PCSK9 Inhibitors in a German Clinical Single-Center Practice – Real-World Treatment of High Cardiovascular Risk Patients Over 68 Weeks

Tim Hollstein*, Ursula Kassner*, Thomas Grenkowitz*, Friederike Schumann*, Thomas Bobbert*, and Elisabeth Steinhagen-Thiessen**

* Department of Endocrinology, Division of Lipid Disorders, Charité Universitätsmedizin Berlin, Berlin, Germany
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* Shared first authors.

** Corresponding author:
Elisabeth Steinhagen-Thiessen
Department of Endocrinology, Division of Lipid Disorders, Charité Universitätsmedizin Berlin
Augustenburger Platz 1, Ostring 3, Berlin 13353, Germany.
Email: elisabeth.steinhagenthiessen@charite.de
## Supplementary Table S1. Patient characteristics and lipids at baseline

| Variables                        | Alirocumab 75 mg Q2W (n=125) | Alirocumab 150 mg Q2W (n=195) | Evolocumab 140 mg Q2W (n=315) |
|----------------------------------|-------------------------------|-------------------------------|-------------------------------|
| Age, years, mean (SD)            | 63.0 (11.0)                   | 62.2 (11.2)                   | 62.7 (11.1)                   |
| Male, n (%)                      | 73 (58.4)                     | 113 (57.9)                    | 186 (59.0)                    |
| Race, white, n (%)               | 120 (96.0)                    | 182 (93.3)                    | 305 (96.8)                    |
| BMI, kg/m², mean (SD)            | 28.4 (4.2)                    | 27.6 (4.8)                    | 28.3 (4.9)                    |
| CVD, n (%)                       | 115 (92.0)                    | 171 (87.7)                    | 272 (86.3)                    |
| CHD                              | 64 (51.2)                     | 113 (57.9)                    | 156 (49.5)                    |
| Stroke                           | 5 (4.0)                       | 8 (4.1)                       | 14 (4.4)                      |
| PAD                              | 7 (5.6)                       | 2 (1.0)                       | 11 (3.5)                      |
| Carotid stenosis                 | 5 (4.0)                       | 12 (6.2)                      | 23 (7.3)                      |
| Multiple manifestations          | 28 (22.4)                     | 34 (17.4)                     | 54 (17.1)                     |
| Other/unknown                    | 6 (4.8)                       | 2 (1.0)                       | 17 (5.4)                      |
| Hypertension, n (%)              | 76 (60.8)                     | 111 (56.9)                    | 210 (66.7)                    |
| Current smoker, n (%)            | 18 (14.4)                     | 27 (13.8)                     | 37 (11.7)                     |
| Diabetes mellitus (type 1 or type 2), n (%) | 33 (26.4) | 38 (19.5) | 61 (19.4) |
| Renal impairment                 | 18 (14.4)                     | 35 (17.9)                     | 36 (11.4)                     |
| Moderate (GFR 30 to < 60 mL/min) | 18 (14.4)                     | 35 (17.9)                     | 33 (10.5)                     |
| Severe (GFR 15 to < 30 mL/min)   | 0                             | 0                             | 3 (1.0)                       |
| CV risk, n (%)                   |                               |                               |                               |
| High                             | 5 (4.0)                       | 12 (6.2)                      | 28 (8.9)                      |
| Very high                        | 120 (96.0)                    | 183 (93.8)                    | 287 (91.1)                    |
| HeFH, n (%)                      | 17 (30.6)                     | 45 (23.1)                     | 72 (22.9)                     |
| Confirmation by genotyping       | 13 (10.4)                     | 29 (14.9)                     | 49 (15.6)                     |
| Statins, n (%)                   | 62 (49.6)                     | 80 (41.0)                     | 125 (39.7)                    |
| High intensity                   | 40 (32.0)                     | 45 (23.1)                     | 76 (24.1)                     |
