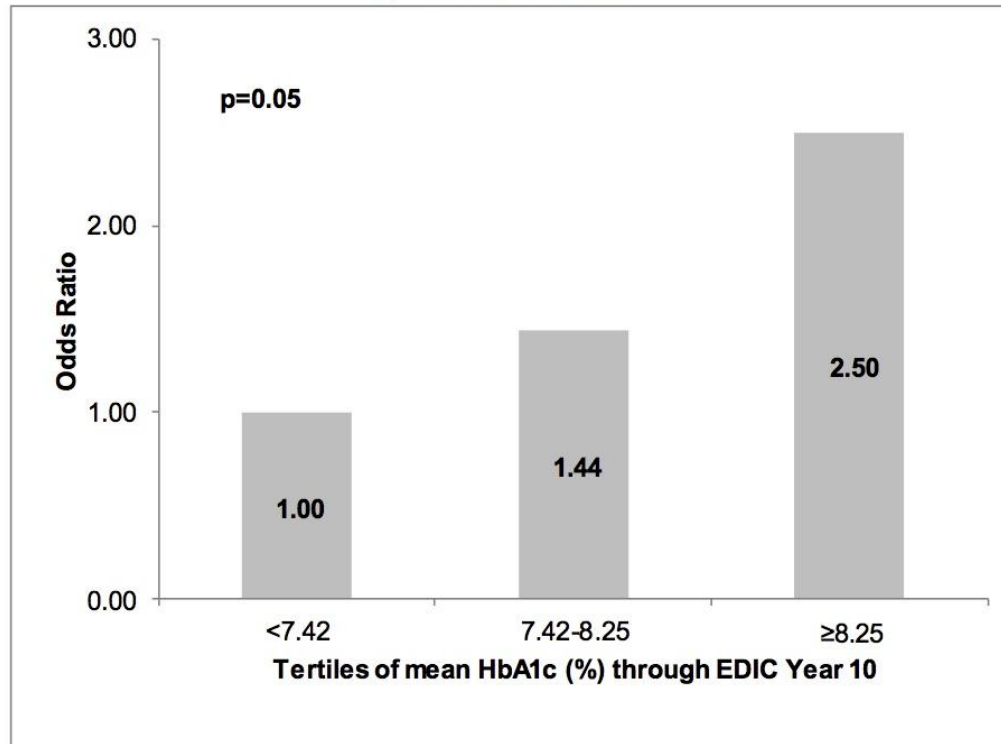


Glycemic control and Urinary Dysfunction

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Urinary Incontinence

Figure 2. Multivariable adjusted odds ratios* of incident weekly UI at EDIC year 17 by tertiles of HbA1c[†]



Note: p-value based on overall Wald chi square test for parameter estimate of HbA1c in multivariable logistic regression model.

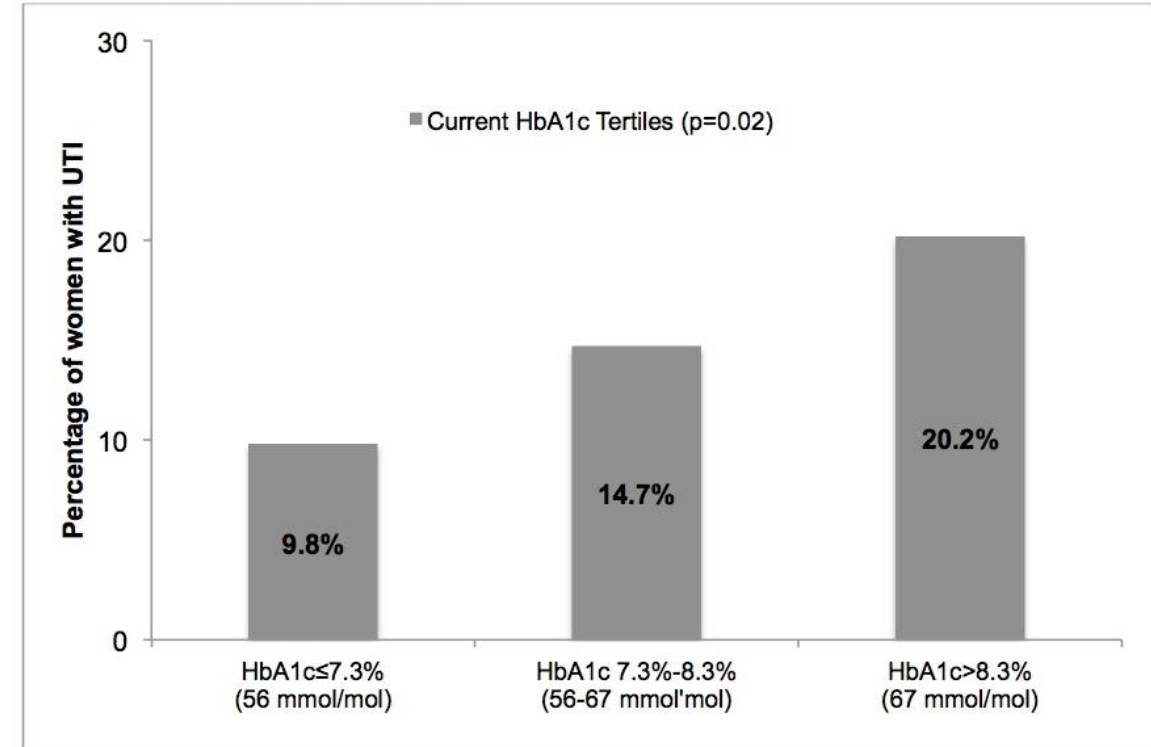
* Odds of incident weekly UI adjusted for attained age, DCCT cohort assignment, DCCT treatment group, EDIC mean daily insulin dose, BMI, parity, hysterectomy, autonomic neuropathy, and UTI during EDIC.

