Journal of Psychiatric Research 119 (2019) 84–94

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

# The effect of melatonin on depressive symptoms and anxiety in patients after acute coronary syndrome: The MEDACIS randomized clinical trial

Michael Tvilling Madsen[a,b,c,d,e,f,g,h,*], Jawad Ahmad Zahid[a], Christine Hangaard Hansen[a], Ole Grummedal[a], Jessica Roberts Hansen[g], Anders Isbrand[i], Ulla Overgaard Andersen[c], Lars Juel Andersen[d], Mustafa Taskiran[f], Erik Simonsen[g,h,1], Ismail Gögenur[a,h,1]

[a] Department of Surgery, Zealand University Hospital, Lykkebaekvej 1, 4600, Koege, Denmark
[b] Department of Cardiology, Zealand University Hospital, Lykkebaekvej 1, 4600, Koege, Denmark
[c] Department of Cardiology, Holbaek Hospital, Smedelundsgade 60, 4300, Holbaek, Denmark
[d] Department of Cardiology, Zealand University Hospital, Koegevej 7-13, 4000, Roskilde, Denmark
[e] Department of Cardiology, Slagelse Sygehus, Ingemannsvej 18, 4200, Slagelse, Denmark
[f] Department of Cardiology, Hvidovre Hospital, Kettegaard Alle 30, 2650, Hvidovre, Denmark
[g] Psychiatric Research Unit, Region Zealand, Faelledvej 6, 4200, Slagelse, Denmark
[h] Institute of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark
[i] Department of Clinical Physiology and Nuclear Medicine, Herlev Hospital, Herlev Ringvej 75, 2730, Herlev, Denmark

ARTICLE INFO

*Keywords:*
Acute coronary syndrome
Depression
Melatonin
Randomized controlled trial
Placebo
Primary prophylactic

ABSTRACT

*Background:* Depression following acute coronary syndrome is prevalent and associated with increased mortality and morbidity. Melatonin may function as a primary prophylactic antidepressant substance and alleviate depressive symptoms. The study was undertaken to determine if melatonin administered following an acute coronary syndrome (ACS) could prevent development of depression.

*Methods:* The study was a double-blinded, placebo-controlled, multicenter, randomized clinical trial performed in five primary care cardiology departments at Zealand, Denmark. Included patients were adults patients, free of depression at baseline, included at the latest 4 weeks after acute coronary syndrome. Twenty-five mg melatonin or placebo was administered 1 h before participants' bedtime for 12 weeks. The primary outcome is Major Depression Inventory (MDI) measured every two weeks throughout the trial. Incidence of depression was apriori defined as MDI score ≥ 21 during the trial. Reported exploratory outcomes were patterns of dropout and safety outcomes.

*Results:* 1220 patients were screened and 252 participants were randomized in a 1:1 ratio. Baseline MDI score in the melatonin and placebo group were, respectively, 6.18 (CI 5.32–7.05) and 5.98 (CI 5.19–6.77). No significant intergroup differences were found during the study in the intention-to-treat analysis or per-protocol analysis. Cumulative events of depressive episodes during the 12 weeks were six in the melatonin group and four in the placebo group. A significant drop in depressive symptoms were present throughout the study period. No intergroup differences were present in dropouts or adverse events.

*Conclusions:* Melatonin showed no prophylactic antidepressant effect following acute coronary syndrome. The non-significant results might be due to a type II error or melatonin might not be able to prevent development of depressive symptoms following ACS.

* Corresponding author. Center for surgical science Department of Surgery, Zealand University Hospital, Koege, University of Copenhagen, Lykkebaekvej 1, 4600, Koege, Denmark.;

*E-mail addresses:* michael_madsen88@hotmail.com, mitm@regionsjaelland.dk, Michael_madsen88@hotmail.com (M.T. Madsen), ja_zahid@yahoo.dk (J.A. Zahid), christine.hangaard@gmail.com (C.H. Hansen), olegrummedal@gmail.com (O. Grummedal), jfernisr1@gmail.com (J.R. Hansen), andersisbrand@gmail.com (A. Isbrand), uoa@regionsjaelland.dk (U.O. Andersen), laad@regionsjaelland.dk (L.J. Andersen), mustafa.taskiran.01@regionh.dk (M. Taskiran), es@regionsjaelland.dk (E. Simonsen), igo@regionsjaelland.dk (I. Gögenur).

[1] These two authors shall have a shared last authorship and contributed equally to the manscript.

https://doi.org/10.1016/j.jpsychires.2019.09.014
Received 23 May 2019; Received in revised form 17 September 2019; Accepted 23 September 2019

## 1. Introduction

Depression and depressive symptoms are prevalent and represent a heavy burden for affected patients following acute coronary syndrome (ACS). The prevalence of depression has consistently been shown to be around 20% and depressive symptoms (distress or minor depression) even higher (Thombs et al., 2006). This has recently been confirmed in a Danish register study (98,000 first time ACS patients 2001–2009) showing that 20% experienced depression in the following 2 years (Osler et al., 2016). Based on the same cohort the cumulative 2-year incidence of depression was 13.4% in woman and 9.8% in men (Joergensen et al., 2016).

Several trials have shown the efficacy of antidepressant treatment (predominantly selective serotonin reuptake inhibitors – SSRI) following ACS (Glassman et al., 2002; Kim et al., 2015; Lespérance et al., 2007; Roose et al., 1998; Strik et al., 2000). A systematic review showed no convincing evidence of any prophylactic antidepressant treatment tested in patients following ACS (Christiansen et al., 2017). Two out of six studies showed an prophylactic effect; however, all six included studies had high risk of bias (Christiansen et al., 2017). One trial investigated SSRI in a double-blinded randomized controlled trial showing, an effect in favor of escitalopram, and no group difference in adverse events or cardiovascular safety (Hanash et al., 2012; Hansen et al., 2012). Pharmacological treatment with SSRI in patients with coronary artery disease has been shown to be well tolerated (Dowlati et al., 2010). However, citalopram and escitalopram have been shown to result in prolonged QT intervals (Castro et al., 2013; Cooke and Waring, 2013). A meta-analysis investigated adverse events in relation to SSRI treatment compared with placebo, and showed that it increased the risk of serious adverse events (OR 1.37; 95% CI 1.08 to 1.75) (Jakobsen et al., 2017). The review excluded trials which exclusively included participants with somatic disease and depression as a co-morbid disease, hence, generalizability to cardiac patients is not completely known. An older Cochrane review of SSRI treatment in primary care showed numbers needed to harm associated with SSRI treatment between 20 and 90 (Arroll et al., 2009). In light of this finding, newer treatment options with larger treatment effects and more favorable safety profiles are needed.

In a prophylaxtic setting a safer alternative might be melatonin, which has been shown to have a primary prophylactic antidepressant effect in patients with breast cancer (Hansen et al., 2014). This trial was a double-blinded placebo-controlled randomized clinical trial which showed a 75% relative risk reduction with administration of melatonin compared to placebo. Melatonin is a non-toxic endogenous hormone, which has been shown to be safe for use in humans (L. P. Andersen et al., 2016). Melatonin release from the pineal gland is regulated by the supra-ciasmatic nuclei, which has the function of synchronizing the body's circadian rhythm, thereby, ensuring a stable sleep-wake rhythm among other processes (Claustrat et al., 2005). Disturbed sleep-wake rhythm is an integrated part of depression and antidepressant drugs improving sleep-wake disturbances are likely to have substantial therapeutic value (Lam, 2006). Agomelatine (a melatonin agonist) has been marketed as an antidepressant acting through its' effect on the MT1 and MT2 melatonergic receptors (partly antagonist 5-HT2c receptor) with similar receptor affinity as melatonin (Cardinali et al., 2012). Therefore, the antidepressant effect of melatonin is assumed to act through stabilization of the sleep-wake rhythm and central receptor activity (MT1 and MT2).

In light of this the MEDACIS trial (Madsen et al., 2017) was undertaken with the primary objective of investigating the prophylactic antidepressant effect of melatonin over a 12 week period in patients following ACS.

## 2. Methods

### 2.1. Study oversight

The MEDACIS trial was an investigator-initiated trial sponsored by several grants from non-profit agencies and funds. The trial was approved by the Ethics Committee of Region Zealand, the Danish Health and Medicines Authority, and the Danish Data Protection Agency before commencement of the trial. The corresponding author had the role of sponsor/investigator and had responsibility of conducting the trial, data-analysis and drafting the manuscript. All authors approved and reviewed the manuscript; furthermore, they assume full responsibility for all data presented in the current publication. The study is reported in line with the CONSORT statement (supplementary material).

### 2.2. Study participants

Eligible patients should provide written informed consent, be over 18 years, be admitted to a recruiting department of cardiology with ACS, and be included at the latest 1 month after discharge from the department. Patients were excluded if they had or were: (1) Known allergic reaction to melatonin; (2) Ongoing or previous pharmacologically treated depression or bipolar disorder; (3) Dementia defined as a Mini Mental State Examination (MMSE) score < 24; (4) At the point of inclusion participating in other pharmacological intervention trial; (5) Diagnosis of Rotor syndrome or Dubin-Johnson syndrome, epilepsy, sleep apnea syndrome, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), or multiple sclerosis; (6) Severe liver disease, defined as transaminases above three times normal levels, or severe kidney disease defined as an eGRF under 40 ml/min; (7) Chronically using hypnotic treatment prior to the ACS; (8) Known sleep disorder (e.g., insomnia, restless legs, etc.); (9) Working nightshifts; (10)Daily alcohol consumption above 5 units of alcohol (1 unit = 12 g alcohol); (11)Predictable poor compliance (not speaking fluent Danish); (12) Pregnant or breastfeeding women; (13) Severe, life-threatening medical condition that implied that the patient could not participate in the study course (e.g., cancer, stroke); (14)Indication for coronary artery bypass graft (CABG) (Madsen et al., 2017). Participants were recruited from five cardiology departments in Denmark. All study related participant contact was handled in the respective cardiology department's outpatient clinic during phase II cardiac rehabilitation.

