Supplementary materials

Table S1 Plasma concentration distribution of atorvastatin and metabolites for the certain dose

Table S2 Plasma concentration distribution of rosuvastatin and metabolites for the certain dose

Table S3–S4 Patient characteristics and their effects on plasma concentration of AT and metabolites. Estimates were calculated by applying a linear regression model

Table S5 Patient characteristics and their effects on plasma concentration of RST and metabolites. Estimates were calculated by applying a linear regression

Figure S1 Histogram of Plasma concentration distribution of atorvastatin and metabolites for the certain dose. AT, atorvastatin; 2-AT, 2-hydroxy atorvastatin; 4-AT, 4-hydroxy atorvastatin; ATL, atorvastatin lactone; 2-ATL, 2-hydroxy atorvastatin lactone; 4-ATL, 4-hydroxy atorvastatin lactone.

Figure S2 Histogram of Plasma concentration distribution of rosuvastatin and metabolites for the certain dose. RST, rosuvastatin; RSTL, rosuvastatin lactone; DM-RST, rosuvastatin lactone.

Figure S3 Correlations between plasma concentration of AT and its metabolites 2-AT (A), 4-AT (B), ATL (C), 2-ATL (D) and 4-ATL (E). AT, atorvastatin; 2-AT, 2-hydroxy atorvastatin; 4-AT, 4-hydroxy atorvastatin; ATL, atorvastatin lactone; 2-ATL, 2-hydroxy atorvastatin lactone; 4-ATL, 4-hydroxy atorvastatin lactone.

Figure S4 Correlations between plasma concentration of RST and its metabolites DM-RST (A) and RSTL (B). RST, rosuvastatin; RSTL, rosuvastatin lactone; DM-RST, rosuvastatin lactone.
| AT and metabolites | Plasma concentration for 10mg, ng/ml | Plasma concentration for 20mg, ng/ml | Plasma concentration for 40mg, ng/ml |
|--------------------|-------------------------------------|-------------------------------------|-------------------------------------|
|                    | Value n (%) | mean+SD | Value n (%) | mean+SD | Value n (%) | mean+SD |
| AT                 |             |         |             |         |             |         |
| low                | 15 (57.69%) | 0.58 ± 0.34 | 360 (25.10%) | 0.62 ± 0.35 | 36 (19.57%) | 0.51 ± 0.33 |
| Mid                | 9 (34.62%) | 2.85 ± 0.92 | 743 (51.81%) | 2.81 ± 1.12 | 70 (38.04%) | 2.90 ± 1.11 |
| High               | 2 (7.69%) | 5.71 ± 0.44 | 331 (23.08%) | 11.24 ± 8.91 | 78 (42.39%) | 13.24 ± 8.56 |
| 2-AT               |             |         |             |         |             |         |
| low                | 14 (53.85%) | 0.66 ± 0.41 | 356 (24.83%) | 0.72 ± 0.36 | 41 (22.28%) | 0.64 ± 0.394 |
| Mid                | 12 (46.15%) | 2.77 ± 1.09 | 747 (52.09%) | 2.80 ± 1.00 | 63 (34.24%) | 2.98 ± 1.09 |
| High               | /           | /        | 331 (23.08%) | 8.63 ± 4.83 | 80 (43.48%) | 10.56 ± 7.24 |
| 4-AT               |             |         |             |         |             |         |
| low                | 9 (34.62%) | 0.21 ± 0.07 | 373 (26.01%) | 0.18 ± 0.10 | 29 (15.76%) | 0.16 ± 0.10 |
| Tier | Count (%) | Median | Q1 | Median | Q1 | Q3 | Median | Q1 | Q3 | Median | Q1 | Q3 |
|------|-----------|--------|----|--------|----|----|--------|----|----|--------|----|----|
| Mid  | 13 (50.00%) | 0.65 ± 0.31 | 736 (51.32%) | 0.79 ± 0.32 | 73 (39.67%) | 0.80 ± 0.30 |
| High | 4 (15.38) | 1.99 ± 0.36 | 325 (22.66%) | 3.99 ± 4.20 | 82 (44.57%) | 4.32 ± 3.56 |
| ATL  | low | 14 (53.85%) | 0.42 ± 0.254 | 369 (25.73%) | 0.47 ± 0.29 | 28 (15.22%) | 0.34 ± 0.24 |
| Mid  | 10 (38.46%) | 1.98 ± 0.75 | 737 (51.39%) | 2.42 ± 1.01 | 75 (40.76%) | 2.67 ± 1.06 |
| High | 2 (7.69%) | 5.89 ± 0.30 | 328 (22.87%) | 10.66 ± 8.34 | 81 (44.02%) | 14.13 ± 13.50 |
| 2-ATL | low | 16 (61.54%) | 1.46 ± 0.88 | 365 (25.45%) | 1.54 ± 0.85 | 30 (16.30%) | 1.12 ± 0.75 |
| Mid  | 9 (34.62%) | 6.38 ± 2.66 | 737 (51.39%) | 6.55 ± 2.51 | 76 (41.30%) | 6.83 ± 2.60 |
| High | 1 (3.85%) | 13.07 ± 0 | 332 (23.15%) | 21.63 ± 11.63 | 78 (42.39%) | 28.20 ± 14.51 |
| 4-ATL | low | 10 (38.46%) | 0.28 ± 0.13 | 377 (26.29%) | 0.24 ± 0.15 | 24 (13.04%) | 0.19 ± 0.16 |
| Mid  | 14 (53.85%) | 0.90 ± 0.38 | 727 (50.70%) | 1.07 ± 0.41 | 81 (44.02%) | 1.12 ± 0.41 |
| High | 2 (7.69%) | 3.58 ± 2.12 | 330 (23.01%) | 4.55 ± 4.153 | 79 (42.93%) | 5.11 ± 3.52 |
*AT = atorvastatin; 2-AT = 2-hydroxy atorvastatin; 4-AT = 4-hydroxy atorvastatin; 2-ATL = 2-hydroxy atorvastatin lactone; 4-ATL = 4-hydroxy atorvastatin lactone; ATL = atorvastatin lactone
Table S2. Plasma concentration distribution of rosvastatin and metabolites for the certain dose

