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# Stereoselective quantitative analysis of ranolazine in plasma and tissue samples: Application in pharmacokinetics and tissue distribution studies

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**Figure S1** Effect of the sorbent for SPE (A), extract solvent for LLE (B) and volume of MTBE for LLE (C) on the recoveries of analytes

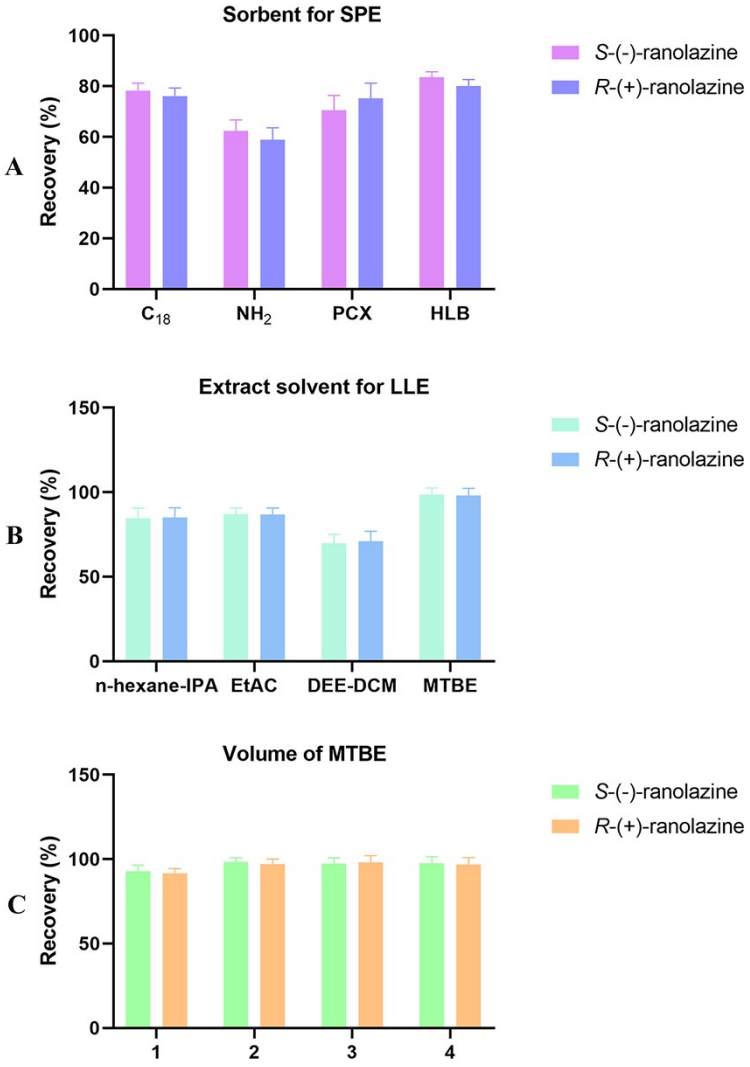

**Figure S2** Product ion mass spectra of (A) ranolazine and (B) ornidazole (IS)

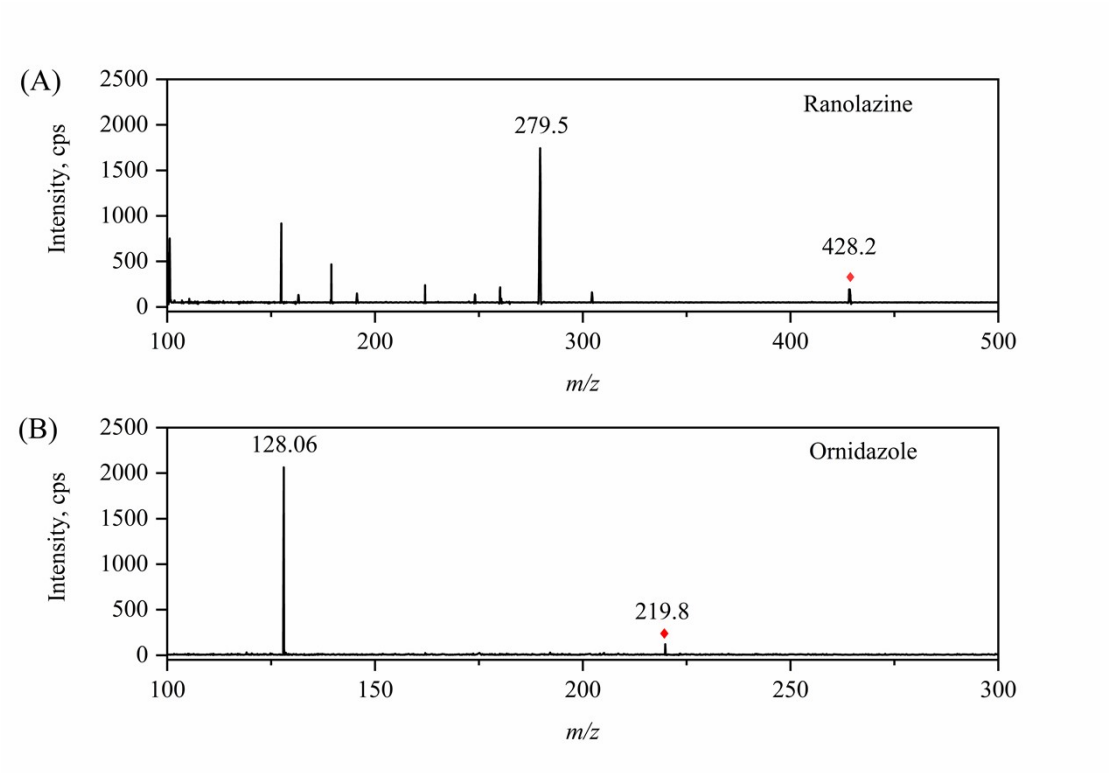

**Table S1** Intra- and inter-day accuracy and precision of *R*-(+)- and *S*-(-)-ranolazine in plasma and tissue samples at LLOQ[a] and three QC[b] levels