### 2.3. Study design

The study design for MEDACIS has previously been described (Madsen et al., 2017). In short, the MEDACIS trial (clinicaltrial.gov, *NCT0245129*) was a randomized, placebo-controlled, double-blinded, multicenter trial with 1:1 allocation of 25 mg melatonin or placebo for a duration of 12 weeks following acute coronary syndrome. No changes to eligibility criteria were made after commencement of the trial. Study medication were delivered in uniform boxes at the end of the inclusion meeting. Medication compliance was checked at clinical visits at weeks 2 and 12 and compliance below 75% was considered non-adherence.

The Regional Pharmacy in Region Zealand Denmark handled randomization and allocation concealment. A randomization list was produced by applying online software (http://www.randomization.com/) and used a 1:1 allocation in blocks containing six participants (three melatonin and three placebo) with no stratification. The randomization list was kept at the Regional Pharmacy and was not available to the investigators. To ensure allocation concealment during the trial the Regional Pharmacy produced two sets of coded envelopes (an opaque, sealed envelope for each patient, containing the randomization code). The blinding was preserved throughout the trial and no cases of “code break” were performed (no formal test of blinding integrity was performed), and the data management and analysis were performed blinded to allocation. A dedicated monitor from the department of

**Table 1**
Baseline characteristics of ACS patients randomized in trial.

| Outcome | Melatonin N = 126 | Placebo N = 126 | Statistical differences |
|---|---|---|---|
| **Demographics** | | | |
| Age, mean (SD) | 62.90 (11.32) | 62.10 (10.81) | P = 0.57 |
| Male, n (%) | 95 (75.4) | 101 (80.16) | P = 0.45 |
| Height (cm) | 175.1 (8.22) | 177.1 (8.69) | P = 0.08 |
| Weight (kg) | 87.64 (17.71) | 85.99 (14.63) | P = 0.42 |
| *Civil status (%)* | | | |
| Married | 105 (83.33) | 97 (76.98) | P = 0.17 |
| Divorced | 8 (6.35) | 5 (3.97) | |
| Widowed | 5 (3.97) | 13 (10.32) | |
| Unmarried | 8 (6.35) | 11 (8.73) | |
| *No. of children (%)* | | | |
| 0 | 6 (4.76) | 13 (10.32) | P = 0.09 |
| 1 | 18 (14.29) | 15 (11.90) | |
| 2 | 47 (37.30) | 61 (48.41) | |
| 3 | 39 (30.95) | 27 (21.43) | |
| > 3 | 16 (12,69) | 10 (7.93) | |
| *Employment (%)* | | | |
| Student | 0 (0) | 1 (0.79) | P = 0.59 |
| Employed | 60 (47.62) | 67 (53.17) | |
| Unemployed | 2 (1.59) | 3 (2.38) | |
| Sick leave | 5 (3.97) | 5 (3.97) | |
| Disability pension | 6 (4.76) | 2 (1.59) | |
| Retired | 53 (42.06) | 48 (38.10) | |
| *Educational level (%)* | | | |
| Finished grade 8 | 17 (13.49) | 7 (5.56) | P = 0.24 |
| Finished grade 10 | 11 (8.73) | 16 (12.70) | |
| High school level education | 49 (38.89) | 45 (35.71) | |
| Some college | 26 (20.63) | 26 (20.63) | |
| Bachelor's degree | 12 (9.52) | 17 (13.49) | |
| Master's degree | 11 (8.73) | 15 (11.90) | |
| *Department (%)* | | | |
| Koege | 36 (28.6) | 36 (28.6) | P > 0.99 |
| Roskilde | 15 (11.9) | 15 (11.9) | |
| Holbaek | 30 (23.8) | 30 (23.8) | |
| Slagelse | 39 (30.9) | 39 (30.9) | |
| Hvidovre | 6 (4.7) | 6 (4.7) | |
| **Psychiatric variables (%)** | | | |
| Family history of mental disorder | 22 (17.46) | 25 (19.84) | P = 0.75 |
| Previous mental disorder | 3 (2.38) | 0 (0) | P = 0.25 |
| Baseline MDI, mean + - SD | 6.18 (5.21) | 5.98 (4.95) | P = 0.83 |
| **Cardiac diagnosis and treatment (%)** | | | |
| STEMI | 53 (42.06) | 62 (49.21) | P = 0.52 |
| Non-STEMI | 66 (52.38) | 58 (46.03) | |
| UAP | 7 (5.56) | 6 (4.76) | |
| PCI treatment | 98 (78.40) | 99 (78.57) | P > 0.99 |
| **Cardiac risk factors (%)** | | | |
| Current smoker | 16 (12.70) | 15 (11.90) | P = 0.97 |
| Former smoker | 77 (61.11) | 78 (61.90) | |
| Newer smoker | 33 (26.19) | 33 (26.19) | |
| Previous heart disease | 31 (24.60) | 35 (27.78) | P = 0.67 |
| Previous coronary heart disease | 28 (22.22) | 26 (20.63) | P = 0.88 |
| Diabetes | 17 (13.49) | 11 (8.73) | P = 0.32 |
| Arterial hypertension | 67 (53.17) | 66 (52.38) | P > 0.99 |
| Atrial fibrillation | 4 (3.17) | 3 (2.38) | P > 0.99 |
| Pulmonary disease (COPD or Asthma) | 12 (9.52) | 9 (7.14) | P = 0.65 |
| GI disease | 24 (19.05) | 18 (14.29) | P = 0.40 |
| Musculoskeletal disease | 59 (46.33) | 51 (40.48) | P = 0.37 |
| Alcohol, units a week, mean (SD) | 4.90 (5.95) | 5.93 (6.69) | P = 0.20 |
| Total Cholesterol, mmol/l, mean (SD) | 4.40 (1.24) | 4.36 (1.19) | P = 0.80 |
| LDL, mmol/l, mean (SD) | 2.43 (1.11) | 2.40 (1.00) | P = 0.83 |
| HDL, mmol/l, mean (SD) | 1.22 (0.40) | 1.27 (0.44) | P = 0.36 |
| Left ventricle ejection fraction, % (SD) | 48.67 (10.31) | 49.54 (10.20) | P = 0.50 |
| *CCS class (%)* | | | |
| 0 (no angina) | 121 (96.03) | 119 (94.44) | P = 0.29 |
| 1 | 2 (1.59) | 6 (4.76) | |
| 2 | 3 (2.38) | 1 (0.79) | |
| *NYHA class (%)* | | | |
| I | 84 (66.67) | 92 (73.02) | P = 0.15 |
| II | 34 (26.98) | 32 (25.40) | |
| III | 8 (6.35) | 2 (1.59) | |
| **Baseline medication (%)** | | | |
| Aspirin | 120 (95.24) | 120 (95.24) | P > 0.99 |
| Thrombocyte inhibitor | 115 (91.27) | 120 (95.24) | P = 0.32 |
| Other anticoagulant treatment (incl. NOAC) | 9 (7.14) | 12 (9.52) | P = 0.65 |
| Statins | 114 (90.48) | 116 (92.06) | P = 0.82 |
| No-statin Cholesterol lowering drugs | 16 (12.70) | 8 (6.35) | P = 0.13 |
| Beta-blockers | 98 (77.78) | 97 (76.98) | P > 0.99 |
| Oral antidiabetics | 17 (13.49) | 9 (7.14) | P = 0.14 |
| Insulin | 7 (5.56) | 4 (3.17) | P = 0.54 |
| Calcium antagonists | 33 (26.19) | 30 (23.81) | P = 0.77 |
| Long acting nitrates | 11 (8.73) | 7 (5.56) | P = 0.46 |
| Nitro-glycerine – discretionary | 77 (61.11) | 75 (59.52) | P = 0.90 |
| Other angina medication | 4 (3.17) | 1 (0.79) | P = 0.37 |
| ACE inhibitors | 42 (33.33) | 42 (33.33) | P > 0.99 |
| Angiotensin-II antagonists | 16 (12.70) | 18 (14.29) | P = 0.85 |
| Diuretics | 36 (28.57) | 25 (19.84) | P = 0.14 |
| Anti-arrhythmic treatment | 1 (0.79) | 0 (0.00) | P > 0.99 |
| Eltroxin | 5 (3.97) | 1 (0.79) | P = 0.21 |
| PPI's | 38 (30.16) | 29 (23.02) | P = 0.25 |
| **ITT POPULATION – Medicine compliance** | | | |
| N | 126 | 126 | P > 0.99 |
| Medicine compliance day 14% (95% CI) | 91.30(87.64; 95.05) | 94.22(91.55; 96.89) | P = 0.26* |
| Medicine compliance day 84% (95% CI) | 84.42(79.33; 89.52) | 88.51(84.58; 92.43) | P = 0.71* |
| N Compliance below 75% day 14 | 10 | 5 | P = 0.29 |
| N Compliance below 75% day 84 | 19 | 13 | P = 0.34 |
| **PP POPULATION** | | | |
| Dropout from ITT (n) | 10 | 5 | P = 0.29 |
| N | 116 | 121 | P = 0.20 |
| Medicine compliance day 14% (95% CI) | 97.22 (96.40; 98.05) | 96.94 (95.89; 97.99) | P = 0.58* |
| Medicine compliance day 84% (95% CI) | 91.41 (88.29; 94.53) | 91.98 (89.37; 94.58) | P = 0.84* |
| N Compliance below 75% day 14 | 0 | 0 | P > 0.99 |
| N Compliance below 75% day 84 | 9 | 8 | P = 0.80 |
| **DROPOUT during the trial** | | | |
| Overall | 19 | 9 | P = 0.07 |
| Withdrawal of informed consent | 9 | 5 | P = 0.41 |
| **Adverse events** | 4 | 2 | P = 0.68 |
| *Fatique* | 2 | 0 | P = 0.50 |
| *Dizzines* | 1 | 0 | P > 0.99 |
| *Sleep disturbance* | 1 | 1 | P > 0.99 |
| *Angina pectoris* | 0 | 1 | P > 0.99 |
| Re-infarction | 2 | 1 | P > 0.99 |
| Other trial | 1 | 0 | P > 0.99 |
| Depression | 1 | 0 | P > 0.99 |
| Prolonged hospitalization | 2 | 0 | P = 0.50 |
| CABG | 0 | 1 | P= > 0.99 |

Legend: Baseline demographics of study participants. * Mann Whitney test – else Fishers exact. Previous mental disorder does not refer to depression or bipolar disorder.

