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THE EFFECT OF METOPROLOL AND ASPIRIN ON CARDIOVASCULAR RISK IN BEREAVEMENT: A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

BACKGROUND: Bereavement is associated with an increased risk of cardiovascular disease; however, no reports exist of interventions to reduce risk. In a randomised, double-blind, placebo-controlled trial of 85 recently bereaved participants, we determined whether beta-blocker (metoprolol 25mg) and aspirin (100mg) reduce cardiovascular risk markers and anxiety, without adversely affecting bereavement intensity.

METHODS: Participants were spouses (n=73) or parents (n=12) of deceased from 5 hospitals in Sydney, Australia, 55 females, 30 males, aged 66.1±9.4 years. After assessment within 2 weeks of bereavement, subjects were randomised to 6 weeks of daily treatment or placebo, and the effect evaluated using ANCOVA, adjusted for baseline values (primary analysis).

RESULTS: Participants on metoprolol and aspirin had lower levels of home systolic pressure (P=0.03), 24-hour average heart rate (P<0.001) and anxiety (P=0.01) platelet response to arachidonic acid (P<0.001) and depression symptoms (p=0.046) than placebo with no difference in Standard Deviation of NN intervals index (SDNNi), von Willebrand Factor antigen, platelet-granulocyte aggregates or bereavement intensity. No significant adverse safety impact was observed.

CONCLUSIONS: In early bereavement, low dose metoprolol and aspirin for 6 weeks reduces physiological and psychological surrogate measures of cardiovascular risk. Although further research is needed, results suggest a potential preventive benefit of this approach during heightened cardiovascular risk associated with early bereavement.

KEY WORDS: Prevention, Cardiovascular Diseases, Bereavement, Psychological

INTRODUCTION

The importance of psychosocial factors in cardiovascular disease is increasingly recognised. [1-4] Bereavement due to the death of a loved one is one of the most stressful experiences to which almost every human is exposed, and is associated with symptoms of depression, anxiety, anger and grief [5,6] that often persist for weeks and months and for some may become prolonged.[7,8] While most people adjust to the loss, there is a heightened risk of mortality up to 6 months with cardiovascular disease accounting for up to half of the excess deaths during spousal bereavement. [6,9] In the Determinants of Myocardial Infarction Onset Study, the relative risk of non-fatal infarction peaked in the first day following bereavement and remained 4-fold increased between 7 days to one month following bereavement. [10]

The mechanism of the increased cardiovascular risk in bereavement has not been well studied, however potential contributors include increased systolic blood pressure and heart rate, reduced heart rate variability, prothrombotic and immune changes, and anxiety, depression and anger. [6,11-15]

Considering the large numbers of bereaved individuals at increased risk for cardiovascular disease, it is important to identify strategies that reduce risk without having a deleterious impact on the bereavement process.

Prior studies suggest that beta adrenergic blocking drugs and/or aspirin modify pathways activated in bereavement.[16-20] In this trial, we therefore tested the hypothesis that the combination of low dose metoprolol and aspirin would reduce cardiovascular risk markers, including symptoms of anxiety, without an adverse impact on bereavement intensity.

METHODS

The present study was a prospective, double-blind, placebo-controlled trial. The protocol was approved by the Institutional Review Board of Northern Sydney Health Ethics

Committee, Australia, and all participants signed informed consent. An independent data and safety monitoring committee reviewed safety and efficacy data. Trial registration was with the Australia and New Zealand Clinical Trials Registry, Registration Number ACTRN12618001387213, Registry URL ttp://www.anzctr.org.au/BasicSearch.aspx. Funding support was provided by a grant from Heart Research Australia. The authors are solely responsible for the design and conduct of this study, all study analyses, and drafting and editing of the paper.

Participants

We recruited spouses, partners or parents of patients who died in hospital wards, intensive care units and emergency departments of 5 participating hospitals in Northern Sydney, Australia. Exclusions were any severe illness, current use of beta blockers, other heart rate lowering drugs, aspirin or other antiplatelet or antithrombotic medication, or having a contra-indication to their use, heart rate <60 bpm, systolic blood pressure <120 mmHg at screening or first assessment, nursing home resident, or cannot speak or read English. Participants lived within 60 minutes driving time from the Core Hematology Laboratory to allow standardisation of blood collection and transport to the laboratory. Assessments were conducted in participants' homes between 8am and noon. Withdrawal was allowed at any time at subject request, or investigator discretion if participation was considered to be causing undue psychological distress or adverse physiological change.

