### SUPPLEMENTARY TABLES

**Supplementary Table 3. Hospital admissions for high-risk conditions 3-years prior to cohort entry, by interaction analysis.**

| #  | Interaction analysis                          | Previous hospitalizations | ICD-9-CM code |
|----|---------------------------------------------|---------------------------|---------------|
| 1  | ACEIs/ARBs plus NSAIDs                      | Hypertensive crisis       | 401.xx-405.xx |
|    |                                            | Acute myocardial infarction | 410.xx        |
|    |                                            | Heart failure              | 428.xx        |
|    |                                            | Kidney failure             | 580.xx-589.xx |
| 2  | ACEIs/ARBs or diuretics plus glucocorticoids| Hypertensive crisis       | 401.xx-405.xx |
|    |                                            | Acute myocardial infarction | 410.xx        |
|    |                                            | Heart failure              | 428.xx        |
|    |                                            | Kidney failure             | 580.xx-589.xx |
| 3  | Diuretics plus NSAIDs                       | Hypertensive crisis       | 401.xx-405.xx |
|    |                                            | Acute myocardial infarction | 410.xx        |
|    |                                            | Heart failure              | 428.xx        |
|    |                                            | Kidney failure             | 580.xx-589.xx |
| 4  | SSRIs plus NSAIDs                           | Hypertensive crisis       | 401.xx-405.xx |
|    |                                            | Cerebrovascular event      | 430.xx-438.xx |
|    |                                            | Intracranial bleeding      | 430.xx, 431.xx, 432.xx |
|    |                                            | Gastrointestinal bleeding  | 578.xx, 569.3x, 562.12, 535.71, 535.61, 535.51, 535.41, 535.31, 535.21, 535.11, 535.01, 534.6x, 534.4x, 534.2x, 534.0x, 533.6x, 533.4x, 533.2x, 533.0x, 532.6x, 532.4x, 532.2x, 532.0x, 531.6x, 531.4x, 531.2x, 531.0x, 530.82, 530.7x, 530.4x, 530.21, 459.0x |
|    |                                            | Other hemorrhagic diathesis| 287.9x, 287.8x, 286.5x |
| 5  | Vitamin K antagonists plus NSAIDs           | Hypertensive crisis       | 401.xx-405.xx |
|    |                                            | Cerebrovascular event      | 430.xx-438.xx |
|    |                                            | Intracranial bleeding      | 430.xx, 431.xx, 432.xx |
|    |                                            | Gastrointestinal bleeding  | 578.xx, 569.3x, 562.12, 535.71, 535.61, 535.51, 535.41, 535.31, 535.21, 535.11, 535.01, 534.6x, 534.4x, 534.2x, 534.0x, 533.6x, 533.4x, 533.2x, 533.0x, 532.6x, 532.4x, 532.2x, 532.0x, 531.6x, 531.4x, 531.2x, 531.0x, 530.82, 530.7x, 530.4x, 530.21, 459.0x |
|    |                                            | Other hemorrhagic diathesis| 287.9x, 287.8x, 286.5x |
| 6  | NOACs plus NSAIDs                           | Hypertensive crisis       | 401.xx-405.xx |
|    |                                            | Cerebrovascular event      | 430.xx-438.xx |
|    |                                            | Intracranial bleeding      | 430.xx, 431.xx, 432.xx |
|    |                                            | Gastrointestinal bleeding  | 578.xx, 569.3x, 562.12, 535.71, 535.61, 535.51, 535.41, 535.31, 535.21, 535.11, 535.01, 534.6x, 534.4x, 534.2x, 534.0x, 533.6x, 533.4x, 533.2x, 533.0x, 532.6x, 532.4x, 532.2x, 532.0x, 531.6x, 531.4x, 531.2x, 531.0x, 530.82, 530.7x, 530.4x, 530.21, 459.0x |
| 7 | Vitamin K antagonists plus antibiotics or antimycotics | Other hemorrhagic diathesis | 287.9x, 287.8x, 286.5x |
|---|------------------------------------------------------|-----------------------------|-----------------------|
|   | Hypertensive crisis                                  |                             | 401.xx-405.xx          |
|   | Cerebrovascular event                                |                             | 430.xx-438.xx          |
|   | Intracranial bleeding                                |                             | 430.xx, 431.xx, 432.xx |
|   | Gastrointestinal bleeding                            |                             | 578.xx, 569.3x, 562.12, 535.71, 535.61, 535.51, 535.41, 535.31, 535.21, 535.11, 535.01, 534.6x, 534.4x, 534.2x, 534.0x, 533.6x, 533.4x, 533.3x, 533.2x, 533.0x, 532.6x, 532.4x, 532.2x, 532.0x, 531.6x, 531.4x, 531.2x, 531.0x, 530.82, 530.7x, 530.4x, 530.21, 459.0x |
|   | Other hemorrhagic diathesis                          |                             | 287.9x, 287.8x, 286.5x |
| 8 | Antihypertensives plus α-blockers                    | Syncope                     | 780.2, 992.1          |
|   |                                                     | Orthostatic hypotension     | 458.0, 458.29, 458.8, 458.9, 785.50-785.59, 796.3 |
| 9 | Antidiabetics plus fluoroquinolones                  |                             | -                     |
| 10| SSRIs plus ASA                                       | Hypertensive crisis         | 401.xx-405.xx          |
|   |                                                     | Cerebrovascular event       | 430.xx-438.xx          |
|   |                                                     | Intracranial bleeding       | 430.xx, 431.xx, 432.xx |
|   |                                                     | Gastrointestinal bleeding   | 578.xx, 569.3x, 562.12, 535.71, 535.61, 535.51, 535.41, 535.31, 535.21, 535.11, 535.01, 534.6x, 534.4x, 534.2x, 534.0x, 533.6x, 533.4x, 533.3x, 533.2x, 533.0x, 532.6x, 532.4x, 532.2x, 532.0x, 531.6x, 531.4x, 531.2x, 531.0x, 530.82, 530.7x, 530.4x, 530.21, 459.0x |
|   |                                                     | Other hemorrhagic diathesis | 287.9x, 287.8x, 286.5x |
## Supplementary Table 4. Odds ratios (ORs) of hospitalization associated with current (last month) and past (≥2 months before) exposure to DDI.

