

## Supplemental Material

Supplemental Table 1. Percentage of data completion of the baseline characteristics in studied patients

Supplemental Table 2. Baseline characteristics of 1,982,488 subjects aged 18 years or above with baseline eGFR  $\geq 60$ ml/min/1.73m<sup>2</sup> in different drug groups before weighting

Supplemental Table 3. Follow-up period by NSAID treatment groups

Supplemental Figure 1. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  with NSAID usage defined by at least 7 consecutive days

Supplemental Figure 2. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  with NSAID usage defined by at least 14 consecutive days

Supplemental Figure 3. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  with NSAID usage defined by at least 21 consecutive days

Supplemental Figure 4. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  in complete case analysis

Supplemental Figure 5. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  for patients with at least 1-year follow-up

Supplemental Figure 6. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  without weighting

Supplemental Figure 7. Associations of NSAID use with incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$  using two consecutive eGFR values with at least 2 months in between to define outcome

Supplemental Figure 8. Associations of NSAID use with the risk of both incident eGFR < 60mL/min/1.73m<sup>2</sup> and eGFR decline  $\geq 30\%$

Supplemental Figure 9. Association between NSAIDs usage and eGFR < 60ml/min/1.73m<sup>2</sup>, eGFR decline  $\geq 30\%$  and the composite outcome within subgroups

Supplemental Table 1. Percentage of data completion of the baseline characteristics in studied patients

Baseline Characteristic	Number (Percentage of data completion)
Age	1,982,488 (100.0%)
Gender	1,982,488 (100.0%)
Smoking status	1,982,488 (100.0%)
Body mass index	751,712 (37.9%)
Systolic blood pressure	1,062,984 (53.6%)
Diastolic blood pressure	1,062,926 (53.6%)
Fasting glucose	1,147,314 (57.9%)
Low-density lipoprotein-cholesterol	1,051,612 (53.0%)
Estimated glomerular filtration rate	1,982,488 (100.0%)
Charlson's Index	1,982,488 (100.0%)
Use of anti-diabetic drugs	1,982,488 (100.0%)
Use of anti-hypertensive drugs	1,982,488 (100.0%)
Use of lipid-lowering agents	1,982,488 (100.0%)
Use of aspirin	1,982,488 (100.0%)

Supplemental Table 2. Baseline characteristics of 1,982,488 subjects aged 18 years or above with baseline eGFR  $\geq$  60ml/min/1.73m<sup>2</sup> in different drug groups before weighting