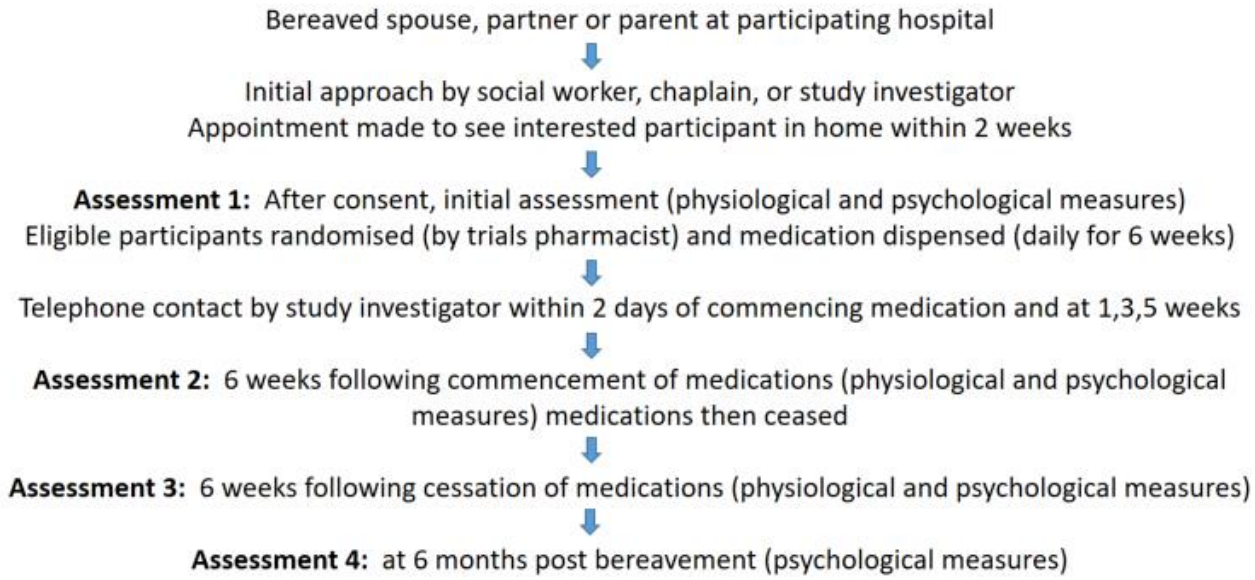
Study Design (see figure 1)

At enrolment, data were obtained on sociodemographic and clinical history, cardiovascular risk factors, body mass index, prior illness, medications, smoking, alcohol use, social support[21] and the specifics of the bereavement. After satisfactory review of the enrolment assessment (Assessment 1) by investigators, subjects were randomised to active therapy or placebo using a randomization code.

Intervention

The active therapy was metoprolol tartrate (25mg mane Metohexal) and low dose immediate release aspirin (100mg mane DBR). Blinding was assured by the provision of placebos identical to the active treatment.

Figure 1: Study Design



Assessment 2 was after 6 weeks on study treatment, following which the medication was ceased. Assessment 3 was 6 weeks following assessment 2 (and cessation of medication). At 6 months, a questionnaire was mailed, and if needed, followed up by telephone or visit.

Questionnaires and Surrogate Measures of Cardiovascular Risk

At each assessment, including at 6 months, questionnaires were administered for symptoms of anxiety and anger (Spielberg State−trait Anxiety and Anger questionnaires),[22,23] depression (Centre for Epidemiological Studies-Depression (CES-D) Scale), [24] and bereavement intensity (Core Bereavement Items Questionnaire, CBI-17).[25] Internal consistency reliability (Cronbach's alpha) of the questionnaires were as follows: State

Anxiety (0.90,0.92, 0.93), State Anger (0.88, 0.93, 0.90), CES-D (0.76, 0.91, 0.89) and CBI-17 (0.95, 0.95, 0.95). For blood pressure recordings, we used a UA 787 Digital monitor (Grade A/A). The study investigator obtained blood pressure measurements for eligibility (mean of 3 measurements). Then the participant was instructed by the investigator in obtaining duplicate measurements at 3 time points (morning, afternoon and evening) over a 24-hour period during each assessment. Adequate subject technique was verified by the investigator. For 24-hour ECG Holter monitor, we used the Medtel Digital System, and the Medilog Optima system (Oxford Instruments Medical Systems Division) for analysis. Average, minimum and maximum heart rate was obtained. Autonomic data were obtained on the 24-hour Holter tracings, for standard deviation of the NN intervals index (SDNNi) and the square root of the mean squared differences of successive intervals. (rMSSD).[12]

For blood sampling, a 21-gauge butterfly needle with a Vacutainer system was used. Blood analyses were performed in Core Hematology and pathology laboratories at Royal North Shore Hospital. Platelet-granulocyte aggregates were measured using flow cytometry,[26] von Willebrand Factor antigen using immunoturbidimetric method,[13] and Multiplate ASPI test with Arachidonic Acid Stimulation 0.5mM.[27]