† EDIC mean HbA1c through Year 10 (HbA1c reference <7.42%).

41% increase in odds of UI per HbA1c% increase over the long term - *sustained glycemic control*

Urinary Tract Infections

Figure 2. Percentage of women with UTI* at EDIC Year 17 per tertile of current EDIC Year 16 HbA1c



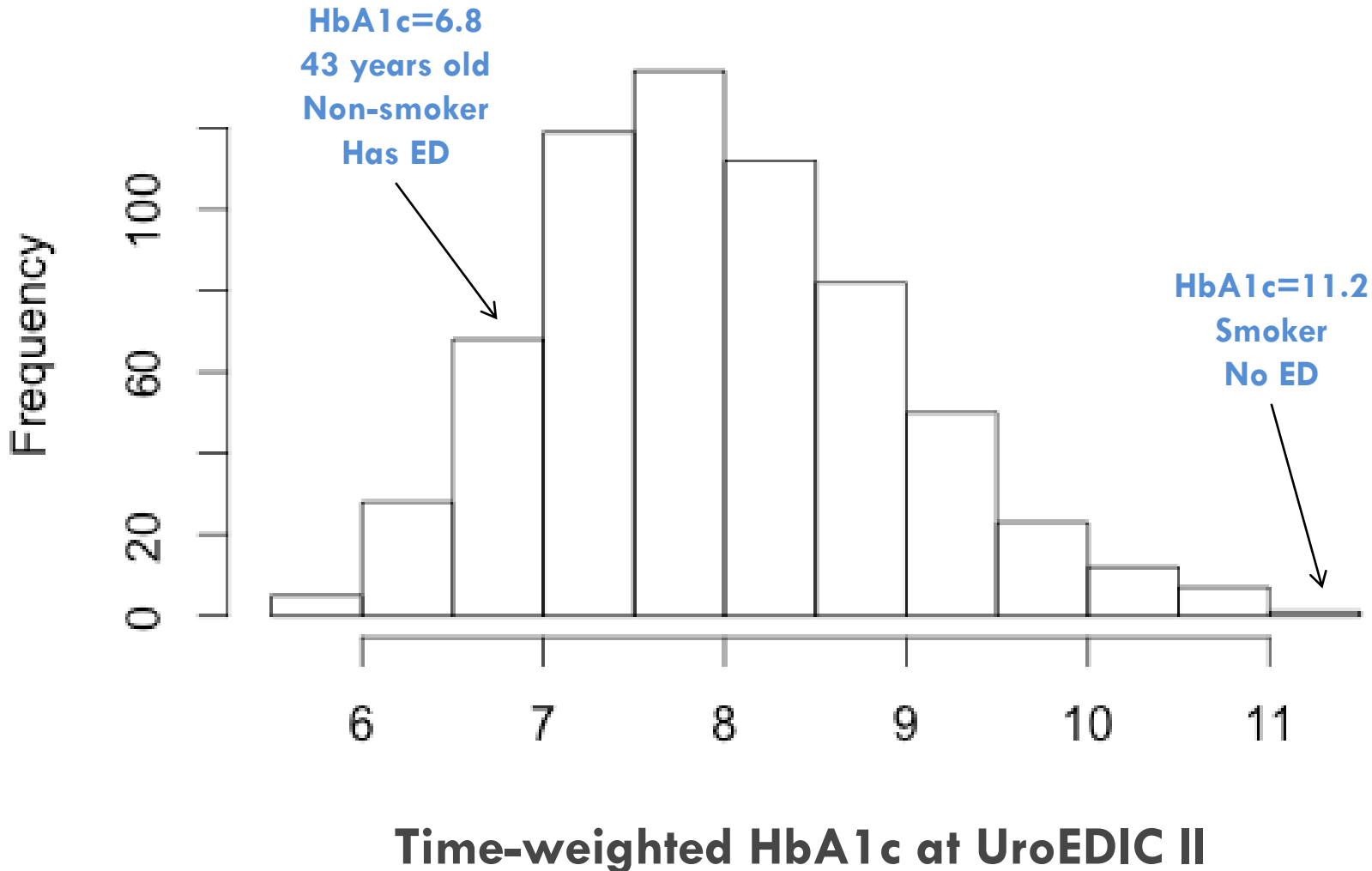
Note: p-values based on Mantel-Haenszel chi square test

* UTI defined as ≥1 episode in past 12 months.

