



Clinical trial results:

The effect of vitamin D on all-cause mortality in congestive heart failure patients

Summary

EudraCT number	2010-020793-42
Trial protocol	DE
Global end of trial date	31 December 2016

Results information

Result version number	v1 (current)
This version publication date	24 June 2022
First version publication date	24 June 2022
Summary attachment (see zip file)	Main Results of the EVITA trial (2017 Eur Heart J EVITA.pdf) Main Results of the EVITA trial; Supplemental material (2017 Eur Heart J EVITA Supplemental Data.pdf) EVITA trial secondary analysis of vitamin D supplementation on anemia risk (2017 Nutrition J Evita Anemia.pdf) EVITA trial secondary analysis of vitamin D supplementation on bone turnover (2017 Osteoporos Int EVITA Bone turnover.pdf) EVITA trial secondary analysis of vitamin D supplementation on the RAAS system (2018 Int J Endocrinol Vitamin D and RAAS.pdf) EVITA trial secondary analysis of vitamin D supplementation on cardiovascular risk markers (2019 Ann Nutr Metab EVITA Cardiovascular Risk Markers.pdf) EVITA trial secondary analysis of vitamin D supplementation on testosterone levels (2019 Eur J Nutr EVITA Testosterone.pdf) EVITA trial secondary analysis of vitamin D supplementation on cardiac function (2019 Int J Cardiol EVITA Cardiac Function.pdf) Evita trial secondary analysis of vitamin D supplementation on cardiac function; Supplemental material (2019 Int J Cardiol EVITA Cardiac Function, Supplemental Material.pdf) EVITA trial follow-up data of vitamin D supplementation on clinical outcomes (2020 ESC Heart Fail vitamin D.pdf)

Trial information

Trial identification

Sponsor protocol code	170782
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01326650
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herz- und Diabeteszentrum NRW
Sponsor organisation address	Georgstraße 11, Bad Oeynhausen, Germany, 32545
Public contact	Scientific Team Leader, Herz- und Diabeteszentrum NRW, +49 5731971912, azittermann@hdz-nrw.de

Scientific contact	Scientific Team Leader, Herz- und Diabeteszentrum NRW, +49 573197912, azittermann@hdz-nrw.de
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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	27 September 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2016
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare in congestive heart failure patients the effect of a daily vitamin D supplement of 4000 IU versus placebo for three years on all-cause mortality.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized in the study. Safety lab was performed every six months. An independent data monitoring committee reviewed the data. Appropriate medical equipment was also available on site in case of any adverse reactions.

Background therapy:

All study participants received evidence-based treatment for heart failure patients.

Evidence for comparator:

Mortality is high in end-stage heart failure patients. There was evidence that poor vitamin D status is associated with poor cardiac function and nonfatal and fatal heart failure events. We therefore investigated whether a daily vitamin D supplement versus placebo for 3 years is able to reduce mortality in end-stage heart failure patients.

Actual start date of recruitment	18 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 400
Worldwide total number of subjects	400
EEA total number of subjects	400

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)	353
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with heart failure with NYHA class II or higher who attended the heart failure unit of Clinic for Thoracic and Cardiovascular Surgery at the Herz- und Diabeteszentrum NRW in Bad Oeynhausen, Germany.

Pre-assignment

Screening details:

Of 892 patients who met the inclusion and exclusion criteria and were screened, 400 were randomized to the vitamin D or placebo group.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Monitor, Data analyst, Investigator

Blinding implementation details:

Participants, their treating physicians, and any individual of the heart failure unit of our clinic were masked to treatment allocation. Likewise, the independent data safety board was blinded to treatment allocation. In addition, data analysis was performed by a blinded external biostatistician.

Arms

Are arms mutually exclusive?	Yes
Arm title	vitamin D arm

Arm description:

Patients had to take 4000 IU vitamin D daily (eight drops of an oily vitamin D preparation; Vigantol oil, Merck, Darmstadt, Germany) during a meal.

Arm type	Experimental
Investigational medicinal product name	Vigantol oil, Merck, Darmstadt, Germany
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

Patients had to take 4000 IU vitamin D daily (eight drops of an oily vitamin D preparation) during a meal.

Arm title	placebo
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Arm description:

Patients had to take eight drops of a vitamin D-free oil daily (Migliol oil; Merck) during a meal.

Arm type	Placebo
Investigational medicinal product name	Migliol oil; Merck, Darmstadt, Germany
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops
Routes of administration	Oral use

Dosage and administration details:

eight drops of a vitamin D-free oil daily during a meal.

Number of subjects in period 1	vitamin D arm	placebo
Started	199	201
Completed	199	201

Baseline characteristics

Reporting groups

Reporting group title	vitamin D arm
Reporting group description: Patients had to take 4000 IU vitamin D daily (eight drops of an oily vitamin D preparation; Vigantol oil, Merck, Darmstadt, Germany) during a meal.	
Reporting group title	placebo
Reporting group description: Patients had to take eight drops of a vitamin D-free oil daily (Migliol oil; Merck) during a meal.	