Statistical Analysis: Differences between treatment groups in sociodemographic data were analysed using Student's t-test for interval data and Chi Square test of Independence for categorical data using intention-to-treat analysis. The primary physiological outcome variables were haemodynamic: home systolic blood pressure (mean of morning, afternoon and evening levels) and 24-hour average heart rate; heart rate variability: SDNNi; and thrombotic: von Willebrand factor antigen and platelet-granulocyte aggregates. Secondary physiological outcomes were morning, afternoon and evening systolic and diastolic pressures considered separately, minimum and maximum heart rates, rMSSD and platelet response to arachidonic acid (Multiplate ASPI test). The primary psychological outcomes were

symptoms of anxiety and bereavement intensity, and secondary psychological outcomes were symptoms of depression and anger. The primary analysis of the primary and secondary outcomes compared the effect of 6 weeks of daily therapy or placebo, using analysis of covariance (ANCOVA) on the post-treatment scores (assessment 2), with pre-treatment score as a covariate and treatment as an independent variable. Secondary analyses of the primary and secondary outcomes compared active and placebo scores at baseline and at 6 weeks following cessation of therapy (assessment 3), and psychological outcomes at 6 months. We calculated that a total sample size of 80 participants (40 completed participants per group) would provide >80% power to identify a between-group difference in systolic pressure of 8mm Hg and heart rate of 5bpm. SPSS Version 24, (IBM Corporation Armonk, NYI, USA) was used for all analyses, with two-sided alpha set to $P<0.05$. There was no adjustment for multiple testing as all outcomes were pre-specified. Because the baseline data showed a statistically significant difference in sex distribution, a post hoc analysis was conducted using analysis of covariance (ANCOVA) on the post-treatment scores, with pre-treatment scores as covariate, and sex and treatment as independent variables. Subjects were analysed based on intention to treat. Data from participants who did not complete the 6-week assessment, were not included in the primary analysis.

RESULTS

Study Population

Between 2011-2015, we screened 5183 hospital deaths (figure 1). The main study exclusion was the absence of a spouse or partner. Of the 598 patients who were eligible by screening, 485 declined to participate, and 28 were excluded due to a low resting heart rate or blood pressure, resulting in 85 subjects who were randomised to active or placebo treatment.

The participants comprised spouses (n=73) or parents (n=12) of deceased from 5 hospitals in Northern Sydney, Australia. Participants were aged 66.1± 9.4 years (SD) (range 36-85 years), and comprised 55 females and 30 males. The average duration from bereavement to enrolment did not differ between groups, 12.7 (SD 3.2) in the treatment group and 11.86 (3.2) in controls, p=0.20. There was no difference between groups in the duration of the intervention (mean ± SD 42.3 ±7.8 vs 43,2 ±4.35 days or in the number of medications taken from post intervention pill count (0=0.47). The earliest enrolment was at day 5, with the Holter monitor being placed prior to the funeral service. The groups were well matched for risk factors other than more women in the active treatment group. There was no significant difference between women and men in baseline measures of anxiety (48.0±11.4 versus 56.0 ±10.9) or depression (27.5 ±11.3 versus 33.7 ±10.0).

There was also no difference in proportion of spouses and parents within the two groups (intervention group: spouses n=37, parents n=5 versus control group: spouses n=34, parents n=9. Although the number of bereaved parents was small, there were no significant differences between parents and spouses in baseline measures of anxiety (53.6 ± 14.6 versus 49.4 ±11.4) or depression (30.8 ± 11.5 versus 28.7 ±11.3).

There were no significant differences between the active versus placebo groups in whether the death occurred suddenly (73.8 vs 88.4%), how prepared they felt for the death (possible score 1-7) (3.3±2.0 vs 2.7±1.8) or whether the participant was the primary carer (78.6 vs 81.4%). Adherence, which was verified by the counting of medication returned at the conclusion of the study period, showed no significant difference between the treatment and control groups.