| | Analytes | Nominal concentration (ng/mL) | Intra-day (n=6) | | | Inter-day (n=18) | | |
|---|---|---|---|---|---|---|---|---|
| | | | Calculated concentration (ng/mL) | RE[c] (%) | RSD[d] (%) | Calculated concentration (ng/mL) | RE (%) | RSD (%) |
| Plasma | *R*-(+)-ranolazine | 2.0 | 2.1 ± 0.1 | 5.0 | 4.8 | 1.9 ± 0.1 | -5.0 | 5.3 |
| | | 6.0 | 6.3 ± 0.4 | 5.0 | 6.3 | 6.1 ± 0.2 | 1.7 | 3.3 |
| | | 40.0 | 41.1 ± 2.2 | 2.8 | 5.4 | 42.0 ± 1.9 | 5.0 | 4.5 |
| | | 80.0 | 78.4 ± 3.7 | -2.0 | 4.7 | 81.4 ± 3.0 | 1.8 | 3.7 |
| | *S*-(-)-ranolazine | 2.0 | 2.1 ± 0.1 | 5.0 | 4.8 | 1.8 ± 0.1 | -10.0 | 5.6 |
| | | 6.0 | 6.2 ± 0.3 | 3.3 | 4.8 | 6.1 ± 0.3 | 1.7 | 4.9 |
| | | 40.0 | 41.9 ± 2.5 | 4.8 | 6.0 | 41.7 ± 1.7 | 4.3 | 4.1 |
| | | 80.0 | 78.0 ± 3.6 | -2.5 | 4.6 | 81.8 ± 3.1 | 2.3 | 3.8 |
| Heart | *R*-(+)-ranolazine | 2.0 | 2.1 ± 0.2 | 5.0 | 9.5 | 1.9 ± 0.1 | -5.0 | 5.3 |
| | | 6.0 | 6.4 ± 0.4 | 6.7 | 6.3 | 5.9 ± 0.2 | -1.7 | 3.4 |
| | | 80.0 | 78.4 ± 2.5 | -2.0 | 3.2 | 82.4 ± 2.9 | 3.0 | 3.5 |
| | | 160.0 | 165.5 ± 4.0 | 3.4 | 2.4 | 165.0 ± 5.8 | 3.1 | 3.5 |
| | *S*-(-)-ranolazine | 2.0 | 2.1 ± 0.2 | 5.0 | 9.5 | 1.9 ± 0.1 | -5.0 | 5.3 |
| | | 6.0 | 6.3 ± 0.3 | 5.0 | 4.8 | 5.8 ± 0.3 | -3.3 | 5.2 |
| | | 80.0 | 78.9 ± 2.3 | -1.4 | 2.9 | 81.9 ± 3.2 | 2.4 | 3.9 |
| | | 160.0 | 166.0 ± 3.4 | 3.8 | 2.0 | 163.9 ± 5.1 | 2.4 | 3.1 |
| Liver | *R*-(+)-ranolazine | 2.0 | 2.1 ± 0.2 | 5.0 | 9.5 | 1.9 ± 0.2 | -5.0 | 10.5 |
| | | 6.0 | 6.4 ± 0.5 | 6.7 | 7.8 | 6.2 ± 0.4 | 3.3 | 6.5 |
| | | 200.0 | 193.0 ± 3.2 | -3.5 | 1.7 | 204.3 ± 5.0 | 2.2 | 2.4 |
| | | 400.0 | 408.7 ± 7.3 | 2.2 | 1.8 | 397.3 ± 3.8 | -0.68 | 1.0 |
| | *S*-(-)-ranolazine | 2.0 | 2.1 ± 0.2 | 5.0 | 9.5 | 1.8 ± 0.2 | -10.0 | 11.1 |
| | | 6.0 | 6.5 ± 0.6 | 8.3 | 9.2 | 6.3 ± 0.3 | 5.0 | 4.8 |
| | | 200.0 | 195.0 ± 5.8 | -2.5 | 3.0 | 205.7 ± 6.1 | 2.9 | 3.0 |
