SUPPLEMENTAL MATERIAL
Data S1

Evaluation of adherence based on serum concentrations

Good adherence is commonly defined as CMA ≥80% (40), when estimated by prescription rates or pill counts. When other objective methods such as Directly Observed Therapy (DOT) or serum drug concentrations are used, only a single snapshot of adherence is revealed and we detect the number of drugs below the defined lower threshold at each different time point to define total or partial non-adherence. Any deviation from prescribed antihypertensive treatment, absence of at least 1 prescribed BP-lowering medication or metabolite in biochemical analysis of body fluids, have previously been used to define nonadherence to antihypertensive treatment. Partial/total nonadherence are further identified as incomplete presence/complete absence of prescribed antihypertensive medications in urine/serum, respectively. (7,23).

Since our samples had been stored for 7 years, not obtained specifically for this analysis and we lacked information on whether steady-state of the drug was obtained before sampling, we decided to use very strict limits for labeling nonadherence; not the expected serum reference ranges as recently published (33), but the lowest calibrator value of the calibration range. This means that when drugs are reported as “not detected”, more than one dose has probably been missed (dependent on pharmacokinetic and pharmacodynamic properties of the drug along with the patient’s metabolic characteristics). Our strict definition may have contributed to overestimation of adherence, on the other hand, we have considered it correct to define patients as partially nonadherent even if only one drug was undetectable. Our limited number of patients made it necessary to treat all non-adherent patients as one group without sub-analyses.
It is of course of interest to follow a patient’s adherence at different visits as we did, but the definition will most often be based on one single measurement, since there is no consensus on how often adherence should be tested by serum concentrations.

Since adherence evaluation is restricted to the proximity of the visits, we have no data regarding adherence status between these consultations. This implies that when drugs are undetectable in serum, the patient must have omitted doses, but we cannot distinguish whether only one single dose is missing or several have been omitted, thus limiting the possibility to evaluate drug persistence.

To illustrate some of the challenges by using serum drug measurements as a tool to evaluate non-adherence, two patients are further discussed, patient D and G. Patient D is classified as partially non-adherent based on undetectable s-[lisinopril] only at the 6-month visit, despite unchanged prescribed dose during the 7 years. To achieve undetectable s-[lisinopril], not only one but several doses have to be omitted due to the half-life of this drug.

Patient G actually admitted non-adherence; he/she had not taken any of the morning medications the day before the 7-year visit, and the time interval from the last ingested dose was reported to be 46 hours. Nevertheless, all drugs except bendroflumethiazide were measurable due to longer half-lives. This illustrates the importance of knowledge of drug pharmacokinetics and metabolism when evaluating adherence based on serum drug measurements. Since this patient actually admitted non-adherence of all morning medications and bendroflumethiazide was undetectable, it seemed correct/appropriate to classify the patient as partially non-adherent even if this was just an occasional missed dose. There are, however, few patients who are neither adherent nor non-adherent all the time, non-adherent patients are more or less partially non-adherent as reflected in our study. Interestingly, the
information that serum drug concentrations were to be measured at the last visit, opened up the doctor-patient conversation, and the patient then admitted non-adherence.

**Pharmacogenetic Analyses and Definitions**

The CYP2D6 pharmacogenetic panel included the non-functional alleles 2D6*3, 2D6*4, 2D6*5 and 2D6*6, and the reduced-function variants 2D6*9, 2D6*10 and 2D6*41. Absence of the assayed variant alleles was interpreted as 2D6*1 (wild-type). Patients were classified into four phenotypic groups based on the consensus recommendations from the Clinical Pharmacogenetic Implementation Consortium and Dutch Pharmacogenetics Working Group (14). Patients with two non-functional alleles with subsequent absent enzyme activity were classified as poor metabolizers (PM). Intermediate metabolizers (IM) have enzyme activity ranging from some loss of function in patients with one non-functional allele in combination with wild-type allele, to the more severe loss of function when a non-functional allele is found together with a reduced-function allele. Normal metabolizers (NM) include homozygote wildtype alleles with normal enzyme activity and heterozygote wildtype and reduced-function alleles with almost normal enzyme activity. CYP2D6 may also have duplications of alleles, leading to increased enzyme activity in patients, classified as ultra-rapid metabolizers (UM).