Figure 2 Screening, recruitment and flow of participants throughout study

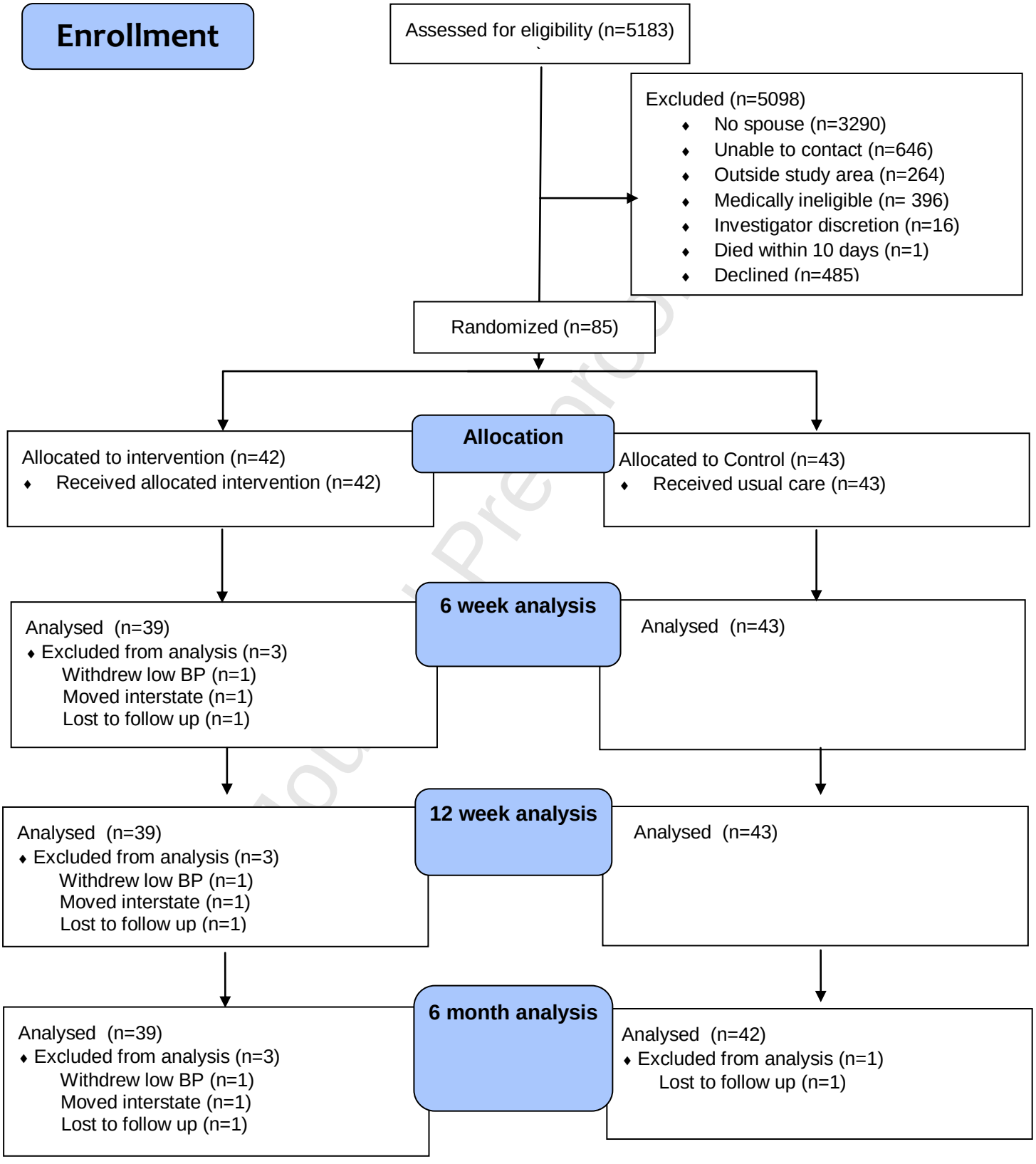


Table 1 Characteristics of study participants at baseline assessment

	Intervention group N=42	Placebo group N=43
Characteristic		
Age, mean (SD)	65.3 ±8.8	67.0 ±10.0
Females, n (%)	32 (76%)	23 (53%)*
BMI (kg/m2) mean (±SD)	27.0 ±6.7	27.0 ±6.0
Waist circumference cm mean (±SD)	92.8 ±15.3	95.4 ±13.9
History of Hypertension	20 (48%)	18 (42%)
History of Diabetes	4 (9%)	6 (14%)
History of High Cholesterol	12 (29%)	12 (28%)
Family history heart disease	11 (26%)	11 (25%)
History of acute myocardial infarction	0	0
History of anxiety disorder	4 (9%)	5 (11%)
History of depression	5 (12%)	8 (19%)
Social support+ – availability mean (±SD)	5.2 (2.4)	4.7 (2.2)
Social support+ – satisfaction mean (±SD)	5.5 (0.7)	5.3 (0.9)
Days from death to enrolment mean (±SD)	12.7 ±3.2	11.9 ±3.2
Standard drinks past week mean (±SD)	8.2 ±7.3	10.2 ±8.0
Reported sleep duration per night past week mean (±SD) hours	5.8 ±1.3	5.9 ±1.2

*p=0.02, +Social Support Scale (SSQ-6)

Outcomes: Mean levels and between-group ANCOVA results adjusted for baseline values for the physiological and psychological variables are shown in Tables 2 and 3.

After 6 weeks on treatment

Blood pressure: The intervention group had lower levels of the primary outcome of mean home systolic blood pressure (P=0.03) and morning systolic pressure (P=0.04) adjusted for baseline. There were no differences for afternoon or evening systolic or diastolic pressures.

Heart Rate: The intervention group had lower levels of the primary outcome of average 24-hour heart rate (P<0.001), as well as minimum (P=0.002) and maximum heart rate (P=0.002).

