



Clinical trial results:

Randomized Evaluation of Decreased Usage of betablocCkErs after myocardial infarction in the SWEDEHEART registry

REDUCe SWEDEHEART

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2017-002336-17 |
| Trial protocol | SE EE |
| Global end of trial date | 16 November 2023 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 14 June 2024 |
| First version publication date | 14 June 2024 |

Trial information

Trial identification

| | |
|-----------------------|-------------------|
| Sponsor protocol code | REDUCe_2017-05-22 |
|-----------------------|-------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03278509 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Karolinska Institutet |
| Sponsor organisation address | Entrévägen 2, target J, floor 5, Stockholm, Sweden, |
| Public contact | Tomas Jernberg, Karolinska Institutet, +46 0701671474, tomas.jernberg@sll.se |
| Scientific contact | Tomas Jernberg, Karolinska Institutet, +46 0701671474, tomas.jernberg@sll.se |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 08 March 2024 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 November 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 November 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine whether long-term treatment with oral beta-blockade in patients with MI and preserved LV systolic ejection fraction reduces the composite of death of any cause or new MI

Protection of trial subjects:

The steering committee appointed a data safety monitoring board (DSMB). The DSMB ensured the safety of the intervention as well as the general execution of the trial on behalf of the trial participants. The responsibilities of the DSMB were defined in a separate charter agreed upon by the steering committee and the DSMB members. Two interim analyses of patient safety were performed by the DSMB after 2 and 4 years of recruitment. No other assessment or reporting of adverse events was to be performed in this study.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 29 September 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Sweden: 4788 |
| Country: Number of subjects enrolled | Estonia: 32 |
| Country: Number of subjects enrolled | New Zealand: 200 |
| Worldwide total number of subjects | 5020 |
| EEA total number of subjects | 4820 |

Notes:

Subjects enrolled per age group

| | |
|---|------|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 2431 |

| | |
|---------------------|------|
| From 65 to 84 years | 2487 |
| 85 years and over | 102 |

Subject disposition

Recruitment

Recruitment details:

A total of 5023 patients with myocardial infarction, who had undergone coronary angiography and echocardiography with a preserved left ventricular ejection fraction ($\geq 50\%$), were enrolled in the trial. Prior to randomization, 3 patients were excluded due to lack of documented informed consent.

Pre-assignment

Screening details:

Patients that were residents of the three trial countries, and who were treated for myocardial infarction with preserved left ventricular ejection fraction and obstructive coronary artery disease, were eligible to enroll in the trial. Major exclusion criteria were an indication for or contraindication to beta-blocker treatment.

Pre-assignment period milestones

| | |
|------------------------------|------|
| Number of subjects started | 5020 |
| Number of subjects completed | 5020 |

Period 1

| | |
|------------------------------|---------------------------------------|
| Period 1 title | Treatment initiation (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Beta-blockers |

Arm description:

Patients assigned treatment with either metoprolol or bisoprolol.

| | |
|--|----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Metoprolol succinate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral, 100 mg daily

| | |
|--|------------|
| Investigational medicinal product name | Bisoprolol |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Oral, 5 mg daily

| | |
|------------------|------------------|
| Arm title | No beta-blockers |
|------------------|------------------|

Arm description:

Patients not assigned beta-blockers

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Beta-blockers | No beta-blockers |
|---------------------------------------|---------------|------------------|
| Started | 2508 | 2512 |
| Completed | 2508 | 2512 |

Baseline characteristics

Reporting groups

| | |
|---|------------------|
| Reporting group title | Beta-blockers |
| Reporting group description: Patients assigned treatment with either metoprolol or bisoprolol. | |
| Reporting group title | No beta-blockers |
| Reporting group description: Patients not assigned beta-blockers | |