| RST and metabolites | Plasma concentration for 5mg, ng/ml | Plasma concentration for 10mg, ng/ml | Plasma concentration for 20mg, ng/ml | Plasma concentration for 40mg, ng/ml |
|---------------------|-----------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| Value n (%)         | mean ± SD                         | mean ± SD                         | mean ± SD                         | mean ± SD                         |
| 16 (1.99%)          | 176 (25.07%)                      | 0.08 ± 0.13                       | 19 (23.75%)                       | 0.05 ± 0.08                       |
|                     | 19 (23.75%)                       |                                   | 0.05 ± 0.08                       | 3 (50.00%)                        |
|                     | 164 (23.36%)                      | 7.91 ± 3.65                       | 32 (40.00%)                       | 10.59 ± 7.50                      |
| RSTL                |                                   |                                   | 2 (33.33%)                        | 7.81 ± 1.05                       |
| low                 | 3 (18.75%)                        | 0.02 ± 0.02                       | 174 (24.79%)                      | 0.02 ± 0.01                       |
|                     | 4 (25.00%)                        | 0.02 ± 0.01                       | 0.02 ± 0.01                       | 4 (66.67%)                        |
|                      |                                   |                                   | 19 (23.75%)                       | 0.02 ± 0.01                       |
| Mid                 | 10 (62.50%)                       | 1.72 ± 0.48                       | 362 (51.57%)                      | 2.29 ± 1.03                       |
|                     | 2 (33.33%)                        | 2.40 ± 1.01                       | 29 (36.25%)                       | 2.40 ± 1.01                       |
|                      |                                   |                                   | 16 (23.36%)                       | 0.30 ± 0.13                       |
| High                | 3 (18.75%)                        | 7.97 ± 1.76                       | 164 (23.36%)                      | 1.45 ± 0.79                       |
|                     | 5 (31.25%)                        | 1.21 ± 0.69                       | 16 (23.36%)                       | 1.81 ± 0.79                       |
| DMGST               |                                   |                                   |                                   |                                   |
|       |     |         |         |         |         |         |
|-------|-----|---------|---------|---------|---------|---------|
|       |     | N-moles | N-moles | N-moles | N-moles | N-moles |
| low   | 4 (25.00%) | 0.05 ± 0.03 | 176 (25.07%) | 0.07 ± 0.02 | 20 (25.00%) | 0.07 ± 0.01 | 1 (16.67%) | 0.07 ± 0 |
| Mid   | 5 (31.25%) | 0.20 ± 0.06 | 358 (51.00%) | 0.26 ± 0.12 | 35 (43.75%) | 0.31 ± 0.14 | 4 (66.67%) | 0.20 ± 0.10 |
| High  | 7 (43.75%) | 0.68 ± 0.17 | 168 (23.93%) | 1.09 ± 0.74 | 25 (31.25%) | 1.79 ± 3.02 | 1 (16.67%) | 0.87 ± 0 |

*DM-RST = N-desmethyl rosuvastatin; RST = rosuvastatin; RSTL = rosuvastatin lactone*
Table S3. Patient characteristics and their effects on plasma concentrations of AT, 2-AT and 4-AT. Estimates were calculated by applying a linear regression model.

