Aims

- Explore the availability of patients for FDA approved renal outcomes in T2 Diabetes according to CKD stages and ACR subgroups
- Develop recruitment criteria for T2D patients at risk for FDA approved renal outcomes

Joslin T2 Diabetes Cohort

- Subjects received treatment at the Joslin Diabetes Center between 2003 and 2009
- Age at study enrollment between 35 and 69 years
- Diagnosed with diabetes between 40 and 64 years or diagnosed beween 20 and 39 years with no Insulin treatment within 2 years of diagnosis
- Exclude Prevalent ESRD and CKD Stages 4 and 5
- Exclude non-diabetic renal disease

Methods

Subjects were assessed for albuminuria status. We attempted to recruit all Microalbuminuria and Proteinuria subjects.

We attempted to recruit an equal number of Normo-albuminuria subjects (about 1/3 of the available population)

Subjects were classified based on median ACR values in the 2 years prior to study enrollment.

Blood, Urine and Medical History was collected at baseline.

Subjects were followed over time in a number of methods:
- Examination by recruiters at Joslin clinic visits or at home
- Lab results from Joslin medical records
- Matching with United States Renal Data Service Rosters
- Matching with National Death Index Rosters

Samples sent to University of Minnesota Lab for measurement of ACR and eGFR.

Serial eGFR measurements were used to calculate linear slopes for rates of eGFR loss.

Slopes were used to calculate an estimated time to lose 30% of baseline eGFR.

Plasma levels of TNFR1 were measured at EKF Diagnostics.

Plasma land urine evels of KIIM1 were measured using an ELISA by R&D.

Urine levels of MCP-1 were measured on Luminex with an EMD Millipore assay.

Results

Summary of Clinical Characteristics

Table 1	Normo-albuminuria N = 706	Micro-albuminuria N = 478	Proteinuria N = 137
Male	47%	68%	78%
Age at Examination	55.9±7.8	55.5±7.5	57.5±7.6
Age at Diabetes Dx	44.0±9.2	44.1±9.0	42.5±10.1
Diabetes Duration	11.0 ±7.6	11.4±7.7	15.0±8.4
HbA1c	7.7±1.2	8.1±1.8	8.0±1.8
Alb.-Creat. Ratio	9±51	76±125	1313±1263
eGFR	93 ±17	90±22	70±26
CKD Stage 1	63%	60%	27%
CKD Stage 2	34%	27%	33%
CKD Stage 3	4%	13%	40%

FDA Approved Renal Outcomes During 5 Years of Follow Up

Table 2		Normoalbuminuria	Microalbuminuria	Proteinuria
CKD Stage 1	ESRD eGFR Loss 30%	1 / 443 0.2% 20 / 443 5%	1 / 287 0.4% 26 / 287 9%	2 / 37 5% 17 / 37 46%
CKD Stage 2	ESRD eGFR Loss 30%	1 / 238 0.4% 20 / 238 8%	1 / 131 0.8% 20 / 131 15%	7 / 45 16% 24 / 45 53%
CKD Stage 3	ESRD eGFR Loss 30%	0 / 25 0% 3 / 25 12%	2 / 60 3% 17 / 60 28%	17 / 55 31% 43 / 55 78%
TOTAL	ESRD eGFR Loss 30%	2 / 706 0.3% 43 / 706 6%	4 / 478 0.8% 63 / 478 13%	26 / 137 47% 84 / 137 61%
Number of Non-Renal Deaths in all CKD Stages		16	26	26

Proportion of Decliners by Quartiles of plasma TNFR1

Table 3	Q1	Q2	Q3	Q4
Normoalb.	N=237	N=200	N=184	N=85
Decliners	3%	4%	8%	14%
Microalb.	N=91	N=126	N=121	N=140
Decliners	5%	7%	15%	22%
Proteinuria	N=3	N=5	N=21	N=108
Decliners	0%	20%	33%	70%

Proportion of Decliners by Quartiles of urinary MCP-1

Table 5	Q1	Q2	Q3	Q4
Normoalb.	N=184	N=179	N=148	N=121
Decliners	4%	5%	9%	10%
Microalb.	N=85	N=118	N=134	N=115
Decliners	10%	11%	13%	18%
Proteinuria	N=3	N=16	N=30	N=78
Decliners	66%	25%	40%	78%

Proportion of Decliners by Quartiles of plasma KIM1

Table 4	Q1	Q2	Q3	Q4
Normoalb.	N=220	N=204	N=169	N=91
Decliners	4%	6%	7%	13%
Microalb.	N=95	N=106	N=131	N=143
Decliners	7%	9%	14%	21%
Proteinuria	N=6	N=16	N=19	N=93
Decliners	17%	25%	37%	75%

Proportion of Decliners by Quartiles of urinary KIM1

Table 6	Q1	Q2	Q3	Q4
Normoalb.	N=234	N=205	N=144	N=90
Decliners	4%	7%	6%	10%
Microalb.	N=76	N=98	N=142	N=134
Decliners	12%	13%	11%	17%
Proteinuria	N=2	N=10	N=27	N=88
Decliners	50%	50%	41%	70%

Conclusions

- Although incidence was highest in the proteinuria group, two-thirds of FDA approved events are occurring in Normo and Microalbuminuria groups.
- One third of all events are occurring with a baseline eGFR above 90 ml/min/1.73m^2.
- Circulating levels of plasma TNFR1 and KIM1 and urinary levels of MCP-1 and KIM1 are associated with the risk of these outcomes and might be useful for screening potential patients
- Further tests need to be developed that have better sensitivity and specificity.
- Increased clinical trial enrollment of patients with FDA approved outcomes can be achieved by including patients with normal renal function and Micro and Normoalbuminuria.