	No NSAID (n=1,821,067)	NSAID (n=161,421)	Celecoxib (n=1,348)	Etoricoxib (n=1,095)	Diclofenac (n=94,035)	Ibuprofen (n=15,838)	Indomethacin (n=5,402)	Mefenamic acid (n=11,479)	Naproxen (n=30,342)	Piroxicam (n=1,333)	Sulindac (n=549)
Male	866,144 (48%)	62,026 (38%)	493 (37%)	455 (42%)	38,607 (41%)	6,060 (38%)	3,048 (56%)	608 (5%)	7,486 (49%)	2,299 (44%)	5,157 (48%)
Age, years	55 (18)	57 (15)	62 (16)	58 (16)	58 (15)	59 (15)	56 (16)	42 (12)	55 (16)	55 (16)	54 (17)
Current smoker	61,779 (3%)	4,835 (3%)	20 (1%)	23 (2%)	2,828 (3%)	585 (4%)	192 (4%)	185 (2%)	452 (3%)	160 (3%)	333 (3%)
Systolic BP, mmHg	132 (20)	131 (20)	132 (21)	133 (21)	132 (19)	131 (19)	133 (20)	124 (19)	131 (20)	132 (20)	131 (20)
Diastolic BP, mmHg	76 (12)	76 (12)	75 (12)	77 (12)	76 (12)	75 (12)	77 (12)	74 (12)	76 (12)	76 (12)	76 (12)
Fasting glucose, mg/dL	104 (30)	102 (26)	101 (23)	102 (28)	102 (26)	103 (28)	103 (28)	96 (22)	103 (28)	103 (28)	103 (29)
BMI, kg/m <sup>2</sup>	24.4 (4.1)	24.9 (4.2)	24.0 (4.4)	23.8 (4.1)	25.0 (4.2)	24.9 (4.2)	25.4 (4.2)	24.0 (4.2)	24.7 (4.0)	24.8 (4.0)	24.7 (4.2)
LDL cholesterol, mg/dL	118 (36)	116 (35)	105 (34)	104 (34)	117 (35)	116 (35)	114 (35)	112 (35)	117 (35)	117 (35)	116 (36)
eGFR, ml/min/1.73m <sup>2</sup>	115 (46)	114 (30)	113 (28)	115 (29)	113 (29)	112 (31)	110 (30)	130 (32)	114 (28)	115 (30)	114 (27)
Charlson comorbidity index	2.4 (2.0)	2.7 (1.9)	3.4 (2.0)	3.1 (2.1)	2.8 (1.9)	2.9 (1.9)	2.6 (1.9)	1.0 (1.2)	2.5 (1.8)	2.5 (1.9)	2.4 (1.9)
Coronary heart disease	88,798 (5%)	8,622 (5%)	105 (8%)	56 (5%)	5,145 (5%)	929 (6%)	344 (6%)	109 (1%)	704 (5%)	227 (4%)	564 (5%)
Heart failure	31,580 (2%)	2,434 (2%)	27 (2%)	23 (2%)	1,292 (1%)	317 (2%)	106 (2%)	56 (0.5%)	198 (1%)	69 (1%)	128 (1%)
Diabetes mellitus	240,682 (13%)	20,257 (13%)	169 (13%)	139 (13%)	12,247 (13%)	2,513 (16%)	628 (12%)	548 (5%)	1,856 (12%)	659 (13%)	1,475 (14%)
Atrial fibrillation	38,647 (2%)	2,938 (2%)	52 (4%)	30 (3%)	1,628 (2%)	347 (2%)	110 (2%)	78 (0.7%)	267 (2%)	94 (2%)	137 (1%)
Peripheral vascular disease	4,587 (0.3%)	585 (0.4%)	2 (0.1%)	4 (0.4%)	369 (0.4%)	62 (0.4%)	22 (0.4%)	15 (0.1%)	46 (0.3%)	21 (0.4%)	55 (0.5%)
Stroke	104,913 (6%)	7,587 (5%)	82 (6%)	74 (7%)	4,322 (5%)	938 (6%)	278 (5%)	222 (2%)	763 (5%)	275 (5%)	539 (5%)
Amputation	1,829 (0.1%)	262 (0.2%)	2 (0.1%)	1 (0.1%)	179 (0.2%)	22 (0.1%)	8 (0.1%)	14 (0.1%)	19 (0.1%)	4 (0.1%)	15 (0.1%)
Dementia	15,565 (0.9%)	695 (0.4%)	11 (0.8%)	6 (0.5%)	357 (0.4%)	121 (0.8%)	16 (0.3%)	10 (0.1%)	82 (0.5%)	15 (0.3%)	68 (0.6%)
Lung disease	59,532 (3%)	5,520 (3%)	67 (5%)	38 (3%)	3,236 (3%)	626 (4%)	183 (3%)	202 (2%)	488 (3%)	155 (3%)	337 (3%)
Connective tissue disease	6,415 (0.4%)	2,192 (1%)	26 (2%)	14 (1%)	972 (1%)	199 (1%)	52 (1%)	105 (0.9%)	50 (0.3%)	9 (0.2%)	31 (0.3%)
Peptic ulcer	43,086 (2%)	3,561 (2%)	85 (6%)	37 (3%)	2,092 (2%)	363 (2%)	109 (2%)	103 (1%)	329 (2%)	123 (2%)	253 (2%)
Liver disease	43,060 (2%)	4,462 (3%)	49 (4%)	37 (3%)	2,612 (3%)	475 (3%)	145 (3%)	180 (2%)	351 (2%)	116 (2%)	251 (2%)
Hemiplegia	18,239 (1%)	1,114 (0.7%)	12 (0.9%)	4 (0.4%)	602 (0.6%)	173 (1%)	33 (0.6%)	41 (0.4%)	73 (0.5%)	31 (0.6%)	38 (0.4%)
Leukemia	2,260 (0.1%)	170 (0.1%)	3 (0.2%)	0 (0.0%)	71 (0.1%)	28 (0.2%)	6 (0.1%)	11 (0.1%)	26 (0.2%)	6 (0.1%)	15 (0.1%)
Malignant lymphoma	2,725 (0.1%)	305 (0.2%)	3 (0.2%)	3 (0.3%)	159 (0.2%)	32 (0.2%)	8 (0.1%)	10 (0.1%)	27 (0.2%)	6 (0.1%)	18 (0.2%)
Cancer	94,278 (5%)	15,585 (10%)	214 (16%)	240 (22%)	9,147 (10%)	1,114 (7%)	299 (6%)	344 (3%)	830 (5%)	300 (6%)	864 (8%)
Use of anti-diabetic drugs	236,348 (13%)	20,381 (13%)	178 (13%)	134 (12%)	12,279 (13%)	2,426 (15%)	685 (13%)	531 (5%)	1,858 (12%)	639 (12%)	1,536 (14%)
Use of lipid-lowering agents	195,247 (11%)	21,732 (13%)	331 (25%)	258 (24%)	13,194 (14%)	2,462 (16%)	638 (12%)	457 (4%)	1,634 (11%)	555 (11%)	1,491 (14%)
Use of anti-hypertensive drugs	656,493 (36%)	62,696 (39%)	583 (43%)	412 (38%)	36,864 (39%)	7,111 (45%)	2,285 (42%)	2,134 (19%)	5,455 (36%)	1,838 (35%)	4,421 (41%)
Use of aspirin	198,914 (11%)	18,525 (11%)	221 (16%)	134 (12%)	10,897 (12%)	1,968 (12%)	660 (12%)	347 (3%)	1,617 (11%)	526 (10%)	1,220 (11%)

All parameters are expressed in either number (percentage) or mean (SD)