| Reporting group values | Beta-blockers | No beta-blockers | Total |
|--|---------------|------------------|-------|
| Number of subjects | 2508 | 2512 | 5020 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 1203 | 1228 | 2431 |
| From 65-84 years | 1257 | 1230 | 2487 |
| 85 years and over | 48 | 54 | 102 |
| Age continuous Units: years | | | |
| median | 65.0 | 65.0 | |
| inter-quartile range (Q1-Q3) | 57.0 to 73.0 | 57.0 to 73.0 | - |
| Gender categorical Units: Subjects | | | |
| Female | 563 | 568 | 1131 |
| Male | 1945 | 1944 | 3889 |
| In hospital course, Coronary angiography Units: Subjects | | | |
| No stenosis | 26 | 25 | 51 |
| One-vessel disease | 1378 | 1378 | 2756 |
| Two-vessel disease | 676 | 668 | 1344 |
| Left main or three-vessel disease | 404 | 420 | 824 |
| Missing | 24 | 21 | 45 |
| In-hospital course, PCI or CABG Units: Subjects | | | |
| PCI | 2387 | 2376 | 4763 |
| CABG | 92 | 103 | 195 |
| Missing | 29 | 33 | 62 |
| Medication at discharge, Aspirin Units: Subjects | | | |
| Aspirin | 2450 | 2440 | 4890 |
| No aspirin | 57 | 72 | 129 |
| Missing | 1 | 0 | 1 |
| Medication at discharge, P2Y12 receptor blocker Units: Subjects | | | |
| P2Y12 receptor blocker | 2411 | 2398 | 4809 |
| Other | 8 | 21 | 29 |
| No antiplatelet therapy | 88 | 93 | 181 |

| | | | |
|---|------|------|------|
| Missing | 1 | 0 | 1 |
| Medication at discharge, Beta-blocker Units: Subjects | | | |
| Beta-blocker | 2399 | 247 | 2646 |
| No beta-blocker | 106 | 2265 | 2371 |
| Missing | 1 | 0 | 1 |
| Unknown | 2 | 0 | 2 |
| Medication at discharge, ACE inhibitor or ARB Units: Subjects | | | |
| ACE inhibitor or ARB | 1985 | 2040 | 4025 |
| No ACE inhibitor or ARB | 522 | 472 | 994 |
| Missing | 1 | 0 | 1 |
| Medication at discharge, Statins Units: Subjects | | | |
| Statins | 2481 | 2461 | 4942 |
| No statins | 26 | 49 | 75 |
| Missing | 1 | 0 | 1 |
| Unknown | 0 | 2 | 2 |
| Medication at discharge, Diuretic agent Units: Subjects | | | |
| Diuretic agents | 211 | 191 | 402 |
| No diuretic agent | 2296 | 2321 | 4617 |
| Missing | 1 | 0 | 1 |
| Medication at discharge, Calcium-channel blocker Units: Subjects | | | |
| Ca-channel blocker | 416 | 496 | 912 |
| No Ca-channel blocker | 2091 | 2015 | 4106 |
| Missing | 1 | 0 | 1 |
| Unknown | 0 | 1 | 1 |
| Risk factors, Current smoking Units: Subjects | | | |
| Smoker | 478 | 530 | 1008 |
| Previous smoker | 915 | 860 | 1775 |
| Never | 1073 | 1093 | 2166 |
| Unknown | 42 | 29 | 71 |
| Risk factors, Hypertension Units: Subjects | | | |
| Hypertension | 1155 | 1163 | 2318 |
| No hypertension | 1352 | 1346 | 2698 |
| Unknown | 1 | 3 | 4 |
| Risk factors, Diabetes mellitus Units: Subjects | | | |
| DM Type II | 185 | 177 | 362 |
| DM Type I | 10 | 21 | 31 |
| Unclear what type | 151 | 156 | 307 |
| No DM | 2159 | 2154 | 4313 |
| Unknown | 2 | 3 | 5 |
| Missing | 1 | 1 | 2 |
| Previous Cardiovascular disease, Myocardial infarction | | | |

