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RESPOSTAS PRESSÓRICAS AO TREINAMENTO COMBINADO EM MULHERES HIPERTENSAS APÓS A MENOPAUSA SOB EFEITO DE MEDICAMENTOS BETA-BLOQUEADORES OU BLOQUEADORES DE RECEPTORES DE ANGIOTENSINA

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Igor Moraes Mariano

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Resumo

Introdução: Mulheres após a menopausa fazem parte dos grupos de risco para hipertensão e uma das formas de tratar essa condição é a prática regular de exercícios físicos. Contudo, ainda não se tem bem descrito se as drogas anti-hipertensivas influenciam a capacidade dos exercícios de auxiliar no controle da pressão arterial (PA). **Objetivo**: Verificar as diferenças das respostas pressóricas ao treinamento com exercícios combinados entre mulheres hipertensas após a menopausa sob influência de β-bloqueadores ou bloqueadores de receptores de angiotensina. **Métodos**: 21 mulheres hipertensas após a menopausa foram divididas em 2 grupos: BRA+Ex - usuárias de bloqueadores de receptores AT1 de Angiotensina II (n=11); e BB+Ex - usuárias de β-bloqueadores adrenérgicos (n=10). Antes e após 12 semanas de treinamento combinado (Exercícios aeróbios e resistidos) de intensidade moderada, foram submetidas a uma bateria de avaliações que incluíam: antropometria, medidas de repouso e ambulatoriais de PA, frequência cardíaca (FC) e duplo produto (DP), além de análise de variabilidade de PA (VPA). **Resultados**: As equações de estimação generalizadas de dois fatores (grupo * tempo) demonstraram efeitos do tempo com reduções na PA sistólica (PAS) de repouso (p=0,009; ΔBRA+Ex = -5,2±6,4; ΔBB+Ex= -1,6±6,0 mmHg), de vigília (p=0,002) e de 24h (p=0,006; 24h ΔBRA+Ex = -5,7±8,3; 24h ΔBB+Ex = -3,1±6,7 mmHg), além de quedas em DP, Desvios padrões de PAS (i.e. VPA), Cargas pressóricas de PAS e na área abaixo da curva de PAS de 24h em ambos os grupos (p=0,005). Foram encontrados efeitos de grupo com menores valores em BB+Ex em FC de repouso (p=0,009), vigília (p=0,005), sono (p=0,003) e 24h (p=0,004), além de DP de repouso (p=0,002), vigília (p=0,002), sono (p=0,001) e 24h (p=0,001). Ademais, demonstramos efeitos de interação com melhoras mais acentuadas na VPA de BB+Ex evidenciados nos desvios padrões de vigília da PAS (p=0,047; ΔBRA+Ex = -0,1±2,2; ΔBB+Ex = -2,3±2,8 mmHg) e PA diastólica (PAD) (p=0,018; ΔBRA+Ex = -0,7±1,6; ΔBB+Ex = -1,3±1,6 mmHg). **Conclusões**: As respostas pressóricas após treinamento com exercícios combinados de média intensidade foram similares entre BB+Ex e BRA+Ex. Este treinamento foi capaz de reduzir PAS e DP durante os períodos de vigília e 24h e reduzir a variabilidade de PAS em ambos os grupos, mas estas respostas de variabilidade parecem ser mais acentuadas em BB+Ex.

Palavras chave: Hipertensão. Exercício Aeróbio. Exercício Resistido. Pressão Arterial. Variabilidade De Pressão Arterial. Pressão Arterial Ambulatorial. Anti-Hipertensivos.

Abstract

Introduction: Postmenopausal women are a hypertension risk group, and one of the ways of treating this condition is the practice of regular physical exercises. However, it has not been well described whether antihypertensive drugs influence this ability of exercises to assist in blood pressure control. **Objective**: The different blood pressure responses were investigated after combined exercise training in hypertensive postmenopausal women under influence of β-blockers or angiotensin receptor blockers. **Methods**: 21 postmenopausal hypertensive patients were divided into 2 groups: ARB+Ex - angiotensin AT1 receptor blockers users (n=11); and BB+Ex - β-adrenergic blockers users (n=10). Before and after 12 weeks of combined (aerobic and resistance) moderate intensity exercise training, volunteers underwent a battery of evaluations that included: anthropometry, resting and outpatient measures of BP, heart rate (HR) and double product (DP), as well as BP variability analysis (BPV). **Results**: The generalized two-factor estimation equation test (GEE; time * group) showed time effects with reductions in systolic BP (SPB) at rest (p=0.009; ΔARB+Ex = -5.2±6.4; ΔBB+Ex= -1.6±6.0 mmHg), awake and 24h (p=0.006; 24h ΔARB+Ex = -5.7±8.3; 24h ΔBB+Ex = -3.1±6.7 mmHg), as well as falls in Double Product, SBP standard deviations (i.e. BPV), SPB pressure loads and 24h SBP area under curve in both groups (p=0.005). Group effects were observed with lower values in BB+Ex in HR at rest (p=0.009), awake (p=0.005), sleep (p=0.003) and 24h (p=0.004), as well as DP at rest (p=0.002), awake (p=0.002), sleep (p=0.001) and 24h (p=0.001). Furthermore, were found interaction effects with greater BB+Ex improvements in BPV in awake SBP standard variation (p=0.047; ΔARB+Ex = -0.1±2.2; ΔBB+Ex = -2.3±2.8 mmHg) and awake Diastolic BP (DBP) standard variation (p=0.018; ΔARB+Ex = -0.7±1.6; ΔBB+Ex = -1.3±1.6 mmHg). **Conclusions**: Resting and ambulatorial BP responses after moderate intensity combined exercise training are similar between BB+Ex and ARB+Ex. This training can reduce SBP and DP during awake and 24h values and reduce SBP variability in both groups, but it seems that these variability responses are greater in BB+Ex.

Key Words: Hypertension. Aerobic Exercise. Resistance Exercise. Climacteric. Blood Pressure Variability. Ambulatory Blood Pressure. Antihypertensive.