Two alleles of CYP2C9 were examined, the reduced-functional 2C9*2 and the non-functional 2C9*3, as well as the non-functional alleles CYP3A4*22 and CYP3A5*3. In the Norwegian population the non-functional allele CYP3A5*3 is the most common form. Presence of the wildtype CYP3A5*1 allele will increase the function of 3A5 compared to normal circumstances.

**Clinical Relevance for Effect of Antihypertensive Drugs**
CYP2D6 is the best studied polymorphism affecting antihypertensive drugs, and is important for metabolism of beta-blockers, especially metoprolol, but also bisoprolol, carvedilol and propranolol. Patients being CYP2D6 IM and PM have increased plasma concentrations of these drugs, leading to decreased heart rate and the possibility of more pronounced side effects (35,37,38).

Losartan is metabolized by the CYP2C9 enzyme to losartan carboxylic acid which is 10-40 times more potent than losartan itself, and lack of this metabolism will lead to reduced effect of this drug. Other angiotensin receptor blockers, like candesartan and irbesartan, are metabolized by CYP2C9 to some degree. Metabolism through CYP3A4 and CYP 3A5 is closely linked and more complex. Of the antihypertensive drugs, mainly calcium channel blockers, but also doxazosin, are metabolized by these enzymes (33).

There are indications that patients with reduced CYP2C9 activity experience a lower reduction in blood pressure and proteinuria when treated with losartan, but for other calcium channel blockers and drugs metabolized through CYP3A4/3A5 clinical data are sparse (32,9).

**CYP Analyses in the Present Study**

See Table S3 for genotypes of CYP2D6, CYP2C9, CYP3A4/3A5 detected in our population (n=19). Two patients (10.5%) had CYP2C9*1/*3 and reduced CYP2C9 activity, which does not differ from the European reference population of 12% (p=0.84) (36). One patient (5.6%) had a non-functional CYP3A4 allele (*1/*22), and one patient (5.3%) had a wild-type CYP3A5 allele (*1/*3), this in line with the European reference population, were
CYP3A4*1/*22 is found in 10% (p=0.53) and CYP3A5 *1/*3 in 14% (p=0.27) respectively (36).

Various CYP2D6 polymorphisms were found in 15 patients (78.9%). Four patients (21.1%), a significantly higher prevalence than in the European reference population (6.5%, p=0.01) (38), were classified as PM. 11 patients (57.9%) were classified as intermediate metabolizers (European reference population: 56%, p=0.57) (36). Four of the IM patients had a non-functional/*41 genotype, which only has 7% enzyme activity and a phenotype more like PM (39). None of the patients had duplication of their CYP2D6 genes (ultra-rapid metabolizer).
Table S1. Overview of drugs and the method`s lowest calibrator (used as cut-off).

| Antihypertensive drugs (21 drugs and 4 metabolites) | Lowest calibrator nmol/L* |
|---------------------------------------------------|---------------------------|
| **Alpha-blockers**                                |                           |
| Doxazosin (depot)                                 | 10                        |
| **Beta-blockers**                                 |                           |
| Atenolol                                          | 20                        |
| Bisoprolol                                        | 1                         |
| Carvedilol                                        | 1                         |
| Labetolol                                         | 1                         |
| Metoprolol (depot)                                | 10                        |
| **CCBs**                                          |                           |
| Amlodipine                                        | 1                         |
| Diltiazem (depot)                                 | 10                        |
| Lercanidipine                                     | 1                         |
| Nifedipine (depot)                                | 1                         |
| Verapamil (depot)                                 | 9                         |
| **ACEIs**                                         |                           |
| Enalaprilat (metabolite of enalapril)              | 1                         |
| Lisinopril                                        | 10                        |
| Ramiprilat (metabolite of ramipril)                | 1                         |
| **ARBs**                                          |                           |
| Candesartan                                       | 1                         |
| Irbesartan                                        | 240                       |
| Losartan carboxylic acid (metabolite of losartan)  | 10                        |
| Telmisartan                                       | 4                         |
| Valsartan                                         | 240                       |
| **Thiazide diuretics**                            |                           |
| Bendroflumethazide                                 | 10                        |
| Hydrochlorothiazide                                | 10                        |
| **Loop diuretics**                                |                           |
| Bumetanide                                        | 10                        |
| Furosemide                                        | 1000                      |
| **Potassium sparing diuretics**                   |                           |
| Canrenone (metabolite of spironolactone)           | 1                         |
| Eplerenone                                        | 20                        |