| Characteristics | Value N (%) or mean ± SD | Plasma AT concentration, ng/mL | Plasma 2-AT concentration, ng/mL | Plasma 4-AT concentration, ng/mL |
|-----------------|---------------------------|-------------------------------|----------------------------------|----------------------------------|
|                 |                           | Univariable Analysis          | Multivariable Analysis           | Univariable Analysis             | Multivariable Analysis           |
|                 |                           | mean ± SD                     | Estimate                         | p-value                          | mean ± SD                       | Estimate                         | p-value                          | Estimate                         | p-value                          |
| Demographic data|                           |                               |                                  |                                  |                                |                                  |                                  |                                |                                  |                                |
| Total number    | 1644                      | 4.46 ± 6.16                   | 3.84 ± 4.19                      | 1.45 ± 2.54                      |                                |                                  |                                  |                                |                                  |                                |
| Age (years)     | 62.74 ± 9.98              | 0.0118                        | < 0.0001                         | 0.0140                           | 0.0002                          | 0.0118                          | < 0.0001                         | 0.0146                          | < 0.0001                         | 0.0162                          | < 0.0001                         | 0.0172                          | < 0.0001                         |
| Sex             | Female                    | 372 (22.63)                   | 4.89 ± 7.06                      | 0.0090                           | 0.9009                          | 4.31 ± 5.23                     | -0.0719                          | 0.2565                          | 1.62 ± 3.23                      | -0.0152                          | 0.8347                          | 1.40 ± 2.30                      |                                  |                                |
|                 | Male                      | 1272 (77.37)                  | 4.33 ± 5.87                      | 3.70 ± 3.82                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                  |                                |                                |
| Dosage (mg)     | 10                        | 26 (1.58)                     | 1.76 ± 1.69                      | 0.0217                           | < 0.0001                        | 0.0219                          | < 0.0001                        | 1.63 ± 1.32                     | 0.0178                          | < 0.0001                        | 0.0193                          | < 0.0001                        | 0.70 ± 0.64                     | 0.0265                          | < 0.0001                        | 0.0257                          | < 0.0001                        |
|                 | 20                        | 1434 (87.23)                  | 4.20 ± 5.89                      | 3.63 ± 3.76                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                  |                                |                                |
|                 | 40                        | 184 (11.19)                   | 6.81 ± 7.91                      | 5.75 ± 6.46                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                  |                                |                                |
| Syntax score    | 14.47±11.75               | 0.0082                        | 0.0014                           | 0.0057                           | 0.0122                          |                                |                                  |                                |                                  |                                  |                                |                                |                                  |                                |
| Medical history |                           |                               |                                  |                                  |                                |                                  |                                  |                                |                                  |                                |                                  |                                |                                |                                |
| Arrhythmia      | No                        | 1485 (90.71)                  | 4.38 ± 5.79                      | -0.0713                          | 0.4921                          | 3.78 ± 4.03                     | -0.0262                          | 0.7745                          | 1.42 ± 2.42                      | 0.0914                           | 0.3838                          | 1.74 ± 3.52                      |                                  |                                |                                  |                                |
|                 | Yes                       | 152 (9.29)                    | 4.98 ± 8.40                      | 4.18 ± 4.94                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                |                                |                                |                                |
| Diabetes        | No                        | 1214 (74.16)                  | 4.37 ± 6.06                      | -0.0148                          | 0.8301                          | 3.74 ± 4.04                     | 0.0312                           | 0.6069                          | 1.30 ± 2.22                      | 0.3142                           | < 0.0001                        | 0.2802                          | < 0.0001                        |                                  |                                |
|                 | Yes                       | 423 (25.84)                   | 4.63 ± 6.13                      | 4.06 ± 4.35                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                |                                |                                |                                |
| Heart failure   | No                        | 1500 (91.63)                  | 4.35 ± 5.87                      | -0.0556                          | 0.6092                          | 3.78 ± 3.88                     | -0.1392                          | 0.1459                          | 1.38 ± 2.36                      | 0.1875                           | 0.0883                          | 2.10 ± 3.97                      |                                  |                                |                                  |                                |
|                 | Yes                       | 137 (8.37)                    | 5.40 ± 8.00                      | 4.31 ± 6.23                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                |                                |                                |                                |
| Hypertension    | No                        | 688 (41.98)                   | 4.25 ± 5.97                      | 0.0398                           | 0.5147                          | 3.71 ± 3.74                     | -0.0045                          | 0.9338                          | 1.33 ± 2.49                      | 0.1128                           | 0.0675                          | 1.53 ± 2.58                      |                                  |                                |                                  |                                |
|                 | Yes                       | 951 (58.02)                   | 4.62 ± 6.31                      | 3.93 ± 4.48                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                |                                |                                |                                |
| Hyperlipidemia  | No                        | 1452 (88.59)                  | 4.52 ± 6.37                      | 0.0397                           | 0.6758                          | 3.84 ± 4.06                     | 0.0098                           | 0.9062                          | 1.47 ± 2.57                      | -0.0856                          | 0.3719                          | 1.25 ± 2.32                      |                                  |                                |                                  |                                |
|                 | Yes                       | 187 (11.41)                   | 4.03 ± 4.34                      | 3.83 ± 5.08                      |                                |                                  |                                  |                                |                                  |                                  |                                |                                |                                |                                |                                |
### Biochemical measurements