Good Clinical Practice (GCP) of Bispebjerg University Hospital monitored the study. Recruitment, enrollment, clinical visits, and phone calls were all handled by a clinical investigator team consisting of the

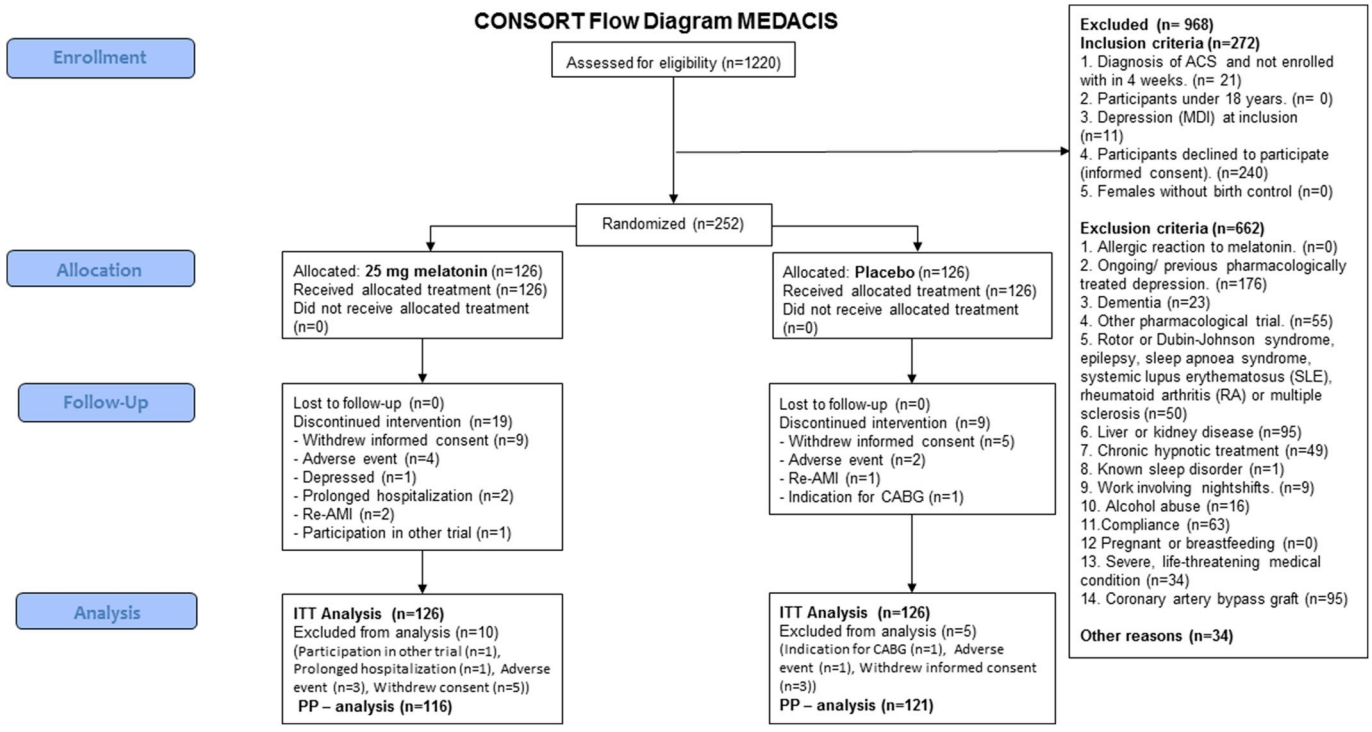


**Fig. 1.** Consort flow diagram for the MEDACIS trial.

**Table 2**
Intergroup comparison on intention to treat population.

| | Melatonin | Placebo | Mean difference |
|---|---|---|---|
| **MDI absolute scores** | | | |
| MDI assessment | Mean (CI 95%) | Mean (CI 95%) | Mean (CI 95%) P-value |
| Baseline | 6.18 (5.32; 7.05) | 5.98 (5.19; 6.77) | 0.198 (−1.06; 1.46) p = 0.76 |
| Day 14 | 5.95 (5.02; 6.87) | 5.10 (4.30; 5.80) | 0.882 (−0.32; 2.1) p = 0.15 |
| Day 28 | 5.15 (4.32; 5.97) | 5.04 (4.15; 5.93) | 0.108 (−1.01; 1.2) p = 0.86 |
| Day 42 | 5.03 (4.05; 6.02) | 4.44 (3.60; 5.30) | 0.593 (−0.69; 1.87) p = 0.36 |
| Day 56 | 4.83 (3.84; 5.83) | 4.59 (3.72; 5.43) | 0.259 (−1.04; 1.56) p = 0.69 |
| Day 70 | 4.47 (3.44; 5.50) | 3.97 (3.33; 4.71) | 0.496 (−0.74; 1.74) p = 0.43 |
| Day 84 | 3.54 (2.76; 4.32) | 4.10 (3.23; 4.97) | - 0.561 (−1.73; 0.61) p = 0.34 |
| **Depression (MDI ≥ 21)** | | | |
| *MDI ≥ 21* | *N* | *N* | *P-value* |
| Day 14 | 2 | 0 | p = 0.24 |
| Day 28 | 1 | 1 | p > 0.99 |
| Day 42 | 3 | 1 | p = 0.37 |
| Day 56 | 2 | 1 | p = 0.61 |
| Day 70 | 3 | 2 | p = 0.35 |
| Day 84 | 1 | 2 | p > 0.99 |
| **HADS data** | | | |
| *HADS-A* | *Mean (CI 95%)* | *Mean (CI 95%)* | *Mean (CI 95%) P-value* |
| Day 0 | 2.98 (2.50; 3.46) | 2.81 (2.28; 3.34) | 0.176 (−0.54; 0.89) p = 0.63 |
| Day 14 | 2.53 (2.01; 3.06) | 2.39 (1.86; 2.93) | 0.14 (−0.60; 0.89) p = 0.71 |
| Day 84 | 1.75 (1.19; 2.03) | 2.28 (1.68; 2.87) | - 0.53 (−1.28; 0.23) p = 0.17 |
| *HADS-A ≥ 8* | *N* | *N* | *P-value* |
| Day 0 | 8 | 12 | p = 0.36 |
| Day 14 | 8 | 12 | p = 0.49 |
| Day 84 | 3 | 9 | p = 0.14 |
| *HADS-D* | *Mean (CI 95%)* | *Mean (CI 95%)* | *Mean (CI95%) P-value* |
| Day 0 | 1.68 (1.31; 2.05) | 1.35 (1.00; 1.70) | 0.33 (−0.18; 0.84) p = 0.20 |
| Day 14 | 1.61 (1.19; 2.03) | 1.11 (0.76; 1.47) | 0.50 (−0.05; 1.04) p = 0.07 |
| Day 84 | 1.19 (0.80; 1.57) | 1.48 (1.09; 1.88) | - 0.30 (−0.85; 0.25) p = 0.29 |
| *HADS-D ≥ 8* | *N* | *N* | *P-value* |
| Day 0 | 3 | 5 | p = 0.50 |
| Day 14 | 3 | 3 | p > 0.99 |
| Day 84 | 3 | 3 | p > 0.99 |

Legend: Mean values for melatonin or placebo during the follow-up of the trial. Intergroup comparison compared via students t-test. Depression (MDI score ≥ 21) during follow-up during the MEDACIS trial on available data. HADS data presented at baseline and follow-up.

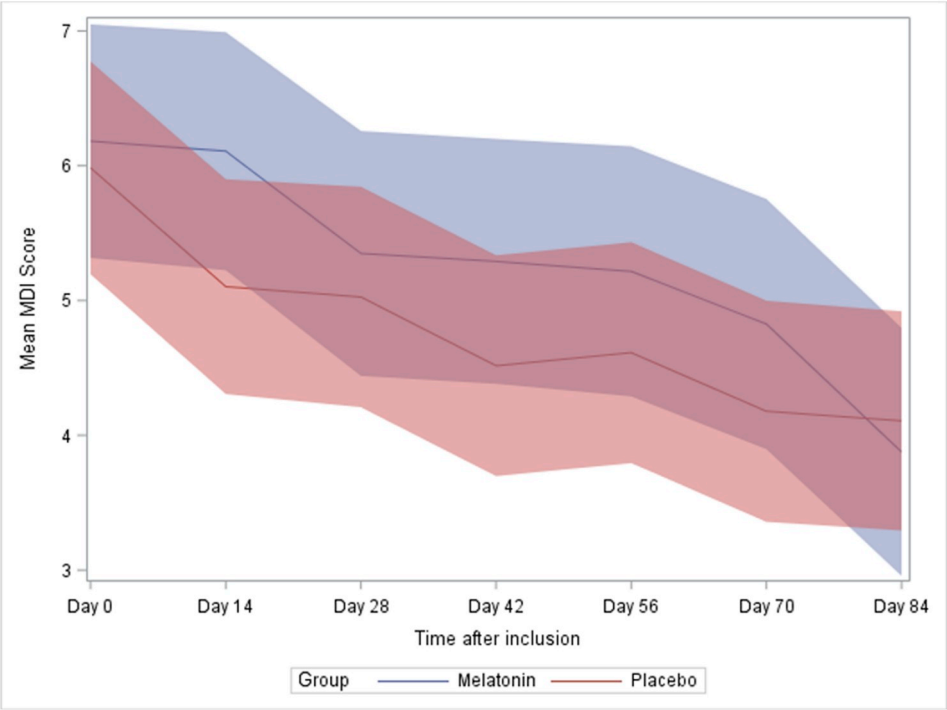


**Fig. 2.** Legend: Mean MDI scores for melatonin and placebo group throughout the MEDACIS trial with 95% CI.

first four authors (MTM, JAZ, CHH and OGC). Two additional recruiting centers were added due to slow recruitment, and a sub-trial consisting of a single-center measurement of endothelial dysfunction using EndoPAT were also added.