| Moderate intensity               | 13 (10.4)                     | 26 (13.3)                     | 34 (10.8)                     |
| Low intensity                    | 9 (7.2)                       | 9 (4.6)                       | 15 (4.8)                      |
| Statin intolerance, n (%)        | 63 (50.4)                     | 115 (59.0)                    | 190 (60.3)                    |
| Other LLT (non-statin)           | 79 (63.2)                     | 105 (53.8)                    | 148 (47.0)                    |
| Ezetimibe                        | 70 (56.0)                     | 84 (43.1)                     | 126 (40.0)                    |
| Apheresis                        | 1 (0.8)                       | 1 (0.5)                       | 5 (1.6)                       |
| Lipids, mmol/L [mg/dL], mean (SD)|                               |                               |                               |
| Pre-LLT LDL-C, calculated        | 5.3 (1.8)                     | 6.1 (2.5)                     | 6.2 (2.9)                     |
| [203.5 (69.9)]                   | [236.3 (98.4)]                | [238.0 (113.4)]               |
| LDL-C, measured                  | 3.5 (1.3)                     | 4.3 (1.4)                     | 4.4 (1.6)                     |
| [135.6 (49.4)]                   | [167.7 (55.8)]                | [170.2 (61.9)]                |
| Non-HDL-C                        | 4.1 (1.5)                     | 4.8 (1.5)                     | 5.0 (1.8)                     |
| [159.5 (59.9)]                   | [187.5 (59.5)]                | [192.4 (68.6)]                |
| Total cholesterol                | 5.4 (1.5)                     | 6.2 (1.6)                     | 6.3 (1.8)                     |
| [209.9 (59.7)]                   | [240.1 (60.7)]                | [245.2 (68.9)]                |
| HDL-C                            | 1.3 (0.4)                     | 1.4 (0.4)                     | 1.4 (0.4)                     |
| [50.4 (15.4)]                    | [52.6 (15.8)]                 | [52.8 (16.9)]                 |
| Lp(a), median (IQR), mmol/L [mg/dL] | 131.9 (196.6) | 101.4 (163.2) | 111.7 (203.2) |
| TG, median (IQR), mmol/L [mg/dL]  | 2.0 (1.4)                     | 1.5 (1.0)                     | 1.6 (1.1)                     |
| [141.0 (126.0)]                  | [137.0 (89.0)]                | [143.0 (101.0)]               |
| Apo B, g/L [mg/dL]               | 1.2 (0.3)                     | 1.3 (0.4)                     | 1.4 (0.4)                     |
| [115.3 (31.1)]                   | [115.3 (31.1)]                | [136.0 (39.9)]                |
| Apo A1, g/L [mg/dL]              | 1.5 (0.3)                     | 1.5 (0.3)                     | 1.5 (0.3)                     |
| [148.5 (27.0)]                   | [150.2 (28.1)]                | [151.8 (29.0)]                |
Apo apolipoprotein, BMI body mass index, CHD coronary heart disease, CVD cardiovascular disease, GFR glomerular filtration rate, HDL-C high-density lipoprotein cholesterol, HeFH heterozygous familial hypercholesterolaemia, IQR interquartile range, LDL-C low-density lipoprotein cholesterol, LLT lipid-lowering therapy, Lp(a) lipoprotein(a), PAD peripheral arterial disease, Q2W every 2 weeks, SD standard deviation, TG triglycerides.
## Supplementary Table S2. Treatment at Week 68 according to treatment allocation at baseline

| Treatment allocation at baseline | Alirocumab 75 mg Q2W | Alirocumab 150 mg Q2W | Evolocumab 140 mg Q2W | Total |
|----------------------------------|----------------------|-----------------------|------------------------|-------|
| Alirocumab 75 mg Q2W            | 51 (81.0)\(^a\)      | 10 (15.9)             | 2 (3.2)                | 63 (100) |
| Alirocumab 150 mg Q2W           | 16 (14.8)            | 81 (75.0)\(^a\)      | 11 (10.2)              | 108 (100) |
| Evolocumab 140 mg Q2W           | 16 (11.5)            | 5 (3.6)               | 118 (84.9)\(^a\)      | 139 (100) |
| Total                            | 83 (26.8)            | 96 (31.0)             | 131 (42.3)             | 310 (100) |

\(^a\) Study participants who remained on the same treatment throughout.