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Lista de abreviaturas e siglas

ABPM	*Ambulatorial Blood Pressure Monitoring*
ARB	*Angiotensin II AT1 Receptor Blocker*
ARB+Ex	*ARB user and exercise training*
AUC	*Area Under the Curve*
BB	β-bloqueadores adrenérgicos ou *β-Adrenergic Blocker*
BB+Ex	*BB users and exercise training*
BP	*Blood Pressure*
BPV	*Blood Pressure Variability*
BRA	Bloqueadores de receptores AT1 de Angiotensina II
DBP	*Diastolic Blood Pressure*
DP	*Double Product*
HA	Hipertensão Arterial
HR	*Heart Rate*
HT	*Hypertension*
MAPA	Monitorização Ambulatorial de Pressão Arterial
MBP	*Mean Blood Pressure*
PA	Pressão Arterial
PAD	Pressão Arterial Diastólica
PAS	Pressão Arterial Sistólica
PP	*Pulse Pressure*
SBP	*Systolic Blood Pressure*
VPA	Variabilidade de Pressão Arterial

Sumário

1 Introdução

O climatério compreende o período de transição fisiológica da fase reprodutiva para a não reprodutiva na mulher (WARD; DENERIS, 2018). Existem alguns conceitos importantes para o entendimento desta fase, dos quais o principal marco é a menopausa, um ponto determinado retroativamente após 12 meses sem ciclo menstrual. Assim, o período sintomático anterior a este evento é chamado de pré-menopausa e o período após este evento é chamado de pós-menopausa (WARD; DENERIS, 2018). Neste sentido, a amenorreia permanente a partir da menopausa se deve a falência total da função ovariana na produção e liberação de estrogênio e da ovulação (ABBAS *et al*., 2018; WARD; DENERIS, 2018). Desta forma, o déficit hormonal desta fase pode causar aumento do peso corporal, alterações do perfil lipídico, mudança nos depósitos de gordura, aparecimento de doenças metabólicas, bem como aumento na incidência de hipertensão arterial (HA) e outras doenças cardiovasculares (ABBAS *et al*., 2018).

A HA, por sua vez, é caracterizada pelo aumento sustentado da pressão arterial (PA) acima dos níveis normais de repouso e é considerada como uma doença crônica degenerativa (MALACHIAS *et al*., 2016). Desta forma, é considerado hipertenso pela Sociedade Brasileira de Cardiologia (MALACHIAS *et al*., 2016) um indivíduo que, na ausência de terapia farmacológica, tem níveis pressóricos de repouso cronicamente maiores ou iguais a 140 mmHg para a PA sistólica (PAS) e/ou 90 mmHg para PA diastólica (PAD). Num contexto mais amplo, a diretriz Americana (WHELTON *et al*., 2017) redefiniu os valores mínimos de PA para considerar HA em 130 mmHg de PAS por 80 mmHg de PAD, dado que estes valores já aumentam o risco de complicações cardiovasculares futuras (WHELTON *et al*., 2017).

Assim, estudos envolvendo doenças cardiovasculares são de grande importância no âmbito da saúde pública, pois são as principais causas de morbidade e de mortalidade no Brasil, com impacto socioeconômico elevado nos sistemas de saúde (MALACHIAS *et al*., 2016). Além disso, a incidência de doenças cardiovasculares é elevada em mulheres após a menopausa quando comparadas aos homens de mesma faixa etária e às mulheres na pré-menopausa (DI GIOSIA *et al*., 2018; ZILBERMAN *et al*., 2015), o que torna este um grupo importante para estudarmos formas de combater este problema.

A prática de exercício físico regular por sua vez, é sugerida como uma estratégia fundamental para o controle e o tratamento da HA, por promover reajuste da PA de repouso em curto (CARVALHO *et al*., 2014; HALLIWILL *et al*., 2013) e longo prazo (CARVALHO *et al*., 2014; DE SOUSA *et al*., 2017; TIBANA *et al*., 2015), inclusive em mulheres hipertensas

após a menopausa (LIN; LEE, 2018; SON *et al*., 2017a, 2017b). Além disso, há indícios de que em pacientes hipertensos, os mecanismos de redução e regulação da PA pelos exercícios são melhores evidenciados que em normotensos (CORNELISSEN; SMART, 2013), o que pode contribuir para a prevenção de eventos cardiovasculares futuros, como infarto do miocárdio e acidente vascular encefálico (BUNDY *et al*., 2017).

Entretanto, apesar dos resultados relevantes do treinamento físico em hipertensos, não se sabe se algumas características idiossincráticas desta população interferem nestas respostas, como o tipo do medicamento anti-hipertensivo utilizado. Neste sentido, em uma robusta meta analise (NACI *et al*., 2018), que envolveu 197 estudos sobre efeitos do exercício e 194 estudos sobre efeitos dos anti-hipertensivos na PA sistólica, publicados entre 1976 e 2018, Naci e colaboradores não encontraram nenhum estudo que confrontasse as respostas da PA ao exercício e aos medicamentos, ressaltando a existência desta lacuna. Além disso, reforçam a importância da compreensão deste tema para garantir a eficiência do tratamento anti-hipertensivo. Portanto, compreender melhor os métodos de tratamento e prevenção de doenças cardiovasculares, assim como o papel do exercício físico regular no controle pressórico é de grande relevância para área da saúde pública, tanto no que se refere à melhoria na qualidade de vida, quanto aos gastos com medicamentos e do sistema de atendimento à saúde para essa população. Além disso, compreender as interações entre os tratamentos farmacológicos e não farmacológicos pode influenciar nas escolhas de combinações entre estes e garantir a efetividade deste tratamento de forma individualizada.

2 Fundamentação Teórica

A HA atinge 32,5% dos indivíduos adultos e contribui para cerca de 50% das mortes por doenças cardiovasculares no Brasil (MALACHIAS *et al*., 2016). É caracterizada por níveis elevados de PA em repouso (MALACHIAS *et al*., 2016; WHELTON *et al*., 2017), frequentemente associada ao risco de eventos cardiovasculares, acidentes cerebrais e doenças renais (BHAGANI; KAPIL; LOBO, 2018). Com o avanço da idade, diferenças no comportamento da PA são observadas, com maior incidência de HA em mulheres a partir da quinta década de vida (DI GIOSIA *et al*., 2018) e que podem causar lesões de órgão alvo graves nesta população (MUIESAN *et al*., 2018). Essa incidência pode ser explicada pelo climatério: o período de transição fisiológica da fase reprodutiva para a não reprodutiva nas mulheres, caracterizado por deficiência de estrogênio, alterações no perfil lipídico, ganho de peso e altos índices de sedentarismo (WARD; DENERIS, 2018), que levam ao aparecimento de doenças cardiovasculares e metabólicas, bem como aumento da incidência de HA nesta população (DI GIOSIA *et al*., 2018). Dentre estes, um dos fatores mais relevantes é a falta de estrogênio, pois este hormônio interfere na modulação da PA de forma substancial através de ação endotelial (WASSERTHEIL-SMOLLER *et al*., 2000), já que este hormônio age em receptores específicos do endotélio, que elevam a produção de substâncias vasodilatadoras, como Prostaciclinas e Oxido Nítrico (CARDOSO JUNIOR *et al*., 2007; ZANESCO; ZAROS, 2009).