### 2.4. Study endpoints

The primary outcome of the trial was the Major Depressive Inventory (MDI) assessed continuously throughout the trial every 2 weeks (see SPIRIT figure (Madsen et al., 2017)). In short, the MDI is a self-rating scale consisting of 12 questions covering the ICD-10 criteria of depression. The MDI has a maximum score of 50 points indicating a maximum number of depressive symptoms. Each question supplies between 0 or 5 points; however, for subsets of question 8 and 10 (restlessness/subdued and appetite) only the highest score counts. It was developed and validated in a Danish population (Olsen et al., 2004, 2003). In the current study, an MDI $\geq 21$ was considered to indicate the presence of depression.

Dropout rates and study medication compliance were reported throughout the study period (SPIRIT figure (Madsen et al., 2017)). Safety outcomes (i.e. harm and adverse events) were assessed every 2 weeks throughout the trial, either at clinical visits or as an interview over the phone. Additionally, the self-administered UKU side-effect rating scale was administered every 2 weeks in an effort to make harm and adverse event monitoring more thorough (Lingjaerde et al., 1987).

The Hospital Anxiety and Depression Scale (HADS) was administered in the current trial three times (at baseline, 2 and 12 weeks) (Zigmond and Snaith, 1983). The HADS was developed as a screening tool for anxiety and depression in a hospital setting and supplies a score of 0–21. As shown by Bjelland et al. (2002), a cut-off of 8 points or higher on the HADS-D or HADS-A subscales gives a sensitivity and specificity of 0.8, and this cut-off was applied in the current study.

### 2.5. Statistical methods

Sample size was based on an estimate that 31% of patients following ACS would present with depressive symptoms [4]. An intervention effect of a reduction of depressive symptoms by 15.5%, power of 0.80, and a significance level of 5% yielded a required sample size in each group of 116. In case of withdrawal or medicine-compliance below 75% at the 2-week clinical visit additional patients would be included. No interim efficacy analysis was planned or performed in the current trial.

Baseline characteristics of participants are presented as mean, SD or CI for continuous data and frequency for categorical data collectively presented in a tabular format. Data distribution was visually checked using histograms and QQ-plots and, if relevant, transformation of data was applied. $P < 0.05$ was considered statistically significant and the SAS-enterprise guide 7.1 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. The R Statistical Software version 3.4.3 (*R Core Team. R: A language and environment for statistical computing*, 2017) with the "survminer" add-on package (Kassambara, 2017) was used to produce the cumulative incidence figure.

The data analysis was performed by the sponsor/investigator and in accordance with an analysis plan developed and consulted with a dedicated biostatistician from Region Zealand (Madsen et al., 2017). The primary hypothesis was tested using Fisher's exact test comparing developed cases of depression (defined as an MDI score $\geq 21$) during the trial. Comparisons of absolute MDI scores between groups were performed using student's t-test and squared transformation was applied. For the primary analysis a linear mixed model was applied with effects of age, gender, co-morbidity and cardiac risk factors assessed in marginal analysis.

Missing data of MDI scores were addressed using multiple imputation where "proc MI" in SAS was used under an assumption of missing at random. Baseline MDI scores were used to impute onto the following 2-week MDI assessments using a chain-wise imputation until the last MDI assessment. Predictive mean matching method matching with the five closest in the same treatment group was chosen and a total of 100 imputations were performed. Gender, age, ACS diagnosis, left ventricle ejection fraction, diabetes, hypertension, smoking status, baseline MDI, and treatment group were incorporated into the imputation. Other baseline characteristics (see Table 1) were examined in marginal correlation analyses, but were found not to be relevant in the imputation model.

**Table 3**
Repeated measure analysis on intention to treat population.

*Linear mixed model - unadjusted ITT population*

| Effect | DF | F Value | P value | Comment |
|---|---|---|---|---|
| Inter group comparison | 1 | 0.11 | 0.7402 | No group difference |
| MDI assessments (Day 0 - day 84) | 6 | 4.45 | 0.0002 | Significant drop over time |
| Group x time | 6 | 1.43 | 0.1997 | No sign group x time effect |

**RM-ANOVA - Multiple imputation ITT population**

| Day | % missing data | Time trend P-value | Inter group difference P-value |
|---|---|---|---|
| 0 | 0,00 | < 0.0001 | 0.9117 |
| 14 | 5,95 | < 0.0001 | 0.1904 |
| 28 | 16,67 | < 0.0001 | 0.4256 |
| 42 | 14,68 | < 0.0001 | 0.2036 |
| 56 | 17,86 | < 0.0001 | 0.2086 |
| 70 | 17,06 | 0.0077 | 0.3332 |
| 84 | 11,51 | Ref. | Ref. |

**Cox-proportional Hazard model**

| **Unadjusted model** | P-value | Hazard Ratio | 95% Hazard Ratio Confidence interval |
|---|---|---|---|
| Melatonin | 0.47 | 1.59 | 0.45; 5.65 |
| Placebo | . | . | . |
| **Adjusted model** | | | |
| Melatonin | 0.50 | 1.60 | 0.40; 6.35 |
| Placebo | . | . | . |

Legend: Linear mixed model on available data on intention to treat population in an unadjusted model. Marginal analysis with adjustment for age, gender, department, ACS diagnosis, previous ACS, hypertension, diabetes, or smoking did not affect the model.
Missing data handles using Multiple imputation by predictive mean matching method (regpmm SAS) using 100 imputations in a chain vice imputation matching at 5 closest in treatment group. Gender, age, ACS diagnosis, LVEF, Diabetes, Hypertension, smoking status, baseline MDI and treatment group were incorporated into the imputation. Other baseline characteristics (see Table 1) were searched in marginal correlation analysis not to be relevant in the imputation model.
Cox proportional hazard models of risk of depression (MDI ≥ 21) in depression vs. placebo. Unadjusted model simple log rank test. Adjusted model adjusted for age, gender, ACS diagnosis, Diabetes, Hypertension, and smoking status.

A preplanned secondary analysis of the primary outcome, the cumulative incidence of depressive symptoms, was plotted for the two groups and compared using the Cox proportional hazards regression analyzing incidence of depression (MDI score ≥21). The effect of age, gender, comorbidity and cardiac risk factors at baseline were investigated in the Cox-model. For the exploratory outcomes (HADS and adverse events) intergroup comparisons were performed using Fisher's exact test for frequencies and *t*-test for continuous data.

The intention-to-treat population (ITT) consisted of all patients included and randomized into the trial. As defined in the protocol only patients completing the 2-week clinical visit with a medicine compliance of at least 75% were considered per protocol (PP).

## 3. Results

### 3.1. Study patients

A total of 1220 patients with suspected ACS were screened (Fig. 1). Of these, 968 were excluded for various reasons, predominantly: current or previous medical antidepressant treatment (18.2%), impaired liver or kidney function (9.8%), or indication for coronary artery bypass graft (CABG, 9.8%). A further 240 patients were eligible but did not provide informed consent. A total of 252 patients were included into the trial resulting in an inclusion rate of eligible patients of 51.2% (252/492 patients).

During the trial, 19 patients in the melatonin group and nine in the placebo group did not complete the study. There was no significant difference in dropouts overall or for any specific reasons between the two groups (Table 1). A total of 252 were present for the ITT analysis and 237 for the PP analysis (Fig. 1). The duration of recruitment was 20 months and the average recruitment rate/month/center was 4.2 (supplementary material).

Baseline characteristics of the two groups are presented in Table 1. No significant differences between the baseline characteristics were present between the two groups. Approximately 45% presented with STEMI, 49% with NSTEMI and 78% were treated with PCI. Dropout and medicine compliance (mean and CI) in the groups were as presented in Table 1. No statistically significant difference in medicine compliance existed in the intention to treat or per protocol population. Furthermore, no significant inter-group differences in dropouts existed in the PP.

### 3.2. Efficacy

The mean baseline MDI score in the melatonin and placebo group was 6.18 (95% CI 5.32, 7.05) and 5.98 (95% CI 5.19, 6.77), respectively, as seen in Table 2/Fig. 2. Fisher's exact test on the incidence of depression (MDI score ≥21) on day 14, 28, 42, 56, 70 and 84 showed no significant group differences (Table 2). An unadjusted linear mixed model showed no intergroup difference (p = 0.74) and a significant lowering of the MDI scores (p = 0.0002) throughout the 12 weeks (Table 3). Using multiple imputation and performing a linear mixed model confirmed the findings in the simple linear mixed model (Table 3). The cox proportional hazard model shows a hazard ratio of depression of 1.59 (p = 0.47; CI 0.45–5.65) and 1.60 (p = 0.50; CI 0.40–6.35) in an unadjusted and adjusted model, respectively (Table 3). Cumulative incidence of depression was six in the melatonin group and four in the placebo group at the 12-week follow-up (Fig. 3). No difference was present between ITT and PP populations. HADS-A and HADS-D values were as presented in Table 2. There were no significant differences between the two groups concerning the HADS-A or HADS-D in absolute scores or cut-off values at day 14 or day 84.