21% increase in UTI count per HbA1c% increase contemporaneously - *glucotoxic event*

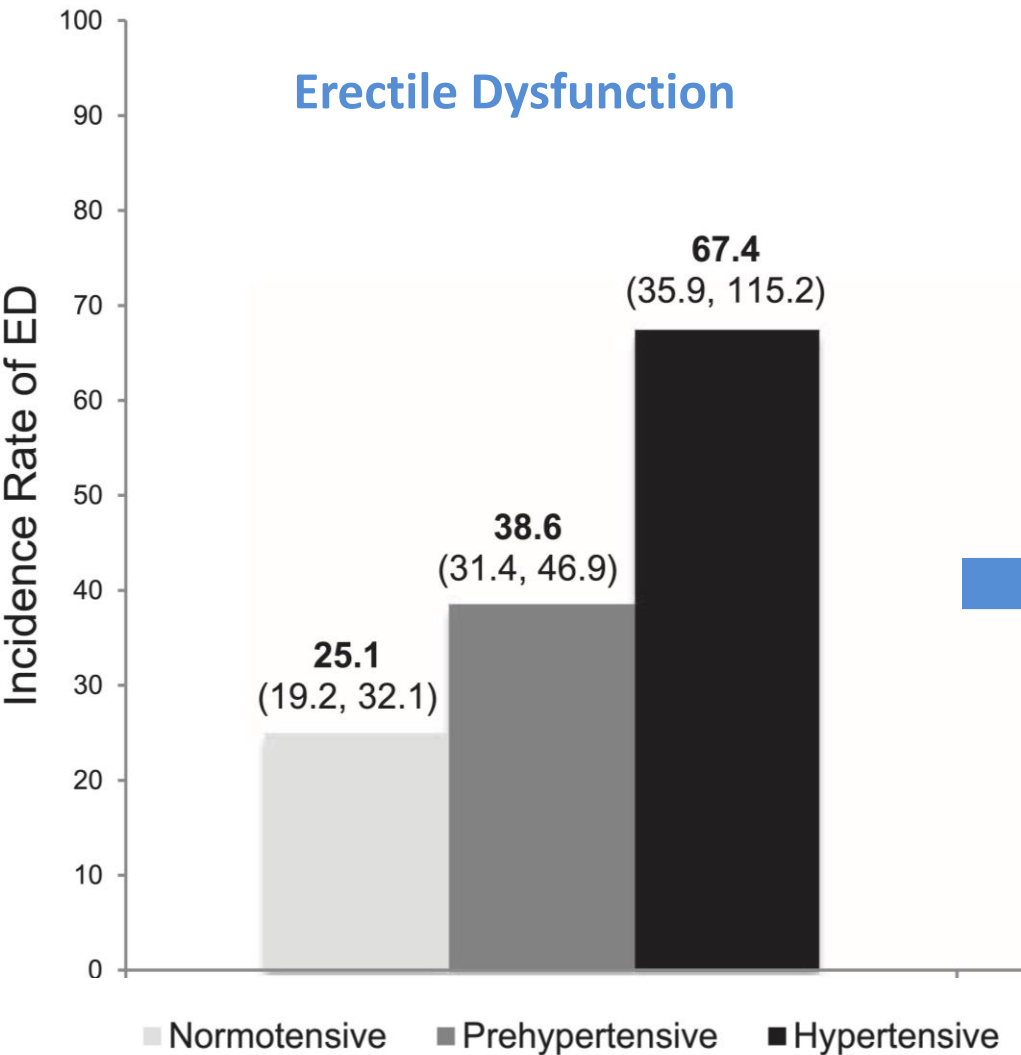


Not all about glycemic control





Blood Pressure & Hypertension



Normo & Pre Hypertensive



Table 3. Multivariable Adjusted Hazard Ratios (95%CI)* for Risk of ED by Preceding 3 Year Mean Systolic, Diastolic and Pulse Pressure

Characteristic	No Antihypertensive Use
Systolic Blood Pressure (per 10mmHg increase)	1.21 (1.04, 1.41)
Diastolic Blood Pressure (per 10mmHg increase)	1.25 (0.99, 1.59)
Pulse Pressure (SBP-DBP) (per 10mmHg increase)	1.17 (0.96, 1.42)

*Adjusted for time-dependent versions of Age, Cigarette Smoking and time-weighted HbA1c
Note: Separate Cox proportional hazards models built for each blood pressure variable