Autonomic Function: There were no statistically significant between-group differences for SDNNi (P=0.44) or rMSSD (P=0.60).

Thrombotic: There were no significant differences for the primary thrombotic outcomes of platelet-granulocyte aggregates (P=0.44) or von Willebrand Factor (P=0.63). The platelet response to Arachidonic Acid was reduced in the active treatment group (P<0.001).

Psychological Outcomes: The intervention group had lower levels of anxiety (P=0.01) and depression symptoms (P=0.046), adjusted for baseline (Table 3) whereas there were no between-group differences in bereavement intensity (P=0.52) or anger (P=0.98).

Off Treatment: After 6 weeks off treatment, the morning systolic pressure and anxiety levels remained lower in the treatment group compared to placebo, adjusted for baseline, although there were no other persisting between-group differences (Table 2). At 6 months, the anxiety level remained lower in the treatment group, with no other between-group differences in psychosocial outcomes (Table 3).

Table 2: Physiological outcomes at baseline (prior to randomisation), on treatment and 6 weeks off treatment

	Intervention group			Control group		
	Baseline	6-weeks on treatment	12-weeks off treatment	Baseline	6-weeks on placebo	12-weeks off placebo
Primary Outcomes						
Systolic BP home+ (mmHg)	135.8 ±1.9	129.0 ±2.1*	129.95 ±1.7	136.0 ±2.3	135.4 ±2.1	134.5 ±1.7
Heart rate average 24 hours (bpm)	75.4 ±1.0	67.1 ±0.8***	75.4 ±0.9	73.1 ±1.0	73.6 ±0.8	74.1 ±0.9
SDNNi 24 hours (ms)	38.9 ±2.0	45.5 ±2.5	38.4 ±2.9	41.7 ±3.0	44.3 ±2.4	46.8 ±2.7
Platelet granulocyte aggregates (x 10^6/ l)	484.4 ±58.0	378.5 ±38.9	384.6 ±37.6	410.0 ±31.0	420.0 ±37.0	403.9 ±35.2
Von Willebrand Factor (%)	130.9 ±7.5	129.2 ±3.0	129.4 ±3.5	135.7 ±6.5	131.3 ±2.8	131.8 ±3.3
Secondary Outcomes						
Systolic BP morning (mmHg)	137.2 ±2.2	132.1 ±2.6*	132.2 ±2.1*	136.5 ±2.1	139.5 ±2.4	141.6 ±2.0
Systolic BP afternoon (mmHg)	138.0 ±2.6	130.0 ±2.6	134.6 ±2.3	140.7 ±2.8	135.2 ±2.4	136.2 ±2.1
Systolic BP evening (mmHg)	131.9 ±2.3	129.2 ±2.6	131.4 ±2.3	134.8 ±2.9	131.8 ±2.6	136.4 ±2.3
Diastolic BP home+ (mmHg)	86.1 ±1.3	81.6 ±1.0	81.5±0.9	83.3 ±1.2	83.2 ±1.1	82.1 ±0.9
Heart rate – minimum (bpm)	54.4 ± 0.9	50.0 ±0.7**	53.0 ±0.8	52.4 ±0.9	53.23 ±0.7	53.2 ±0.7
Heart rate – maximum (bpm)	123.2 ±2.0	110.4 ±1.8**	119.5 ±2.1	117.0 ±2.7	118.3 ±1.7	119.5 ±2.0
RMSSD 24 hours (ms)	42.0 ±3.8	54.1 ±5.1	42.6 ±5.1	46.1 ±5.9	51.3 ±4.9	56.4 ±4.9
Multiplate ASPI test	78.5 ±3.4	10.6 ±2.5***	73.5 ±3.7	79.1 ±2.9	77.4 ±2.4	79.6 ±3.5

All values mean ± SE. Between-group differences adjusted for baseline values at * P<0.05, ** P <0.01, *** P < 0.001. Follow-up means are estimated marginal means ± standard error (SE). Multiplate ASPI test - platelet response to arachidonic acid. +Average of morning, afternoon, evening home BP levels.

Table 3: Psychological outcomes at baseline (prior to randomisation), on treatment, 6 weeks off treatment and at 6 months

	Intervention group				Control group			
	Baseline	6 weeks on treatment	12 weeks off treatment	6-months	Baseline	6 weeks on placebo	12 weeks off treatment	6-months
State Anxiety	49.9 ±1.8	38.1 ±1.2**	37.7 ±1.4*	36.4 ±1.5*	45.5 ±1.7	42.4 ±1.2	41.1 ±1.4	40.8 ±1.5
Depression	29.1 ±1.7	16.4 ±1.4*	15.1 ±1.3	13.64 ±1.5	25.1 ±1.5	20.3 ±1.3	17.8 ±1.2	17.01 ±1.4
State Anger	20.51 ±1.0	18.5 ±0.7	17.7 ±0.5	17.1 ±0.5	19.1 ±0.8	18.5 ±0.7	18.3 ±0.5	17.5 ±0.4
Bereavement intensity	44.3 ±1.8	41.0 ±1.1	39.5 ±1.0	38.9 ±1.2	43.7 ±1.5	42.0 ±1.1	41.2 ±1.0	39.5 ±1.1