### 3.3. Safety

No statistically significant differences between the groups for SUSAR, SAR or SAE were present throughout the trial (Table 4). One SAR was present in the placebo group and represented a participant admitted to hospital for observation for AMI due to chest pain. The patients was in the end diagnosed with stable angina.

### 3.4. Supplementary analysis

In depth details regarding timing of recruitment at individual centers are available in Table 5. Full analysis of Per Protocol population analog to the ITT analysis is available in Table 6 (supplementary material).

## 4. Discussion

The MEDACIS trial showed no effect of 25 mg melatonin for preventing the development of depression or depressive symptoms following ACS. There was a significant drop in mean MDI scores during the 12 weeks of the trial. No intergroup differences were found for the safety or HADS outcomes.

A recent systematic review of primary prophylactic antidepressant to ACS patients showed an effect in two out of six trials of depression

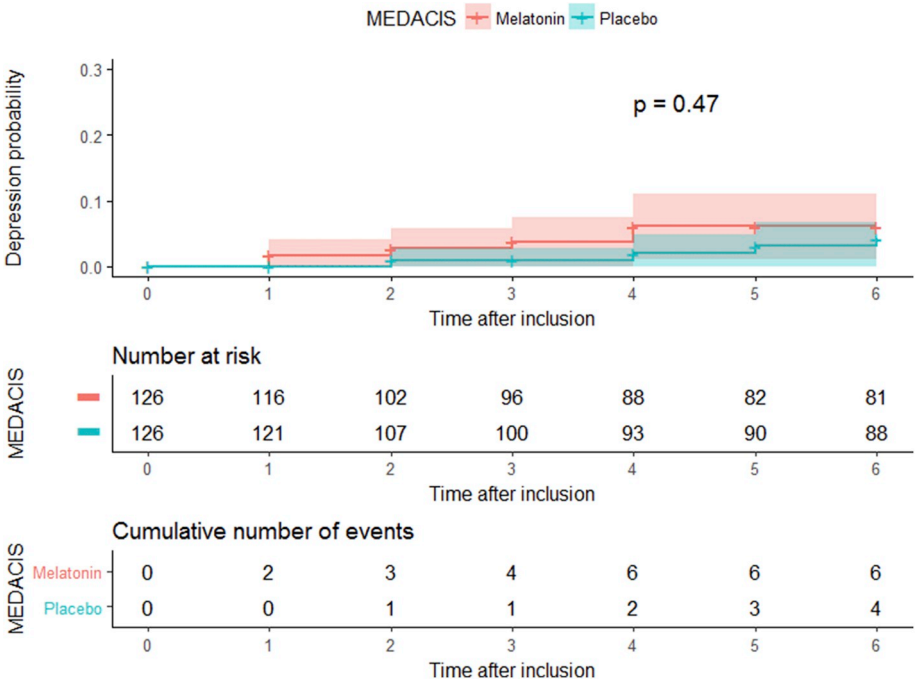


**Fig. 3.** Cumulative incidence curve on depression in the MEDACIS trial with numbers at risk and cumulative number of event. P-value = log rank test. Cumulative 10 events during 2328 weeks (10 depressions/44.77 risk years = 22.34 depressions per 100 person years.

and depressive symptoms (Christiansen et al., 2017). The results of the MEDACIS trial adds to these results of non-significant prophylactic antidepressant effects of known tested interventions. As previously mentioned, the DECARD trial (Hansen et al., 2012) showed a prophylactic antidepressant effect of 10 mg Escitalopram in time to event analysis (log rank p = 0.022), an absolute risk reduction of 6.8% and a number needed to treat of 15 (Hansen et al., 2012). A total of 239 patients following an ACS were randomized and followed for a 12-month period with a total of 9 diagnostic interviews during follow-up. In spite of being a high-quality trial the DECARD trial has been criticized for selective outcome reporting and exposing patients with no depression to SSRI with possible side-effects (Thombs and Ziegelstein, 2012). The DECARD and the MEDACIS trial differ in several important ways; in the former the follow-up was shorter; patients undergoing CABG were not included; and patients were excluded based on previous antidepressant usage.

Following participants for a longer period would prolong the time at risk of developing depression; however, the MEDACIS showed a significant drop in the MDI score as the study progressed. As with our results, some studies report an initial peak followed by a decline in depressive symptoms (Gu et al., 2016; Martin et al., 2003; Mayou et al., 2000; Parashar, 2006), whereas others report a consistent level of depression (Hanssen et al., 2009; Lane et al., 2002). This inconsistency might be due to differences in assessment timing, depression-screening tools, comorbidity, and demographics. In an unselected Danish population of first-time ACS patients the crude rate of incident depression was 17.6 and 6.5 per 100 person years from within 30 days and 2 years, respectively (Joergensen et al., 2016). Choosing to follow participants for only 12 weeks might be a partial explanation for the few cumulative events of depression in the current trial. However, in light of the high rate of incident depression immediately following ACS and drop in depressive symptoms in the study, the effect should be limited. Eliminating participants undergoing CABG was decided because their phase II cardiac rehabilitation starts later than those treated with PCI/conservatively. CABG constitutes major surgery and complications are prevalent. In particular, postoperative cognitive dysfunction may lead to reduced participation in rehabilitation and reduced quality of life (Goto and Maekawa, 2014; Indja et al., 2017). One study showed higher depression in a CABG population compared to PCI before cardiac rehabilitation (Pourafkari, 2015). Thus choosing not to include CABG patients might have excluded participants with an increased risk of depression. Choosing to exclude participants with previous and current antidepressant treatment would have affected the incidence of depression as patients with previous depression are known to have an increased risk of developing recurrent depression (Post, 2007). We cannot rule out that choosing to exclude on prior/current antidepressant treatment resulted in lower incidence of depression.

Melatonin was chosen as the intervention in the current trial based on previous significant prophylactic antidepressant effect shown in women with breast cancer (Hansen et al., 2014). This study showed a large effect in favor of melatonin with a relative risk of 0.25 (95% CI 0.077 to 0.80, number needed to treat = 3) to prevent depressive episodes. However, it should be noted that the trial was terminated early due to slow inclusion (54 out of planned 220) and had uneven dropout, which was higher in the placebo group. Hence, in light of the large effect size shown in women with breast cancer, melatonin holds promise as a preventive intervention. Compared to the previous trial (Hansen et al., 2014) which used 6 mg, the choice of 25 mg melatonin in the current trial might seem like a high dosage. Common dosages as a sleeping aid are between 3 and 10 mg (Hansen et al., 2015; Herxheimer and Petrie, 2002); however, dosages as high as 100 mg orally have been reported (Vakkuri et al., 1985). A recent review on melatonin safety demonstrated both short- and intermediate-term usage to be safe and only associated with mild adverse effects comparable to placebo levels (L. P. Andersen et al., 2016). Furthermore, it was pointed out that the optimal dosing for most indications has not been established (L. P. Andersen et al., 2016). As argued by Cardinali et al. (2012), to elucidate the antidepressant effect of melatonin equipotent dosages to antidepressants (Agomelatine) should be administered. The melatonin agonist Agomelatine administered as an antidepressant has an induction dosage of 25 mg and has similar MT1 and MT2 receptor affinity as melatonin. As melatonin is a safe non-toxic drug, where long-term treatment showed only mild adverse events comparable to placebo (L. P. H. Andersen et al., 2016), choosing a dosage of 25 mg melatonin was a balanced choice.

The major limitation of the current trial results from the low

**Table 4**
HARMS and adverse events.

| Outcome (%) | Melatonin N = 126 | Placebo N = 126 | Statistical differences |
|---|---|---|---|
| **Suspected unexpected serious adverse reaction (SUSAR)** | | | |
| SUSAR | 0 (0) | 0 (0) | P > 0.99 |
| **Serious adverse reactions (SAR)** | | | |
| Angina | 0 (0) | 1 (0.79) | P > 0.99 |
| **Serious adverse events (SAE)** | | | |
| N participants experienced SAE | 17 (13.49) | 18 (14.29) | P > 0.99 |
| Re-NSTEMI | 2 | 0 | P = 0.50 |
| Angina pectoris | 2 | 1 | P > 0.99 |
| Admission for observation for AMI | 2 | 6 | P = 0.28 |
| Chest pain | 1 | 3 | P = 0.62 |
| Heart Surgery | 0 | 1 | P > 0.99 |
| Pericarditis | 1 | 0 | P > 0.99 |
| Mitral insufficiency | 0 | 1 | P > 0.99 |
| Cardiac pulmonary edema | 2 | 0 | P = 0.50 |
| Pressure pulmonary edema | 1 | 0 | P > 0.99 |
| Tachycardia | 3 | 1 | NS |
| Suspected arrhythmia | 1 | 0 | P > 0.99 |
| Transitory cerebral Ischemia (TCI) | 1 | 0 | P > 0.99 |
| Pneumonia | 0 | 2 | P = 0.50 |
| Dyspnoea | 1 | 0 | P > 0.99 |
| Diverticulitis | 1 | 0 | P > 0.99 |
| Melena | 0 | 1 | P > 0.99 |
| Gout | 0 | 1 | P > 0.99 |
| Urinary retention | 0 | 2 | P = 0.50 |
| Macroscopic haematuria | 0 | 3 | P = 0.25 |
| Dehydration | 1 | 0 | P > 0.99 |
| Head ache caused by nitrate medication | 1 | 0 | P > 0.99 |
| Discomfort | 0 | 1 | P > 0.99 |
| Fainting | 0 | 1 | P > 0.99 |
| Suicide screening | 1 | 0 | P > 0.99 |
| **Adverse reactions (AR)** | | | |
| Fatigue | 2 | 0 | P = 0.50 |
| Head ache | 0 | 1 | P > 0.99 |
| Dizziness | 2 | 0 | P = 0.50 |
| Nausea and vomiting | 1 | 0 | P > 0.99 |
| Sleep disturbance | 0 | 1 | P > 0.99 |
| **Adverse events (AE)** | | | |
| Altered bowel habits | 27 | 16 | P = 0.09 |
| Sleep disturbance | 11 | 9 | P = 0.82 |
| Musculoskeletal pain | 13 | 16 | P = 0.69 |
| Dry mouth | 12 | 7 | P = 0.34 |
| Influenza | 9 | 11 | P = 0.82 |
| Palpitations | 10 | 15 | P = 0.40 |
| Dizziness | 12 | 5 | P = 0.13 |
| Fatigue | 6 | 5 | P > 0.99 |
| Nausea | 6 | 2 | P = 0.28 |
| Itching | 1 | 8 | P = 0.04 |
| Orthostatic hypotension | 5 | 4 | P > 0.99 |
| Pneumonia | 2 | 3 | P > 0.99 |
| Rash | 3 | 2 | P > 0.99 |