| | | | |
|--|------|------|------|
| Units: Subjects | | | |
| Previous myocardial infarction | 165 | 192 | 357 |
| No myocardial infarction | 2338 | 2315 | 4653 |
| Unknown | 5 | 5 | 10 |
| Previous Cardiovascular disease, PCI | | | |
| Units: Subjects | | | |
| Previous PCI | 147 | 175 | 322 |
| No PCI | 2357 | 2330 | 4687 |
| Unknown | 4 | 7 | 11 |
| Previous Cardiovascular disease, Cardiac surgery | | | |
| Units: Subjects | | | |
| CABG | 33 | 36 | 69 |
| Other heart surgery | 7 | 7 | 14 |
| No previous cardiac surgery | 2464 | 2464 | 4928 |
| Unknown | 4 | 5 | 9 |
| Previous Cardiovascular disease, Stroke | | | |
| Units: Subjects | | | |
| Previous stroke | 52 | 67 | 119 |
| No stroke | 2454 | 2440 | 4894 |
| Unknown | 2 | 5 | 7 |
| Previous Cardiovascular disease, Chronic heart failure | | | |
| Units: Subjects | | | |
| Heart failure with normal LVEF (>=50%) | 0 | 3 | 3 |
| Heart failure with slightly reduced LVEF (40-49%) | 10 | 18 | 28 |
| Heart failure with moderately reduced LVEF (30-39%) | 0 | 0 | 0 |
| Heart failure with severely reduced LVEF (<30%) | 1 | 0 | 1 |
| Heart failure with unknown LVEF | 2 | 1 | 3 |
| No heart failure | 2473 | 2459 | 4932 |
| Unknown | 22 | 31 | 53 |
| Reason for admission | | | |
| Units: Subjects | | | |
| Chest pain | 2421 | 2417 | 4838 |
| Dyspnea | 23 | 27 | 50 |
| Cardiac arrest | 1 | 6 | 7 |
| Other | 62 | 62 | 124 |
| Unknown | 1 | 0 | 1 |
| Characteristics at presentation, CPR | | | |
| Units: Subjects | | | |
| CPR before hospitalization | 10 | 11 | 21 |
| No CPR | 2473 | 2474 | 4947 |
| Unknown | 25 | 27 | 52 |
| Characteristics at presentation, Pulmonary rales | | | |
| Units: Subjects | | | |
| Basal rales | 28 | 41 | 69 |
| Rales above the basal half of the lungs | 0 | 1 | 1 |
| Pulmonary edema | 1 | 1 | 2 |

| | | | |
|--|------------|------------|------|
| No pulmonary rales | 2416 | 2419 | 4835 |
| Unknown | 63 | 50 | 113 |
| Characteristics at presentation, Atrial fibrillation | | | |
| Units: Subjects | | | |
| AF/AFF | 21 | 23 | 44 |
| Sinus rythm | 2451 | 2467 | 4918 |
| Other | 30 | 14 | 44 |
| Unknown | 6 | 8 | 14 |
| Characteristics at presentation, Infarct type | | | |
| Units: Subjects | | | |
| STEMI | 877 | 892 | 1769 |
| NSTEMI | 1623 | 1597 | 3220 |
| No myocardial infarction | 7 | 23 | 30 |
| Unknown | 1 | 0 | 1 |
| Characteristics at presentation, Current oral beta-blocker treatment | | | |
| Units: Subjects | | | |
| Oral beta-blocker treatment | 269 | 302 | 571 |
| No oral beta-blockers | 2199 | 2170 | 4369 |
| Unknown | 40 | 40 | 80 |
| Heart rate | | | |
| Units: beats/min | | | |
| median | 74 | 73 | |
| inter-quartile range (Q1-Q3) | 65 to 85 | 64 to 84 | - |
| Systolic blood pressure | | | |
| Units: mmHg | | | |
| median | 150 | 151 | |
| inter-quartile range (Q1-Q3) | 135 to 170 | 136 to 170 | - |

End points

End points reporting groups

| | |
|--|---------------------------------|
| Reporting group title | Beta-blockers |
| Reporting group description: Patients assigned treatment with either metoprolol or bisoprolol. | |
| Reporting group title | No beta-blockers |
| Reporting group description: Patients not assigned beta-blockers | |
| Subject analysis set title | Beta-blockers |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Subjects followed for a median of 3.5 (2.2-4.7) years | |
| Subject analysis set title | No beta-blockers |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Subjects followed for a median of 3.5 (2.2-4.7) years | |
| Subject analysis set title | Beta-blockers, SEPHIA 6-10w |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All subjects included in the SEPHIA registry, attending the follow-up visit at 6-10 weeks after myocardial infarction | |
| Subject analysis set title | No beta-blockers, SEPHIA 6-10w |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All subjects included in the SEPHIA registry, attending the follow-up visit at 6-10 weeks after myocardial infarction | |
| Subject analysis set title | Beta-blockers, SEPHIA 11-13m |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All subjects included in the SEPHIA registry, attending the follow-up visit at 11-13 months after myocardial infarction | |
| Subject analysis set title | No beta-blockers, SEPHIA 11-13m |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: All subjects included in the SEPHIA registry, attending the follow-up visit at 11-13 months after myocardial infarction | |