Autonomic neuropathy

Erectile Dysfunction / LUTS in Men

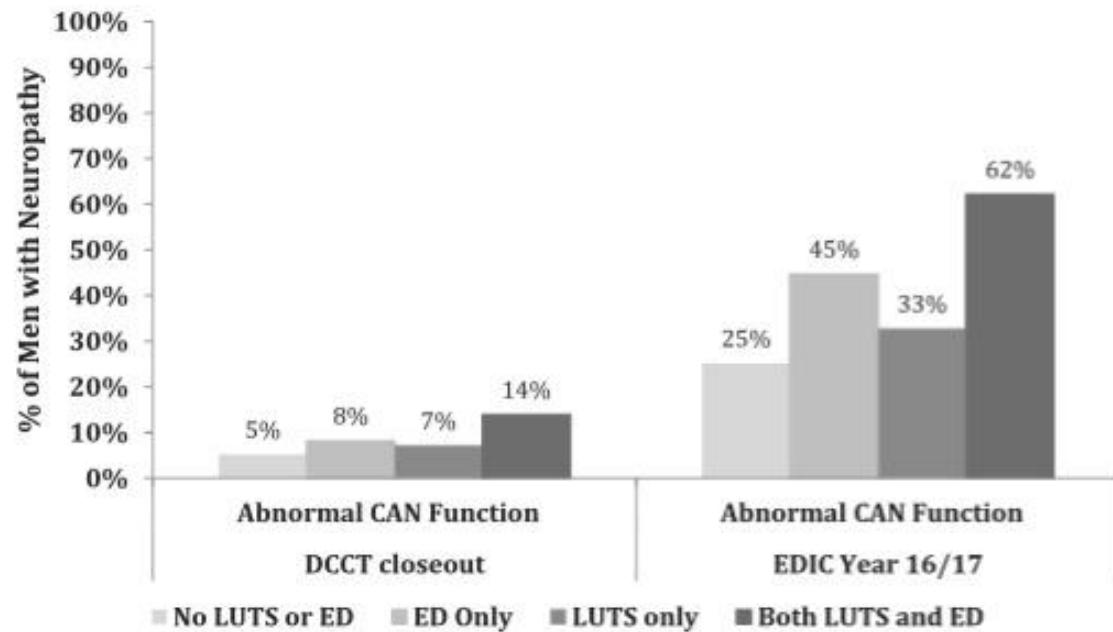


Figure 3. Prevalence of CAN at DCCT closeout and EDIC year 16/17 by ED and LUTS status at EDIC year 17.