Legend: Overview of specific safety outcomes and harms in the MEDACIS trial.

incidence of depression, leading the current trial to be underpowered. The low incidence of depression might have been due to the selected eligibility criteria resulting in "healthy" participants being less likely to develop depression. "Healthy" participants would consistently score lower on the MDI resulting in a low variance and few scores above 21, which could be a possible explanation for the non-significant antidepressant effect of melatonin (i.e. type II error). Possibly a placebo effect could be present in the current study, resulting in fewer depressive events in both groups. As a result, the a priori assumed relative risk reduction of the intervention would be lowered and with a fixed alpha ($p = 0.05$) the power of the trial would decrease with increased risk of a type II error. However, a placebo-effect in the context of prevention trials has not been part of the Cochrane placebo-effect review (Hróbjartsson and Gøtzsche, 2010), hence, the size of a potential placebo-effect remains unknown. The BDI estimated prevalence of depression was used in the sample size calculation. However, whether MDI and BDI have overlapping cut-off (diagnostic test accuracy) is currently unknown, which is a limitation of the current trial. The current trial excluded based on treatment of current or previous pharmacological treatment of depression; however, this did not include psychotherapy and no-treatment options. Thus it cannot be ruled out that patients with previous depression were part of the study population.

A strength of the current trial is the study design; i.e., using a randomized controlled trial, using double blinding, recruitment at multiple sites, and blinded data-analysis. These were all factors placing the trial at the higher end of the evidence hierarchy. The study had high internal validity, as can be seen from a balanced randomization, high medication compliance, low and balanced dropout rate, and no significant differences between ITT and PP.

External validity of the trial is questionable, since only 20.6% (252/1220) of the screened participants ended up being included in the trial; however, 51.2% of the eligible patients participated in the trial. Randomization rate of 20.6% for screened and 51.2% rate for eligible participants could be considered high as recruitment into prevention trials was found to be lower than treatment trials (Cooper et al., 2015) (comparable rates with metformin 6.2% and 48.6%, respectively). A recruitment rate of 4.2 participants/center/month was higher than trials from the UK's National Institute for Health Research (NIHR) median rate 0.92 (Walters et al., 2017). Non-participants in the DECARD trial tended to be older (Hansen et al., 2011) and increasing age results in increased incidence of depression (Joergensen et al., 2016), therefore more depression in non-participants. Non-participation in post-ACS studies (Grace et al., 2004; Sorensen et al., 2005) has shown that it is likely that being female, being unmarried, and diagnosed with unstable angina pectoris are all associated with increased incidence of depression (Joergensen et al., 2016). Investigation into external validity linking clinical trial data and clinical registers would therefore be highly relevant (Kilburn et al., 2017).

**Table 5**
Recruitment rate divided by centre.

| Centre | Screening start | Screening end | Months | Recruited pr. centre | Recruitment/month |
|---|---|---|---|---|---|
| Koege Sygehus | 18 JAN 2016 | 10 MAY 2017 | 16.0 | 72 | 4.5 |
| Roskilde Sygehus | 09 FEB 2016 | 24 APR 2017 | 14.5 | 30 | 2.0 |
| Holbaek Sygehus | 01 MAR 2016 | 18 APR 2017 | 13.5 | 60 | 4.4 |
| Hvidovre hospital | 22 AUG 2016 | 06 MAR 2017 | 6.5 | 12 | 1.8 |
| Slagelse Sygehus | 03 AUG 2016 | 20 APR 2017 | 8.5 | 78 | 9.2 |
| Total/average | - | - | 59 | 252 | 4.2 |

Legend: Inclusion timing, period and number of participants divided by including centre.

**Table 6**
Intergroup comparison on Per protocol population.

| | Melatonin N = 116 | Placebo N = 121 | Difference |
|---|---|---|---|
| **MDI absolute scores** | | | |
| MDI assessment | Mean (CI 95%) | Mean (CI 95%) | Mean (CI 95%) P-value |
| Baseline | 5.97 (5.02; 6.92) | 5.93 (5.04; 6.83) | 0.032 (−1.27; 1.33) p = 0.98 |
| Day 14 | 5.95 (5.02; 6.88) | 5.07 (4.30; 5.83) | 0.882 (−0.31; 2.1) p = 0.16 |
| Day 28 | 5.15 (4.23; 5.97) | 5.04 (4.15; 5.93) | 0.108 (−1.01; 1.32) p = 0.41 |
| Day 42 | 5.04 (4.05; 6.02) | 4.44 (3.62; 5.27) | 0.593 (−0.69; 1.87) p = 0.23 |
| Day 56 | 4.84 (3.84; 5.83) | 4.58 (3.72; 5.43) | 0.259 (−1.04; 1.56) p = 0.40 |
| Day 70 | 4.47 (3.44; 5.50) | 3.97 (3.24; 4.71) | 0.498 (−0.76; 1.74) p = 0.40 |
| Day 84 | 3.54 (2.76; 4.32) | 4.10 (3.23; 4.97) | - 0.561 (−1.73; 0.60) p = 0.90 |
| **Depression (MDI ≥ 21)** | | | |
| *MDI ≥ 21* | *N* | *N* | *P-value* |
| Day 14 | 2 | 0 | p = 0.24 |
| Day 28 | 1 | 1 | p = 1.00 |
| Day 42 | 3 | 1 | p = 0.37 |
| Day 56 | 2 | 1 | p = 0.61 |
| Day 70 | 3 | 1 | p = 0.35 |
| Day 84 | 1 | 2 | p = 1.00 |
| **HADS data** | | | |
| *HADS-A* | *Mean (CI 95%)* | *Mean (CI 95%)* | *Mean (CI 95%) P-value* |
| Day 0 | 2.97 (2.47; 3.48) | 2.71 (2.19; 3.25) | 0.258 (−0.47; 0.99) p = 0.18 |
| Day 14 | 2.53 (2.01; 3.06) | 2.36 (1.82; 2.89) | 0.18 (−0.58; 0.93) p = 0.28 |
| Day 84 | 1.75 (1.29; 2.21) | 2.28 (1.68; 2.87) | - 0.53 (−1.28; 0.23) p = 0.31 |
| *HADS-A ≥ 8* | *N* | *N* | *P-value* |
| Day 0 | 8 | 10 | p = 0.8076 |
| Day 14 | 8 | 12 | p = 0.4873 |
| Day 84 | 3 | 9 | p = 0.1382 |
| *HADS-D* | *Mean (CI 95%)* | *Mean (CI 95%)* | *Mean (CI95%) P-value* |
| Day 0 | 1.62 (1.26; 1.99) | 1.32 (0.96; 1.67) | 0.30 (−0.20; 0.81) p = 0.20 |
| Day 14 | 1.61 (1.19; 2.03) | 1.08 (0.73; 1.44) | 0.53 (−0.02; 1.07) p = 0.07 |
| Day 84 | 1.19 (0.80; 1.57) | 1.48 (1.09; 1.88) | - 0.30 (−0.85; 0.25) p = 0.29 |
| *HADS-D ≥ 8* | *N* | *N* | *P-value* |
| Day 0 | 2 | 5 | p = 0.45 |
| Day 14 | 3 | 3 | p = 1.00 |
| Day 84 | 3 | 3 | p = 1.00 |

Linear mixed model - unadjusted ITT population

| Effect | F Value | P value | Comment |
|---|---|---|---|
| Inter group comparison | 0.11 | 0.7402 | No group difference |
| MDI assessments (Day 0 - day 84) | 4.45 | 0.0002 | Significant drop over time |
| Group x time | 1.43 | 0.1997 | No sign group x time effect |

| **RM-ANOVA - Multiple imputation ITT population** | **Time trend P-value** | **Inter group difference P-value** |
|---|---|---|
| Day 0 | < 0.0001 | 0.9117 |
| Day 14 | < 0.0001 | 0.1904 |
| Day 28 | < 0.0001 | 0.4256 |
| Day 42 | < 0.0001 | 0.2036 |
| Day 56 | < 0.0001 | 0.2086 |
| Day 70 | 0.0077 | 0.3332 |
| Day 84 | Ref. | Ref. |

| **Cox-proportional Hazard model** Unadjusted **model** | P-value | Hazard Ratio | 95% Hazard Ratio Confidence Limits |
|---|---|---|---|
| Melatonin | 0.47 | 1.59 | 0.45; 5.65 |
| . | . | | .s |
| **Adjusted model** | | | |
| Melatonin | 0.50 | 1.6 | 0.40; 6.35 |
| Placebo | . | . | . |

Legend: Mean values for melatonin or placebo during the follow-up of the trial. Intergroup comparison compared via students t-test. Depression (MDI score ≥ 21) during follow-up during the MEDACIS trial on available data. HADS data presented at baseline and follow-up.
Linear mixed model on available data on intention to treat population in an unadjusted model. Marginal analysis with adjustment for age, gender, department, ACS diagnosis, previous ACS, hypertension, diabetes, or smoking did not affect the model.
Missing data handles using Multiple imputation by predictive mean matching method (regpmm SAS) using 100 imputations in a chain vice imputation matching at 5 closest in treatment group. Gender, age, ACS diagnosis, LVEF, Diabetes, Hypertension, smoking status, baseline MDI and treatment group were incorporated into the imputation. Other baseline characteristics (see Table 1) were searched in marginal correlation analysis not to be relevant in the imputation model.
Cox proportional hazard models of risk of depression (MDI ≥ 21) in depression vs. placebo. Unadjusted model simple log rank test. Adjusted model adjusted for age, gender, ACS diagnosis, Diabetes, Hypertension, and smoking status.

