



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
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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,
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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
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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
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End point description:

End point type	Secondary
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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
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Comparison groups	Beta-blockers v No beta-blockers
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Number of subjects included in analysis	5020
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.739
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Method	Regression, Cox
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Parameter estimate	Cox proportional hazard
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Point estimate	0.957
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Confidence interval

level	95 %
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sides	2-sided
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lower limit	0.738
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upper limit	1.24
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Secondary: Readmission because of atrial fibrillation

End point title	Readmission because of atrial fibrillation
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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End point description:

End point type	Secondary
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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
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Dictionary used

Dictionary name	N/A
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Dictionary version	N/A
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Reporting groups

Reporting group title	Beta-blockers
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Reporting group description: -

Reporting group title	No beta-blockers
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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>