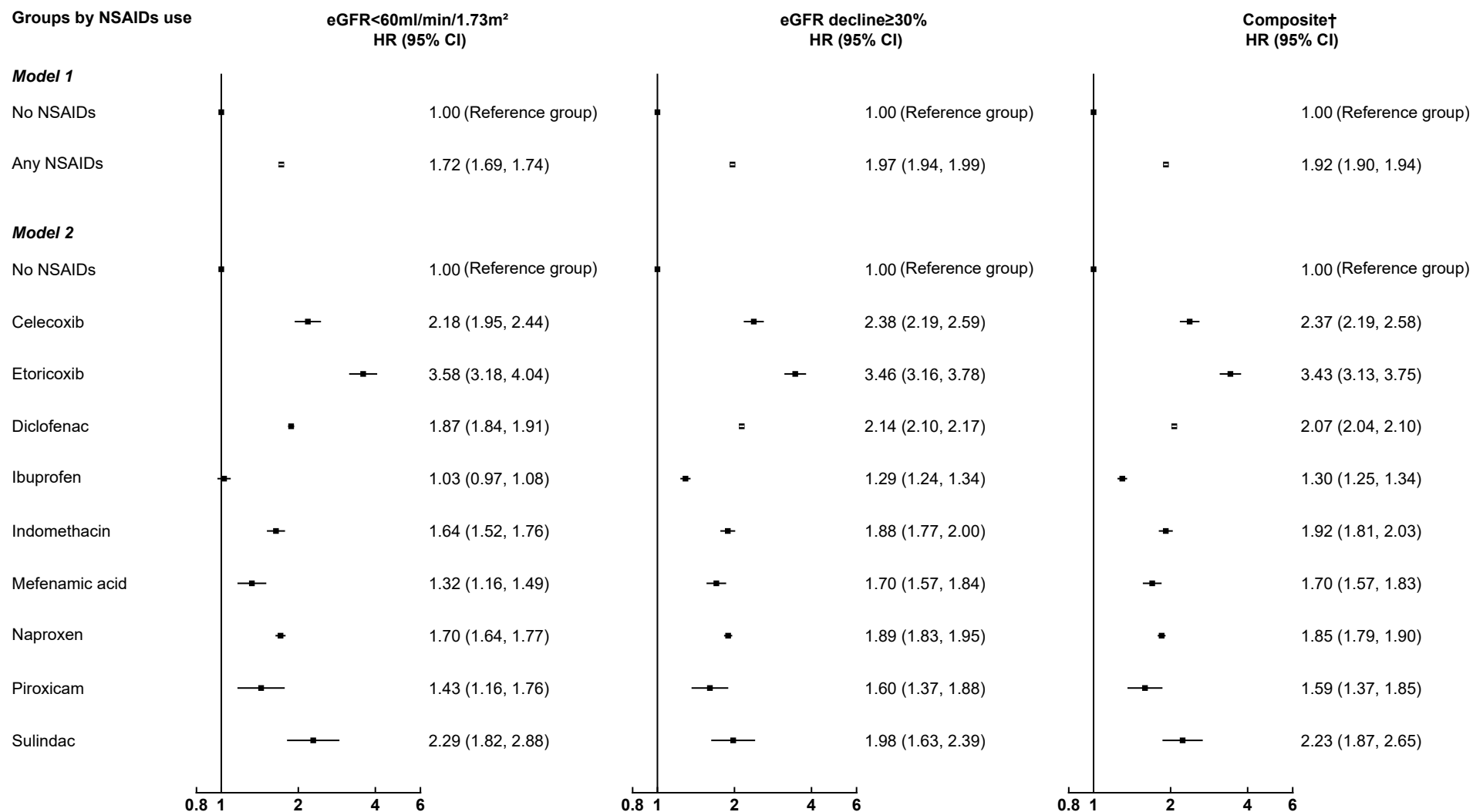
NSAID = non-steroidal anti-inflammatory drug; BP = blood pressure; BMI = body mass index; LDL cholesterol = low-density lipoprotein-cholesterol; eGFR = estimated glomerular filtration rate.

Supplemental Table 3. Follow-up period by NSAID treatment groups

	eGFR < 60 ml/min/1.73 m <sup>2</sup>
	Median of follow-up (interquartile range), year
No NSAIDs	6.3 (3.3,9.4)
Any NSAIDs	7.0 (4.0,9.6)
Celecoxib	7.5 (4.2,10.2)
Etoricoxib	7.1 (3.5,10.0)
Diclofenac	7.3 (4.2,9.8)
Ibuprofen	7.5 (4.6,10.0)
Indomethacin	8.5 (5.1,10.4)
Mefenamic acid	7.6 (4.7,10.0)
Naproxen	7.7 (4.4,10.0)
Piroxicam	10.3 (8.0,10.8)
Sulindac	8.0 (3.5,10.5)

NSAID = non-steroidal anti-inflammatory drug.

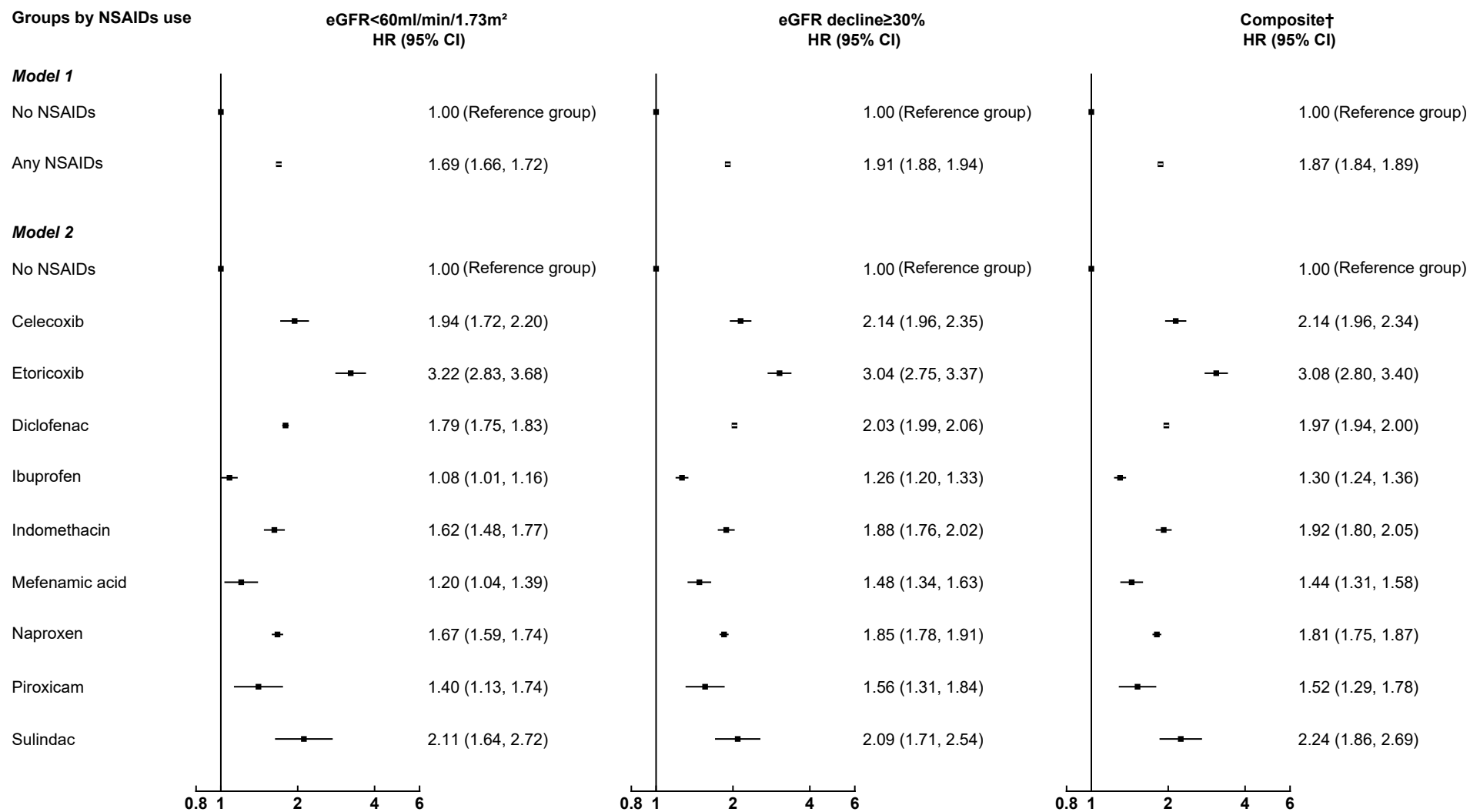
Supplemental Figure 1. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% with NSAID usage defined by at least 7 consecutive days