*For each drug six calibrators were used for the calibration curve and the calibration equations were quadratic or linear with $R^2 > 0.97$ for all drugs.

CCB=calcium channel blocker, ACEI=angiotensin converting enzyme inhibitor, ARB=angiotensin receptor blockers
Table S2. Antihypertensive agents, doses, dosing intervals and serum concentrations at baseline, 6 months, 3 years and 7 years (n=19). Drugs that were undetectable in serum are marked in grey.

| Prescribed medication | Serum conc. nmol/L | Prescribed medication | Serum conc. nmol/L | Prescribed medication | Serum conc. nmol/L | Prescribed medication | Serum conc. nmol/L |
|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|-----------------------|---------------------|
| **Baseline**          |                     | **6 months**          |                     | **3 years**           |                     | **7 years**           |                     |
| **Nonadherent patients** |                     |                       |                     |                       |                     |                       |                     |
| A                     |                     |                       |                     |                       |                     |                       |                     |
| Lercanidipine 20 mg x 1 | <1                  | Lercanidipine 20 mg x 1 | 382.8               | Amlodipine 10 mg x 1  | <1                  |                       |                     |
| Telmisartan 80 mg x 1  | <4                  | Carvedilol 25 mg x 2  | 4.63                | Valsartan 320 mg x 1  | <240                |                       |                     |
| Hydrochlorothiazide 12.5 mg x 1 | <10                | Moxonidine 0.2 mg x 1* |                     | Hydrochlorothiazide 25 mg x 1 | <1                |                       |                     |
| Carvedilol 25 mg x 2   | <1                  |                       |                     | Carvedilol 25 mg x 2  | <1                  |                       |                     |
| Moxonidine 0.2 mg x 1* |                      |                       |                     |                       |                     |                       |                     |
| B                     |                     |                       |                     |                       |                     |                       |                     |
| Candesartan 16 mg x 2 | <3                  | Losartan 100 mg x 1   | 104.3               | Losartan 100 mg x 1   | 76.6                | Metoprolol d. 50 mg x 1 | 246.61              |
| Furosemid d. 30 mg x 1 | <1000               | Hydrochlorothiazide 25 mg x 1 | 94.8               | Hydrochlorothiazide 25 mg x 1 | 116.9              | Spironolactone 25 mg x 1 | 93                  |
| Metoprolol d. 200 mg x 1 | 423.93             | Metoprolol d. 100 mg x 1 | 498.29             | Metoprolol d. 100 mg x 1 | 631.93             |                       |                     |
| Spironolactone 25 mg x 1 | 9                   | Doxazosin d. 4 mg x 1 | 34.8                | Spironolactone 25 mg x 1 | <1                  |                       |                     |
| Moxonidine 0.2 mg +0.4 mg* |                     | Spironolactone 25 mg x 1 | 9                   | Moxonidine 0.2 mg +0.4 mg* |                     |                       |                     |
| C                     |                     | Moxonidine 0.2 mg +0.4 mg* |                     |                       |                     |                       |                     |