| Parameter      | Value          | Std Dev | Mean          | Median  | 25th Percentile | 75th Percentile | Min       | Max        | Numbers | Proportion |
|----------------|----------------|---------|---------------|---------|-----------------|-----------------|-----------|------------|---------|------------|
| ALT, U/L       | 29.06 ± 17.28  | 0.0067  | 0.0003        | 0.0059  | 0.0041          | 0.0039          | 0.0169    | 0.0039     | 0.0358  | 0.0061     |
| AST, U/L       | 30.96 ± 29.74  | 0.0040  | < 0.0001      | 0.0027  | 0.0025          | 0.0027          | 0.0025    | 0.0033     | 0.0015  | 0.0033     |
| CREA, umol/L   | 87.85 ± 32.56  | 0.0043  | < 0.0001      | 0.0026  | 0.0195          | 0.0024          | 0.0040    | 0.0063     | < 0.0001| 0.0046     |
| eGFR, ml/min/1.73 m² | 95.04 ± 77.73 | -0.0010 | 0.0126        | -0.0005 | 0.1686          | -0.0008         | 0.0353    | 0.0061     | 0.0010  | 0.0056     |
| CK, U/L        | 152.66 ± 380.24| 0.0000  | 0.5627        | 0.0000  | 0.7453          | -0.0001         | 0.3685    | 380.24     |        |            |
| CKMB, U/L      | 8.77 ± 14.29   | 0.0035  | 0.1252        | 0.0029  | 0.1391          | 0.0020          | 0.3690    |            |        |            |
| CHOL, mmol/L   | 4.31 ± 1.13    | 0.0806  | 0.0028        | 0.0495  | 0.0377          | -0.0970         | 0.0004    | -0.09269   | 0.0084  |            |
| LDLC, mmol/L   | 2.60 ± 0.93    | 0.1178  | 0.0003        | 0.1199  | 0.0016          | 0.0789          | 0.0060    | -0.0751    | 0.0232  |            |
| HDLC, mmol/L   | 0.98 ± 0.26    | -0.3281 | 0.0057        | -0.0411 | 0.6953          | -0.4712         | < 0.0001  |            |        |            |
| TRIG, mmol/L   | 1.61 ± 1.08    | 0.0427  | 0.1307        | -0.0071 | 0.7760          | -0.0880         | 0.0022    | -0.07498   | 0.0388  |            |
| GLUC, mmol/L   | 6.63 ± 2.60    | 0.0199  | 0.0887        | 0.0196  | 0.0566          | 0.0548          | < 0.0001  | 0.05257    | 0.0001  |            |
| Lpa, mg/L      | 288.79 ± 312.66| 0.0002  | 0.0947        | 0.0001  | 0.1707          | 0.0000          | 0.9914    |            |        |            |
| APOA, g/L      | 1.05 ± 0.28    | -0.5130 | < 0.0001      | -0.4192 | 0.0011          | -0.2969         | 0.0061    | -0.24401   | 0.0309  | -0.5855    |

### Medication

| Category       | Value          | Std Dev | Mean          | Median  | 25th Percentile | 75th Percentile | Min       | Max        |
|----------------|----------------|---------|---------------|---------|-----------------|-----------------|-----------|------------|
| β-blockers     | No 185 (11.29) | 3.92 ± 4.56 | 0.501        | 0.5986  | 3.43 ± 3.24     | 0.1075          | 0.2002    | 1.15 ± 1.56 |
|                | Yes 1453 (88.71)| 4.49 ± 6.13 | 0.0501       | 0.5986  | 3.88 ± 4.27     | 0.1075          | 0.2002    | 1.15 ± 1.56 |
| ACEIs          | No 639 (39.01) | 4.53 ± 6.24 | -0.0140      | 0.8209  | 3.94 ± 4.20     | -0.0281         | 0.6059    | 1.40 ± 2.23 |
|                | Yes 999 (60.99)| 4.36 ± 5.81 | 0.0347       | 0.6058  | 3.75 ± 4.15     | -0.0281         | 0.6059    | 1.46 ± 2.68 |
| CCBs           | No 1184 (72.28)| 4.25 ± 5.49 | 0.0347       | 0.6058  | 3.78 ± 3.75     | -0.0309         | 0.6022    | 1.38 ± 2.32 |
|                | Yes 454 (27.72)| 4.89 ± 7.08 | 0.0347       | 0.6058  | 3.95 ± 5.09     | -0.0309         | 0.6022    | 1.60 ± 2.95 |

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Variables with \( P < 0.05 \) were entered into the multivariable model, and only variables with \( P < 0.05 \) were retained in the model.