Q2W every 2 weeks.
### Supplementary Table S3. Mean change from baseline in lipids at Weeks 4 and 68

|                | Alirocumab 75 mg Q2W | Alirocumab 150 mg Q2W | Evolocumab 140 mg Q2W |
|----------------|----------------------|-----------------------|-----------------------|
|                | Absolute change, mmol/L [mg/dL], mean (95% CI) | Percentage change from baseline, % | Absolute change, mmol/L [mg/dL], mean (95% CI) | Percentage change from baseline, % | Absolute change, mmol/L [mg/dL], mean (95% CI) | Percentage change from baseline, % |
| **Week 4**     |                      |                       |                       |                           |                           |                           |
| LDL-C          | -1.7 (-1.8 to -1.5)  | -48.1 (-50.7 to -45.5) | -2.5 (-2.6 to -2.2)  | -59.0 (-61.3 to -56.6)  | -2.4 (-2.5 to -2.3)  | -57.5 (-59.2 to -55.8) |
|                | [-64.5 (-69.7 to -59.3)] |                       | [-94.7 (-99.3 to -90.2)]  |                           | [-94.0 (-99.3 to -90.2)] |                           |
| Non-HDL-C      | -0.8 (-0.9 to -0.7)  | -45.5 (-47.9 to -43.1) | -1.1 (-1.2 to -1.1)  | -55.8 (-58.0 to -53.5)  | -1.1 (-1.2 to -1.1)  | -54.2 (-55.8 to -52.6) |
|                | [-71.9 (-77.7 to -66.1)] |                      | [-101.0 (-105.9 to -96.0)] |                           | [-100.5 (-104.6 to -96.4)] |                           |
| Total cholesterol | -1.8 (-1.9 to -1.6) | -32.0 (-33.9 to -30.0) | -2.5 (-2.6 to -2.4)  | -41.1 (-42.9 to -39.4)  | -2.5 (-2.6 to -2.4)  | -39.8 (-41.0 to -38.5) |
|                | [-68.0 (-73.4 to -62.2)] |                      | [-97.0 (-102.0 to -92.1)] |                           | [-96.4 (-100.6 to -92.3)] |                           |
| HDL-C          | 0.1 (0.1 to 0.1)     | 8.3 (5.7 to 10.9)     | 0.1 (0.1 to 0.1)     | 8.4 (6.5 to 10.3)       | 0.1 (0.1 to 0.1)     | 9.7 (7.6 to 11.9)       |
|                | [3.9 (2.6 to 5.2)]   |                       | [4.0 (3.0 to 5.0)]   |                       | [4.1 (3.2 to 5.0)]   |                       |
| Lp(a), absolute change from baseline, nmol/L | -16.6 (-24.8 to -11.1) | -22.8 (-27.4 to -18) | -15.8 (-23.7 to -13.3) | -28.7 (-32.5 to -24.8) | -15.9 (-18.9 to -12.3) | -25.4 (-28.3 to -22.4) |
|                |                      |                       |                       |                           |                           |                           |
| Triglycerides  | -0.2 (-0.3 to -0.1)  | -14.9 (-19.9 to -7.3) | -0.3 (-0.4 to -0.2)  | -21.6 (-24.6 to -15.9)  | -0.3 (-0.4 to -0.2)  | -20.5 (-25.6 to -16.1) |