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.

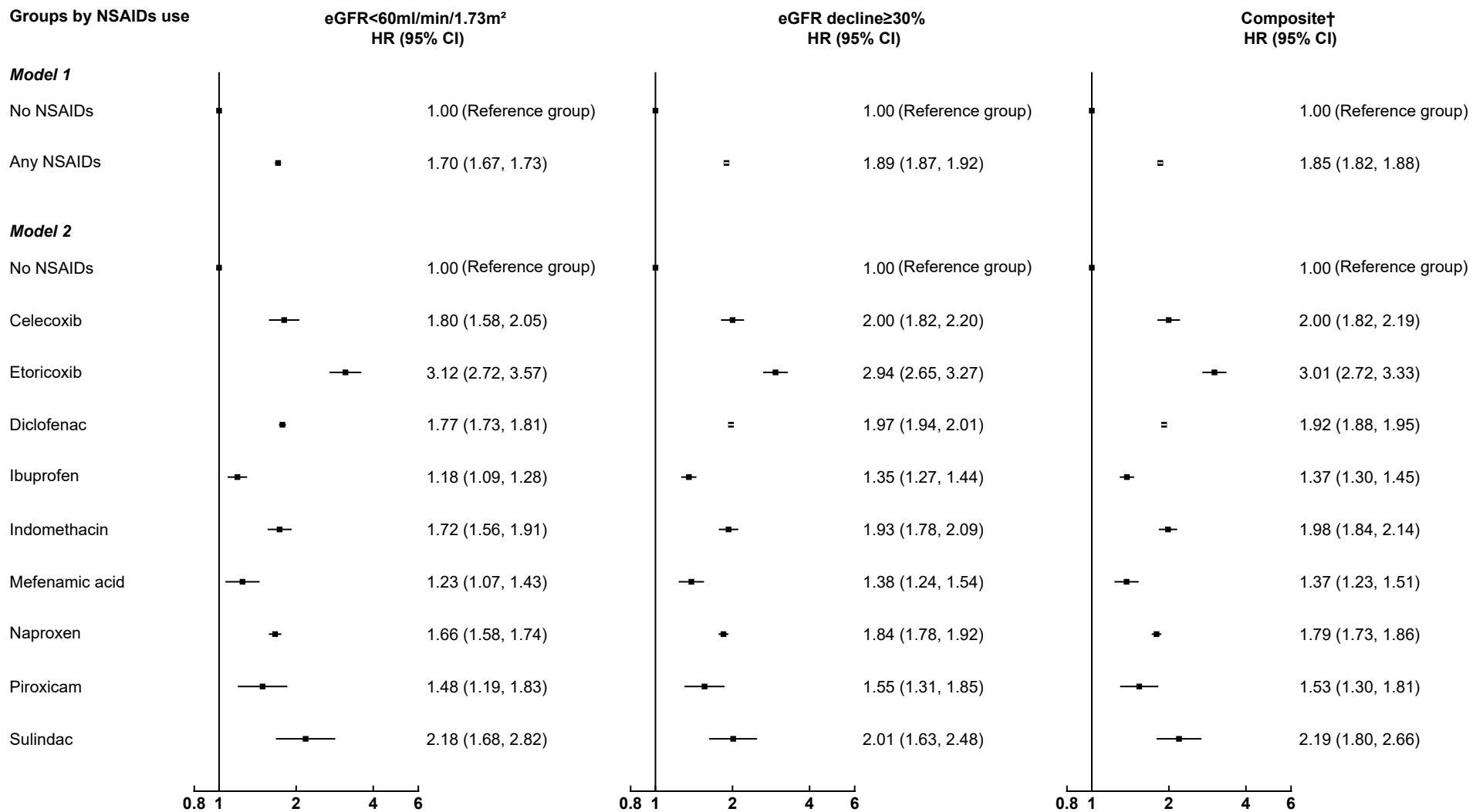
Supplemental Figure 2. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% with NSAID usage defined by at least 14 consecutive days



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.