| # | Interaction analysis | Exposure to DDI | Cases | Matched controls | Adjusted OR (95% CI) | Users | Prevalent | Incident |
|---|----------------------|------------------|-------|------------------|----------------------|-------|-----------|----------|
| 1 | ACEIs/ARBs plus NSAIDs | No               | 1549 (91.8) | 14 676 (91.9) | Ref.                  | 16 478 (93.3) | 1177 (6.7) |
|  |                      | Past             | 78 (4.6)   | 776 (4.9)      | 0.93 (0.72-1.18)     |       |           |          |
| 2 | ACEIs/ARBs or diuretics plus glucocorticoids | Current | 60 (3.6) | 516 (3.2) | 1.05 (0.80-1.39) | 19 464 (93.8) | 1291 (6.2) |
|  |                      | No               | 1698 (85.2) | 17 299 (92.2) | Ref.                  |       |           |          |
|  |                      | Past             | 142 (7.1)  | 904 (4.8)      | 1.36* (1.12-1.64)    |       |           |          |
| 3 | Diuretics plus NSAIDs | Current | 153 (7.7) | 559 (3.0) | 2.35* (1.93-2.86) | 8491 (82.5) | 1804 (17.5) |
|  |                      | No               | 1038 (94.3) | 8734 (95.0) | Ref.                  |       |           |          |
|  |                      | Past             | 36 (3.3)   | 228 (2.5)      | 1.26 (0.87-1.83)     |       |           |          |
| 4 | SSRIs plus NSAIDs    | Current | 58 (84.1) | 577 (90.4) | Ref.                  | 543 (76.8) | 164 (23.2) |
|  |                      | No               | 27 (2.5)   | 232 (2.5)      | 0.96 (0.64-1.46)     |       |           |          |
|  |                      | Past             | 6 (8.7)    | 42 (6.6)       | 1.12 (0.47-3.11)     |       |           |          |
| 5 | Vitamin K antagonists plus NSAIDs | Current | 5 (7.2) | 19 (3.0) | 2.88 (0.97-8.59) | 424 (78.7) | 115 (21.3) |
|  |                      | No               | 57 (93.4)  | 467 (97.7)     | Ref.                  |       |           |          |
|  |                      | Past             | 2 (3.3)    | 7 (1.5)        | 1.88 (0.37-9.59)     |       |           |          |
| 6 | NOACs plus NSAIDs    | Current | 2 (3.3) | 4 (0.8) | 7.60 (0.98-58.7) | 224 (77.0) | 67 (23.0) |
|  |                      | No               | 27 (96.4)  | 255 (97.0)     | Ref.                  |       |           |          |
|  |                      | Past             | 0 (0.0)    | 5 (1.9)        | n/a                   |       |           |          |
| 7 | Vitamin K antagonists plus antibiotics or antimycotics | Current | 1 (3.6) | 3 (1.1) | 4.07 (0.38-43.6) | 449 (80.2) | 111 (19.8) |
|  |                      | No               | 57 (93.4)  | 449 (90.0)     | Ref.                  |       |           |          |
| 8 | Antihypertensives plus α-blockers | Current | 1289 (91.6) | 11 958 (91.2) | Ref.                  | 13 791 (95.0) | 728 (5.0) |
|  |                      | No               | 54 (3.8)   | 498 (3.8)      | 1.01 (0.74-1.37)     |       |           |          |
| 10 | SSRIs plus ASA      | Current | 64 (4.5) | 656 (5.0) | 0.89 (0.67-1.18) | 552 (79.9) | 139 (20.1) |
|  |                      | No               | 42 (60.9)  | 400 (64.3)     | Ref.                  |       |           |          |
|  |                      | Past             | 15 (21.7)  | 119 (19.1)     | 1.38 (0.71-2.68)     |       |           |          |
|  |                      | Current | 12 (17.4) | 103 (16.6) | 1.21 (0.59-2.49) |       |           |          |