De forma ampla, recomendam-se intervenções medicamentosas e não-medicamentosas para o tratamento da HA (WHELTON *et al*., 2017). Dentre as medidas farmacológicas, as principais escolhas de classes de drogas de primeira linha são: Diuréticos tiazídicos, Inibidores de Enzima conversora de Angiotensina, Bloqueadores de canais de cálcio, Bloqueadores de receptores de Angiotensina (BRA) e β-bloqueadores adrenérgicos (BB). Dentre estes, destacamos neste trabalho as duas últimas, por serem classes de medicamentos amplamente prescritas, além de agir por mecanismos fisiológicos díspares.

Neste sentido, os BRA agem de forma bastante sistêmica, bloqueando os receptores AT1 de Angiotensina II. Estes receptores são abundantes em diversos tecidos relacionados ao controle de PA, como: vasos, coração, rins, suprarrenais e nervos, mas sua ação anti-hipertensiva primária ocorre nos vasos periféricos (ABRAHAM; WHITE; WHITE, 2015). Ao efetivar o bloqueio dos receptores alvo, há aumento de adenosina monofosfato cíclica e diminuição da liberação de inositol trifosfato e de vários metabolitos do ácido araquidônico, o que causa relaxamento da musculatura vascular e portanto queda de PA (ABRAHAM; WHITE;

WHITE, 2015). Adicionalmente, este bloqueio resulta em redução da liberação de catecolaminas e consequente redução da hiperatividade nervosa simpática (ABRAHAM; WHITE; WHITE, 2015) e na diminuição da liberação e produção de aldosterona, o que por sua vez causa diminuição de reabsorção de sódio e água no túbulo proximal e portanto da PA (MALACHIAS *et al*., 2016). Além de ter poucos efeitos adversos, com raras observações de exantemas, esta classe de medicamentos proporciona redução da morbimortalidade cardiovascular e por nefropatias principalmente em populações de alto risco ou com outras doenças associadas (MALACHIAS *et al*., 2016). Alguns exemplos desses medicamentos comercializados no Brasil são: Losartana, Olmesartana e Valsartana.

Os BB por sua vez tem um mecanismo anti-hipertensivo complexo que pode envolver o bloqueio de canais adrenérgicos do tipo β em diversas partes do corpo, como: coração, rins e musculatura esquelética (MALACHIAS *et al*., 2016). Contudo, seus efeitos tem caráter mais central, causando diminuição do débito cardíaco com grande regulação da frequência cardíaca, redução da secreção de renina pelos rins, adaptação de barorreceptores e diminuição das catecolaminas nas sinapses nervosas (LÓPEZ-SENDÓN *et al*., 2004; MALACHIAS *et al*., 2016). Medicamentos de primeira geração, como o propranolol, tem ação não seletiva com afinidade similar entre os receptores β1 (localizados principalmente no coração) e β2 (localizados especialmente nos vasos e músculos esqueléticos), já os medicamentos de segunda geração, como o atenolol, tem ação seletiva em receptores do tipo β1 (WIYSONGE *et al*., 2017). Além disso, medicamentos de 3ª geração, como o nebivolol, têm efeito vasodilatador adicional, seja por bloqueio receptor α_1 adrenérgico ou por aumentar a síntese e liberação de óxido nítrico no endotélio vascular (LÓPEZ-SENDÓN *et al*., 2004; MALACHIAS *et al*., 2016). De acordo com a diretriz supracitada (MALACHIAS *et al*., 2016), são eficazes no tratamento da HA e tem redução de morbidade e mortalidade cardiovasculares bem documentada em grupos com idade inferior a 60 anos. Contudo, apresentam diversos efeitos adversos (MALACHIAS *et al*., 2016), dos quais destacamos: broncoespasmo, bradicardia e vasoconstrição periférica.

Entretanto, antes da indicação de agentes terapêuticos é recomendado em todos os níveis de hipertensão, alterações no estilo de vida visando melhora e manutenção do resultado hipotensor a partir de fatores de risco modificáveis, dentre eles: redução no consumo de álcool, sódio e tabaco (MALACHIAS *et al*., 2016), aquisição de hábitos alimentares adequados (ASHOR; LARA; SIERVO, 2017) e a prática de exercícios físicos regulares (DE SOUSA *et al*., 2017). O último contribui com quedas na PA a curto (CARVALHO *et al*., 2014;

HALLIWILL *et al*., 2013) e longo prazo (CARVALHO *et al*., 2014; DE SOUSA *et al*., 2017; TIBANA *et al*., 2015), além de colaborar no controle de diversos fatores de risco, como: controle lipídico (GIOLO *et al*., 2018), função endotelial (SANTOS-PARKER; LAROCCA; SEALS, 2014), perfil oxidativo (ASHOR; LARA; SIERVO, 2017; GIOLO *et al*., 2018), regulação autonômica (COTE *et al*., 2015), sintomas do climatério (COSTA *et al*., 2017) e da saúde cardiovascular de forma geral em mulheres hipertensas após a menopausa (LIN; LEE, 2018)