Primary: Death from any cause or new myocardial infarction

| | |
|---|---|
| End point title | Death from any cause or new myocardial infarction |
| End point description: | |
| End point type | Primary |
| End point timeframe: Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number | 199 | 208 | | |

Statistical analyses

| Statistical analysis title | Primary analysis |
|---|----------------------------------|
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.645 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.955 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.787 |
| upper limit | 1.16 |

Secondary: All-cause mortality

| | |
|---|---------------------|
| End point title | All-cause mortality |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| All-cause mortality | 97 | 103 | | |

Statistical analyses

| Statistical analysis title | Secondary analyses |
|----------------------------|----------------------------------|
| Comparison groups | Beta-blockers v No beta-blockers |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.663 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.713 |
| upper limit | 1.241 |

Secondary: Cardiovascular mortality

| | |
|---|--------------------------|
| End point title | Cardiovascular mortality |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Cardiovascular death | 38 | 33 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Secondary analyses |
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.553 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.152 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.722 |
| upper limit | 1.836 |

Secondary: New myocardial infarction

| | |
|-----------------|---------------------------|
| End point title | New myocardial infarction |
|-----------------|---------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Subjects followed for a median of 3.5 (2.2-4.7) years

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Myocardial infarction | 112 | 117 | | |

Statistical analyses

| | |
|----------------------------|--------------------|
| Statistical analysis title | Secondary analyses |
|----------------------------|--------------------|

| | |
|-------------------|----------------------------------|
| Comparison groups | Beta-blockers v No beta-blockers |
|-------------------|----------------------------------|

| | |
|---|------|
| Number of subjects included in analysis | 5020 |
|---|------|

| | |
|------------------------|---------------|
| Analysis specification | Pre-specified |
|------------------------|---------------|

| | |
|---------------|-------------|
| Analysis type | superiority |
|---------------|-------------|

| | |
|---------|---------|
| P-value | = 0.739 |
|---------|---------|

| | |
|--------|-----------------|
| Method | Regression, Cox |
|--------|-----------------|

| | |
|--------------------|-------------------------|
| Parameter estimate | Cox proportional hazard |
|--------------------|-------------------------|

| | |
|----------------|-------|
| Point estimate | 0.957 |
|----------------|-------|

Confidence interval

| | |
|-------|------|
| level | 95 % |
|-------|------|

| | |
|-------|---------|
| sides | 2-sided |
|-------|---------|

| | |
|-------------|-------|
| lower limit | 0.738 |
|-------------|-------|

| | |
|-------------|------|
| upper limit | 1.24 |
|-------------|------|

Secondary: Readmission because of atrial fibrillation

| | |
|-----------------|--|
| End point title | Readmission because of atrial fibrillation |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Subjects followed for a median of 3.5 (2.2-4.7) years

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Atrial fibrillation | 27 | 34 | | |

Statistical analyses

| Statistical analysis title | Secondary analyses |
|---|----------------------------------|
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3666 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.792 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.478 |
| upper limit | 1.313 |

Secondary: Readmission because of heart failure

| | |
|---|--------------------------------------|
| End point title | Readmission because of heart failure |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Heart failure | 20 | 22 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Secondary analyses |
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.757 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.909 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.496 |
| upper limit | 1.665 |

Secondary: Readmission because of bradycardia, AV-block 2-3, need for pacemaker, hypotension or syncope

| | |
|---|--|
| End point title | Readmission because of bradycardia, AV-block 2-3, need for pacemaker, hypotension or syncope |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|--|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Bradycardia, AV-block, PPM, hypotension, syncope | 86 | 80 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Secondary analyses |
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.641 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 1.075 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.793 |
| upper limit | 1.458 |