These ORs are adjusted for covariates shown in Table 2 and for prevalent user status (≥1 prescriptions for the drug of interest 6-months prior to cohort entry). Values are counts (percentages) unless stated otherwise. Analysis #9 (antidiabetics plus fluoroquinolones) is not presented because previous use of antidiabetics is included in the first model (Table 3).

* Significant at the 0.05 level
### Supplementary Table 5. Indications for NSAIDs use (source: HDRs).

| Chronic/acute condition | Indication                                                          | ICD-9-CM code                      |
|-------------------------|---------------------------------------------------------------------|------------------------------------|
| **Chronic**             | Osteoarthrosis                                                     | 715.xx, 718.0x                     |
|                         | Disorders causing back pain                                        | 721.0x, 721.1x, 721.2x, 721.3x, 721.4x, 721.9x, 722.0x, 722.1x, 722.2x, 723.1x, 724.1x, 724.2x, 724.3x, 724.5x, 711.2x, 713.xx, 714.xx, 719.3x, 720.xx, 725.xx, 733.6x, 730.xx, 733.1x, 711.0x, 711.1x, 711.3x, 711.4x, 711.5x, 711.6x, 711.7x, 711.8x, 711.9x, 712.xx, 716.xx, 717.xx, 818.2x, 718.3x, 718.4x, 719.4x, 719.2x, 726.xx, 727.xx, 728.0x, 729.1x, 729.3x, 729.5x, 574.xx |
| **Acute**               | Osteomyelitis, pathological fracture                               | 730.xx, 733.1x                     |
|                         | Infectious Arthritis                                               | 7.11.0x, 711.1x, 711.3x, 711.4x, 711.5x, 711.6x, 711.7x, 711.8x, 711.9x, 712.xx |
|                         | Chrystal arthropathies                                             | 712.xx                             |
|                         | Non-chronic arthropathies                                          | 716.xx, 717.xx, 818.2x, 718.3x, 718.4x, 719.4x, 719.2x, 726.xx, 727.xx |
|                         | Soft tissue disorders, esenthesopathies, bursopathies, synovitis   | 719.2x, 726.xx, 727.xx             |
|                         | Muscle related pain with NSAID indication                          | 728.0x, 729.1x, 729.3x, 729.5x, 574.xx |