| | | 400.0 | 405.9 ± 6.1 | 1.5 | 1.5 | 395.2 ± 3.1 | -1.2 | 0.8 |
| Spleen | *R*-(+)-ranolazine | 2.0 | 1.9 ± 0.1 | -5.0 | 5.3 | 2.1 ± 0.2 | 5.0 | 9.5 |
| | | 6.0 | 5.7 ± 0.4 | -5.0 | 7.0 | 6.2 ± 0.4 | 3.3 | 6.5 |
| | | 80.0 | 78.2 ± 1.4 | -2.3 | 1.8 | 81.2 ± 2.6 | 1.5 | 3.2 |
| | | 160.0 | 164.3 ± 3.2 | 2.7 | 1.9 | 166.3 ± 4.8 | 3.9 | 2.9 |
| | *S*-(-)-ranolazine | 2.0 | 1.9 ± 0.1 | -5.0 | 5.3 | 2.2 ± 0.3 | 10.0 | 13.6 |
| | | 6.0 | 5.8 ± 0.3 | -3.3 | 5.2 | 6.3 ± 0.3 | 5.0 | 4.8 |
| | | 80.0 | 78.8 ± 1.6 | -1.5 | 2.0 | 82.0 ± 3.1 | 2.5 | 3.8 |
| | | 160.0 | 165.0 ± 3.0 | 3.1 | 1.8 | 167.4 ± 5.0 | 4.6 | 3.0 |
| Lung | *R*-(+)-ranolazine | 2.0 | 2.1 ± 0.1 | 5.0 | 4.8 | 1.9 ± 0.2 | -5.0 | 10.5 |
| | | 6.0 | 5.7 ± 0.2 | -5.0 | 3.5 | 6.2 ± 0.4 | 3.3 | 6.5 |
| | | 80.0 | 76.1 ± 1.8 | -4.9 | 2.4 | 84.6 ± 2.4 | 5.8 | 2.8 |
| | | 160.0 | 165.4 ± 4.1 | 3.4 | 2.5 | 155.0 ± 5.1 | -3.1 | 3.3 |
| | *S*-(-)-ranolazine | 2.0 | 2.1 ± 0.1 | 5.0 | 4.8 | 1.9 ± 0.2 | -5.0 | 10.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 6.0 | 5.8 ± 0.3 | -3.3 | 5.2 | 6.3 ± 0.5 | 5.0 | 7.9 |
| | | 80.0 | 77.0 ± 2.0 | -3.8 | 2.6 | 83.8 ± 3.0 | 4.8 | 3.6 |
| | | 160.0 | 166.9 ± 6.2 | 4.3 | 3.7 | 158.3 ± 4.2 | -1.1 | 2.7 |
| | | 2.0 | 2.2 ± 0.2 | 10.0 | 9.1 | 1.9 ± 0.1 | -5.0 | 5.3 |
| | *R*-(+)- | 6.0 | 6.3 ± 0.4 | 5.0 | 6.3 | 6.2 ± 0.3 | 3.3 | 4.8 |
| | ranolazine | 100.0 | 97.7 ± 1.6 | -2.3 | 1.6 | 102.1 ± 1.7 | 2.1 | 1.7 |
| Kidney | | 200.0 | 204.9 ± 3.2 | 2.5 | 1.6 | 191.5 ± 4.8 | -4.3 | 2.5 |
| | | 2.0 | 2.1 ± 0.2 | 5.0 | 9.5 | 1.9 ± 0.1 | -5.0 | 5.3 |
| | *S*-(-)- | 6.0 | 6.2 ± 0.3 | 3.3 | 4.8 | 6.4 ± 0.4 | 6.7 | 6.3 |
| | ranolazine | 100.0 | 98.0 ± 2.1 | -2.0 | 2.1 | 105.4 ± 2.1 | 5.4 | 2.0 |
| | | 200.0 | 202.7 ± 2.5 | 1.4 | 1.2 | 193.0 ± 5.2 | -3.5 | 2.7 |