4-AT = 2-hydroxy atorvastatin; 4-AT = 4-hydroxy atorvastatin; ACEIs = angiotensin converting enzyme inhibitors; ALT = alanine aminotransferase; APOA = apolipoprotein a; AST = aspartate aminotransferase; AT = atorvastatin; CCBs = calcium channel blockers; CHOL = cholesterol; CK = creatine kinase; CKMB = creatine kinase MB; eGFR = estimated glomerular filtration rate; GLUC = glucose; HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; Lpa = lipoprotein (a); PPIs = proton pump inhibitors; Scr = serum creatinine; SD = standard deviation; TRIG = triglyceride.
Table S4. Patient characteristics and their effects on plasma concentrations of ATL, 2-ATL and 4-ATL. Estimates were calculated by applying a linear regression model.

| Characteristics      | Value N (%) or mean ± SD | Plasma ATL concentration, ng/mL | Plasma 2-ATL concentration, ng/mL | Plasma 4-ATL concentration, ng/mL |
|----------------------|--------------------------|----------------------------------|-----------------------------------|-----------------------------------|
|                      |                          | Univariable Analysis             | Multivariable Analysis            | Univariable Analysis              | Multivariable Analysis            |
|                      |                          | mean ± SD                        | Estimate                          | p-value                           | mean ± SD                        | Estimate                          | p-value                           |
| Demographic data     |                          |                                  |                                   |                                   |                                  |                                  |                                   |
| Total number         | 1644                     | 4.16 ± 6.44                      | 9.37 ± 10.35                      | 1.76 ± 2.66                       |
| Age (years)          | 62.74 ± 9.98             | 0.0157 < 0.0001                  | 0.0170 < 0.0001                   | 0.0152 < 0.0001                   | 0.0168 < 0.0001                   | 0.0199 < 0.0001                   | 0.0211 < 0.0001                   |
| Sex                  | Female                   | 3.85 ± 5.60                      | 0.1345 0.0871                     | 9.78 ± 11.15                      | 0.0118 0.8637                     | 1.77 ± 2.94                       | 0.1000 0.1962                     |
|                      | Male                     | 4.25 ± 6.67                      | 0.2982 0.871                      | 9.26 ± 10.10                      | 0.1650 0.772                      | 1.76 ± 2.57                       | 0.1962                            |
| Dosage (mg)          | 26 (1.58)                | 1.44 ± 1.59                      | 0.0302 < 0.0001                   | 3.61 ± 3.47                       | 0.0248 < 0.0001                   | 0.0253 < 0.0001                   | 0.0275 < 0.0001                   |
|                      | 1434 (87.23)             | 3.80 ± 5.57                      | 0.0294 < 0.0001                   | 8.76 ± 9.43                       | 0.2250 0.592                      | 1.65 ± 2.58                       | 0.1962                            |
|                      | 184 (11.19)              | 7.36 ± 10.81                     | 0.006 0.014                       | 14.96 ± 15.00                     | 0.0158 < 0.0001                   | 0.00841 0.0113                    |
| SYNTAX score         | 14.47±11.75              | 0.0083 0.0029                    | 0.006 0.014                       | 0.0158 < 0.0001                   | 0.00841 0.0113                    |

Medical history

| Arrhythmia No        | 1485 (90.71)             | 4.11 ± 6.26                      | 0.0230 0.8393                     | 9.26 ± 10.13                      | 0.0486 0.6230                     | 1.73 ± 2.53                       | 0.1878 0.0933                     |
|                      | Yes                      | 152 (9.29)                       | 4.54 ± 7.91                       | 10.19 ± 11.71                     | 0.2030 2.046                      | 2.04 ± 3.67                       |                                   |
| Diabetes No          | 1214 (74.16)             | 4.12 ± 6.26                      | -0.0796 0.2899                    | 9.18 ± 10.07                      | -0.0047 0.9429                    | 1.68 ± 2.67                       | 0.2465 0.0009                     |
|                      | Yes                      | 423 (25.84)                      | 4.25 ± 6.91                       | 9.84 ± 10.85                      | -0.0088 0.9325                    | 1.98 ± 2.62                       | 0.2153 0.0049                     |
| Heart failure No     | 1500 (91.63)             | 4.07 ± 6.41                      | 0.0919 0.4398                     | 9.21 ± 10.09                      | -0.0088 0.9325                    | 1.67 ± 2.43                       | 0.1914 0.1026                     |
|                      | Yes                      | 137 (8.37)                       | 5.10 ± 6.60                       | 10.87 ± 12.08                     | -0.0147 0.8002                    | 1.73 ± 2.62                       | 0.1294 0.0491                     |
| Hypertension No      | 688 (41.98)              | 4.30 ± 7.03                      | -0.0106 0.8737                    | 9.38 ± 10.21                      | -0.0147 0.8002                    | 1.78 ± 2.69                       |                                   |
|                      | Yes                      | 951 (58.02)                      | 4.07 ± 6.00                       | 9.37 ± 10.46                      | 0.0129 0.8864                     | 1.81 ± 2.78                       | -0.1016 0.3197                    |
| Hyperlipidemia No    | 1452 (88.59)             | 4.28 ± 6.74                      | -0.0364 0.7254                    | 9.53 ± 10.65                      | 0.0129 0.8864                     | 1.81 ± 2.78                       | -0.1016 0.3197                    |
## Biochemical measurements