FSD / Urinary Incontinence in Women

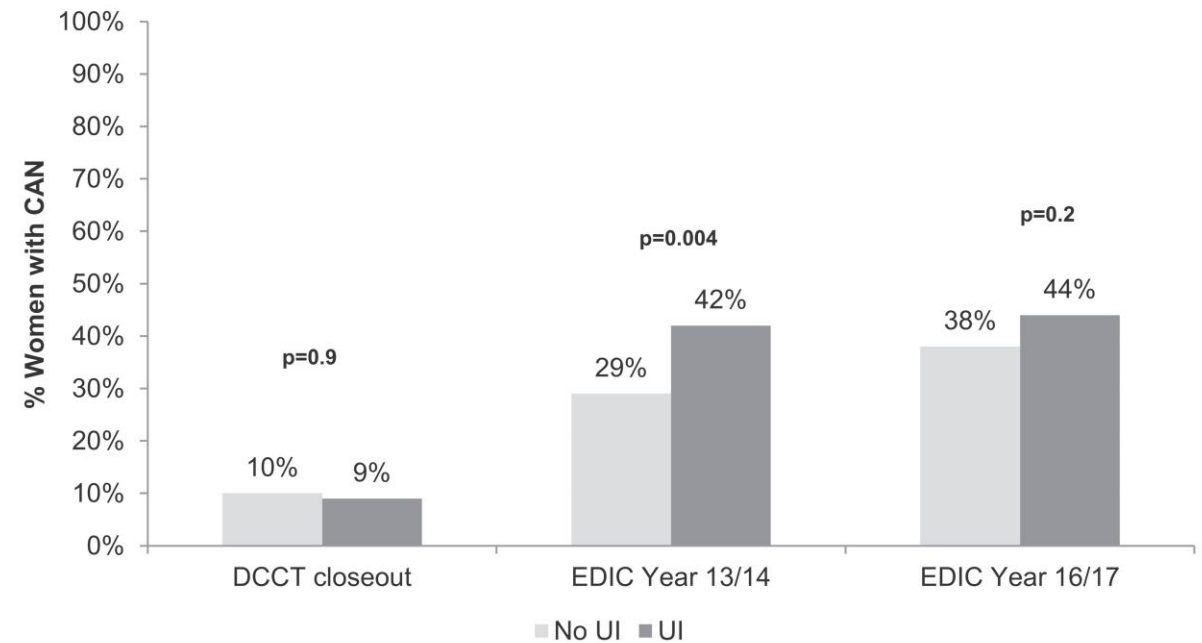
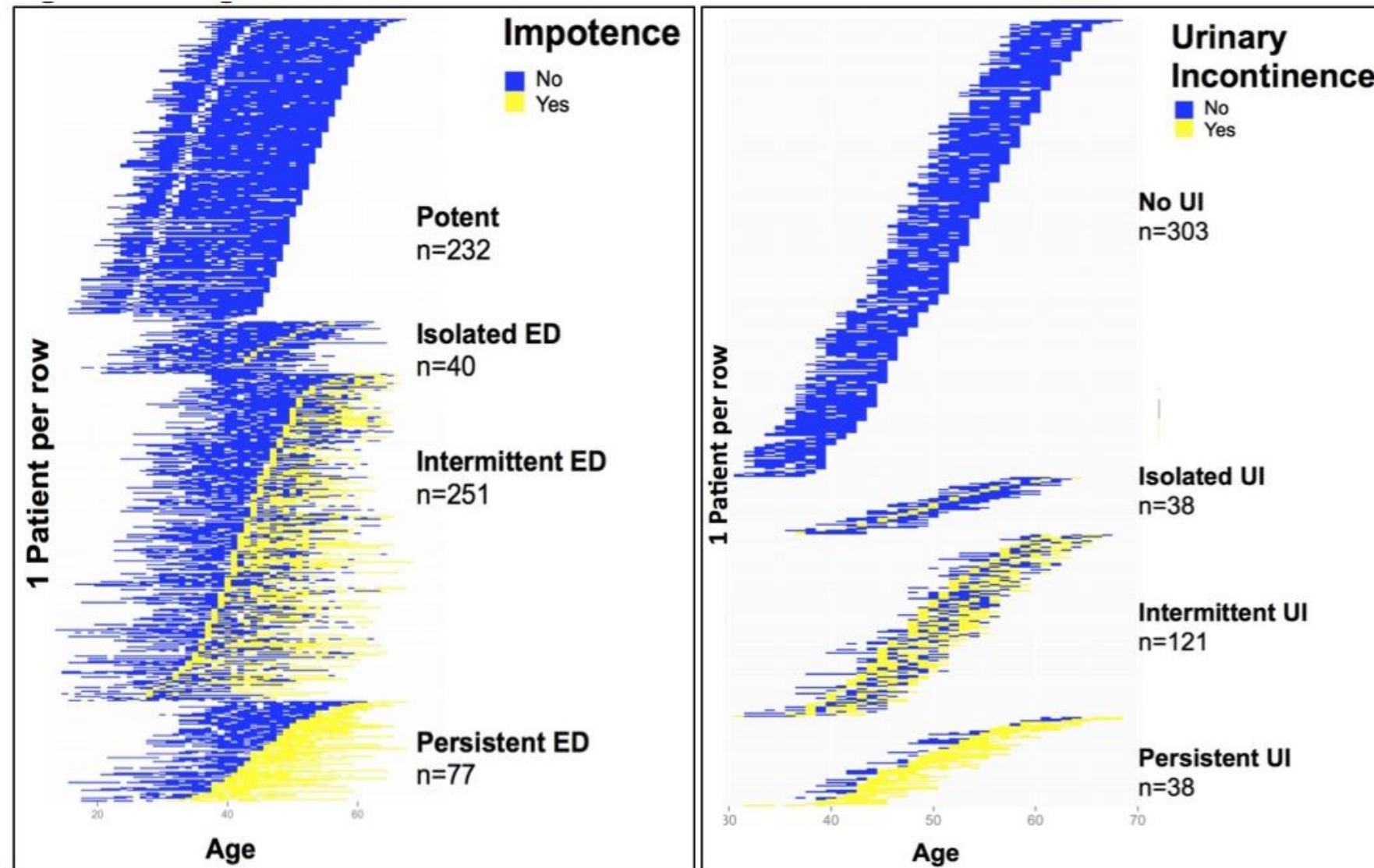


Figure 2—Prevalence of CAN among women with FSD and UI in DCCT/EDIC. CAN defined as an R-R variation <15 or R-R variation between 15 and 19.9 plus a Valsalva ratio ≤ 1.5 or a supine-to-standing drop of 10 mmHg in DBP (20).



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Longitudinal ED and UI Phenotypes



Intermittent Phenotype:

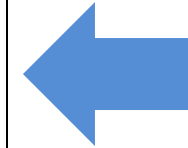
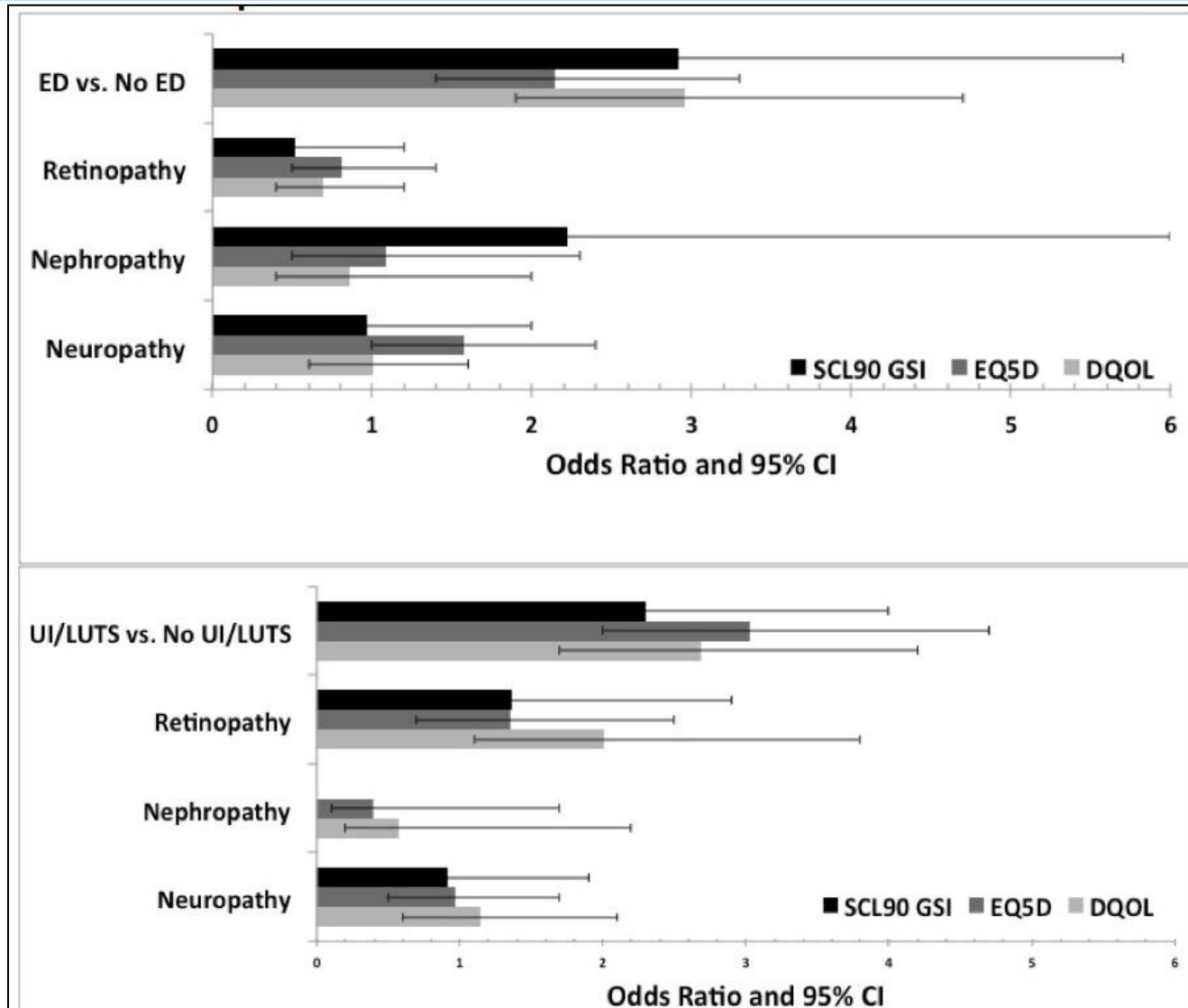
- Traditional Risk Factors (BMI, hysterectomy)
- HbA1c

Persistent Phenotype:

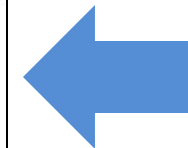
- Autonomic Dysfunction



Urologic Complications and Quality of Life



- Odds of poor QOL defined by lowest quartile of QOL scores
- Effect of ED/UI on poor QOL higher than those observed for other complications



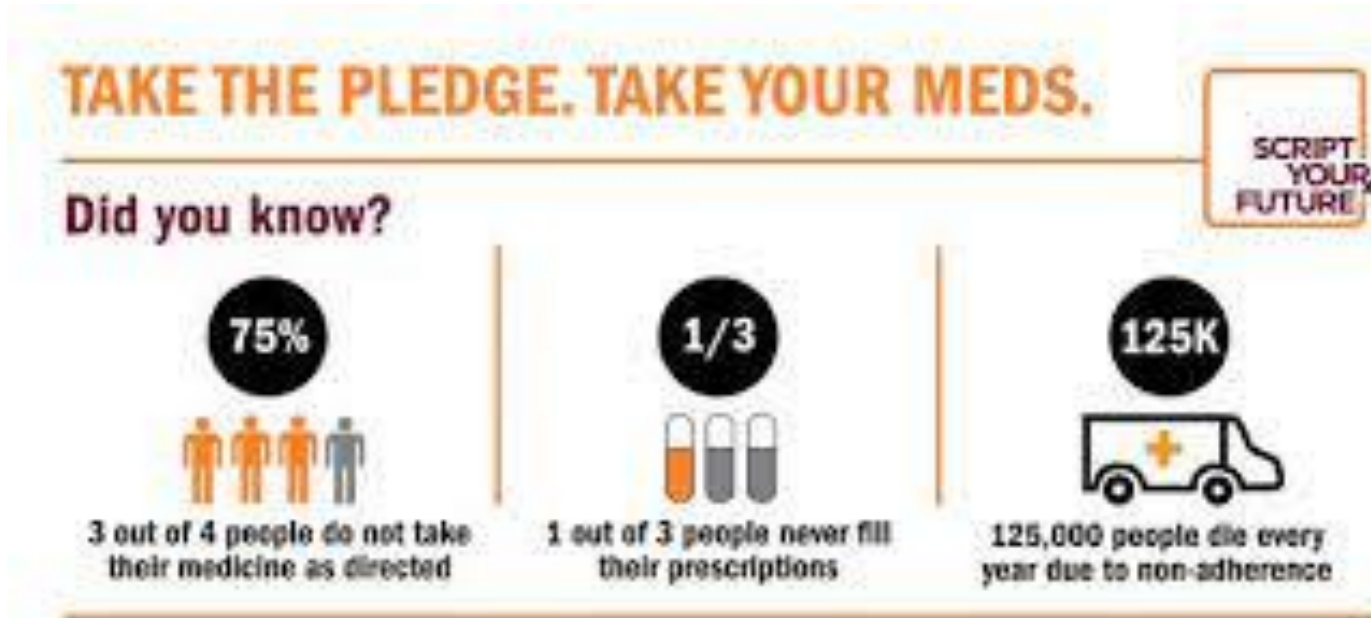
- **Participants significantly impacted by urologic disorders**