Reporting group values	vitamin D arm	placebo	Total
Number of subjects	199	201	400
Age categorical			
Randomization was computer based in blocks of six and stratified by sex.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
18-79	199	201	400
Age continuous			
Randomization was computer based in blocks of six and stratified by sex.			
Units: years			
arithmetic mean	54	53	
standard deviation	± 11	± 10	-
Gender categorical			
Units: Subjects			
Female	33	35	68
Male	166	166	332

Subject analysis sets

Subject analysis set title	vitamin D arm
Subject analysis set type	Full analysis
Subject analysis set description: baseline characteristics	
Subject analysis set title	placebo arm
Subject analysis set type	Full analysis
Subject analysis set description: baseline characteristics	

Reporting group values	vitamin D arm	placebo arm	
Number of subjects	199	201	
Age categorical			
Randomization was computer based in blocks of six and stratified by sex.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
18-79	199	201	
Age continuous			
Randomization was computer based in blocks of six and stratified by sex.			
Units: years			
arithmetic mean	54	53	
standard deviation	± 11	± 10	
Gender categorical			
Units: Subjects			
Female	33	35	
Male	166	166	

End points

End points reporting groups

Reporting group title	vitamin D arm
Reporting group description: Patients had to take 4000 IU vitamin D daily (eight drops of an oily vitamin D preparation; Vigantol oil, Merck, Darmstadt, Germany) during a meal.	
Reporting group title	placebo
Reporting group description: Patients had to take eight drops of a vitamin D-free oil daily (Migliol oil; Merck) during a meal.	
Subject analysis set title	vitamin D arm
Subject analysis set type	Full analysis
Subject analysis set description: baseline characteristics	
Subject analysis set title	placebo arm
Subject analysis set type	Full analysis
Subject analysis set description: baseline characteristics	

Primary: overall mortality

End point title	overall mortality
End point description: Primary endpoint was all-cause mortality. We used four sources of information to identify the primary endpoint: repeated contacts with the participants, contacts with family physicians, a regular review of medical records, and consultation of the respective registration office. Causes of death were assessed from the medical records or by contacting the family physicians.	
End point type	Primary
End point timeframe: period of 3 years	

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in mortality rates
Statistical analysis description: differences in mortality rates between the placebo and vitamin D group.	
Comparison groups	vitamin D arm v placebo arm

Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Cox proportional hazard
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.71

Notes:

[1] - lower mortality in the vitamin D versus placebo group was considered

Secondary: hospitalization

End point title	hospitalization
End point description:	
End point type	Secondary
End point timeframe:	
3 years	

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in hospitalization rates
Statistical analysis description:	
difference in hospitalization rates in the vitamin D versus placebo group	
Comparison groups	vitamin D arm v placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.63

Notes:

[2] - lower hospitalization rate in the vitamin D versus placebo group

Secondary: mechanical circulators support implantation

End point title	mechanical circulators support implantation
End point description: lower rate of MCS implantation in the vitamin D versus placebo group	
End point type	Secondary
End point timeframe: 3 years	

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in MCS implantation rates
Comparison groups	vitamin D arm v placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	3.66

Notes:

[3] - lower MCS implantation rate in the vitamin D versus placebo group

Secondary: High urgent listing for heart transplantation

End point title	High urgent listing for heart transplantation
End point description: difference in high urgent listing for heart transplantation between the vitamin D and placebo group	
End point type	Secondary

End point timeframe:

3 years

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in high urgent listing for HTx
Comparison groups	vitamin D arm v placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	2.03

Secondary: heart transplantation

End point title	heart transplantation
End point description:	
End point type	Secondary
End point timeframe:	
3 years	

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in heart transplantation
Statistical analysis description: lower transplantation rate in the vitamin D versus placebo group	
Comparison groups	vitamin D arm v placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	2.07

Secondary: resuscitation

End point title	resuscitation
End point description: difference in resuscitation rate	
End point type	Secondary
End point timeframe: 3 years	

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in resuscitation
Comparison groups	vitamin D arm v placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	4.01

Notes:

[4] - lower resuscitation rate in the vitamin D versus placebo group

Secondary: hypercalcemia

End point title	hypercalcemia
End point description: difference in hypercalcemia rate	
End point type	Secondary
End point timeframe: 3 years	

End point values	vitamin D arm	placebo arm		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	201		
Units: number	199	201		

Statistical analyses

Statistical analysis title	difference in hypercalcemia rates
Comparison groups	vitamin D arm v placebo arm
Number of subjects included in analysis	400
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.05
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	5.98

Notes:

[5] - lower hypercalcemia risk in the placebo versus vitamin D group

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years

Adverse event reporting additional description:

hypercalcemia and hypervitaminosis D were assessed at each 6-month visit during the entire three years of study duration.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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Reporting groups

Reporting group title	vitamin D group
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Reporting group description:

experimental group

Reporting group title	placebo group
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Reporting group description:

placebo group

Serious adverse events	vitamin D group	placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 199 (0.00%)	0 / 201 (0.00%)	
number of deaths (all causes)	39	36	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	vitamin D group	placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 199 (5.03%)	5 / 201 (2.49%)	
Endocrine disorders			
hypercalcemia			
subjects affected / exposed	10 / 199 (5.03%)	5 / 201 (2.49%)	
occurrences (all)	10	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

A major limitation is the aforementioned low-statistical power to detect significant treatment differences in the primary endpoint. A further limitation is that the study is largely restricted to male Caucasian patients.
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Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28498942>