| **C**                 |                     |                       |                     |                       |                     |                       |                     |
| Spironolactone 100 mg x 1 | <1                  | Spironolactone 100 mg x 1 | <1                  | Furosemide d. 60 mg x 1 | Small top           | Furosemide d. 60 mg x 1 | 311                 |
| Metoprolol d. 200 mg x 1 | <10                 | Metoprolol d. 200 mg x 1 | <10                 | Aliskiren 150 mg x 1* |                     | Aliskiren 150 mg x 1* |                     |
| Doxazosin d.8 mg x 2   | <10                 | Doxazosin d. 8 mg x 2 | <10                 |                       |                     |                       |                     |
| Amlodipine 10 mg x 1   | <1                  | Amlodipine 10 mg x 1 | <1                  |                       |                     |                       |                     |
| Valsartan 320 mg x 1   | <240                | Valsartan 320 mg x 1  | <240                |                       |                     |                       |                     |
| Hydrochlorothiazide 25 mg x 1 | <10              | Hydrochlorothiazide 25 mg x 1 | <10                |                       |                     |                       |                     |
| Drug                        | Dose | Drug                        | Dose |
|-----------------------------|------|-----------------------------|------|
| Nifedipine 60 mg x 1        |      | Nifedipine 60 mg x 1        |      |
| Furosemide d. 60 mg x 1     | <1   | Furosemide d. 60 mg x 1     | <1000|
| Moxonidine 0.4 mg x 1*      |      | Moxonidine 0.4 mg x 1*      |      |
| Alikiren 150 mg x 1*        |      | Alikiren 150 mg x 1*        |      |
| Lisinopril 20 mg x 1        | 58   | Lisinopril 20 mg x 1        | <10  |
| Hydrochlorothiazide 12.5 mg x 1 | 105.9 | Hydrochlorothiazide 50 mg x 1 | 126.6 |
| Lercanidipine 20 mg x 1     | 2.47 | Lercanidipine 20 mg x 1     | 3.9  |
| Metoprolol d. 100 mg x 1    | 98.8 | Metoprolol d. 100 mg x 1    | 74.88|
| Moxonidine 0.4 + 0.2 mg*    |      | Doxazosin d. 4 mg x 1 vesp   | 42.2 |
| Amlorid 5 mg x 1*           |      | Amlorid 2.5 mg x 2*         |      |
| Moxonidine 0.4 + 0.2 mg*    |      | Moxonidine 0.4 + 0.2 mg*    |      |
| Spironolactone 25 mg x 1    | <1   | Spironolactone 25 mg x 1    | 6    |
| Candesartan 32 mg x 1       | 254.6| Candesartan 32 mg x 1       | 47.8 |
| Nifedipine d.30 mg x 2      | 46.8 | Hydrochlorothiazide 37.5 mg x 1 | 197 |
| Bisoprolol 5 mg x 1         | 103.2| Nifedipine d.30 mg x 2      | 54.9 |
| Moxonidine 0.4 mg x 1*      |      | Bisoprolol 5 mg x 1         | 25.4 |
| Amlorid 0.4 mg x 1*         |      | Moxonidine 0.4 mg x 1*      |      |
| Amlorid 2.5 mg x 1*         |      | Amlorid 2.5 mg x 1*         |      |
| Hydrochlorothiazide 12.5 mg x 1 | 29.3 | Hydrochlorothiazide 12.5 mg x 1 | 47 |
| Nifedipine d.30 mg x 1      | 47.9 | Nifedipine d.30 mg x 1      | 22.6 |
| Lercanidipine 10 mg x 1     | 0.72 | Lercanidipine 10 mg x 1     | 0.94 |
| Furosemide 40 mg x 1        | 238.8| Furosemide 40 mg x 1        | 61.3 |
| Losartan 100 mg x 1         | 65.7 | Losartan 100 mg x 1         | 94.7 |
| Hydrochlorothiazide 12.5 mg x 1 | 29.3 | Hydrochlorothiazide 12.5 mg x 1 | 47 |
| Nifedipine d.30 mg x 1      | 47.9 | Nifedipine d.30 mg x 1      | 22.6 |
| Lercanidipine 10 mg x 1     | 0.72 | Lercanidipine 10 mg x 1     | 0.94 |
| Hydrochlorothiazide 25 mg x 1 | 79.5 | Hydrochlorothiazide 25 mg x 1 | 30.28|
| Doxazosin d. 4 mg x 2       | 100.5| Doxazosin d. 8 mg x 1       | 90.9 |