## 5. Conclusion

The current trial showed no prophylactic antidepressant effect of 25 mg melatonin compared with placebo in a selected group of patients with ACS.

**Registration** The trial was registered at clinicaltrial.gov under *NCT02451293* identifier prior to inclusion of any patients.

**Protocol** A protocol has been published and is available at - https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-017-1806-x.

## Contributions by authors

MTM: Designed the protocol, conducted the study as sponsor/investigator, collected data, analyzed and interpreted all the data. Prepared the first draft of the manuscript, revised and coordinated revision of the manuscript, and approved the final manuscript.

JAZ: Collected the data, interpreted the data, revised the manuscript, and approved the final manuscript.

CHH: Collected the data, interpreted the data, revised the manuscript, and approved the final manuscript.

OGC: Collected the data, interpreted the data, revised the manuscript, and approved the final manuscript.

JRH: Collected the data, revised the manuscript, and approved the final manuscript.

AI: Collected the data, revised the manuscript, and approved the final manuscript.

UOA: Designed the study, revised the manuscript, and approved the final manuscript.

LJA: Designed the study, revised the manuscript, and approved the final manuscript.

MT: Designed the study, revised the manuscript, and approved the final manuscript.

ES: Designed the study, revised the manuscript, and approved the final manuscript.

IG: Planned the study, designed the study, initiated the study, interpreted the data, revised the manuscript, and approved the final manuscript.

## Ethics approval and consent to participate

The trial was approved by the Ethics Committee of Region Zealand, the Danish Health and Medicines Authority, and the Danish Data Protection Agency before commencement of the trial. All participants gave informed consent based on both oral and written information provided to the patient by study investigators.

## Consent to publish

All participants within the trial have given consent to publish the results of the trial. As stated in the following section, no individual level data are publicly available.

## Availability of data and material

Upon reasonable request to the corresponding author, aggregate data that support the findings of this study are available. The individual level data are not publicly available, as the data were collected in adherence with the legal framework governing use of confidential personally identifiable information.

## Role of the funding source

The work is funded by a Ph.D. grant from the University of Copenhagen, Faculty of Health Sciences, the Beckett-foundation, the A.P.Møller foundation for the Advancement of Medical Science, the Else and Mogens Wedell Wedellborgs Foundation, Direktør Kurt Bønnelycke foundation, Grosserer L.F. Foght foundation, Direktør Jacob Madsen og Hustru Olga Madsens foundation, Henry and Astrid Møllers foundation, Lægeforeningens foundation, Axel Muusfeldt foundation and Region Zealand Research Foundation.None of the above mention funding bodies had any influence in the design of the study and collection, analysis, and interpretation of data or in writing the manuscript should be declared.

## Declaration of competing interest

None.

## Acknowledgements

The authors would like to thank Gunnar Hellmund Laier, biostatistician from Region Zealand who helped develop the statistical analysis plan and aided the corresponding in the data analysis. M.D. Ragnar Klein Olsen should be acknowledged for assistance with the Hamilton assessment during the trial. Furthermore, our thanks goes to PharmaNord Aps (Vejle, Denmark) for their role in the study. PharmaNord produced, packaged and shipped the study medication to the Pharmacy of Region Zealand, who handled the further process. PharmaNord had no influence on study design, conduct, data collection or analysis, results reporting, and/or publication of results of the trial. Many thanks are warranted to the participants of the trial and to the departments of cardiology at Koege, Roskilde, Holbaek, Slagelse/Naestved, and Hvidovre Hospitals.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.09.014.

## References

Andersen, L.P., Gogenur, I., Rosenberg, J., Reiter, R.J., 2016a. The safety of melatonin in humans. Clin. Drug Investig. 36, 169–175. https://doi.org/10.1007/s40261-015-0368-5.

Andersen, L.P.H., Gögenur, I., Rosenberg, J., Reiter, R.J., 2016b. The safety of melatonin in humans. Clin. Drug Investig. 36, 169–175. https://doi.org/10.1007/s40261-015-0368-5.

Arroll, B., Elley, C.R., Fishman, T., Goodyear-Smith, F.A., Kenealy, T., Blashki, G., Kerse, N., MacGillivray, S., 2009. Antidepressants versus placebo for depression in primary care. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD007954.

Bjelland, I., Dahl, A.A., Haug, T.T., Neckelmann, D., 2002. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. J. Psychosom. Res. 52, 69–77.

Cardinali, D.P., Srinivasan, V., Brzezinski, A., Brown, G.M., 2012. Melatonin and its analogs in insomnia and depression. J. Pineal Res. 52, 365–375. https://doi.org/10.1111/j.1600-079X.2011.00962.x.

Castro, V.M., Clements, C.C., Murphy, S.N., Gainer, V.S., Fava, M., Weilburg, J.B., Erb, J.L., Churchill, S.E., Kohane, I.S., Iosifescu, D.V., Smoller, J.W., Perlis, R.H., 2013. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ 346, f288.

Christiansen, O.G., Madsen, M.T., Simonsen, E., Gögenur, I., 2017. Prophylactic antidepressant treatment following acute coronary syndrome: a systematic review of randomized controlled trials. J. Psychiatr. Res. 94, 186–193. https://doi.org/10.1016/j.jpsychires.2017.07.016.

Claustrat, B., Brun, J., Chazot, G., 2005. The basic physiology and pathophysiology of melatonin. Sleep Med. Rev. 9, 11–24. https://doi.org/10.1016/j.smrv.2004.08.001.

Cooke, M.J., Waring, W.S., 2013. Citalopram and cardiac toxicity. Eur. J. Clin. Pharmacol. 69, 755–760. https://doi.org/10.1007/s00228-012-1408-1.

Cooper, C.L., Hind, D., Duncan, R., Walters, S., Lartey, A., Lee, E., Bradburn, M., 2015. A rapid review indicated higher recruitment rates in treatment trials than in prevention trials. J. Clin. Epidemiol. 68, 347–354. https://doi.org/10.1016/j.jclinepi.2014.10.007.

Dowlati, Y., Herrmann, N., Swardfager, W.L., Reim, E.K., Lanctôt, K.L., 2010. Efficacy and tolerability of antidepressants for treatment of depression in coronary artery disease: a meta-analysis. Can. J. Psychiatry Rev. Can. Psychiatr. 55, 91–99. https://doi.org/10.1177/070674371005500205.

Glassman, A.H., O'Connor, C.M., Califf, R.M., Swedberg, K., Schwartz, P., Bigger, J.T., Krishnan, K.R.R., van Zyl, L.T., Swenson, J.R., Finkel, M.S., Landau, C., Shapiro, P.A., Pepine, C.J., Mardekian, J., Harrison, W.M., Barton, D., Mclvor, M., Sertraline Antidepressant Heart Attack Randomized Trial (SADHEART) Group, 2002. Sertraline treatment of major depression in patients with acute MI or unstable angina. J. Am.