[a] LLOQ, lower limit of quantitative; [b] QC, quality control; [c] RE, relative error; [d] RSD, relative standard deviation

**Table S2** Extraction recoveries and matrix effect of *R*-(+)- and *S*-(-)-ranolazine in

plasma and tissue samples

| | Analytes | Nominal concentration (ng/mL) | Recovery (mean ± SD, %) | RSD (%) | NMF (mean ± SD, %) | RSD (%) |
|---|---|---|---|---|---|---|
| Plasma | *R*-(+)-ranolazine | 6.0 | 102.4 ± 3.9 | 3.8 | 103.8 ± 9.3 | 9.0 |
| | | 40.0 | 98.3 ± 3.1 | 3.2 | 101.5 ± 6.4 | 6.3 |
| | | 80.0 | 97.6 ± 4.6 | 4.7 | 99.5 ± 6.3 | 6.3 |
| | *S*-(-)-ranolazine | 6.0 | 101.9 ± 4.0 | 3.9 | 104.3 ± 10.5 | 10.1 |
| | | 40.0 | 98.1 ± 2.9 | 3.0 | 100.9 ± 7.1 | 7.0 |
| | | 80.0 | 97.2 ± 4.9 | 5.0 | 99.1 ± 5.0 | 5.0 |
| Heart | *R*-(+)-ranolazine | 6.0 | 97.0 ± 4.5 | 4.6 | 98.3 ± 4.9 | 5.0 |
| | | 80.0 | 101.2 ± 5.9 | 5.8 | 97.0 ± 6.3 | 6.5 |
| | | 160.0 | 98.6 ± 6.1 | 6.2 | 102.8 ± 7.9 | 7.7 |
| | *S*-(-)-ranolazine | 6.0 | 97.6 ± 3.1 | 3.2 | 97.5 ± 4.4 | 4.5 |
| | | 80.0 | 100.9 ± 5.3 | 5.3 | 96.6 ± 6.0 | 6.2 |
| | | 160.0 | 98.5 ± 6.5 | 6.6 | 103.0 ± 7.7 | 7.5 |
| Liver | *R*-(+)-ranolazine | 6.0 | 101.6 ± 8.8 | 8.7 | 101.4 ± 10.9 | 10.7 |
| | | 200.0 | 96.4 ± 3.8 | 3.9 | 101.7 ± 8.5 | 8.4 |
| | | 400.0 | 98.4 ± 2.9 | 2.9 | 97.8 ± 6.3 | 6.4 |
| | *S*-(-)-ranolazine | 6.0 | 102.0 ± 8.0 | 7.8 | 100.8 ± 9.8 | 9.7 |
| | | 200.0 | 97.0 ± 3.5 | 3.6 | 102.0 ± 8.0 | 7.8 |
| | | 400.0 | 98.8 ± 3.0 | 3.0 | 98.1 ± 6.0 | 6.1 |
| Spleen | *R*-(+)-ranolazine | 6.0 | 101.4 ± 5.3 | 5.2 | 101.9 ± 10.4 | 10.2 |
| | | 80.0 | 97.3 ± 9.1 | 9.4 | 98.5 ± 8.4 | 8.5 |
| | | 160.0 | 98.4 ± 5.2 | 5.3 | 102.0 ± 7.6 | 7.5 |
| | *S*-(-)-ranolazine | 6.0 | 100.8 ± 5.0 | 5.0 | 100.7 ± 10.1 | 10.0 |
| | | 80.0 | 97.7 ± 9.0 | 9.2 | 97.6 ± 7.7 | 7.9 |
| | | 160.0 | 98.0 ± 4.8 | 4.9 | 101.6 ± 7.0 | 6.9 |
| Lung | *R*-(+)-ranolazine | 6.0 | 104.3 ± 9.2 | 8.8 | 96.3 ± 5.6 | 5.8 |
| | | 80.0 | 97.7 ± 8.8 | 9.0 | 101.2 ± 6.5 | 6.4 |
| | | 160.0 | 97.4 ± 3.9 | 4.0 | 103.5 ± 8.0 | 7.7 |
| | *S*-(-)- | 6.0 | 103.7 ± 9.1 | 8.8 | 97.5 ± 6.1 | 6.3 |
| | | 80.0 | 97.5 ± 8.9 | 9.1 | 102.3 ± 7.0 | 6.8 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | 160.0 | 98.0 ± 4.0 | 4.1 | 103.3 ± 8.1 | 7.8 |
| Kidney | *R*-(+)-ranolazine | 6.0 | 100.5 ± 6.5 | 6.5 | 102.0 ± 5.8 | 5.7 |
| | | 100.0 | 95.3 ± 9.0 | 9.4 | 98.4 ± 6.9 | 7.0 |
| | | 200.0 | 97.5 ± 4.2 | 4.3 | 100.3 ± 3.9 | 3.9 |
| | *S*-(-)-ranolazine | 6.0 | 100.4 ± 6.3 | 6.3 | 102.2 ± 5.5 | 5.4 |
| | | 100.0 | 95.5 ± 9.6 | 10.1 | 98.8 ± 7.0 | 7.1 |
| | | 200.0 | 98.3 ± 3.8 | 3.9 | 100.1 ± 4.5 | 4.5 |