**Legend:**
- * indicates a tolerance level.
- Vesp indicates a vespafloxacin dosage.
- < indicates a dose range.
- > indicates a concentration range.
- ± indicates a variation range.
### Adherent patients

| Drug                                      | Dose     | Adherence | Blood Pressure (mmHg) |
|-------------------------------------------|----------|-----------|-----------------------|
| Adherent patients                         |          |           |                       |
| Enalapril 20 mg x 1                       | 398.1    | 532.8     | 116.1                 |
| Carvedilol 25 mg x 1                      | 38.2     | 333.8     | 103.5                 |
| Furosemide 40 mg x 1                      | 1150     | 40.3      | 0.95                  |
| Lisinopril 20 mg x 1                      | 82       | 169       | 24                    |
| Nifedipine d. 60 mg x 1                   | 14.8     | 163.1     | 1.66                  |
| Metoprolol d. 25 mg x 1                   | 38.48    | 45.76     | 63.1                  |
| Moxonidine 0.4 mg x 1*                    |          |           |                       |
| Doxazosin d. 12 mg x 1 vesp               |          |           |                       |
| Amlodipine 5 mg x 1                       |          |           |                       |
| Metoprolol d. 50 mg x 1                   | 44.9     | 41.9      | 33.3                  |
| Amilorid 2.5 mg x 1*                      |          |           |                       |
| Lisinopril 20 mg x 1                      | 323.1    | 186.9     | 138.7                 |
| Hydrochlorothiazide 12.5 mg x 1           | 123.5    | 537.7     | 258.6                 |
| Bisoprolol 5 mg x 1                       | 44.9     | 41.9      | 33.3                  |
| Spironolactone 25 mg x 1                  | 69       | 41.9      | 33.3                  |
| Telmisartan 80 mg x 1                     | 202      | 1623      | 46.4                  |
| Hydrochlorothiazide 12.5 mg x 1           | 100.3    | 79.2      | 1418                  |
| Nifedipine d. 60 mg x 1                   | 5.6      | 37.5      | 90.3                  |
| Metoprolol d. 50 mg x 1                   | 37.83    | 90.922    | 93.08                 |
| Doxazosin d. 4 mg x 1                     | 2.86     | 17.4      | 14                    |
| Moxonidine 0.4 mg x 1*                    |          |           |                       |
| Amlodipine 10 mg x 1                      | 12.9     | 13.2      | 16.6                  |
| Valsartan 160 mg x 1                      | 11878    | 2271      | 860                   |
| Hydrochlorothiazide 12.5 mg x 1           | 250.7    | 59.3      | 30.4                  |
| Metoprolol 200 mg x 1                     | 157.82   | 157.3     | 160.29                |
| Doxazosin d. 12 mg x 1 vesp               | 39.3     | 48.1      | 26.2                  | **Note:** Moxonidine and Amlodipine doses are given in milligrams, while other drugs are given in milligrams per day.