| Test         | Mean ± SD    | p-value   | Mean ± SD    | p-value   | Mean ± SD    | p-value   |
|--------------|--------------|-----------|--------------|-----------|--------------|-----------|
| ALT, U/L     | 29.06 ± 17.28 | 0.0074    | 0.0003       | 0.0047    | 0.0078       | 0.0075    |
| AST, U/L     | 30.96 ± 29.74 | 0.0057    | < 0.0001     | 0.0049    | 0.0004       | < 0.0001  |
| CREA, umol/L | 87.85 ± 32.56 | 0.0073    | < 0.0001     | 0.0045    | 0.0002       | < 0.0001  |
| eGFR, ml/min/1.73 m2 | 95.04 ± 77.73 | -0.0021 | < 0.0001   | -0.0014 | 0.0003       | -0.0020   |
| CK, U/L      | 152.66 ±     | 0.0002    | 0.0653       | 0.0001    | 0.1989       | 0.0001    |
| CKMB, U/L    | 8.77 ± 14.29  | 0.0059    | 0.0160       | 0.0050    | 0.0206       | 0.0047    |
| CHOL, mmol/L | 4.31 ± 1.13   | 0.0943    | -0.014       | 0.0651    | 0.0114       | -0.0607   |
| LDL, mmol/L  | 2.60 ± 0.93   | 0.1390    | < 0.0001     | 0.1505    | 0.0006       | -0.0468   |
| HDLC, mmol/L | 0.98 ± 0.26   | -0.3386   | 0.0093       | -0.0272   | 0.8105       | -0.5224   |
| TRIG, mmol/L | 1.61 ± 1.08   | 0.0171    | 0.5804       | -0.0213   | 0.4295       | -0.0555   |
| GLUC, mmol/L | 6.63 ± 2.60   | 0.0163    | 0.2027       | 0.0135    | 0.2260       | 0.0469    |
| Lpa, mg/L    | 288.79 ±     | 0.0003    | 0.0045       | 0.0003    | 0.0053       | 0.0003    |
| APOA, g/L    | 1.05 ± 0.28   | -0.6067   | < 0.0001     | -0.5050   | 0.0004       | -0.3508   |

## Medication

| Test   | No             | Yes            | p-value   | No             | Yes            | p-value   |
|--------|----------------|----------------|-----------|----------------|----------------|-----------|
| β-blockers | 185 (11.29) | 1453 (88.71)  |           | 8.54 ± 8.22    | 9.45 ± 10.51  | 0.857     |
| ACEIs  | 639 (39.01)   | 999 (60.99)   |           | 9.27 ± 9.89    | 9.39 ± 10.53  | 0.0001    |
| CCBs   | 1184 (72.28)  | 1184 (72.28)  |           | 9.22 ± 9.87    | 9.39 ± 10.53  | 0.0001    |
| PPIs |   |   |   |   |
|------|---|---|---|---|
| Yes  | 454 (27.72) | 4.38 ± 6.55 | 9.66 ± 11.29 | 1.85 ± 2.79 |
| No   | 837 (51.1) | 3.69 ± 5.21 | 8.67 ± 9.18 | 1.59 ± 2.37 |
| Yes  | 801 (48.9) | 4.61 ± 7.39 | 10.05 ± 11.28 | 1.90 ± 2.84 |

*Variables with P < 0.05 were entered into the multivariable model, and only variables with P < 0.05 were retained in the model.*

2-ATL = 2-hydroxy atorvastatin lactone; 4-ATL = 4-hydroxy atorvastatin lactone; ATL = atorvastatin lactone; other abbreviations as in Table S3.
Table S5. Patient characteristics and their effects on plasma concentration of RST, RSTL and DM-RST. Estimates were calculated by applying a linear regression model.