|                | [-16.0 (-29.0 to -8.0)] |                      | [-25.0 (-31.0 to -18.0)] |                           | [-29.0 (-35.0 to -22.0)] |                           |
| Apo B          | -0.88 (-0.95 to -0.82) | -39.3 (-41.6 to -37.0) | -1.3 (-1.3 to -1.2)  | -50.0 (-52.2 to -47.8)  | -1.3 (-1.3 to -1.2)  | -48.3 (-50.0 to -46.7) |
|                | [-45.3 (-58.7 to -41.9)] |                      | [-65.2 (-86.5 to -61.8)] |                           | [-64.2 (-86.9 to -61.5)] |                           |
| Apo A1         | 0.12 (0.06 to 0.17)  | 4.3 (2.3 to 6.3)      | 0.14 (0.1 to 0.18)   | 5.1 (3.6 to 6.5)        | 0.13 (0.1 to 0.17)   | 5.2 (3.9 to 6.5)        |
|                | [5.9 (2.9 to 5.2)]   |                       | [7.1 (4.9 to 9.3)]   |                       | [6.9 (5.0 to 8.7)]   |                       |
| **Week 68**    |                      |                       |                       |                           |                           |                           |
| LDL-C          | -1.5 (-1.9 to -1.0)  | -41.7 (-58.2 to -25.2) | -2.3 (-2.6 to -2.1)  | -53.7 (-58.2 to -49.1)  | -2.3 (-2.5 to -2.1)  | -54.1 (-57.8 to -50.5) |
|                | [-56.7 (-75.2 to -38.2)] |                      | [-90.1 (-99.2 to -81.0)]  |                           | [-88.3 (-96.1 to -80.6)] |                           |
| Non-HDL-C      | -1.6 (-2.1 to -1.1)  | -36.6 (-53.2 to -20.0) | -2.4 (-2.7 to -2.2)  | -50.5 (-54.7 to -46.3)  | -2.5 (-2.7 to -2.3)  | -51.3 (-55.1 to -47.4) |
|                | [-61.4 (-82.3 to -40.5)] |                      | [-93.6 (-103.0 to -84.3)] |                           | [-96.6 (-105.5 to -87.8)] |                           |
| Total cholesterol | -1.5 (-2.0 to -1.0) | -24.9 (-36.3 to -13.6) | -2.4 (-2.6 to -2.1)  | -38.0 (-41.3 to -34.6)  | -2.3 (-2.6 to -2.1)  | -37.0 (-40.1 to -34.0) |
|                | [-57.4 (-77.9 to -36.8)] |                      | [-90.9 (-100.4 to -81.3)] |                           | [-90.7 (-99.5 to -81.8)] |                           |
| HDL-C          | 0.1 (0.0 to 0.2)     | 8.7 (2.7 to 14.7)     | 0.1 (0.0 to 0.1)     | 7.1 (3.3 to 11.0)       | 0.2 (0.1 to 0.2)     | 18.6 (4.4 to 32.8)     |
|                | [4.0 (1.1 to 7.1)]   |                       | [2.7 (0.8 to 4.7)]   |                       | [5.9 (4.0 to 7.8)]   |                       |
| Triglycerides  | -0.2 (-0.5 to -0.1)  | 7.1 (-15.8 to 30.1)   | 0 (-0.3 to 0.2)      | 4.8 (-9.3 to 18.8)      | -0.4 (-0.7 to -0.2)  | -7.6 (-15.3 to 0.1)    |
|                | [-15.7 (-43.8 to 12.4)] |                      | [-1.3 (-24.5 to 21.9)] |                           | [-39.5 (-58.4 to -20.7)] |                           |

† P-value < 0.05 versus alirocumab 75 mg Q2W.