**Blood Pressure:** Normal range is 120/80 mmHg.
| Drug                        | Quantity | Quantity | Amount | Quantity | Quantity |
|-----------------------------|----------|----------|--------|----------|----------|
| Spironolactone 50 mg x 1    | 10350    | 418      | 20     | 418      | 2302     |
| Hydrochlorothiazide 37.5 mg x 1 | 1270.6   | 259.8    | 20     | 322.2    | 127.2    |
| Ramipril 20 mg x 1          | 335.1    | 15       | 20     | 13.8     | 24.9     |
| Lercanidipine 20 mg x 1     | 2.36     | 0.99     | 20     | 0.87     | 2.41     |
| Bisoprolol 10 mg x 1        | 147.6    | 60.6     | 20     | 68       | 52.8     |
| Doxazosin d. 8 mg x 1       | 31       | 26.8     | 20     | 56.8     | 33.2     |
| Moxonidine 0.2 mg x 2*      | 92.5     | 88.1     | 20     | 20.9     | 24       |
| Amilorid 2.5 mg x 1*        | 199.8    | 29.5     | 20     | 8.2      | 6.8      |
| Candesartan 16 mg x 1       | 43.2     | 46.7     | 20     | 33.1     | 45.3     |
| Hydrochlorothiazide 12.5 mg x 1 | 214.9  | 63.8     | 20     | 13.8     | <10      |
| Nifedipine d. 60 mg x 1     | 92.5     | 88.1     | 20     | 20.9     | 24       |
| Amlodipine 10 mg x 1        | 71.4     | 65.3     | 20     | 60.9     | 81.9     |
| Moxonidine 0.2 mg x 1*      | 4301     | 1508     | 20     | 1461     | 323.3    |
| Candesartan 16 mg x 1       | 310.1    | 124.1    | 20     | 322.2    | 127.2    |
| Nifedipine 10 mg x 1        | 12.8     | 7.3      | 20     | 19.8     | 19.8     |
| Metoprolol d. 200 mg x 1    | 282.36   | 54.99    | 20     | 118.82   | 118.82   |
| Spironolactone 12.5 mg x 1  | 13       | 15       | 20     | 17       | 17       |
| Furosemide 40 mg x 1*       | <10000   | <10000   | 20     | 223.7    | 223.7    |
| Minoxidil 5 mg x 2*         | 112.4    | 234.7    | 20     | 69.8     | 164      |
| Candesartan 32 mg x 1       | 112.4    | 234.7    | 20     | 69.8     | 164      |
| Atenolol 50 mg x 1          | 189      | 88       | 20     | 118      | 98       |
| Doxazosin d. 8 mg x 1       | 32       | 48.5     | 20     | 38.3     | 50.1     |
| Bumetanide 1 mg x 1 | 67 | Hydrochlorothiazide 25 mg x 1 | 118.6 | Hydrochlorothiazide 25 mg x 1 | 160.5 | Hydrochlorothiazide 25 mg x 1 | 252.6 |
|---------------------|----|-------------------------------|--------|-------------------------------|--------|-------------------------------|-------|
| Felodipine 10 mg x 1* |    | Felodipine 10 mg x 1*         |       | Felodipine 10 mg x 1*         |       | Felodipine 10 mg x 1*         |       |
| Amelodin 2.5 mg x 1* |    | Amelodin 2.5 mg x 1*          |       | Amelodin 2.5 mg x 1*          |       | Amelodin 2.5 mg x 1*          |       |
| Minoxidil 5 mg x 2*  |    | Minoxidil 5 mg x 2*           |       | Minoxidil 5 mg x 2*           |       | Minoxidil 5 mg x 2*           |       |
| Losartan 100 mg x 1 |  1773.6 | Losartan 100 mg x 1 |  65 | Losartan 100 mg x 1 |  2288.6 | Losartan 100 mg x 1 |  57.1 |
| Hydrochlorothiazide 25 mg x 1 |  183.4 | Hydrochlorothiazide 25 mg x 1 |  71 | Hydrochlorothiazide 25 mg x 1† | <10 | Spironolactone 25 mg x 1 |  45 |
| Spironolactone 12.5 mg x 1 |  47 | Spironolactone 12.5 mg x 1 |  24 | Spironolactone 25 mg x 1 |  163 | Felodipine 10 mg x 1 vesp* |       |
| Felodipine d.10 mg x 1 vesp* |    | Felodipine d. 10 mg x 1 vesp* |       |                               |       |                               |       |
| Losartan 100 mg x 1 |  38.7 | Losartan 100 mg x 1 |  48.9 | Losartan 100 mg x 1 |  96.8 | Losartan 100 mg x 1 |  49.6 |
| Hydrochlorothiazide 25 mg x 1 |  28.3 | Hydrochlorothiazide 25 mg x 1 |  59.7 | Hydrochlorothiazide 25 mg x 1 |  65.1 | Hydrochlorothiazide 25 mg x 1 |  35.7 |
| Lercanidipine 20 mg x 1 |  1.77 | Lercanidipine 20 mg x 1 |  2.95 | Lercanidipine 20 mg x 1 |  1.2 | Lercanidipine 20 mg x 1 |  1.97 |
| Metoprolol d. 200 mg x 1 |  88.92 | Metoprolol d. 150 mg x 1 | 107.9 | Metoprolol d. 150 mg x 1 |  81.25 | Metoprolol d. 150 mg x 1 | 102.7 |
| Doxazosin d. 4 mg x 1 |  32.8 | Doxazosin d. 4 mg x 1 vesp |  43 | Spironolactone 50 mg x 1 |  97 | Moxonidine 0.2 mg + 0.4 mg* |       |
| Spironolactone 25 mg x 1 |  44 | Spironolactone 50 mg x 1 |  94 | Moxonidine 0.2 mg + 0.4 mg* |       |                               |       |
| Moxonidine 0.2 mg + 0.4 mg* |    | Moxonidine 0.2 mg + 0.4 mg* |       |                               |       |                               |       |