Secondary: Readmission to hospital because of asthma or COPD

| | |
|---|---|
| End point title | Readmission to hospital because of asthma or COPD |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Asthma or chronic obstructive pulmonary disease | 15 | 16 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Secondary analyses |
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.855 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.937 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.463 |
| upper limit | 1.894 |

Secondary: Readmission because of stroke

| | |
|---|-------------------------------|
| End point title | Readmission because of stroke |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Subjects followed for a median of 3.5 (2.2-4.7) years | |

| End point values | Beta-blockers | No beta-blockers | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 2508 | 2512 | | |
| Units: Number of subjects | | | | |
| Stroke | 36 | 46 | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Secondary analyses |
| Comparison groups | Beta-blockers v No beta-blockers |
| Number of subjects included in analysis | 5020 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2698 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.782 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.506 |
| upper limit | 1.21 |

Secondary: CCS Angina class at 6-10 weeks

| | |
|-----------------|--------------------------------|
| End point title | CCS Angina class at 6-10 weeks |
|-----------------|--------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed at the 6-10 week visit.

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | | |
|-----------------------------|-----------------------------|--------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1909 | 1927 | | |
| Units: Number of subjects | | | | |
| No angina | 1667 | 1669 | | |
| CCS I | 82 | 90 | | |
| CCS II | 29 | 27 | | |
| CCS III | 7 | 5 | | |
| CCS IV | 3 | 0 | | |
| Non-ischaemic | 121 | 136 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CCS Angina Class Proportional Odds |
| Comparison groups | No beta-blockers, SEPHIA 6-10w v Beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3836 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.964 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.78 |
| upper limit | 1.3 |

Secondary: CCS Angina Class at 11-13 months

| | |
|-----------------|----------------------------------|
| End point title | CCS Angina Class at 11-13 months |
|-----------------|----------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed at the 11-13 month visit.

| End point values | Beta-blockers, SEPHIA 11- 13m | No beta- blockers, SEPHIA 11- 13m | | |
|-----------------------------|-------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1832 | 1886 | | |
| Units: Number of subjects | | | | |
| No angina | 1601 | 1652 | | |
| CCS I | 82 | 79 | | |
| CCS II | 28 | 27 | | |
| CCS III | 7 | 8 | | |
| CCS IV | 5 | 4 | | |
| Non-ischaemic | 109 | 116 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | CCS Angina Class Proportional Odds |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3718 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.618 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.07 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.82 |
| upper limit | 1.39 |

Secondary: NYHA Dyspnea Class at 6-10 weeks

| | |
|----------------------------------|----------------------------------|
| End point title | NYHA Dyspnea Class at 6-10 weeks |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at the 6-10 week visit. | |

| End point values | Beta-blockers, SEPHIA 6-10w | No beta- blockers, SEPHIA 6-10w | | |
|-----------------------------|--------------------------------|---------------------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1909 | 1927 | | |
| Units: Number of subjects | | | | |
| No dyspnea | 1524 | 1569 | | |
| NYHA I | 71 | 61 | | |
| NYHA II | 101 | 86 | | |
| NYHA III | 15 | 17 | | |
| NYHA IV | 5 | 2 | | |
| Other reason | 193 | 192 | | |

Statistical analyses

| Statistical analysis title | NYHA Dyspnea Class Proportional Odds |
|---|--|
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3836 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.126 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.95 |
| upper limit | 1.47 |

Secondary: NYHA Dyspnea Class at 11-13 months

| | |
|-----------------------------------|------------------------------------|
| End point title | NYHA Dyspnea Class at 11-13 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at the 11-13 month visit | |

| End point values | Beta-blockers, SEPHIA 11- 13m | No beta- blockers, SEPHIA 11- 13m | | |
|-----------------------------|-------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 1832 | 1886 | | |
| Units: Number of subjects | | | | |
| No dyspnea | 1489 | 1576 | | |
| NYHA I | 84 | 54 | | |
| NYHA II | 66 | 67 | | |
| NYHA III | 12 | 14 | | |
| NYHA IV | 2 | 5 | | |
| Other reason | 179 | 170 | | |