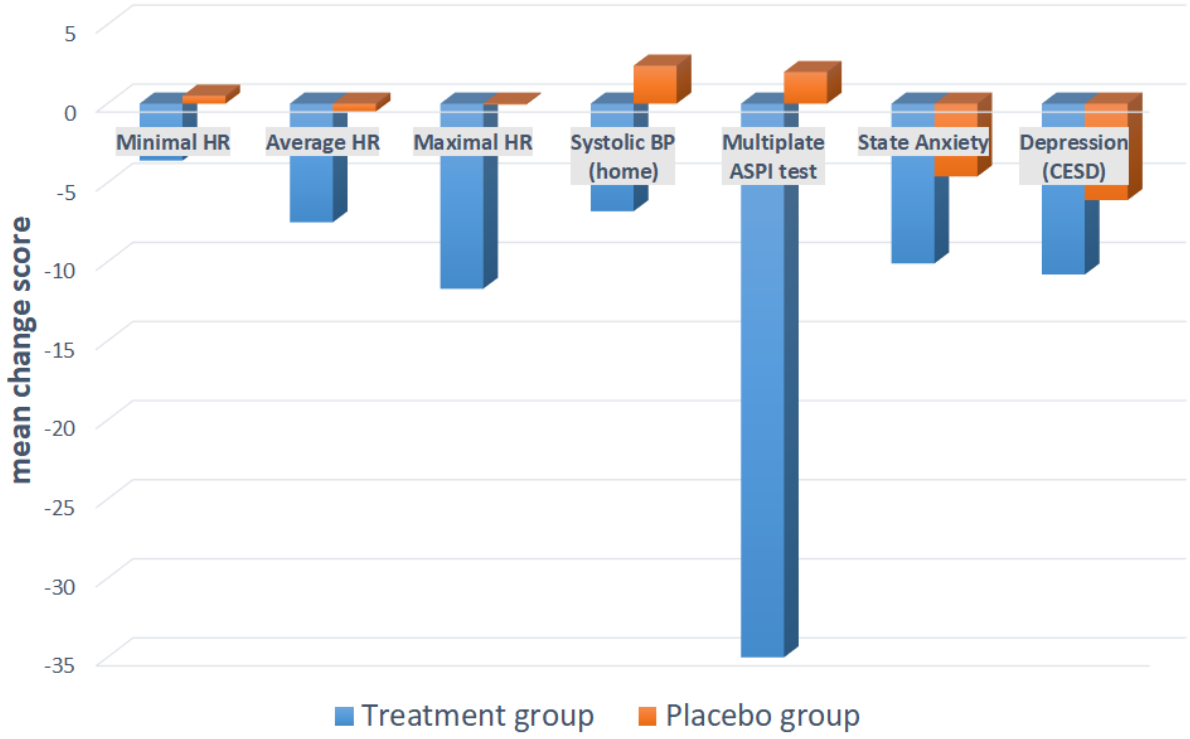
All values mean ± SE. Significant difference between groups adjusted for baseline values at * P<0.05, ** P <0.01. All follow-up means are estimated marginal means ± standard error (SE).

Post hoc analysis additionally adjusted for gender

The findings with the additional adjustment for sex were not different in interpretation from the primary analyses that did not include sex. Thus, after 6 weeks on treatment, the sex-adjusted mean home systolic blood pressure was lower with active treatment (P=0.03) as was morning systolic pressure (P=0.03), average 24-hour heart rate (P<0.001), minimum (P=0.002) and maximum heart rate (P=0.001), platelet response to Arachidonic Acid (p<0.001), and anxiety (p=0.009). The sex-adjusted depression level treatment statistical comparison p value was 0.08, (0.046 when unadjusted for sex).

Figure 3 Change Scores for Treatment (metoprolol 25mg/aspirin 100mg versus Placebo

(All between-group differences depicted are statistically significant (P<0.05) for 6 weeks versus baseline. Home BP = Average of morning, afternoon, evening home measurements)



Safety during the study

There were no major adverse events. Our predetermined protocol to deal with severe grief reactions was not needed by any participant. One subject on active treatment became dizzy and hypotensive after the first dose, and was withdrawn. On review by the data and safety monitoring committee, this participant was a protocol violation, with a pre-randomisation systolic pressure measure below entry criteria. One participant receiving placebo was hospitalised on the day after the second assessment with an episode of chest pain and hypertension (systolic pressure of 210mmHg) and suspected unstable angina. This subject (unblinded only to the chief investigator) responded well to metoprolol with a fall in pressure to 130mmHg. Two other subjects on active treatment withdrew for non-medical reasons.