Apo apolipoprotein, CI confidence interval, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, Lp(a) lipoprotein(a), Q2W every 2 weeks.
| n (%)               | All patients [N=310] (%) |
|---------------------|--------------------------|
| Revascularization\(^a\) | 25 (8.1)                 |
| Heart attack        | 9 (2.9)                  |
| Bypass surgery      | 4 (1.3)                  |
| Stroke              | 1 (0.3)                  |
| Total               | 39 (12.6)                |

\(^a\) Defined as coronary or peripheral revascularization either with stent or drug-eluting balloon.
### Supplementary Table S5. Safety data regardless of treatment allocation at Weeks 2 and 68

| n (%) | Week 2 (n=593) | Week 68 (n=310) |
|-------|----------------|-----------------|
| Any AE | 283 (47.7)     | 146 (47.1)      |
| AE leading to death | 0              | 0               |
| AE leading to treatment discontinuation | 14 (2.4)<sup>a</sup> | 19 (6.1)<sup>b</sup> |
| AE leading to change of PCSK9i | 0              | 27 (8.7)<sup>c</sup> |
| **AE occurring in ≥2% of patients** | | |
| Rhinitis | 103 (17.4)    | 36 (11.6)       |
| Fatigue | 93 (15.7)      | 32 (10.3)       |
| Myalgia | 54 (9.1)       | 39 (12.6)       |
| Joint pain | 45 (7.6)   | 31 (10.0)       |
| Back pain | 41 (6.9)      | 14 (4.5)        |
| Headache | 37 (6.3)       | 12 (3.9)        |
| Sore throat | 36 (6.1)    | 10 (3.2)        |
| Influenza-like symptoms | 34 (5.7) | 11 (3.6) |
| Cough | 30 (5.1)       | 16 (5.2)        |
| Nausea | 28 (4.7)       | 8 (2.6)         |
| Vertigo | 22 (3.8)       | 7 (2.3)         |
| Hyperhidrosis | 22 (3.7) | 17 (5.5) |
| Diarrhoea | 19 (3.2)      | 12 (3.9)        |
| Pruritus | 14 (2.4)       | 14 (4.5)        |
| Weight gain | 13 (2.2) | 13 (4.2) |
| Injection-site reaction | 12 (2.0) | 12 (3.9) |
| **Laboratory parameters** | | |
| CK >400 U/L and >50% increase vs baseline | 2 (0.3) | 1 (0.3) |
| ALT (>2x ULN) or AST (>2x ULN) | 7 (1.1) | 3 (1.0) |

<sup>a</sup> AEs leading to PCSK9i discontinuation were myalgias (n=6), gastrointestinal side effects (n=5), influenza-like symptoms (n=3), skin reaction (n=3), bronchitis, coughing (n=2), elevated liver enzymes (n=1), allergic reaction (n=1), exacerbated rheumatoid arthritis (n=1), and unknown or a combination of multiple factors (n=11).

<sup>b</sup> Excluding discontinuations up to Week 2.

<sup>c</sup> Including patients changing their PCSK9i treatment from alirocumab to evolocumab (n=6; 1.9%); evolocumab to alirocumab (n=15; 4.8%); alirocumab 150 mg Q2W to alirocumab 75 mg Q2W (n=6; 1.9%); no patients increased alirocumab dose from 75 mg Q2W to 150 mg Q2W.

**AE** adverse event, **ALT** alanine aminotransferase, **AST** aspartate aminotransferase, **CK** creatinine kinase, **PCSK9i** protein convertase subtilisin/kexin type 9 inhibitor, **Q2W** every 2 weeks, **ULN** upper normal limit.
## Supplementary Table S6. Adverse events occurring in ≥2% of patients at Week 68 according to gender