Statistical analyses

| Statistical analysis title | NYHA Dyspnea Class Proportional Odds |
|---|--|
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3718 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.1107 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.96 |
| upper limit | 1.53 |

Secondary: EQ-5D VAS at 6-10 weeks and 11-13 months

| | |
|--|--|
| End point title | EQ-5D VAS at 6-10 weeks and 11-13 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at the 6-10 week visit and the 11-13 month visit. | |

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | Beta-blockers, SEPHIA 11-13m | No beta-blockers, SEPHIA 11-13m |
|---------------------------------------|-----------------------------|--------------------------------|------------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1909 | 1927 | 1834 | 1886 |
| Units: Score | | | | |
| median (inter-quartile range (Q1-Q3)) | | | | |
| EQ-5D VAS | 76 (65 to 85) | 75 (65 to 85) | 80 (70 to 90) | 80 (70 to 90) |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ5D-VAS comparison at 6-10 weeks |
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3836 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.25 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -0.72 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.95 |
| upper limit | 0.51 |

| | |
|---|--|
| Statistical analysis title | EQ5D-VAS comparison at 11-13 months |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3720 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.94 |
| Method | Regression, Linear |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 0.04 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.11 |
| upper limit | 1.2 |

Secondary: EQ-5D mobility score at 6-10 weeks and 11-13 months

| | |
|-----------------|---|
| End point title | EQ-5D mobility score at 6-10 weeks and 11-13 months |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Assessed at the 6-10 week and 11-13 month visits

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | Beta-blockers, SEPHIA 11-13m | No beta-blockers, SEPHIA 11-13m |
|---------------------------------------|-----------------------------|--------------------------------|------------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1800 | 1819 | 1745 | 1805 |
| Units: Number of subjects | | | | |
| I have no problems in walking about | 1569 | 1592 | 1487 | 1556 |
| I have some problems in walking about | 227 | 223 | 256 | 244 |
| I am confined to bed | 4 | 4 | 2 | 5 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ5D mobility score comparison at 6-10 weeks |
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3619 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.749 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.26 |

| | |
|---|--|
| Statistical analysis title | EQ5D mobility score comparison at 10-13 months |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3550 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.412 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.08 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.9 |
| upper limit | 1.31 |

Secondary: EQ-5D self-care score at 6-10 weeks and 11-13 months

| | |
|--|--|
| End point title | EQ-5D self-care score at 6-10 weeks and 11-13 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at the 6-10 week and 11-13 month visits | |

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | Beta-blockers, SEPHIA 11-13m | No beta-blockers, SEPHIA 11-13m |
|---|-----------------------------|--------------------------------|------------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1797 | 1818 | 1745 | 1805 |
| Units: Number of subjects | | | | |
| I have no problems with self-care | 1762 | 1788 | 1718 | 1778 |
| I have some problems washing or dressing myself | 33 | 28 | 27 | 22 |
| I am unable to wash or dress myself | 2 | 2 | 0 | 5 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ5D self-care score comparison at 6-10 weeks |
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3615 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.501 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.72 |
| upper limit | 1.95 |

| | |
|---|--|
| Statistical analysis title | EQ5D self-care score comparison at 10-13 months |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3550 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.909 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.03 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 1.77 |

Secondary: EQ-5D usual activities score at 6-10 weeks and 11-13 months

| | |
|--|---|
| End point title | EQ-5D usual activities score at 6-10 weeks and 11-13 months |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at the 6-10 week and 11-13 month visits | |

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | Beta-blockers, SEPHIA 11-13m | No beta-blockers, SEPHIA 11-13m |
|--|-----------------------------|--------------------------------|------------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1795 | 1816 | 1745 | 1804 |
| Units: Number of subjects | | | | |
| I have no problems performing usual activities | 1622 | 1607 | 1590 | 1646 |
| I have some problems performing usual activities | 159 | 191 | 141 | 135 |
| I am unable to perform usual activities | 14 | 18 | 14 | 23 |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | EQ5D usual activity score comparison at 6-10 weeks |
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |

| | |
|---|----------------------|
| Number of subjects included in analysis | 3611 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0667 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.82 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.66 |
| upper limit | 1.01 |

| | |
|---|--|
| Statistical analysis title | EQ5D usual activity score comparison at 10-13m |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3549 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.932 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.27 |