NMF: normalized matrix factor

**Table S3**. Stability results of *R*-(+)- and *S*-(-)-ranoalzine in plasma and tissues under various storage conditions (n = 6)

| | Analytes | Nominal concentration (ng/mL) | Room temperature for 12 h | | On the autosampler tray 4°C for 24 h | | -80°C for 30 days | | Three freeze-thaw cycles | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | RE (%) | RSD (%) | RE (%) | RSD (%) | RE (%) | RSD (%) | RE (%) | RSD (%) |
| Plasma | *R*-(+)-ranolazine | 6.0 | 8.3 | 10.4 | -11.2 | 10.4 | -6.2 | 8.3 | 12.4 | 9.7 |
| | | 40.0 | -5.5 | 6.2 | -5.3 | 5.1 | 4.2 | 5.9 | 9.3 | 4.2 |
| | | 80.0 | 3.6 | 4.3 | 3.8 | 5.8 | 1.9 | 5.1 | -4.2 | 4.0 |
| | *S*-(-)-ranolazine | 6.0 | 8.0 | 11.1 | -10.8 | 9.3 | -5.9 | 9.2 | 13.0 | 9.8 |
| | | 40.0 | -5.7 | 6.0 | -5.0 | 5.5 | 4.9 | 6.3 | 8.0 | 3.6 |
| | | 80.0 | 2.9 | 5.0 | 4.1 | 6.0 | 2.2 | 5.0 | -3.6 | 3.5 |
| Heart | *R*-(+)-ranolazine | 6.0 | -10.6 | 8.2 | 11.4 | 8.5 | -5.2 | 7.8 | -10.4 | 9.4 |
| | | 80.0 | 8.2 | 4.3 | -7.4 | 7.4 | 7.3 | 3.8 | 6.9 | 5.3 |
| | | 160.0 | 5.1 | 1.2 | 2.6 | 4.9 | 3.2 | 4.4 | 4.8 | 4.9 |
| | *S*-(-)-ranolazine | 6.0 | -10.1 | 8.8 | 12.1 | 9.0 | -4.8 | 6.9 | -11.8 | 9.1 |
| | | 80.0 | 8.0 | 4.7 | -7.9 | 7.0 | 7.0 | 4.0 | 7.4 | 5.6 |
| | | 160.0 | 5.5 | 1.0 | 2.5 | 5.5 | 3.0 | 4.9 | 4.7 | 5.2 |
| Liver | *R*-(+)-ranolazine | 6.0 | -10.8 | 5.8 | 6.9 | 7.3 | 8.9 | 8.3 | -9.3 | 8.4 |
| | | 200.0 | 6.4 | 4.9 | 6.8 | 5.4 | -8.5 | 7.1 | 6.4 | 7.3 |
| | | 400.0 | 5.2 | 2.8 | -3.8 | 4.7 | 5.3 | 1.9 | 1.6 | 0.9 |