| Characteristics | Value N (%) | Plasma RST concentration, ng/mL | Plasma RSTL concentration, ng/mL | Plasma DM-RST concentration, ng/mL |
|-----------------|-------------|---------------------------------|----------------------------------|------------------------------------|
|                 |             | Univariable Analysis Multivariable Analysis | Univariable Analysis Multivariable Analysis | Univariable Analysis Multivariable Analysis |
|                 |             | mean ± SD Estimate p-value | mean ± SD Estimate p-value | mean ± SD Estimate p-value |
|                 |             | Mean ± SD p-value | Mean ± SD p-value | Mean ± SD p-value |
| Demographic data |             | | | |
| Total number    | 804         | 3.25 ± 3.89 | 0.44 ± 0.53 | 0.44 ± 0.77 |
| Age (years)     | 62.37 ± 9.70 | 0.0019 | 0.8099 | 0.0065 | 0.2567 | 0.0102 | 0.0101 | 0.0096 | 0.0151 |
| Sex             |             | Male 604 (75.12) | 3.08 ± 3.51 | 0.42 ± 0.51 | 0.41 ± 0.52 |
|                 | Female 200 (24.88) | 3.75 ± 4.83 | -0.1100 | 0.5368 | 0.50 ± 0.57 | -0.0850 | 0.5101 | 0.53 ± 1.24 | -0.0859 | 0.3344 |
| Dosage (mg)     |             | 5 16 (1.99) | 2.57 ± 2.86 | 0.48 ± 0.63 | 0.41 ± 0.54 |
|                 |             | 10 702 (87.31) | 3.05 ± 3.42 | 0.41 ± 0.48 | 0.37 ± 0.42 |
| SYNTAX score    |             | 14.16±12.41 | 0.001804 | 0.7744 | 0.0126 | 0.0056 | 0.0053 | 0.0888 |
| Medical history |             | | | |
| Arrhythmia      |             | No 745 (92.66) | 3.28 ± 3.94 | -0.6050 | 0.44 ± 0.53 | -0.3567 | 0.0953 | 0.45 ± 0.79 | -0.2590 | 0.0791 |
|                 | Yes 59 (7.34) | 2.81 ± 3.18 | 0.41 ± 0.52 | 0.36 ± 0.42 |
| Diabetes        |             | No 599 (74.5) | 3.05 ± 3.31 | -0.0940 | 0.5949 | 0.42 ± 0.49 | -0.0542 | 0.6722 | 0.39 ± 0.45 | 0.1376 | 0.1191 |
|                 | Yes 205 (25.5) | 3.81 ± 5.19 | 0.49 ± 0.63 | 0.62 ± 1.30 |
| Heart failure   |             | No 751 (93.41) | 3.10 ± 3.44 | -0.0517 | 0.8677 | 0.43 ± 0.50 | 0.0908 | 0.6865 | 0.41 ± 0.50 | 0.3445 | 0.0261 | 0.3641 | 0.0297 |
|                 | Yes 53 (6.59) | 5.33 ± 7.61 | 0.63 ± 0.83 | 0.94 ± 2.28 |
| Hypertension    |             | No 365 (45.4) | 3.08 ± 3.43 | -0.0782 | 0.6132 | 0.43 ± 0.53 | -0.0178 | 0.8738 | 0.41 ± 0.54 | 0.0650 | 0.4005 |
|                 | Yes 439 (54.6) | 3.38 ± 4.23 | 0.44 ± 0.53 | 0.47 ± 0.91 |
| Hyperlipidemia  |             | No 707 (87.94) | 3.24 ± 3.88 | -0.2954 | 0.2113 | 0.43 ± 0.50 | -0.0522 | 0.7606 | 0.45 ± 0.80 | -0.1690 | 0.1524 |
| Variable   | Yes | No   | p-value 1 | p-value 2 | p-value 3 | p-value 4 |
|------------|-----|------|-----------|-----------|-----------|-----------|
| **Biochemical measurements** |     |      |           |           |           |           |
| ALT, U/L   | 30.16 ± 19.47 | 0.0006 ± 0.8932 | 0.0047 ± 0.1134 | -0.0020 ± 0.3423 |
| AST, U/L   | 30.94 ± 27.71 | -0.0082 ± 0.0033 | -0.0009 ± 0.6680 | -0.0018 ± 0.2013 |
| CREA, umol/L | 86.86 ± 31.99 | -0.0010 ± 0.6935 | 0.0029 ± 0.0928 | 0.0020 ± 0.1011 |
| eGFR, ml/min/1.73 m² | 100.66 ± 95.81 | 0.0008 ± 0.3377 | -0.0003 ± 0.5889 | -0.0002 ± 0.6865 |
| CK, U/L    | 133.87 ± 250.07 | -0.0011 ± 0.0004 | -0.0002 ± 0.3327 | -0.0002 ± 0.2411 |
| CKMB, U/L  | 7.81 ± 9.11 | -0.0239 ± 0.0052 | 0.0002 ± 0.9737 | -0.0003 ± 0.9466 |
| CHOL, mmol/L | 4.48 ± 1.30 | -0.1476 ± 0.0144 | -0.0206 ± 0.6355 | -0.0799 ± 0.0081 |
| LDLC, mmol/L | 2.75 ± 1.06 | -0.2425 ± 0.0011 | -0.2589 ± 0.0005 | -0.0424 ± 0.4279 |
| HDLC, mmol/L | 1.01 ± 0.25 | -0.3201 ± 0.3059 | -0.0790 ± 0.7250 | -0.4451 ± 0.0044 |
| TRIG, mmol/L | 1.62 ± 1.11 | -0.0131 ± 0.8527 | 0.0084 ± 0.8688 | -0.0145 ± 0.6825 |
| GLUC, mmol/L | 6.79 ± 2.98 | -0.0232 ± 0.3692 | 0.0027 ± 0.8863 | 0.0068 ± 0.6003 |
| Lpa, mg/L  | 266.70 ± 290.59 | 0.0000 ± 0.8960 | 0.0003 ± 0.1268 | 0.0000 ± 0.9135 |
| APOA, g/L  | 1.09 ± 0.28 | -0.1011 ± 0.7451 | -0.4255 ± 0.0630 | -0.4536 ± 0.0037 |
| **Medication** |     |      |           |           |           |           |
| β-blockers | No  | 102 (12.69) | 3.12 ± 3.47 | -0.0470 ± 0.8390 | 0.40 ± 0.48 | 0.1918 ± 0.2525 | 0.38 ± 0.49 | 0.0449 ± 0.6976 |
|           | Yes | 702 (87.31) | 3.26 ± 3.95 | 0.44 ± 0.54 | 0.45 ± 0.80 |    |    |    |    |
|        | No     | Yes    |
|--------|--------|--------|
| ACEIs  | 346 (43.03) | 458 (56.97) |
|        | 3.23 ± 3.29 | 3.26 ± 4.28 |
|        | -0.2217  | 0.45 ± 0.53 |
|        | 0.1538   | 0.45 ± 0.91 |
|        | 0.43 ± 0.53 | 0.45 ± 0.53 |
|        | 0.1227   | 0.42 ± 0.48 |
|        | 0.2760   | 0.45 ± 0.86 |
|        | 0.43 ± 0.52 | -0.0919    |
|        | 0.2369   | 0.6387   |