Secondary: EQ-5D pain/discomfort score at 6-10 weeks and 11-13 months

| | |
|--|--|
| End point title | EQ-5D pain/discomfort score at 6-10 weeks and 11-13 months |
| End point description: | |
| | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed at the 6-10 week and 11-13 month visits | |

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | Beta-blockers, SEPHIA 11-13m | No beta-blockers, SEPHIA 11-13m |
|------------------------------|-----------------------------|--------------------------------|------------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1789 | 1812 | 1745 | 1801 |
| Units: Number of subjects | | | | |
| I have no pain or discomfort | 1140 | 1145 | 1050 | 1067 |

| | | | | |
|------------------------------------|-----|-----|-----|-----|
| I have moderate pain or discomfort | 594 | 608 | 618 | 664 |
| I have extreme pain or discomfort | 55 | 59 | 77 | 70 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ5D pain/discomfort score comparison at 6-10w |
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3601 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.719 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.98 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.12 |

| | |
|---|--|
| Statistical analysis title | EQ5D pain/discomfort score comparison at 10-13m |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3546 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.685 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.97 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.11 |

Secondary: EQ-5D anxiety/depression score at 6-10 weeks and 11-13 months

| | |
|------------------------|---|
| End point title | EQ-5D anxiety/depression score at 6-10 weeks and 11-13 months |
| End point description: | |
| End point type | Secondary |

End point timeframe:

Assessed at the 6-10 week and 11-13 month visits

| End point values | Beta-blockers, SEPHIA 6-10w | No beta-blockers, SEPHIA 6-10w | Beta-blockers, SEPHIA 11-13m | No beta-blockers, SEPHIA 11-13m |
|--------------------------------------|-----------------------------|--------------------------------|------------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 1787 | 1804 | 1736 | 1790 |
| Units: Number of subjects | | | | |
| I am not anxious or depressed | 1204 | 1220 | 1301 | 1320 |
| I am moderately anxious or depressed | 536 | 530 | 402 | 422 |
| I am extremely anxious or depressed | 47 | 54 | 33 | 48 |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | EQ5D anxiety/depression score comparison at 6-10w |
| Comparison groups | Beta-blockers, SEPHIA 6-10w v No beta-blockers, SEPHIA 6-10w |
| Number of subjects included in analysis | 3591 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.936 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 1.01 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.88 |
| upper limit | 1.16 |

| | |
|---|--|
| Statistical analysis title | EQ5D anxiety/depression score comparison at 10-13m |
| Comparison groups | Beta-blockers, SEPHIA 11-13m v No beta-blockers, SEPHIA 11-13m |
| Number of subjects included in analysis | 3526 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.353 |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.93 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.8 |
| upper limit | 1.08 |

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Only serious adverse events that were not considered trial endpoints were collected during the trial.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-----|
| Dictionary name | N/A |
|-----------------|-----|

| | |
|--------------------|-----|
| Dictionary version | N/A |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | Beta-blockers |
|-----------------------|---------------|

Reporting group description: -

| | |
|-----------------------|------------------|
| Reporting group title | No beta-blockers |
|-----------------------|------------------|

Reporting group description: -

| Serious adverse events | Beta-blockers | No beta-blockers | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 2508 (0.00%) | 0 / 2512 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Beta-blockers | No beta-blockers | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 2508 (0.00%) | 0 / 2512 (0.00%) | |

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious events were collected during the trial and no serious adverse events were recorded.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 01 September 2021 | During the trial, the total blinded event counts indicated an actual event rate of 3% per year instead of 7.2%. The sponsor, together with the steering committee and patient representatives, concluded that a 25% lower risk (corresponding to a 0.9-percentage-point lower absolute risk) would still be a clinically relevant effect to detect. To detect a hazard ratio of 0.75, with 80% power at a two-sided significance level of 5%, a total number of 379 primary end-point events would be required, which was expected to occur with the enrollment of approximately 5000 patients instead of the initially planned 7000 patients. In September 2021, the protocol was revised accordingly. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/38587241>