There was no difference between intervention and control groups in reported health related behaviours at 6 weeks: sleep duration (mean ±SD 6.4 ±1.6 vs 6.4 ±1.3 hours, p=0.81) and alcohol consumption (mean ±SD standard drinks in the week prior 5.8 ±6.2 vs 7.9 ±8.1, p=0.19) or at 12 weeks: sleep duration (6.5 ±1.2 vs 6.5 ±1.2, p=0.90) and alcohol intake (6.8 ±6.6 vs 8.9 ±7.7, p=0.19).

DISCUSSION

In this prospective, randomised, placebo-controlled trial, low dose metoprolol (25mg morning) and aspirin (100mg) reduced home systolic blood pressure, 24-hour average heart rate, platelet response to arachidonic acid, and symptoms of anxiety and depression. Heart rate variability, platelet granulocyte aggregates and von Willebrand factor were not altered by the intervention. The six weeks of daily medication commenced an average of 12 days following bereavement of partners or children, was well tolerated with no adverse effect on bereavement intensity up to 6 months.

Low dose metoprolol and aspirin were chosen as the interventions for several reasons. Beta-adrenergic blocking drugs provide protection against emotional triggers of acute coronary syndrome [28,29] and their effect is pronounced during the morning increase in adrenergic activity and peak in CVD. [30] Beta-blockers also attenuate stress-related surges in heart rate, blood pressure and ischemia, decrease arrhythmia, improve autonomic function and may reduce coagulability.[17,31,32] Low dose metoprolol (25 mg daily) has been shown to reduce plaque progression, improves plaque stability while lowering intermediate outcomes of heart rate by 3.2 bpm and systolic blood pressure by 3.1 mmHg compared with placebo.[16] The haemodynamic effects seen with the dose of metoprolol used in the present study, are similar to differences in mean heart rate and blood pressure previously observed between bereaved and non-bereaved controls. [11] The clinical utility of low dose therapy is supported by Barron who showed that patients post MI treated with low doses of beta blockers had reduced cardiovascular mortality compared with those not receiving beta blockers.[33] There is also evidence that aspirin may reduce the relative risk of MI triggered by anger, [29,34] and modify the link between inflammation and depression. [20] Aspirin preferentially reduces morning MI concurrent with peak platelet reactivity.[30,35] Catecholamine surges associated with stressors increase platelet activation.[36] Aspirin inhibits epinephrine-induced aggregation and thromboxane production,[37] although in an animal model, an epinephrine infusion overcame the aspirin inhibition of thrombogenesis.[38] While our findings on heart rate and blood pressure support the hypothesis that the physiologic effects of low dose metoprolol and aspirin in bereavement are similar to those reported in non-bereaved populations, it was important to determine efficacy and tolerability in bereaved subjects, with their fluctuating symptoms of depression, anxiety and anger. While beta blockers do not in general have a negative impact on depression,[39-42] this has not been previously evaluated in bereavement. It is reassuring that we in fact found a reduction in anxiety and depressive symptoms. There are

conflicting data on the effect of aspirin or beta-blocker on von Willebrand factor and platelet aggregates, markers that have been shown to be elevated in bereaved individuals.[13] While we found no significant effect on these markers in the present trial, it is reassuring that aspirin had its expected significant effect on arachidonic acid-induced platelet aggregation, as assesed by the Multiplate ASPI test. A morning dose of short-acting metoprolol was used, to ensure maximal drug effect in the daytime hours where we previously found the bereaved to have a higher heart rate than bereaved. [11] An evening dose of metoprolol was not given, since we had not previously seen a higher heart rate in the bereaved at that time [11] and it enabled a low daily dose (25mg daily) to be used to minimise the potential for side effects in individuals not used to taking this medication. Our regimen was consistent with current guidelines that recommend beta blockers without stipulating dosage, and ongoing daily aspirin therapy of 75-162 mg.[43]

The reductions in systolic blood pressure and heart rate that we found, are consistent with the known effects of beta-blockers that contribute to their cardioprotective effect.[16] The greatest reduction in systolic pressure with treatment occurred in the morning, corresponding to the circadian time of greatest cardiovascular risk, [30] and greatest separation in systolic pressure between bereaved and non-bereaved in our prior study.[11] The morning systolic pressure remained lower in the active arm 6 weeks following treatment cessation, raising the possibility of a legacy effect. Because higher heart rates are associated with increased cardiovascular risk, and are present in bereaved individuals, the reduced average and maximal heart rate seen with treatment represents a potential protective effect.[44]

Although HRV is reduced in bereavement, [12,14] and some studies suggest beta blockers and to a lesser extent aspirin may increase HRV, [17,19] we found no treatment effect on autonomic endpoints.

