

Supplemental Table 1 – Thresholds to define outliers of lab values in screening test for proteinuria

Type of screening test	Unit	Threshold for Outliers	References
24 hour urine albumin	mg/d	>20000	A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists
albumin excretion rate	mg/min	>14 (=20000/1440min)	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists. • 24 hours = 1440 minutes
albumin creatinine ratio (ACR)	mg/g	>20000	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists. • Weight-based Urinary creatinine normal range: 15-25 mg/kg/24h • An average weight 70 kg • The minimum creatinine excretion rate in 24h = 15 mg*70=1050 mg = 1 g
spot urine albumin	mg/dL/ mmol/L	>4000 mg/dL (=20000/(500/100)) >615 mmol/L (=20000/(65*0.5))	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists. • a minimum of daily urine amount being 500 ml (A urine output of 500 mL per day is generally considered adequate for normal function) • Albumin MW=65,000
24 hour urine protein	mg/d	>20000	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists.
urine protein excretion rate	mg/d	>20000	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists.
protein creatinine ratio (PRC)	mg/g	>20000	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists. • Weight-based Urinary creatinine normal range: 15-25 mg/kg/24h • An average weight 70 kg • The minimum creatinine excretion rate in 24h = 15 mg*70=1050 mg = 1 g
spot urine protein	mg/dL	>4000 mg/dL (=20000/(500/100))	<ul style="list-style-type: none"> • A threshold of 20000 mg/d of protein or albumin was recommended by two experienced nephrologists. • a minimum of daily urine amount being 500 ml (A urine output of 500 mL per day is generally considered adequate for normal function) • 1 dl= 100 ml

Note: The molecular weight of serum albumin as determined by physicochemical methods has varied from 65,000 to 69,000, with 65,000 more commonly used.

Supplemental Table 2 – Patient characteristics at baseline and the percentage of patients with at least one test in one year after initiation of antidiabetic drug therapy and at any time during follow-up but without a history of diabetic renal complications

Characteristics	Number of patients (%)	Number of patients with at least one test for proteinuria in one year after cohort entry (%)	P value for Chi-Square test for trend	Number of patients with at least one test for proteinuria during any time in the follow-up (%)*	Time in months to the first test among patients with at least one test (median, P25-P75) †	P value for trend
N	57,114 (100)	43,062 (75.4)	-	51,461 (90.1)	4.8 (1.0 - 11.9)	-
Mean age (SD, years)	61.6 (11.0)	-	-	-	-	-
Age (years)						
40-49	9,506 (16.6)	6,609 (69.5)	<0.0001	8,139 (85.6)	3.8 (0.7 - 10)	<0.0001
50-59	15,503 (27.1)	11,535 (74.4)		13,921 (89.8)	3.8 (0.7 - 9.7)	
60-69	17,398 (30.5)	13,420 (77.1)		15,974 (91.8)	3.9 (0.8 - 9.7)	
70-79	11,082 (19.4)	8,842 (79.8)		10,251 (92.5)	3.8 (0.8 - 9.0)	
80+	3,625 (6.4)	2,656 (73.3)		3,176 (87.6)	4.2 (0.8 - 9.9)	
Sex			0.7211			<0.0001
Male	33,546 (58.7)	25,428 (75.8)		30,370 (90.5)	3.8 (0.7 - 9.6)	
Female	23,568 (41.3)	17,634 (74.8)		21,091 (89.5)	3.9 (0.8 - 9.7)	
Smoking status			0.0309			0.0007
Never	20,963 (36.7)	15,719 (75.0)		18,819 (89.8)	3.9 (0.8 - 9.6)	
Current	10,550 (18.5)	7,740 (73.4)		9,354 (88.7)	3.8 (0.8 - 9.9)	
Former	23,933 (41.9)	18,396 (76.9)		21,867 (91.4)	3.9 (0.8 - 9.7)	
Unknown	1,668 (2.9)	1,207 (72.4)		1,421 (85.2)	3.0 (0.7 - 8.0)	
Year of cohort entry	10,658 (18.7)		<0.0001			<0.0001
2007	10,309 (18.1)	7,910 (76.7)		9,721 (94.3)	4.1 (0.9 - 10.3)	
2008	10,407 (18.2)	8,046 (77.3)		9,742 (93.6)	3.8 (0.8 - 9.9)	
2009	10,980 (19.2)	8,472 (77.2)		10,148 (92.4)	3.7 (0.8 - 9.5)	
2010	10,658 (18.7)	7,910 (74.2)		9,543 (89.5)	4 (0.9 - 9.8)	
2011	9,673 (16.9)	7,023 (72.6)		8,318 (86.0)	3.8 (0.8 - 9.5)	
2012	5,087 (8.9)	3,701 (72.8)		3,989 (78.4)	3.5 (0.5 - 7.9)	
History of hypertension			0.2473			0.6463
No	27,438 (48.0)	20,446 (74.5)		24,376 (88.8)	3.6 (0.7 - 9.3)	
Yes	29,676 (52.0)	22,616 (76.2)		27,085 (91.3)	4.2 (0.9 - 9.9)	

* Patients' follow-up time was censored on the date of the first test for proteinuria.

† History of diabetic renal complications was defined as a diagnosis of albuminuria, proteinuria, diabetic nephropathy, nephrotic syndrome, chronic renal disease, renal failure, dialysis, or renal transplant at any time before cohort entry date.