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Impact

Medication Adherence Significant Problem in Diabetes



Patients could be motivated to prevent urologic disorders





Diabetic Cystopathy

- **Lack of clarity, understanding and standardization of the term diabetic cystopathy:** decreased bladder sensation, poor contractility and increased post-void residual urine diagnosed with urodynamics, uroflow and measurement of post-void residual urine.
- **It has commonly been thought that in older women/men with diabetes diabetic cystopathy leads to a flaccid, hypotonic or atonic bladder.**
- **Lack of validated or standardized clinically significant measures used to diagnose full spectrum of diabetic cystopathy**



Post Void Residuals

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Figure 2. Distribution of PVR among Men and Women with T1D

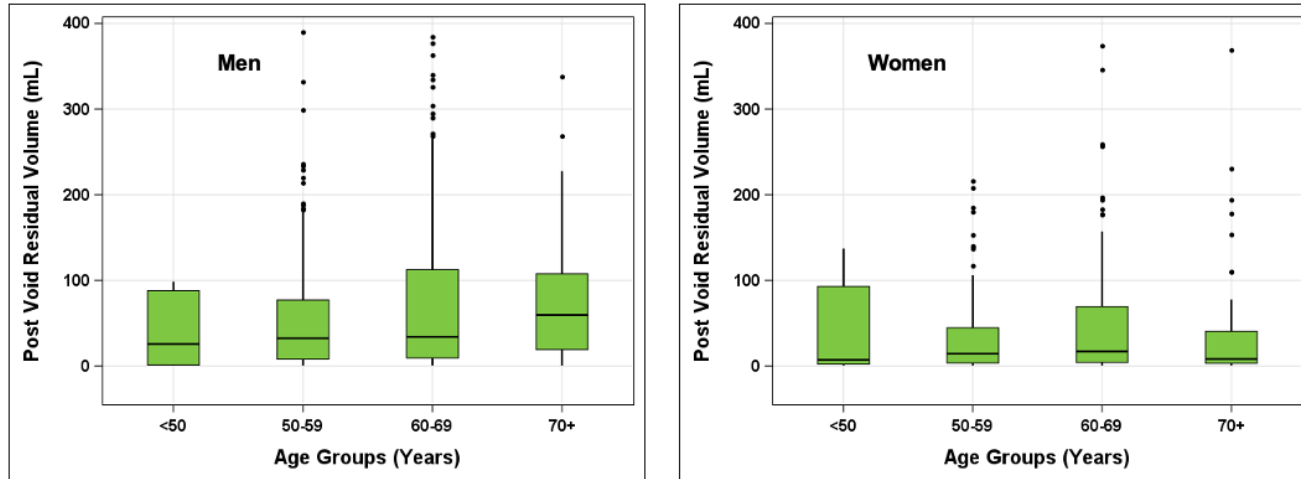
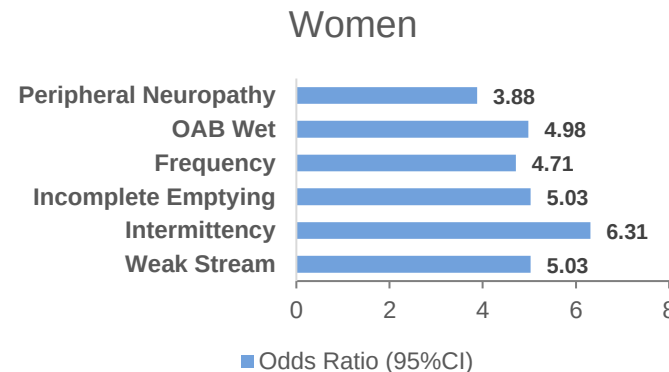
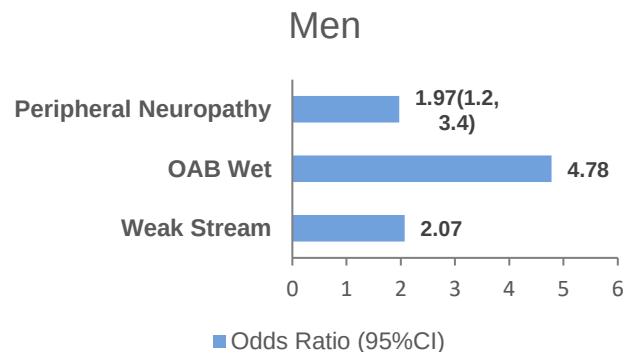