Anxiety, depression and anger, which are commonly found in bereaved individuals, have been linked to increased cardiovascular risk. [1-6] It was therefore important to evaluate whether the medication had favourable or deleterious psychological effects. The reduced anxiety we found with the active treatment is consistent with limited studies that support beta blocker use for acute anxiety and panic attacks.[18] Of note, the reduction in anxiety persisted post-therapy to the 6-month time point. In some studies, beta blockers have resulted in reduced incidence of post-traumatic stress disorder, although data are not conclusive.[45] The reduction in depressive symptoms was reassuring for the safety of the strategy. Aspirin may possibly have improved depressive symptoms, since inflammation and depression have been linked, and some studies, although not all, suggest reduced depressive symptoms with aspirin.[20] A feasibility study in 10 bereaved individuals reported encouraging data for a benefit of aspirin on HRV, attenuated physiological reactivity to a grief-related stress task and a beneficial effect on depressive symptoms.[46] In our study, there were no treatment effect on grief intensity or symptoms of anger either on treatment or at 6 months, and no evidence of a withdrawal effect.

Several limitations of our study should be considered. We only evaluated the medication response after 6 weeks, and a different and possibly greater treatment impact may have been observed had we evaluated the participants after a shorter period, such as after 1 week, when physiological and psychological activation would be greater than at 6 weeks, or if medication had been commenced earlier that our average of day 12 post-bereavement. However, even though stress-related physiologic and psychological changes would likely be higher closer to the bereavement, our time window fitted within the logistics of a randomised study and sensitivity to the bereavement needs of the participants, and was well within the 6-month period of increased cardiovascular risk with bereavement, with similar timing to our prior

case-control study which demonstrated increases in physiological and psychosocial risk factors.[15] The sample size was small although it was based on our prior power calculations. Since both metoprolol and aspirin were used as an active strategy versus two matched placebos, we cannot separate the effects of the individual drugs, especially because beta blockers may have antithrombotic effects, and aspirin may modify HRV and depression. Further research is needed to separate out the actions of these two therapies. Other viable pathways were not assessed in this analysis including physical inactivity, poor eating habits and other maladaptive changes in health behaviour, although there was no difference in sleep duration or alcohol use. Although the average age of our participants is less than that of the overall bereaved population, the age range was broad, including a participant aged 85 years, and the increased cardiovascular risk with bereavement is seen in men and women of all ages.[6] The recruitment rate of 19% of eligible subjects raises a question regarding generalizability, however we consider this rate to be reasonable, since the trial was at the sensitive time of early bereavement, and included randomization to medication, which had not been previously evaluated in this population. Since we enrolled participants where the deaths occurred in hospital, the reactions may have been greater than when deaths occurred at home or in a nursing home. However, while the stress of hospitalisation of a relative is independently associated with increased cardiovascular events,[47] epidemiologic studies of bereavement have not been restricted to hospitalised patients.[5,6,9,10]

Implications and future studies

The finding that low dose metoprolol and aspirin has a positive impact on several surrogate cardiovascular risk markers including anxiety, and is well tolerated in early bereavement with no negative impact on bereavement intensity up to 6 months, enables clinicians to consider this treatment in their patients. While clinicians need to be wary of appearing to medicalize

an almost universal stressful experience, reducing heart attacks among bereaved people is a worthy goal. At a time when the deceased is the focus of attention, our findings remind clinicians to consider the well-being of bereaved individuals more broadly, including encouraging adequate diet and sleep, ensuring medication adherence and reminding the bereaved to seek help for symptoms that may be cardiac. A large randomised trial would be required to see differences in hard endpoints [10] and to identify which individuals would derive particular benefit. Our study was not designed to evaluate prolonged bereavement intensity, however the reduced anxiety seen at 6 months, suggests that the impact may persist beyond the period of treatment, and provides encouragement for further evaluation. While the present study focused on bereavement due to the death of partners and children, our findings are relevant to other causes of bereavement, including job loss, relationship breakdown, trauma and deaths of other loved ones, including pets. The findings also provide encouragement for the evaluation of the beta blocker/aspirin combination in acute stress situations as triggered acute risk prevention (TARP) therapy.[48] Further research is needed into timing and duration of the intervention, possibly beginning earlier in bereavement. Our encouraging findings in bereavement also suggest that this metoprolol and aspirin treatment combination could be considered in other acute stress situations.

Conclusion: In early bereavement, low dose metoprolol (25mg morning) and aspirin (100mg morning) lowered blood pressure and heart rate and platelet responsiveness, and safely reduced anxiety and depressive symptoms. There is a paucity of proven interventions preventing adverse physical health during bereavement, which is a unique life stress with a complex combination of psychological symptoms. This study, the first randomised trial to investigate cardiac risk reduction in early bereavement, suggests that low dose metoprolol and aspirin may have a positive effect on reducing cardiovascular risk.

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