Chronic diseases checked for 3 years prior to cohort entry; acute diseases checked during follow-up or 1 month prior to cohort entry.
Supplementary Table 6. Odds ratios (ORs) of hospitalization associated with current (last month) and past (≥2 months before) exposure to DDI.

| #  | Interaction analysis                      | Exposure to DDI | OR (95% CI)          | Patients excluded |
|----|------------------------------------------|----------------|----------------------|-------------------|
|    |                                          |                | Crude                | Adjusted*         |                   |
| 1  | ACEIs/ARBs plus NSAIDs                    | No             | Ref.                 | Ref.              | 17                |
|    |                                          | Past           | 0.93 (0.73-1.18)     | 0.93 (0.73-1.19)  |                   |
|    |                                          | Current        | 1.11 (0.84-1.46)     | 1.06 (0.80-1.40)  |                   |
| 2  | ACEIs/ARBs or diuretics plus glucocorticoids | No             | Ref.                 | Ref.              | 23                |
|    |                                          | Past           | 1.55† (1.29-1.87)    | 1.36† (1.12-1.65) |                   |
|    |                                          | Current        | 2.91† (2.41-3.52)    | 2.38† (1.95-2.90) |                   |
| 3  | Diuretics plus NSAIDs                     | No             | Ref.                 | Ref.              | 19                |
|    |                                          | Past           | 1.17 (0.81-1.68)     | 1.27 (0.88-1.84)  |                   |
|    |                                          | Current        | 0.94 (0.63-1.41)     | 0.97 (0.64-1.46)  |                   |
| 4  | SSRIs plus NSAIDs                         | No             | Ref.                 | Ref.              | 0                 |
|    |                                          | Past           | 1.34 (0.53-3.39)     | 1.21 (0.47-3.08)  |                   |
|    |                                          | Current        | 2.62 (0.95-7.22)     | 2.88 (0.97-8.59)  |                   |
| 5  | Vitamin K antagonists plus NSAIDs         | No             | Ref.                 | Ref.              | 1                 |
|    |                                          | Past           | 2.14 (0.44-10.4)     | 2.03 (0.37-11.1)  |                   |
|    |                                          | Current        | 5.52 (0.90-33.8)     | 7.00 (0.98-59.7)  |                   |
| 6  | NOACs plus NSAIDs                         | No             | Ref.                 | Ref.              | 2                 |
|    |                                          | Past           | n/a                  | n/a               |                   |
|    |                                          | Current        | 2.99 (0.31-28.8)     | 3.61 (0.35-37.2)  |                   |
| 7  | Vitamin K antagonists plus antibiotics or antifungal agents | No             | Ref.                 | Ref.              | 1                 |
|    |                                          | Past           | 0.27 (0.04-2.04)     | 0.27 (0.03-2.09)  |                   |
|    |                                          | Current        | 0.98 (0.29-3.31)     | 0.82 (0.23-2.89)  |                   |
| 8  | Antihypertensives plus α-blockers         | No             | Ref.                 | Ref.              | 12                |
|    |                                          | Past           | 0.98 (0.73-1.33)     | 1.00 (0.74-1.36)  |                   |
|    |                                          | Current        | 0.90 (0.68-1.19)     | 0.89 (0.67-1.19)  |                   |
| 9  | Antidiabetics plus fluoroquinolones       | No             | Ref.                 | Ref.              | 1                 |
|    |                                          | Past           | 2.00 (0.83-4.77)     | 2.00 (0.81-4.90)  |                   |
|    |                                          | Current        | 4.54† (1.77-11.7)    | 4.42† (1.60-11.3) |                   |
| 10 | SSRIs plus ASA                           | No             | Ref.                 | Ref.              | 0                 |
|    |                                          | Past           | 1.17 (0.63-2.19)     | 1.33 (0.69-2.56)  |                   |
|    |                                          | Current        | 1.12 (0.57-2.21)     | 1.20 (0.58-2.46)  |                   |

These ORs are unbiased estimates of the relative risk of hospitalization. Values are counts (percentages) unless stated otherwise. Patients with >50% of their matched follow-up periods in the hospital are excluded.

* Adjusted for covariates shown in Table 2.
† Significant at the 0.05 level.