*Figure does not include n=7 men with PVR values >400.

- PVR in long standing T1D:
 - largely normal
 - Very rare chronic retention
 - Varies by gender
- LUTS and Neuropathy associated with elevated PVR
- The need for better classification of diabetic cystopathy





What's Next?

- **Longest running diabetes study and urologic study in setting of diabetes**
- Population approaching longevity previously unthinkable
- Unclear impact of other emerging comorbidities of living with T1D:
 - Age (Cognition/Frailty)
 - Duration of diabetes/Long term complication experience
 - Obesity/Metabolic Dysfunction
 - Biologic Senescence



Ferucci Aging Framework

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The Metrics of Aging

Functional Aging (impact on daily life)

- Cognitive Function
- Physical Function
- Mood
- Mental Health



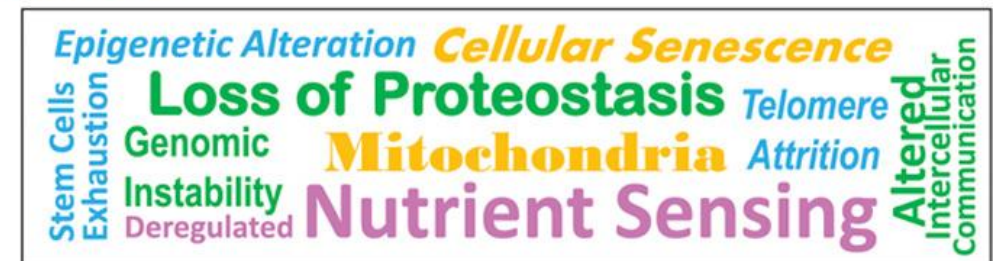
Phenotypic Aging (phenotypes that change)

- Body Composition
- Energetics
- Homeostatic Mechanisms
- Brain health



Biological Aging (root mechanisms)

- Molecular Damage
- Defective Repair
- Energy Exhaustion
- Signal/Noise Reduction



Circulation Research

Volume 123, Issue 7, 14 September 2018; Pages 740-744
<https://doi.org/10.1161/CIRCRESAHA.118.312816>



CARDIOVASCULAR AGING COMPENDIUM

Time and the Metrics of Aging

Luigi Ferrucci, Morgan E. Levine, Pei-Lun Kuo, and Eleanor M. Simonsick



Summary

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SPECIFIC AIM 1: Examine the impact of functional aging—including cognitive decline, physical impairment, and frailty—on urological health in older adults with T1D.

- **Cognitive domains:** executive function, attention, memory
- **Functional domains:** gait speed, grip strength, mobility, and frailty indices

SPECIFIC AIM 2: Evaluate how phenotypic aging—including adiposity, metabolic dysfunction, neuropathy, and myocardial aging—contributes to the development and progression of urological dysfunction in T1D.

SPECIFIC AIM 3: Identify molecular signatures of biological aging—including inflammation and cellular senescence—that drive urological decline in T1D.

- **Systemic Senescence Burden:** serum markers (IL-6, IL-8, TNF- α , MCP-1, GDF15, PAI-1, MMP-3), cell-free DNA, mitochondrial DNA, and inflammaging/metabolic aging markers
- **Bladder Microenvironment Senescence:** Unprocessed urine proteins, oxidative damage (8-OHdG, F2-isoprostanes), urinary mtDNA, and ECM remodeling markers
- **Urothelial Tissue Senescence:** RNA-seq from urine-derived urothelial cells will quantify p16/p21, SASP gene modules, validated senescence signatures (SenMayo, CellAge), mitochondrial aging pathways, and epithelial differentiation states



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UroEDIC TEAM Efforts



Jeanette Brown (1954-2021)

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UroEDIC Team

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UroEDIC I

- Patricia Cleary
- Jeanette Brown
- Leroy Nyberg

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- William Herman
- Eva Feldman
- Rodica Pop-Busui
- Barbara Braffett
- Rod Dunn
- Jim Hotaling
- Melody Palmer
- Alan Jacobson
- Cathy Martin
- Andrew Paterson
- Catherine Kowie
- John Kusek

UroEDIC III

- Matthias Kretlzer
- Quentin Clemens
- Karandeep Singh
- Ziya Kirkali