| CCBs   | 564 (70.15) | 240 (29.85) |
|        | 3.31 ± 4.06 | 3.09 ± 3.46 |
|        | -0.4080   | 0.44 ± 0.50 |
|        | 0.0152   | -0.4789   |
|        | -0.0189  | 0.0055    |
|        | 0.8771   | 0.45 ± 0.86 |
|        | 0.45 ± 0.91 | -0.0395    |
|        | 0.6387   | 0.6461   |

| PPIs   | 385 (47.89) | 419 (52.11) |
|        | 3.06 ± 3.27 | 3.42 ± 4.38 |
|        | -0.0692  | 0.42 ± 0.53 |
|        | 0.6537   | 0.42 ± 0.53 |
|        | 0.45 ± 0.53 | 0.48 ± 0.95 |
|        | -0.0513  | 0.5250    |

*Variables with P < 0.05 were entered into the multivariable model, and only variables with P < 0.05 were retained in the model.*

†DM-RST = N-desmethyl rosuvastatin; RST = rosuvastatin; RSTL = rosuvastatin lactone; other abbreviations as in Table S3.
Figure S1. Histogram of Plasma concentration distribution of atorvastatin and metabolites for the certain dose. AT, atorvastatin; 2-AT, 2-hydroxy atorvastatin; 4-AT, 4-hydroxy atorvastatin; ATL, atorvastatin lactone; 2-ATL, 2-hydroxy atorvastatin lactone; 4-ATL, 4-hydroxy atorvastatin lactone.
Figure S2. Histogram of Plasma concentration distribution of rosuvastatin and metabolites for the certain dose. RST, rosuvastatin; RSTL, rosuvastatin lactone; DM-RST, rosuvastatin lactone.
Figure S3 Correlations between plasma concentration of AT and its metabolites 2-AT (A); 4-AT (B), ATL (C), 2-ATL (D) and 4-ATL (E).

AT, atorvastatin; 2-AT, 2-hydroxy atorvastatin; 4-AT, 4-hydroxy atorvastatin; ATL, atorvastatin lactone; 2-ATL, 2-hydroxy atorvastatin lactone; 4-ATL, 4-hydroxy atorvastatin lactone.
Figure S4 Correlations between plasma concentration of RST and its metabolites DM-RST (A) and RSTL (B). RST, rosuvastatin; RSTL, rosvastatin lactone; DM-RST, rosuvastatin lactone.