| | *S*-(-)-ranolazine | 6.0 | -10.5 | 5.5 | 7.4 | 6.9 | 9.6 | 9.5 | -10.8 | 8.5 |
| | | 200.0 | 6.0 | 5.6 | 6.0 | 5.0 | -7.1 | 6.3 | 6.1 | 7.0 |
| | | 400.0 | 5.1 | 3.0 | -3.3 | 4.1 | 5.1 | 2.2 | 1.5 | 1.2 |
| Spleen | *R*-(+)-ranolazine | 6.0 | -11.8 | 10.5 | -8.2 | 6.9 | -8.4 | 10.5 | 7.7 | 6.4 |
| | | 80.0 | 7.6 | 9.3 | 6.1 | 5.2 | 6.9 | 4.9 | 6.6 | 4.8 |
| | | 160.0 | 5.4 | 4.9 | 4.8 | 3.0 | 0.9 | 4.3 | -9.8 | 6.3 |
| | *S*-(-)-ranolazine | 6.0 | -12.1 | 10.3 | -7.5 | 6.5 | -8.9 | 11.9 | 8.1 | 6.7 |
| | | 80.0 | 8.2 | 8.8 | 6.0 | 5.7 | 7.2 | 5.1 | 6.3 | 4.5 |
| | | 160.0 | 5.0 | 4.6 | 4.3 | 4.1 | 0.6 | 4.0 | -9.3 | 8.0 |
| Lung | *R*-(+)-ranolazine | 6.0 | -12.3 | 8.7 | 8.3 | 6.9 | -9.2 | 5.4 | -9.3 | 6.4 |
| | | 80.0 | 7.4 | 3.9 | 5.9 | 5.8 | 6.4 | 3.8 | -10.2 | 4.9 |
| | | 160.0 | 6.2 | 5.3 | -1.8 | 0.9 | 5.7 | 1.9 | 5.8 | 3.1 |
| | | 6.0 | -11.8 | 8.5 | 8.1 | 7.7 | -9.8 | 5.9 | -8.7 | 6.8 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *S*-(-)-ranolazine | 80.0 | 7.9 | 4.5 | 6.6 | 5.6 | 6.0 | 4.1 | -10.0 | 4.5 |
| | | 160.0 | 6.0 | 5.0 | -1.5 | 0.7 | 5.5 | 1.5 | 6.1 | 2.9 |
| | | 6.0 | 10.4 | 11.7 | 6.4 | 9.8 | 5.3 | 4.8 | 6.0 | 5.3 |
| | *R*-(+)-ranolazine | 100.0 | -8.6 | 8.3 | -5.9 | 6.4 | 4.9 | 3.9 | -7.3 | 4.6 |
| | | 200.0 | 3.6 | 5.4 | 3.2 | 2.5 | 1.8 | 0.8 | 3.6 | 3.9 |
| Kidney | | 6.0 | 10.9 | 10.1 | 6.0 | 9.9 | 5.1 | 4.4 | 5.6 | 5.1 |
| | *S*-(-)-ranolazine | 100.0 | -8.1 | 8.6 | -7.1 | 6.1 | 5.0 | 3.3 | -7.7 | 4.2 |
| | | 200.0 | 3.5 | 5.0 | 3.4 | 2.3 | 2.1 | 0.5 | 3.4 | 4.0 |