*Agents not analyzed by our method. † Hydrochlorothiazid not detected, but patient labeled as adherent since the other components in the poly-pill is present. ‡Low dose loop-diuretic is rapidly excreted, and is excluded from the adherence evaluation. Prolonged release formula is marked d. for depot.
Table S3. Genotypes of CYP2D6, CYP2C9, CYP3A4 and CYP3A5

CYP2D6 phenotype is written in parenthesis.

N=19

PM=poor metabolizer, IM* = intermediate metabolizer with highly reduced enzyme activity, IM = intermediate metabolizer, NM = normal metabolizer

| Non-adherent patients | CYP2D6 | CYP2C9 | CYP3A4 | CYP3A5 |
|-----------------------|--------|--------|--------|--------|
| A                     | *4/*6 (PM) | *1/*3 (↓ metabolism) | *1/*1 | *3/*3 |
| B                     | *3/*4 (PM) | *1/*1 | *1/*1 | *3/*3 |
| C                     | *4/*4 (PM) | *1/*1 | *1/*1 | *3/*3 |
| D                     | *1/*1 (NM) | *1/*1 | *1/*1 | *1/*3 (↑ metabolism) |
| E                     | *1/*9 (NM) | *1/*1 | *1/*1 | *3/*3 |
| F                     | *4/*41 (IM*) | *1/*1 | *1/*1 | *3/*3 |
| G                     | *4/*41 (IM*) | *1/*1 | *1/*1 | *3/*3 |

| Adherent patients | CYP2D6 | CYP2C9 | CYP3A4 | CYP3A5 |
|-------------------|--------|--------|--------|--------|
| h                 | *4/*4 (PM) | *1/*3 (↓ metabolism) | Missing, The patient uses Carbamazepine, inductor of CYP3A4 | *3/*3 |
| i                 | *4/*41 (IM*) | *1/*1 | *1/*1 | *3/*3 |
| j                 | *5/*41 (IM*) | *1/*1 | *1/*1 | *3/*3 |
| k                 | *4/*10 (IM*) | *1/*2 | *1/*1 | *3/*3 |
| l                 | *1/*4 (IM) | *1/*2 | *1/*1 | *3/*3 |
| m                 | *1/*3 (IM) | *1/*1 | *1/*1 | *3/*3 |
| n                 | *1/*6 (IM) | *1/*1 | *1/*22 (↓ metabolism) | *3/*3 |
| o                 | *1/*5 (IM) | *1/*1 | *1/*1 | *3/*3 |
| p                 | *1/*4 (IM) | *1/*1 | *1/*1 | *3/*3 |
| q                 | *1/*4 (IM) | *1/*1 | *1/*1 | *3/*3 |
| r                 | *1/*1 (NM) | *1/*1 | *1/*1 | *3/*3 |
| s                 | *1/*41 (NM) | *1/*2 | *1/*1 | *3/*3 |