Neste sentido, diversos estudos (CORNELISSEN; SMART, 2013; NACI *et al*., 2018) demonstraram resultados positivos ao associar períodos de exercícios físicos regulares à redução da PA em populações hipertensas, demonstrando resultados similares aos apresentados pelo tratamento farmacológico (NACI *et al*., 2018). Contudo, vale destacar que a maioria dos estudos mostra que fases de treinamento com exercícios aeróbicos são eficazes no tratamento da HA (HACKAM *et al*., 2013; HECKSTEDEN; GRÜTTERS; MEYER, 2013). Outros (CORNELISSEN; SMART, 2013; HERROD *et al*., 2018) demonstraram que o treinamento resistido pode ser eficaz. Por fim, poucos abordaram a redução da PA de repouso e ambulatorial e de sua variabilidade (VPA) após treinamento com exercício combinado (PEDRALLI *et al*., 2016; SON *et al*., 2017a), mesmo que estes apresentem resultados meta-analíticos promissores (NACI *et al*., 2018) e que as diretrizes (MALACHIAS *et al*., 2016; WHELTON *et al*., 2017) recomendem sessões de ao menos 30 minutos de exercícios aeróbios de média intensidade e complementação com exercícios resistidos como componentes do treinamento para o hipertenso. Quanto às características do exercício, a meta-análise de Cornelissen e colaboradores (CORNELISSEN; SMART, 2013) demonstrou melhores resultados pressóricos em treinamentos com exercícios de intensidades de moderadas a altas, com sessões de ao menos 30 minutos, supervisionadas, em participantes do sexo masculino e especialmente em hipertensos.

Além disso, vale destacar que o exercício age sobre diversos mecanismos de regulação da PA similares aos dos medicamentos supracitados, causando: **1)** Aumento da sensibilidade barorreflexa (LIN; LEE, 2018); **2)** Melhora de *stiffness* arterial e vasodilatação dependentes do endotélio, associados a biodisponibilidade de oxido nítrico e causada por aumento de atividade enzimática e fosforilação de enzima oxido nítrico sintase, além de aumento nas concentrações disponíveis de nitrito, nitrato e óxidos de nitrogênio (Son *et al*., 2017); **3)** Redução da disfunção autonômica associada a HA, causando aumento do tônus vagal e diminuição do tônus simpático (BESNIER *et al*., 2017; LIN; LEE, 2018); **4)** Melhora da função endotelial induzida por

aumento de produção e liberação de substâncias vasodilatadoras como Acetilcolina e Bradicinina (LIN; LEE, 2018) e; **5)** Melhoras na vasodilatação mediada por fluxo sanguíneo, sendo mais aparentes na macrovasculatura em relação a microvasculatura (VINET *et al*., 2018).

Dadas as semelhanças entre os mecanismos anti-hipertensivos dos medicamentos e dos exercícios, surge a hipótese de que estas respostas poderiam interferir umas nas outras. Assim, a compreensão da interação das diferentes formas de tratamento da HA poderia influenciar na escolha da combinação entre medidas farmacológicas e de estilo de vida de forma a garantir a maior efetividade do tratamento. Contudo, estas respostas ainda não estão claras na literatura e têm sido demonstradas apenas em alguns ensaios com exercícios de forma aguda (QUEIROZ *et al*., 2017; RAMIREZ-JIMENEZ *et al*., 2018b, 2018a). Com relação ao exercício de forma crônica, uma recente meta-análise (NACI *et al*., 2018) que envolveu 391 estudos sobre efeitos dos anti-hipertensivos e dos exercícios na PA sistólica, não encontrou nenhum estudo entre 1976 e 2018 que averiguasse a relação entre as respostas pressóricas ao exercício e aos anti-hipertensivos.

Para tanto, existem diversos métodos de avaliação dos valores de PA após fase de treinamento. O primeiro deles é a medida em repouso de PA, que tem grande importância clínica na prevenção e tratamento de HA, mas que limita a análise do comportamento da PA a apenas um momento do dia, além de exigir a realização de técnicas adequadas de medida e várias visitas dos pacientes para assegurar a consistência dos resultados (HINDERLITER; VOORA; VIERA, 2018). Assim, a monitorização ambulatorial de PA (MAPA) passou a ser utilizada, já que fornece informações sobre os níveis de PA de 24 horas durante as atividades diárias usuais e durante o sono, permitindo a distinção entre os fenótipos da PA (normotensão sustentada, hipertensão sustentada, hipertensão mascarada e hipertensão do jaleco branco) (HINDERLITER; VOORA; VIERA, 2018). Além disso, fornece informações sobre o comportamento temporal da PA (HANSEN *et al*., 2010), técnica conhecida como análise de variabilidade de PA (VPA), sendo que o aumento dessa variabilidade está associado a um maior risco de eventos cardiovasculares e mortalidade (PARATI *et al*., 2013; STEVENS *et al*., 2016).

Desta forma, ao investigar as repostas pressóricas (PA e VPA) aos exercícios combinados em mulheres hipertensas após a menopausa sob efeito de diferentes classes de anti-hipertensivos (BRA e BB), produzimos informações ainda não descritas na literatura e que podem influenciar nas escolhas de combinações entre tratamentos anti-hipertensivos farmacológicos e não farmacológicos. A hipótese inicial foi que haveriam quedas na PA de repouso, sob estresse e na VPA independente dos medicamentos, mas que as respostas em BRA

seriam mais acentuadas que em BB por agirem de forma mais sistêmica, além do efeito cronotrópico negativo de BB (LÓPEZ-SENDÓN *et al*., 2004) que poderia limitar as cargas absolutas de treinamento durante o exercício aeróbio.

3 Objetivos

O objetivo deste estudo foi investigar as repostas da pressão arterial após o treinamento com exercícios aeróbios e resistidos combinados em mulheres hipertensas após a menopausa sob efeito de duas classes distintas de anti-hipertensivos.

3.1. Objetivos específicos

Verificar se as respostas da PA após o treinamento combinado são influenciadas pelo uso de BB e BRA através dos resultados de PA de repouso, da MAPA de 24 horas e da análise de VPA de 24 horas.

Para tanto, o presente estudo será apresentado em formato de artigo científico no próximo capítulo.

4 Blood pressure responses after combined exercise training in hypertensive postmenopausal women under influence of β-blockers or angiotensin receptor blockers: a pilot study.

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Introduction

Hypertension (HT) is a common disease in both sexes, characterized by sustained high blood pressure (BP) at rest (Malachias *et al*., 2016; Whelton *et al*., 2017), often associated with the risk of cardiovascular events, stroke and kidney disease (Bhagani *et al*., 2018). With advancing age, differences in BP behavior are observed, with a higher incidence in women after the 5th decade of life (Di Giosia *et al*., 2018). This incidence can be explained by climacteric: period of physiological transition from reproductive to non-reproductive phase in women, characterized by estrogen deficiency, alterations in the lipid profile, weight gain, high sedentary indices (Ward and Deneris, 2018) and onset of cardiovascular and metabolic diseases, as well as increased incidence of HT (Di Giosia *et al*., 2018) causing specific organ damage in women (Muiesan *et al*., 2018).