Supplemental Table 3 – The percentage of patients with at least one test for proteinuria during one-year period of treatment period/course stratified by a history of diabetic renal complications

History of diabetic renal complications	Antidiabetic treatment course	Number of patients	Number of patients with at least one test for proteinuria during one-year period (%)	Time in months to the first test in one year during treatment period/course (median, P25-P75) ^{*†}
Yes	1 st treatment	6,049	5,975 (98.8)	4.6 (0.9 - 9.8)
	MET [‡]	4,935	4,881 (98.9)	4.6 (0.9 - 9.7)
	SU	884	871 (98.5)	4.1 (0.8 - 9.6)
	2 nd treatment	1,809	1,705 (94.3)	5.6 (2.3 - 10.1)
	MET + SU	1,063	1,005 (94.5)	5.6 (2.3 - 10.2)
	No	1st treatment	39,112	38,494 (98.4)
MET		36,334	35,789 (98.5)	3.9 (0.8 - 9.5)
SU		1,622	1,576 (97.2)	3.9 (0.9 - 9.6)
MET + SU		762	748 (98.2)	2.4 (0.3 - 6.7)
2nd treatment		13,237	12,357 (93.4)	5.9 (2.2 - 10.7)
MET + SU		8,448	7,918 (93.7)	5.8 (2.1 - 10.6)
MET + DPP4I		1,801	1,652 (91.7)	5.8 (2.3 - 10.9)
MET + PIO		869	815 (93.8)	6.5 (2.7 - 11.5)
SU		719	667 (92.8)	6.1 (2.7, 9.8)
3rd treatment		3,628	3,258 (89.8)	6.1 (2.7 - 10.6)
SU + DPP4I		1,158	1,041 (89.9)	6.0 (2.6 - 10.9)

* Only patients who had at least one test for proteinuria during the specified period were counted.

† Only treatment periods/courses that lasted for at least one year were counted; and only proteinuria tests that were done within one year after initiation of each treatment period/course were counted. Data for the most frequently used antidiabetic drug treatment with at least 500 users were presented.

‡ MET: metformin, SU: sulfonylureas, DPP4I: dipeptidyl peptidase 4 inhibitors, PIO: pioglitazone.

Supplemental Table 4 – First and second test results among those with first proteinuria test in one year after initiation of antidiabetic drug therapy

Test type	Patient count (%)
First proteinuria test*	49,707 (75.6)
First proteinuria test positive	6,093 (12.3)
Second proteinuria test done†	1,184 (19.4)
Positive	531 (44.9)
Negative	378 (31.9)
Unknown	275 (23.2)
Second proteinuria test not done	4,909 (80.6)
First proteinuria test negative	22,802 (45.9)
Second proteinuria test done†	2,428 (10.6)
Positive	216 (8.9)
Negative	1,672 (68.9)
Unknown	540 (22.2)
Second proteinuria test not done	20,374 (89.4)
First proteinuria test unknown	20,812 (41.9)
Second proteinuria test done†	2,520 (12.1)
Positive	207 (8.2)
Negative	662 (27.1)
Unknown	1,631 (64.7)
Second proteinuria test not done	18,292 (87.9)

*Any diagnosis or lab test less than 14 days after the first proteinuria test was considered the same test as the first test, considering the lag time of the lab results and the office visit to address the first test.

† Second proteinuria test was defined as any diagnosis or lab test undertaken between 14 and 90 days after the first test.

Supplemental Table 5 – Results of the first proteinuria test within one year after antidiabetic drug initiation stratified by baseline characteristics

Characteristics	Number of patients with a 1 st test done*	% Positive	% Negative	% Result unknown
N	49,707	12.3	45.9	41.9
Age at cohort entry				
40-49	6,836	14.0	44.5	41.5
50-59	12,127	12.2	45.5	42.3
60-69	15,040	10.6	47.2	42.3
70-79	11,414	12.1	46.2	41.7
80+	4,290	15.9	43.8	40.3
Sex				
Female	20,993	10.5	47.4	42.1
Male	28,714	13.6	44.7	41.7
Smoking status				
Never smoker	17,905	11.3	46.7	42.1
Current smoker	8,566	14.1	43.2	42.8
Former smoker	21,950	12.4	46.6	41.0
Unknown	1,286	12.2	40.8	47.1
Year of cohort entry				
2007	9,187	11.3	45.7	43.1
2008	9,287	11.4	46.3	42.4
2009	9,777	12.1	46.1	41.8
2010	9,158	13.2	45.2	41.6
2011	8,066	12.9	46.1	40.9
2012	4,232	13.3	46.0	40.7
History of hypertension				
No	21,845	11.5	46.3	42.3
Yes	27,862	12.9	45.6	41.6
History of diabetic renal complications at cohort entry [†]				
No	43,062	11.2	46.7	42.2
Yes	6,645	19.4	40.8	39.9

*Any diagnosis or lab test less than 14 days after the first proteinuria test was considered the same test as the first test, considering the lag time of the lab results and the office visit to address the first test.

[†] History of diabetic renal complications was defined as a diagnosis of albuminuria, proteinuria, diabetic nephropathy, nephrotic syndrome, chronic renal disease, renal failure, dialysis, or renal transplant any time before cohort entry date.

SUPPLEMENTAL FIGURE LEGEND

Supplemental Figure 1 — Algorithms to obtain valid lab values for proteinuria in CPRD GOLD