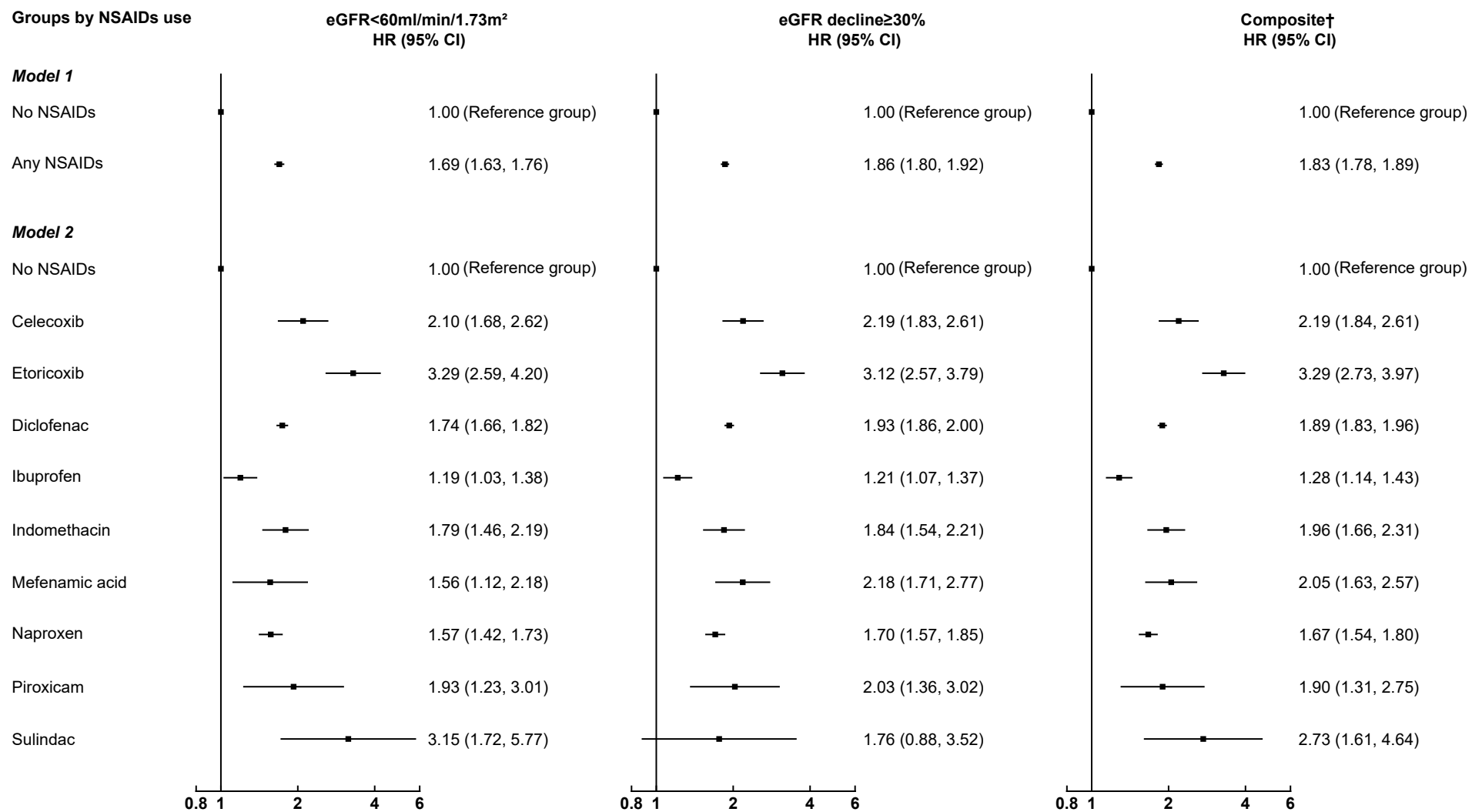
Supplemental Figure 3. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% with NSAID usage defined by at least 21 consecutive days



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.

Supplemental Figure 4. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% in complete case analysis