|                 | Week 2          |          | Odds-ratio (95% CI) | P-value | Week 68          |          | Odds-ratio (95% CI) | P-value |
|-----------------|-----------------|----------|---------------------|---------|------------------|----------|---------------------|---------|
|                 | Male (n=348)    | Female (n=245) |          |         | Male (n=188)    | Female (n=122) |          |         |
| Any AE          | 143 (41.1)      | 140 (57.1) | 0.52 (0.38–0.73)    | 0.001   | 85 (45.2)       | 61 (50.0)  | 0.82 (0.52–1.29)    | 0.4     |
| Rhinitis        | 56 (16.1)       | 47 (19.2)  | 0.81 (0.53–1.24)    | 0.3     | 20 (10.6)       | 16 (13.1)  | 0.81 (0.53–1.24)    | 0.6     |
| Fatigue         | 43 (12.4)       | 50 (20.5)  | 0.55 (0.35–0.85)    | 0.007   | 19 (10.1)       | 13 (10.7)  | 0.89 (0.42–1.89)    | 0.9     |
| Myalgia         | 25 (7.2)        | 29 (11.8)  | 0.58 (0.33–1.01)    | 0.052   | 20 (10.6)       | 19 (15.6)  | 0.65 (0.33–1.27)    | 0.2     |
| Joint pain      | 20 (5.8)        | 25 (10.2)  | 0.54 (0.29–0.99)    | 0.045   | 16 (8.5)        | 15 (12.3)  | 0.67 (0.32–1.41)    | 0.3     |
| Back pain       | 13 (3.6)        | 28 (11.4)  | 0.3 (0.15–0.60)     | 0.0003  | 9 (4.8)         | 5 (4.1)   | 1.2 (0.4–3.6)       | 1.0     |
| Headache        | 11 (3.2)        | 26 (10.7)  | 0.27 (0.13–0.57)    | 0.0002  | 5 (2.7)         | 7 (5.7)   | 0.45 (0.14–1.46)    | 0.2     |
| Sore throat     | 12 (3.5)        | 24 (9.8)   | 0.34 (0.16–0.67)    | 0.0015  | 6 (3.2)         | 4 (3.3)   | 0.98 (0.27–3.54)    | 1.0     |
| Influenza-like symptoms | 21 (6.0) | 13 (5.3) | 1.14 (0.56–2.34) | 0.7 | 7 (3.7) | 4 (3.3) | 1.15 (0.33–4.01) | 1.0 |
| Cough           | 14 (4.0)        | 16 (6.5)   | 0.60 (0.28–1.25)    | 0.17    | 10 (5.3)        | 6 (4.9)   | 1.10 (0.39–3.09)    | 1.0     |
| Nausea          | 5 (1.4)         | 23 (9.4)   | 0.14 (0.05–0.37)    | <0.0001 | 5 (2.7)        | 3 (2.5)   | 0.87 (0.19–3.94)    | 1.0     |
| Vertigo         | 8 (2.3)         | 14 (5.7)   | 0.39 (0.16–0.94)    | 0.03    | 5 (2.7)         | 2 (1.6)   | 1.65 (0.31–8.63)    | 0.7     |
| Hyperhidrosis   | 11 (3.2)        | 11 (4.5)   | 0.70 (0.30–1.64)    | 0.4     | 10 (5.3)        | 7 (5.7)   | 0.93 (0.34–2.51)    | 1.0     |
| Diarrhoea       | 10 (2.9)        | 9 (3.7)    | 0.78 (0.31–1.94)    | 0.6     | 6 (3.2)         | 6 (5.0)   | 0.64 (0.20–2.03)    | 0.6     |
| Pruritus        | 3 (0.9)         | 11 (4.5)   | 0.19 (0.05–0.67)    | 0.004   | 6 (3.2)         | 8 (6.6)   | 0.47 (0.16–1.40)    | 0.18    |
| Weight gain     | 7 (2.0)         | 6 (2.5)    | 0.81 (0.27–2.45)    | 0.7     | 6 (3.2)         | 7 (5.7)   | 0.54 (0.18–1.66)    | 0.4     |
| Injection-site reaction | 1 (0.3) | 11 (4.5) | 0.06 (0.01–0.48) | 0.0003 | 6 (3.2) | 6 (4.9) | 0.64 (0.20–2.03) | 0.6 |

Statistically significant differences between men and women (p≤0.05) are highlighted in bold. Statistical significance determined with chi-square test.

AE, adverse event; CI, confidence interval.