Pharmacological and non-pharmacological interventions are widely recommended for HT treatment (Whelton *et al*., 2017). Among pharmacological treatments, two extensively prescribed antihypertensive classes but with different mechanisms, are β-adrenergic blockers (BB) and Angiotensin Receptor Blockers (ARB). The antihypertensive mechanism of BB involves mainly central mechanisms, with blockade of β-adrenergic receptors, which causes a decrease in cardiac output, renin secretion, synaptic catecholamines and baroreceptors adaptations (Malachias *et al*., 2016). ARB has more systemic effects, antagonizing AT1 receptors of Angiotensin II, causing vasodilation and decreasing aldosterone release and production, which causes sodium and water reabsorption causing BP reductions (Malachias *et al*., 2016).

Regarding non-medication interventions, it is emphasized that physical exercises training may reduce BP in patients with normal or high blood pressure (Cornelissen and Smart, 2013), including in postmenopausal women (Lin and Lee, 2018; Son *et al*., 2017). However, few studies have addressed resting and ambulatory BP (ABPM) and its variability (BPV) changes after combined aerobic and resistance exercise training (Son *et al*., 2017), even though guidelines (Malachias *et al*., 2016; Whelton *et al*., 2017) recommend at least 30 minutes of moderate intensity aerobic exercises associated with resistance exercises. In addition, it should be noted that the exercise acts on several mechanisms of BP regulation similar to those of the aforementioned drugs, causing possible improvements in autonomic regulation (Besnier *et al*., 2017), baroreflex sensitivity and bioavailability of vasodilator agents in hypertensive

postmenopausal women (Lin and Lee, 2018; Son *et al*., 2017). Therefore, the effects of exercise and medication, hypothetically can be added, may be independent or may depend on some saturated pathway.

Then, the objective of this study was to investigate BP responses (resting BP, ABPM and BPV) after combined aerobic and resistance exercises training in hypertensive postmenopausal women under effects of two different antihypertensive-drugs (ARB and BB). Our hypothesis was that BP and BPV could be lower after exercise training, but the use of BB could attenuate these responses by its chronotropic effect, reducing absolute workload of exercise comparing with lager systemic responses of the ARB. This information has not yet been described and may influence the choices of combinations between pharmacological and non-pharmacological antihypertensive treatments.

Material and methods

Participants

Twenty one women volunteered through advertising in electronic and traditional media (Social medias, TV and radio) during 2016 and 2017. From this register were selected those that fit the following inclusion criteria: 1) Women aged between 50 and 70 years; 2) Amenorrhea of at least 12 months and [FSH]>40mIU/mL; 3) Be able to perform physical exercises; 4) Under antihypertensive treatment only with: ARB or BB, without drugs or dose changes for 12 months; 5) Do not present history of other cardiovascular diseases; 6) Non-smokers; 7) No diagnosis of Diabetes Mellitus or renal pathologies; 8) Do not use hormonal therapies; and 9) Do not be uncompensated hypertensive. Before starting the training program, they presented a medical certificate releasing participation in the exercise program and signed the Consent Form, and they were instructed to maintain their eating habits during the study. They were divided into 2 groups: ARB users (ARB+Ex; n=11) and BB users (BB+Ex; n=10). Those who changed dose or medication during the study were discarded from the analyzes, as shown in *Figure 1*.

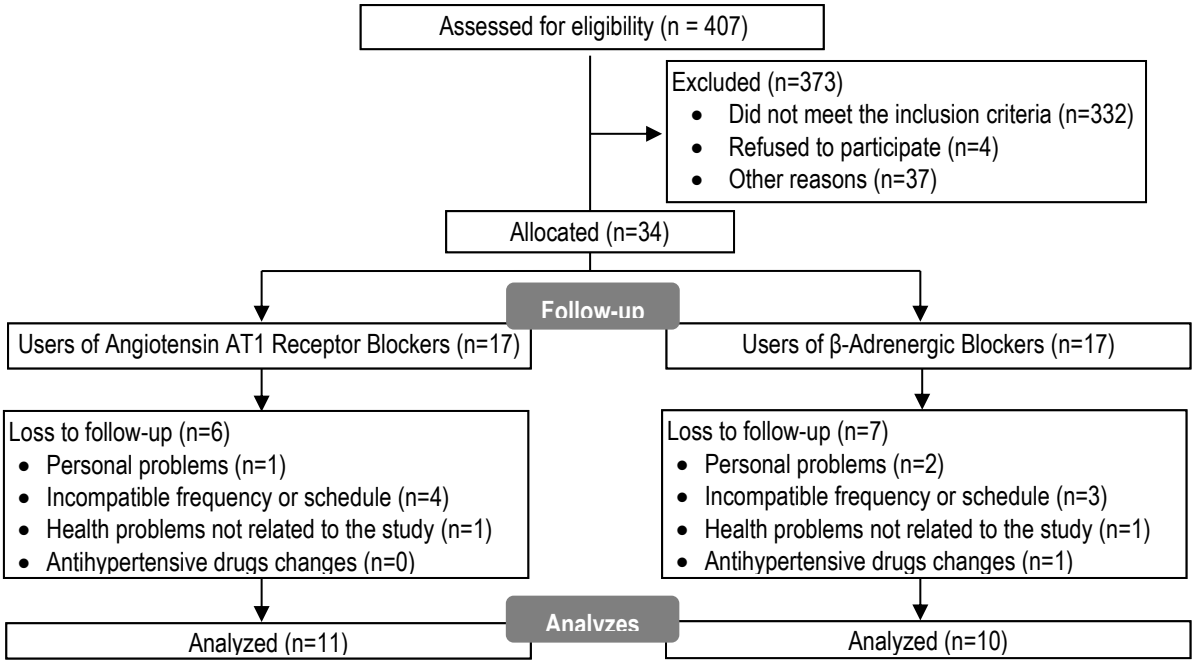

Figure 1 – Follow-up flowchart

General Procedures

This study was a comparative parallel clinical trial and has international registration of clinical studies in "Clinicaltrials.gov" (Registry: NCT03531034) and was approved by local Human Research Ethics Committee (Registry: 40622414.9.0000.5152). The procedures were performed at Federal university of Uberlândia. Before 12 weeks of training, volunteers went through a battery of evaluations which will be better explained below, that include: body composition and anthropometry, physical capacity and cardiovascular measurements. After that, they performed a familiarization with the exercises used in the training. Thus, the sessions for strength evaluation (1 repetition maximum test - 1RM) and an incremental treadmill test for aerobic exercise prescription were started. The exercise program was performed three times a week on non-consecutive days for 12 weeks. Between 48 and 96 hours after the end of the 12 weeks of training all evaluations were performed again.