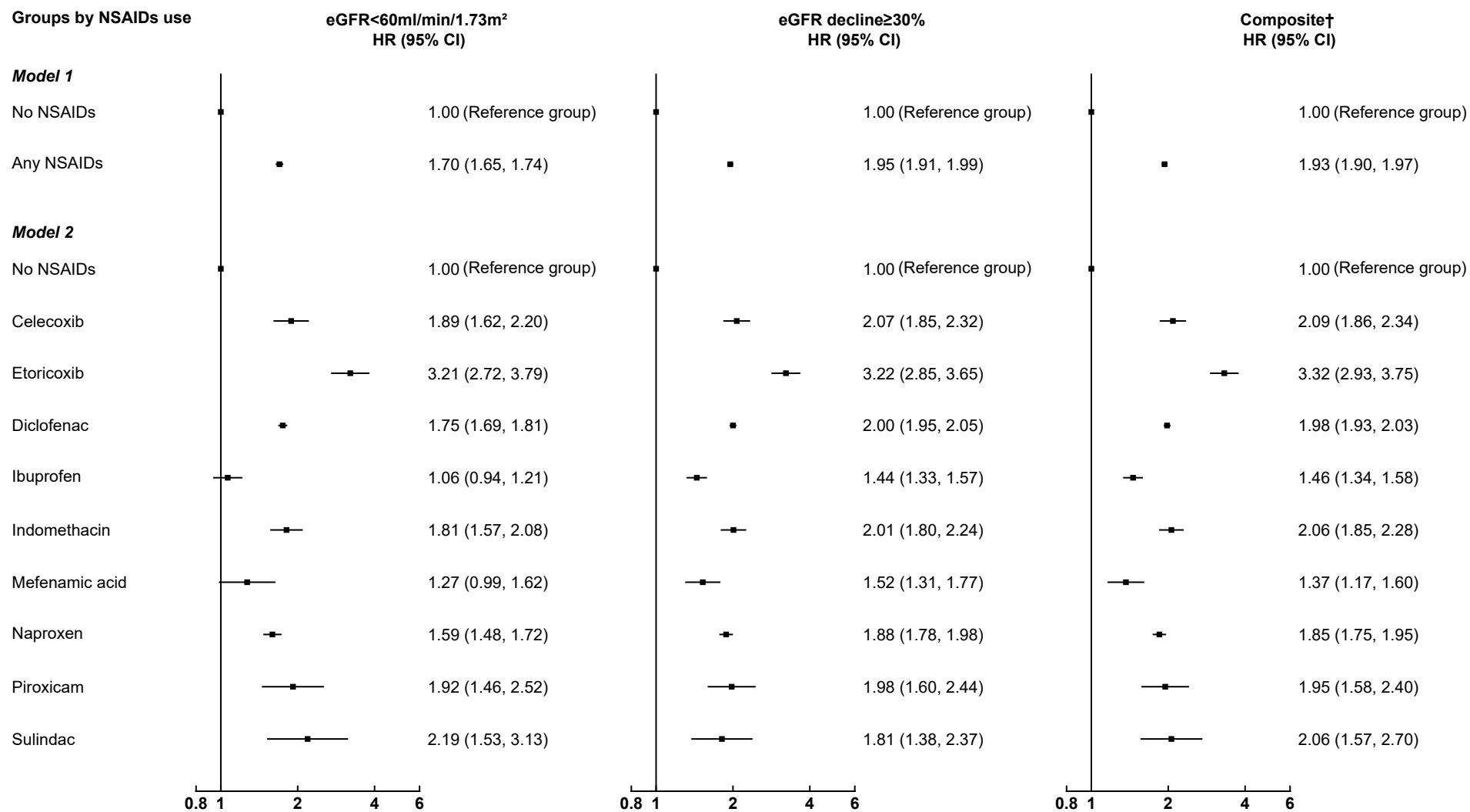


Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.



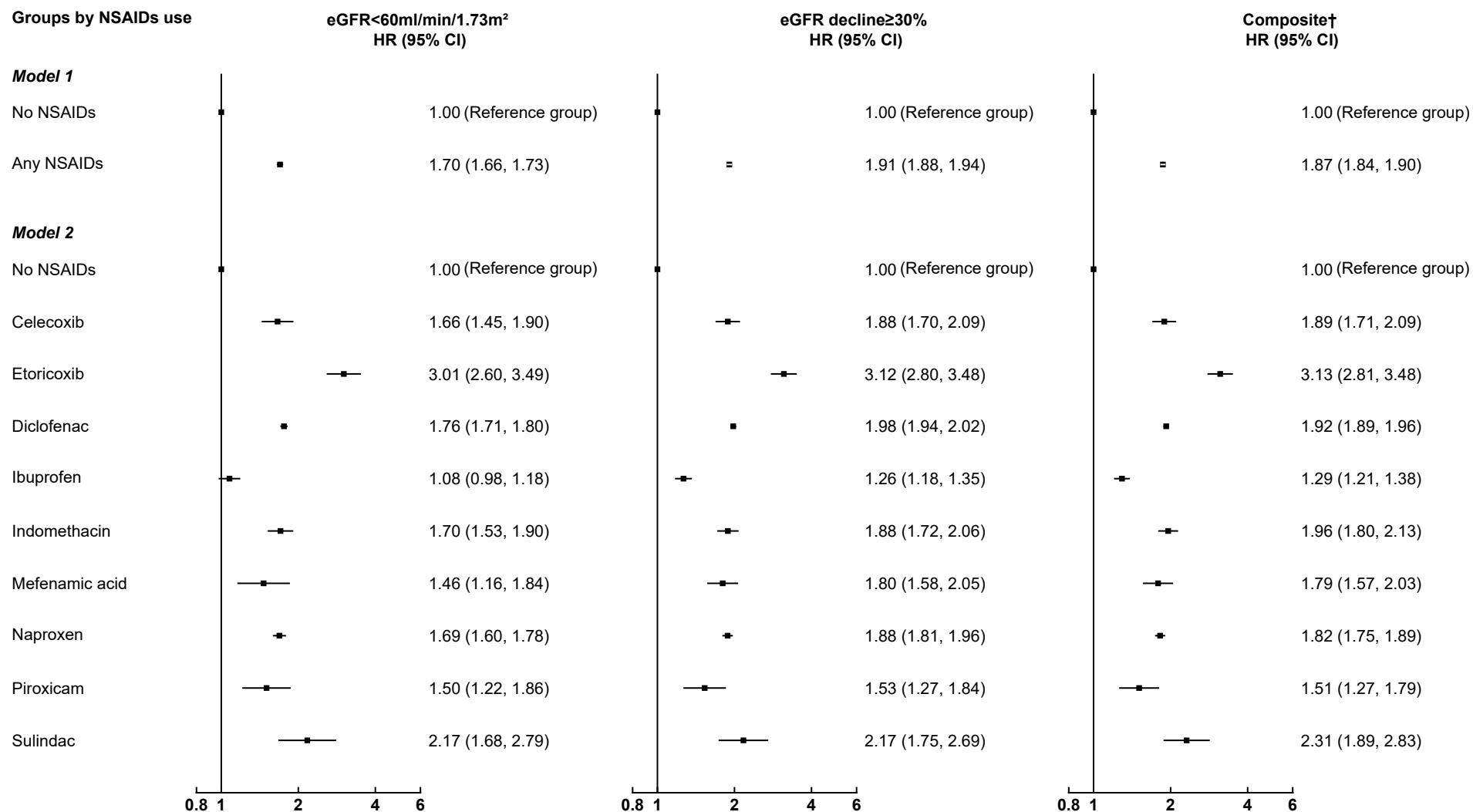
Supplemental Figure 5. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% for patients with at least 1-year follow-up



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.