Med. Assoc. 288, 701–709.
Goto, T., Maekawa, K., 2014. Cerebral dysfunction after coronary artery bypass surgery. J. Anesth. 28, 242–248. https://doi.org/10.1007/s00540-013-1699-0.
Grace, S.L., Abbey, S.E., Irvine, J., Shnek, Z.M., Stewart, D.E., 2004. Prospective examination of anxiety persistence and its relationship to cardiac symptoms and recurrent cardiac events. Psychother. Psychosom. 73, 344–352. https://doi.org/10.1159/000080387.
Gu, G., Zhou, Y., Zhang, Y., Cui, W., 2016. Increased prevalence of anxiety and depression symptoms in patients with coronary artery disease before and after percutaneous coronary intervention treatment. BMC Psychiatry 16. https://doi.org/10.1186/s12888-016-0972-9.
Hanash, J.A., Hansen, B.H., Hansen, J.F., Nielsen, O.W., Rasmussen, A., Birket-Smith, M., 2012. Cardiovascular safety of one-year escitalopram therapy in clinically non-depressed patients with acute coronary syndrome: results from the DEpression in patients with Coronary ARtery Disease (DECARD) trial. J. Cardiovasc. Pharmacol. 60, 397–405. https://doi.org/10.1097/FJC.0b013e3182677041.
Hansen, B.H., Hanash, J.A., Rasmussen, A., Hansen, J.F., Andersen, N.L., Nielsen, O.W., Birket-Smith, M., 2012. Effects of escitalopram in prevention of depression in patients with acute coronary syndrome (DECARD). J. Psychosom. Res. 72, 11–16. https://doi.org/10.1016/j.jpsychores.2011.07.001.
Hansen, B.H., Hanash, J.A., Rasmussen, A., Hansen, J.F., Birket-Smith, M., 2011. Comparison of participants and non-participants in a randomized study of prevention of depression in patients with acute coronary syndrome. Nord. J. Psychiatry 65, 22–25. https://doi.org/10.3109/08039488.2010.485326.
Hansen, M.V., Andersen, L.T., Madsen, M.T., Hageman, I., Rasmussen, L.S., Bokmand, S., Rosenberg, J., Gogenur, I., 2014. Effect of melatonin on depressive symptoms and anxiety in patients undergoing breast cancer surgery: a randomized, double-blind, placebo-controlled trial. Breast Canc. Res. Treat. 145, 683–695. https://doi.org/10.1007/s10549-014-2962-2.
Hansen, M.V., Halladin, N.L., Rosenberg, J., Gogenur, I., Moller, A.M., 2015. Melatonin for pre- and postoperative anxiety in adults. Cochrane Database Syst. Rev. 4, CD009861. https://doi.org/10.1002/14651858.CD009861.pub2.
Hanssen, T.A., Nordrehaug, J.E., Eide, G.E., Bjelland, I., Rokne, B., 2009. Anxiety and depression after acute myocardial infarction: an 18-month follow-up study with repeated measures and comparison with a reference population. Eur. J. Cardiovasc. Prev. Rehabil. 16, 651–659. https://doi.org/10.1097/HJR.0b013e32832e4206.
Herxheimer, A., Petrie, K.J., 2002. Melatonin for the prevention and treatment of jet lag. In: The Cochrane Collaboration (Ed.), Cochrane Database of Systematic Reviews. John Wiley & Sons, Ltd, Chichester, UK. https://doi.org/10.1002/14651858.CD001520.
Hróbjartsson, A., Gøtzsche, P.C., 2010. Placebo interventions for all clinical conditions. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD003974.pub3.
Indja, B., Seco, M., Seamark, R., Kaplan, J., Bannon, P.G., Grieve, S.M., Vallely, M.P., 2017. Neurocognitive and psychiatric issues post cardiac surgery. Heart Lung Circ. 26, 779–785. https://doi.org/10.1016/j.hlc.2016.12.010.
Jakobsen, J.C., Katakam, K.K., Schou, A., Hellmuth, S.G., Stallknecht, S.E., Leth-Møller, K., Iversen, M., Banke, M.B., Petersen, I.J., Klingenberg, S.L., Krogh, J., Ebert, S.E., Timm, A., Lindschou, J., Gluud, C., 2017. Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis. BMC Psychiatry 17, 58. https://doi.org/10.1186/s12888-016-1173-2.
Joergensen, T.S.H., Maartensson, S., Ibfelt, E.H., Joergensen, M.B., Wium-Andersen, I.K., Wium-Andersen, M.K., Prescott, E., Andersen, P.K., Osler, M., 2016. Depression following acute coronary syndrome: a Danish nationwide study of potential risk factors. Soc. Psychiatry Psychiatr. Epidemiol. 51, 1509–1523. https://doi.org/10.1007/s00127-016-1275-7.
Kassambara, A., 2017. Survminer.
Kilburn, L.S., Aresu, M., Banerji, J., Barrett-Lee, P., Ellis, P., Bliss, J.M., 2017. Can routine data be used to support cancer clinical trials? A historical baseline on which to build: retrospective linkage of data from the TACT (CRUK 01/001) breast cancer trial and the National Cancer Data Repository. Trials 18. https://doi.org/10.1186/s13063-017-2308-6.
Kim, J.-M., Bae, K.-Y., Stewart, R., Jung, B.-O., Kang, H.-J., Kim, S.-W., Shin, I.-S., Hong, Y.J., Kim, J.H., Shin, H.-Y., Kang, G., Ahn, Y., Kim, J.-K., Jeong, M.H., Yoon, J.-S., 2015. Escitalopram treatment for depressive disorder following acute coronary syndrome: a 24-week double-blind, placebo-controlled trial. J. Clin. Psychiatry 62–68. https://doi.org/10.4088/JCP.14m09281.
Lam, R.W., 2006. Sleep disturbances and depression: a challenge for antidepressants. Int. Clin. Psychopharmacol. 21, S25–S29. https://doi.org/10.1097/01.yic.0000195658.91524.61.
Lane, D., Carroll, D., Ring, C., Beevers, D.G., Lip, G.Y.H., 2002. The prevalence and persistence of depression and anxiety following myocardial infarction. Br. J. Health Psychol. 7, 11–21. https://doi.org/10.1348/135910702169321.
Lespérance, F., Frasure-Smith, N., Koszycki, D., Laliberté, M.-A., van Zyl, L.T., Baker, B., Swenson, J.R., Ghatavi, K., Abramson, B.L., Dorian, P., Guertin, M.-C., CREATE Investigators, for the, 2007. Effects of citalopram and interpersonal psychotherapy on depression in patients with coronary artery disease: the Canadian cardiac randomized evaluation of antidepressant and psychotherapy efficacy (CREATE) trial. J. Am. Med. Assoc. 297, 367. https://doi.org/10.1001/jama.297.4.367.
Lingjaerde, O., Ahlfors, U.G., Bech, P., Dencker, S.J., Elgen, K., 1987. The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr. Scand. Suppl. 334, 1–100.
Madsen, M.T., Isbrand, A., Andersen, U.O., Andersen, L.J., Taskiran, M., Simonsen, E., Gögenur, I., 2017. The effect of MElatonin on Depressive symptoms, Anxiety, CIrcadian and Sleep disturbances in patients after acute coronary syndrome (MEDACIS): study protocol for a randomized controlled trial. Trials 18, 81. https://doi.org/10.1186/s13063-017-1806-x.
Martin, C.R., Lewin, R.J., Thompson, D.R., 2003. A confirmatory factor analysis of the Hospital Anxiety and Depression Scale in coronary care patients following acute myocardial infarction. Psychiatry Res. 120, 85–94.
Mayou, R.A., Gill, D., Thompson, D.R., Day, A., Hicks, N., Volmink, J., Neil, A., 2000. Depression and anxiety as predictors of outcome after myocardial infarction. Psychosom. Med. 62, 212–219.
Olsen, L.R., Jensen, D.V., Noerholm, V., Martiny, K., Bech, P., 2003. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. Psychol. Med. 33, 351–356.
Olsen, L.R., Mortensen, E.L., Bech, P., 2004. Prevalence of major depression and stress indicators in the Danish general population. Acta Psychiatr. Scand. 109, 96–103.
Osler, M., Martensson, S., Wium-Andersen, I.K., Prescott, E., Andersen, P.K., Jorgensen, T.S., Carlsen, K., Wium-Andersen, M.K., Jorgensen, M.B., 2016. Depression after first hospital admission for acute coronary syndrome: a study of time of onset and impact on survival. Am. J. Epidemiol. 183, 218–226. https://doi.org/10.1093/aje/kwv227.
Parashar, S., 2006. Time course of depression and outcome of myocardial infarction. Arch. Intern. Med. 166, 2035. https://doi.org/10.1001/archinte.166.18.2035.
Post, R.M., 2007. Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. Neurosci. Biobehav. Rev. 31, 858–873. https://doi.org/10.1016/j.neubiorev.2007.04.003.
Pourafkari, L., 2015. The psychological effects of cardiac rehabilitation after coronary revascularization. Turk Kardiyol. Dernegi Arsivi-Arch. Turk. Soc. Cardiol. https://doi.org/10.5543/tkda.2015.56846.
R Core Team, 2017. R: A Language and Environment for Statistical Computing. Foundation for Statistical computing, Vienna, Austria.
Roose, S.P., Laghrissi-Thode, F., Kennedy, J.S., Nelson, J.C., Bigger, J.T., Pollock, B.G., Gaffney, A., Narayan, M., Finkel, M.S., McCafferty, J., Gergel, I., 1998. Comparison of paroxetine and nortriptyline in depressed patients with ischemic heart disease. J. Am. Med. Assoc. 279, 287–291.
Sorensen, C., Brandes, A., Hendricks, O., Thrane, J., Friis-Hasche, E., Haghfelt, T., Bech, P., 2005. Psychosocial predictors of depression in patients with acute coronary syndrome. Acta Psychiatr. Scand. 111, 116–124. https://doi.org/10.1111/j.1600-0447.2004.00430.x.
Strik, J.J., Honig, A., Lousberg, R., Lousberg, A.H., Cheriex, E.C., Tuynman-Qua, H.G., Kuijpers, P.M., Wellens, H.J., Van Praag, H.M., 2000. Efficacy and safety of fluoxetine in the treatment of patients with major depression after first myocardial infarction: findings from a double-blind, placebo-controlled trial. Psychosom. Med. 62, 783–789.
Thombs, B.D., Bass, E.B., Ford, D.E., Stewart, K.J., Tsilidis, K.K., Patel, U., Fauerbach, J.A., Bush, D.E., Ziegelstein, R.C., 2006. Prevalence of depression in survivors of acute myocardial infarction. J. Gen. Intern. Med. 21, 30–38. https://doi.org/10.1111/j.1525-1497.2005.00269.x.
Thombs, B.D., Ziegelstein, R.C., 2012. When prevention is a bad idea: problems with the DECARD trial and the premise behind it. J. Psychosom. Res. 72, 333–335. https://doi.org/10.1016/j.jpsychores.2012.02.005.
Vakkuri, O., Leppäluoto, J., Kauppila, A., 1985. Oral administration and distribution of melatonin in human serum, saliva and urine. Life Sci. 37, 489–495.
Walters, S.J., Bonacho dos Anjos Henriques-Cadby, I., Bortolami, O., Flight, L., Hind, D., Jacques, R.M., Knox, C., Nadin, B., Rothwell, J., Surtees, M., Julious, S.A., 2017. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open 7 e015276. https://doi.org/10.1136/bmjopen-2016-015276.
Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psychiatr. Scand. 67, 361–370.