Body composition and anthropometry

The anthropometric evaluations were performed in an isolated environment, in which are measured: 1) body mass, through an electronic scale (Filizola®, São Paulo, SP, Brazil); 2) height, measured with fixed stadiometer (Sanny®, São Bernardo do Campo, SP, Brazil) and; 3) abdominal circumference, through an inelastic tape measuring 0.5 cm wide (Filizola®, São Paulo, SP, Brazil) placed on the umbilical scar. The evaluation of the body composition was

performed through tetra polar bioimpedance (InBody 230 Trepel®; Perafita, Portugal). The level of physical activity was assessed by the International Physical Activity Questionnaire (IPAQ short version), validated for Brazilian population (Matsudo *et al*., 2001).

Cardiovascular measurements

Resting BP and HR was monitored through calibrated and validated automatic monitors (Asmar *et al*., 2010) (*Omron*® HEM-7113, Shimogyo-ku, Kyoto, Japan) in 3 non-consecutive days. At each moment of measurement, 3 measurements of systolic BP (SBP), diastolic BP (DBP), heart rate (HR) and Double Product (DP) were performed and considered as the mean for analysis. Values outside the 95% confidence interval were discarded, being considered the average of the others. In addition, the ABPM was performed in the pre and post-training periods for 24 hours (Dyna Map + Cardios®, São Paulo, SP, Brazil). Such a device measured SBP, DBP, mean BP (MBP), Pulse Pressure (PP), HR and DP every 15 minutes between 07:00 and 23:00 and every 30 minutes between 23:00 and 07:00.

Thus, the ABPM values associated with daily report information that they filled while they were with the device allowed us to evaluate the following BPV indices in awake, asleep and 24h periods: **1)** Standard deviation ($SD = \sqrt{\Sigma(BP_x - BP_{mean})2/n}$) of BP; **2)** Average real variability ($ARV = \Sigma(BP_x-BP_{x-1})/n$); **3)** Morning surge (MS = the first 2 hours of awakening/ BP_{mean} of the smallest asleep and adjacent BP); **4)** BP Nocturnal dipping ($ND = (BP_{awake} - BP_{asleep})x100/BP_{awake}$**); 5)** BP loads: percentage of 24h SBP greater than 130 mmHg, greater than 135 mmHg during awake and greater than 120 mmHg during sleep; and 24h DBP greater than 80 mmHg, greater than 85 mmHg during awake and greater than 70 mmHg during sleep.

Exercise training program

The exercise training consisted of the combination of aerobic and resistance exercises in the same session, three times a week on non-consecutive days for 12 weeks (36 sessions). Each session lasted approximately 60 minutes, and every day they did about 30 minutes of aerobic exercises and 30 minutes of resistance exercises. In addition, at each session the order of the exercises was reversed and monitored through HR monitors and subjective perceived effort scale to ensure safety.

The intensity of the aerobic physical exercise was determined through an incremental treadmill test with 2-minute stages and 1% of treadmill inclination increments per stage until

the volunteers reached voluntary exhaustion. The speed of the treadmill was fixed at 5.5 km/h and the exercise intensity was imposed by the treadmill inclination (Puga *et al*., 2012). This protocol was chosen because it allows to reach maximum parameters without the motor limitation of the running with this population. At the beginning of each aerobic session a 5-minute warm-up on a treadmill with a velocity of 5.5 km/h and 1% of inclination was performed. After that, the aerobic training consisted of a 25-minute walk with fixed speed (5.5 km/h) and overload imposed by the inclination of the treadmill, aiming to reach the intensity between 65 and 75% of the maximum workload (last completed stage reached in the incremental test). This intensity consisted on the same % (65 to 75%) of the VO_2 peak, with is well described as moderate intensity. The exercise intensity was increased by 20% after 6 weeks of training as exercise training overload.

In order to assess maximum strength in resistance exercises before exercise training, we initially performed 2 familiarizations with the 1 Maximum Repetition test (1RM), and then performed the 1RM test (Brown and Weir, 2001). Briefly, we performed a warm-up protocol consisting of 2 sets of exercise to be performed at intensities around 50 and 80% of the subjective estimate of 1RM, with 8 and 3 repetitions respectively. After this warm up, there was a maximum of 5 attempts per exercise to find the highest workload that they can only make a full movement (concentric and eccentric).

The following resistance exercises were performed: Leg press 45º (hip and knee extension), Chest press in vertical machine (shoulder horizontal abduction with elbow extension), Anterior latissimus dorsi pulldown (shoulder abduction and elbow flexion), Squat with lumbar Swiss ball support (hip and knee extension), and classic Abdominal crunch (spine flexion with fixed hip and flexed knee on a flat surface). These were selected by stimulating large muscle groups, in order to obtain greater cardiovascular and muscular changes. Each exercise was performed in a traditional 3-series format of 8-12 repetitions with 60 seconds rest between sets and exercises. The intensity was determined through repetition zones of 8 to 12 complete movements until there was motor alteration that compromised the correct technique of the exercise or the required execution speed (around 3s per complete movement). The order of the exercises was alternated between agonist muscle groups. The exception to this training format was abdominal, which was performed through maximal repetitions without external load. This phase of the training lasted between 27 and 30 minutes. The load readjustment occurred daily in order to maintain the repetition zone.

Statistical analyzes

The results were presented in mean ± standard deviation of pre and post intervention, besides their variation (Δ) and lower and upper limits of the 95% confidence interval. The chi-square test ($\chi 2$) was used to analyze the distribution between the groups of physical activity level and polytherapy with thiazide diuretics. The calculation of area under the curve (AUC) of 24h SBP and DPB where performed using trapezoidal method. To compare the pre-training general characteristics the student's t-test was used. A two-factor (Time and group) generalized estimating equation (GEE) technique to understand the effects of training and the influence of medications, with Bonferroni post hoc when necessary. All analyzes were performed using IBM® SPSS® Statistics 21 and GraphPad Prism® version 5. The significance level was adopted at $p \leq 0.05$.