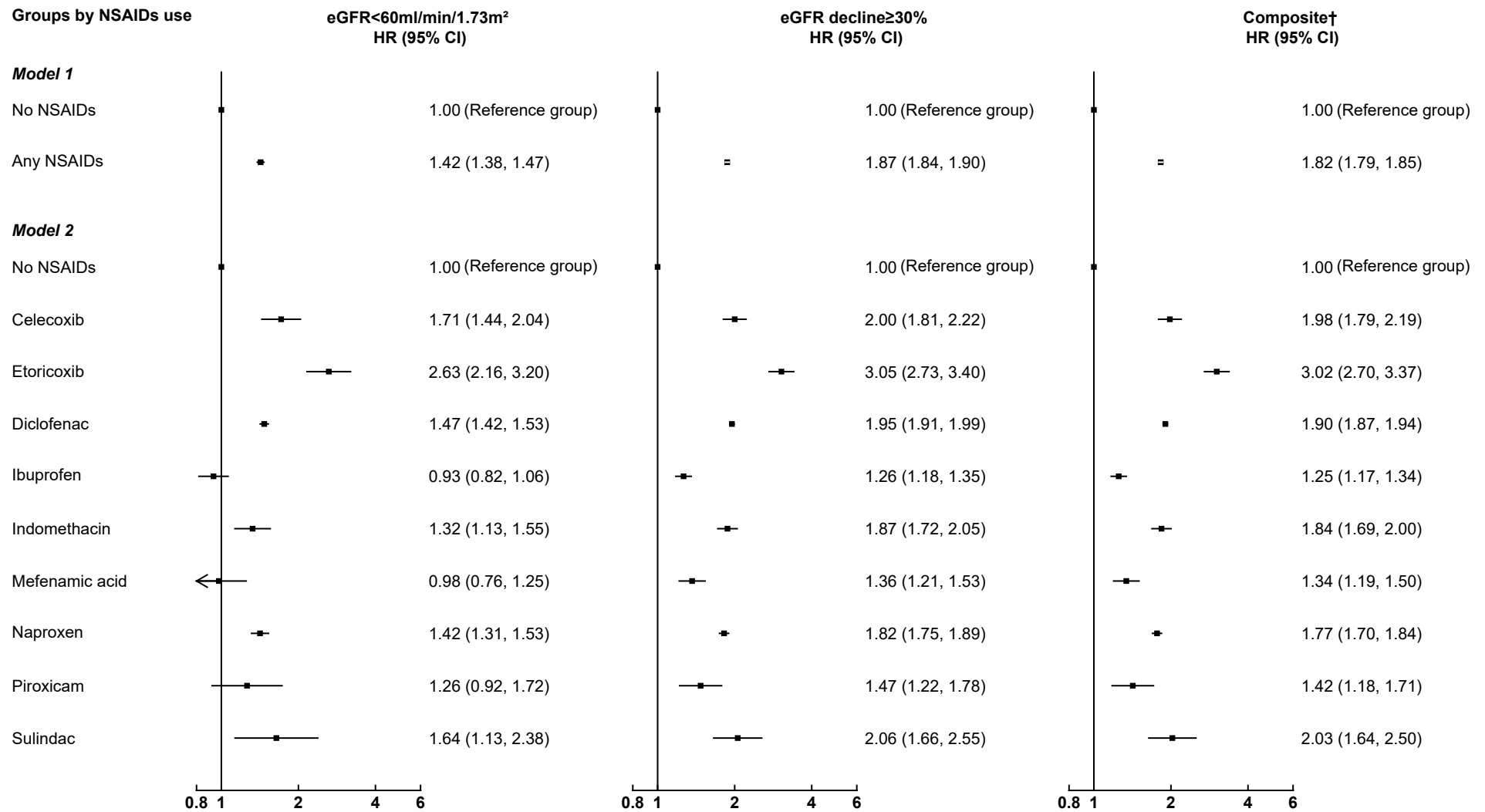
Supplemental Figure 6. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% without weighting



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.

Supplemental Figure 7. Associations of NSAID use with incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30% using two consecutive eGFR values with at least 2 months in between to define outcome



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

† Composite is defined by either incident eGFR<60ml/min/1.73m<sup>2</sup> or eGFR decline≥30%.

Supplemental Figure 8. Associations of NSAID use with the risk of both incident eGFR<60mL/min/1.73m<sup>2</sup> and eGFR decline≥30%

Groups by NSAIDs use

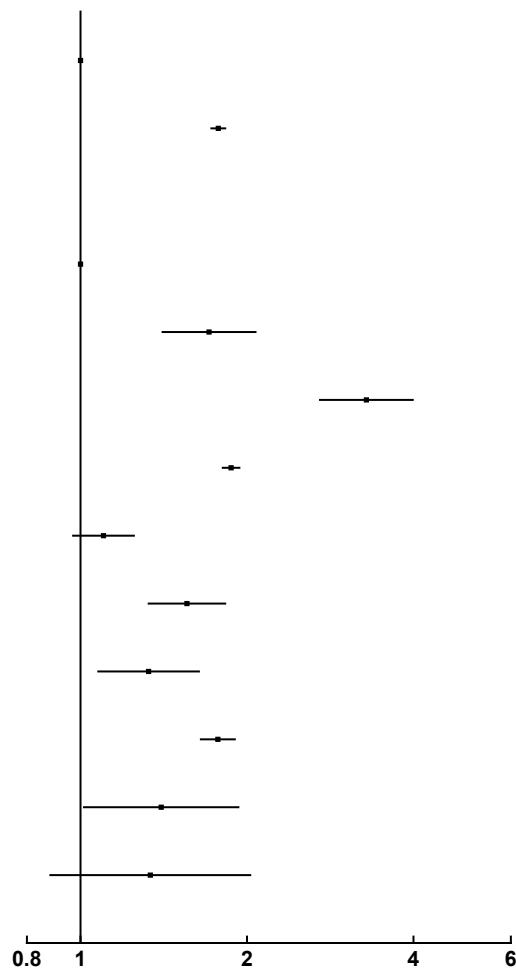
eGFR<60ml/min/1.73m<sup>2</sup> and eGFR decline≥30%  
HR (95% CI)

**Model 1**

No NSAIDs	1.00 (Reference group)
Any NSAIDs	1.77 (1.72, 1.83)

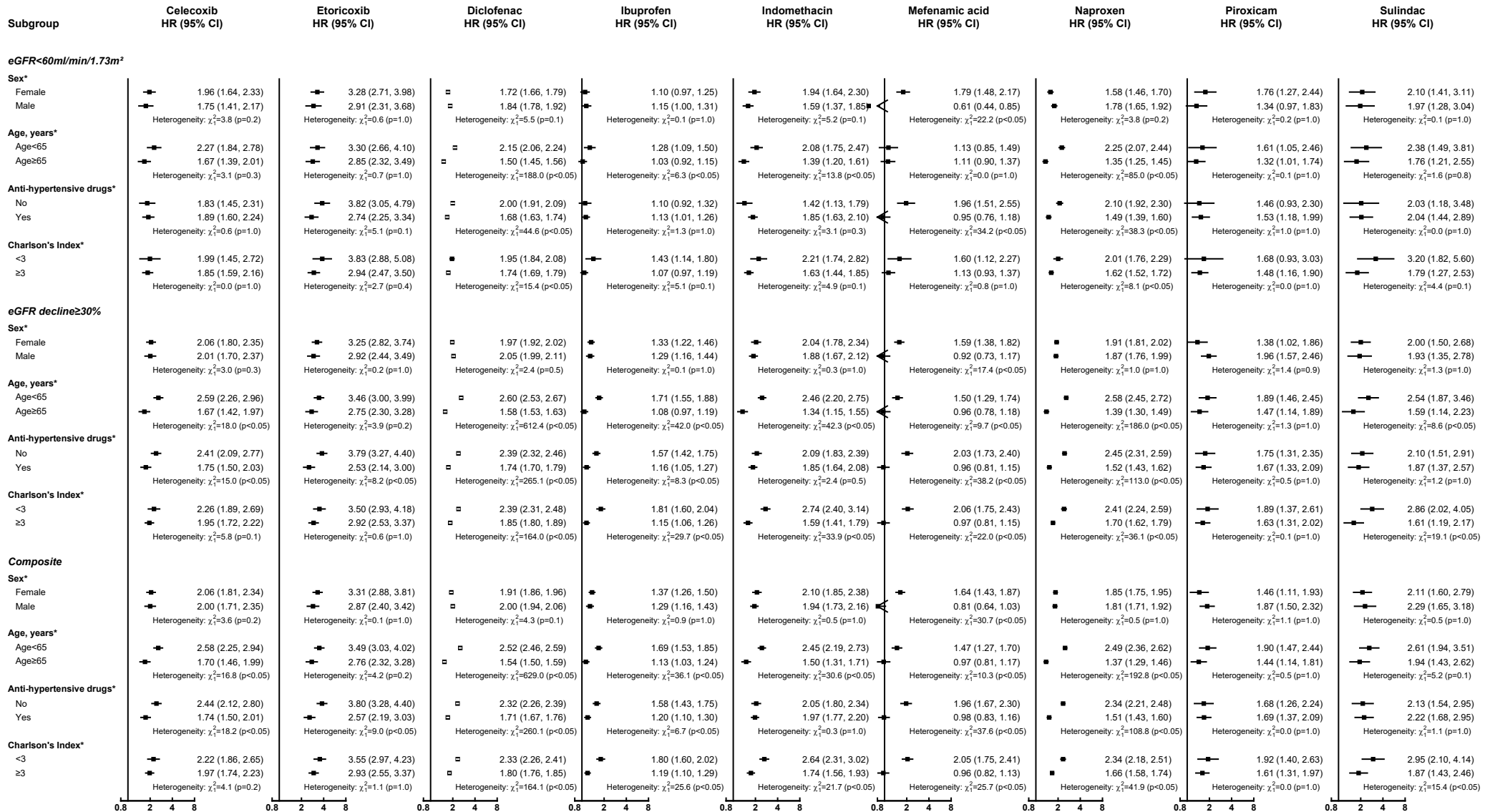
**Model 2**

No NSAIDs	1.00 (Reference group)
Celecoxib	1.71 (1.41, 2.07)
Etoricoxib	3.29 (2.71, 3.99)
Diclofenac	1.87 (1.81, 1.94)
Ibuprofen	1.10 (0.97, 1.25)
Indomethacin	1.56 (1.33, 1.83)
Mefenamic acid	1.33 (1.08, 1.64)
Naproxen	1.77 (1.65, 1.90)
Piroxicam	1.40 (1.01, 1.93)
Sulindac	1.34 (0.88, 2.03)



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

Supplemental Figure 9. Association between NSAIDs usage and eGFR<60ml/min/1.73m<sup>2</sup>, eGFR decline≥30% and the composite outcome within subgroups



Hazard ratio was adjusted by age, gender, smoking status, body mass index, systolic blood pressure, diastolic blood pressure, fasting glucose, low-density lipoprotein-cholesterol, estimated glomerular filtration rate, the usages of anti-hypertensive drugs, anti-diabetic drugs, lipid-lowering agents, and aspirin, and all the comorbidities listed in Table 1 at baseline. NSAID = non-steroidal anti-inflammatory drug; HR = hazard ratio; CI = confidence interval.

\* Significant interaction between NSAID treatment group and studied subgroup (P-value<0.05) by Wald test.