Results

Before the training began, the χ^2 test showed no group differences of previous training level classification (p=0.27) or on polytherapies with thiazide diuretics distribution (p=0.81, 6 polytherapies each group). In ARB+Ex all antihypertensives are losartan and in BB+Ex there are 7 atenolol users and 3 of propranolol. Table 1 shows no group differences in overall characteristics prior to exercise training, except for the maximum HR in the treadmill incremental test (p<0.001). All analyzed volunteers performed at least 80% of the sessions.

Table 1 – General Characteristics prior to exercise training

	ARB (n=11)	BB (n=10)	p
Initial Age (years)	58.1 ± 6.2	57.6 ± 2.7	0.821
Time after menopause (years)	9.4 ± 6.7	9.1 ± 6.1	0.926
Height (m)	1.58 ± 0.05	1.60 ± 0.12	0.730
Abdominal circumference (cm)	96.9 ± 9.7	95.9 ± 10.1	0.819
Body Mass (kg)	74.2 ± 10.5	70.4 ± 9.7	0.404
Body Mass Index (kg/m²)	29.6 ± 4.2	27.7 ± 4.2	0.310
Fat mass (%)	43.1 ± 6.7	38.7 ± 6.6	0.154
Lean mass (%)	53.5 ± 6.3	57.8 ± 6.2	0.150
[LH] (mUI/Ml)	47.4 ± 15.8	44.6 ± 22.2	0.738
[FSH] (U/l)	83.1 ± 22.8	84.4 ± 35.0	0.917
Resting SBP	117.3 ± 11.7	114.8 ± 5.9	0.553
Resting DBP	73.0 ± 7.9	71.3 ± 6.4	0.599
Maximum treadmill inclination (%)	8.4 ± 3.3	7.4 ± 3.3	0.512
Maximum HR (bpm)	157.4 ± 12.3	128.1 ± 16.2	<0.001
Leg Press maximum strength (kg)	185.0 ± 83.5	202.0 ± 48.9	0.581
Chest Press maximum strength (kg)	30.2 ± 6.5	31.3 ± 10.6	0.771
Lat Pulldown maximum strength (kg)	32.4 ± 7.6	36.5 ± 6.5	0.207

HR: Heart Rate; [LH]: Luteinizing Hormone Concentration; [FSH]: Follicle Stimulating Hormone Concentration; ARB+Ex: Angiotensin AT1 receptor blockers users; BB+Ex: β-blockers users.

Figure 2 shows BP, HR and DP values at rest. There were no interaction effects (group * time), but it is noted a decreasing time effect (p=0.009) on resting SBP values (ARB+Ex pre = 117.27±11.66 and post = 112.09±7.86; BB+Ex pre = 114.80±5.86 and post = 113.20±5.13 mmHg) with no group effect and no changes in resting DBP. In addition, there was a group effect with lower BB+Ex values in HR (p=0.009) and DP (p=0.002) and a time effect (p=0.026) with reductions in DP in both groups (ΔARB+Ex = -471.76±982.76; ΔBB+Ex = -252.57±533.26 mmHg.bpm).

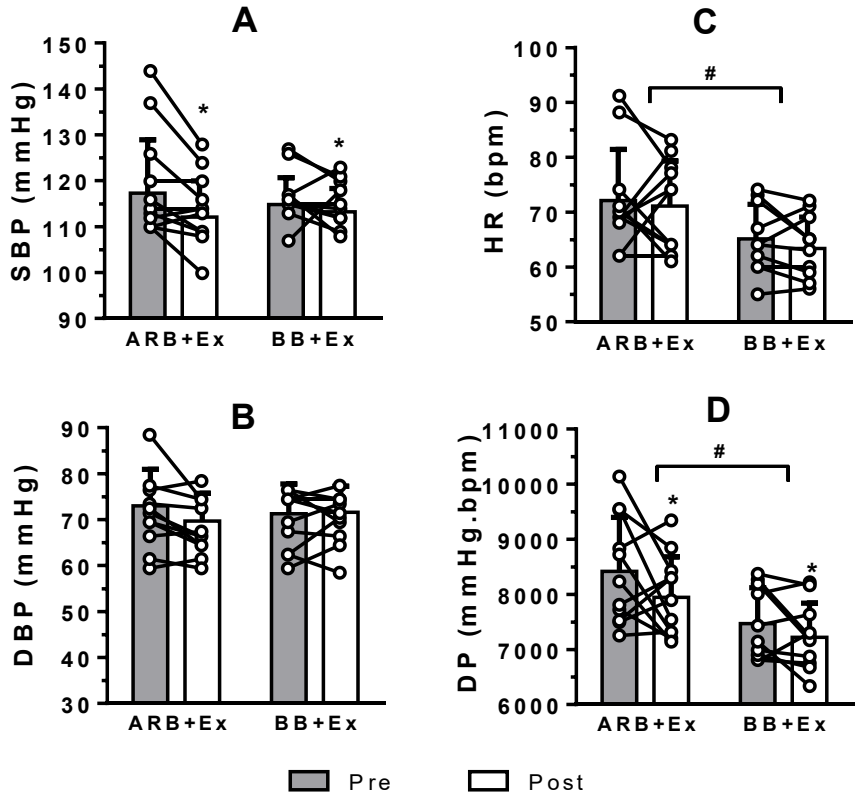

Figure 2 – Blood pressure (A and B), heart rate (C) and double product (D) at rest. BP: Blood Pressure; SBP: systolic BP; DBP: diastolic BP; HR: Heart rate; DP: Double product; *: Time Effect; #: Group effect; ARB+Ex: Angiotensin AT1 receptor blockers users and exercise; BB+Ex: β-blockers users and exercise.

Figure 3 represents 24h ABPM values of BP, HR and DP. There were no interaction effects in any of these variables, but rather reductions (time effects) in 24h (p=0.006; ΔARB+Ex = -5.68±8.32; ΔBB+Ex = -3.14 ± 6.69 mmHg) and awake SBP (p=0.002; ΔARB+Ex = -6.69 ± 9.03; ΔBB+Ex = -3.36 ± 5.93 mmHg) after exercise training. Besides that, PP decreases (time effect) during 24h (p=0.002), awake (p=0.002) and asleep periods (p=0.009). Groups effects with lower values in BB+Ex were evidenced in all day phases in HR (24h p=0.004; awake p=0.005; asleep p=0.003) and DP (24h p=0.001; awake p=0.002; asleep p=0.001), besides time

effects with DP reduction of 24h (p=0.008; ΔARB+Ex = -557.66 ± 978.90 ; ΔBB+Ex = -417.43 ± 748.16 mmHg.bpm) and awake (p<0.001; ΔARB+Ex = -810.38 ± 959.87; ΔBB+Ex = -502.32 ± 809.31 mmHg.bpm).

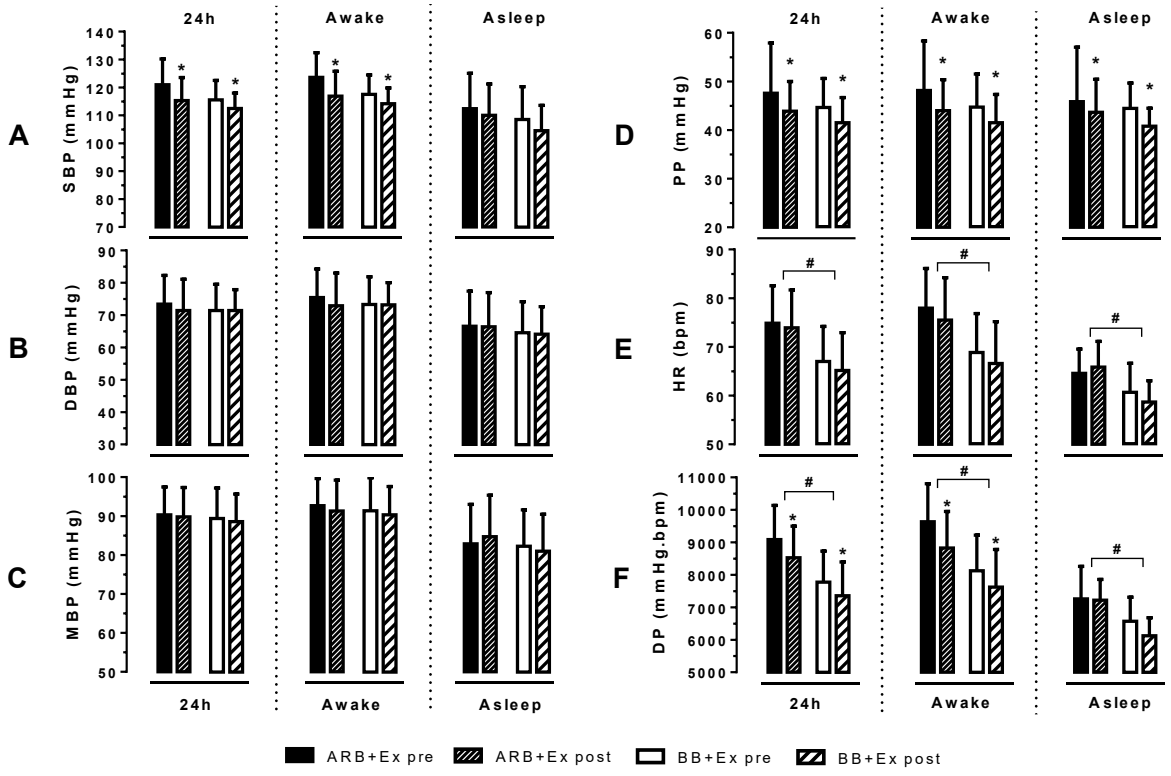

Figure 3 –Ambulatorial blood pressure, heart rate and double product. Panels A-F represents: Systolic (A), Diastolic (B) and Mean (C) Blood pressures, Pulse pressure (D), Heart Rate (E) and Double product (F). SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MBP: Mean blood pressure; PP: Pulse Pressure; HR: Heart rate; DP: Double Product; *: Time effect; #: Group effect; ARB+Ex: Angiotensin AT1 receptor blockers users; BB+Ex: β-blockers users.

Table 2 shows BPV values. There were interactions effects in SBP and DBP awake SD with a greater tendency to fall in BB+Ex. In addition, there was a reduction (time effect) of SBP standard deviations (SD), except in asleep phase, demonstrating training capacity to reduce SBP oscillations during the day. Besides that, the number of SBP peaks above normal values (i.e. pressure loads) was lower after training in the 24 hour and awake phases.

Table 2 – Blood pressure variability indexes and blood pressure loads

ARB+Ex (n=11); BB+Ex (n=10)		M±SD Pre	M±SD Post	Δ	Δ95% IC		p Time	p Group	p Inter.
SBP indexes									
SD 24h (mmHg)	**ARB+Ex**	13.1 ± 2.3	12.8 ± 1.1	-0.3 ± 2.8	-2.0	1.3	.034	.176	.142
	BB+Ex	13.0 ± 2.7	11.1 ± 1.7	-2.0 ± 2.3	-3.4	-0.6			
SD awake (mmHg)	**ARB+Ex**	12.3 ± 2.0	12.2 ± 1.5	-0.1 ± 2.2	-1.4	1.1	.024	.178	.047
	BB+Ex	12.3 ± 3.2	10.0 ± 2.1	-2.3 ± 2.8	-4.0	-0.6			
SD asleep (mmHg)	**ARB+Ex**	9.4 ± 2.4	9.2 ± 2.1	-0.1 ± 3.3	-2.0	1.8	.425	.479	.502
	BB+Ex	10.4 ± 3.1	9.1 ± 2.2	-1.2 ± 4.5	-3.8	1.4			
SDdn (mmHg)	**ARB+Ex**	11.5 ± 1.9	11.4 ± 1.3	-0.1 ± 2.2	-1.4	1.2	.039	.358	.070
	BB+Ex	11.7 ± 2.6	9.9 ± 1.8	-1.9 ± 2.3	-3.2	-0.5			
ARV (mmHg)	**ARB+Ex**	10.5 ± 1.9	10.1 ± 1.4	-0.4 ± 2.5	-1.9	1.0	.095	.668	.330
	BB+Ex	10.9 ± 3.1	9.2 ± 1.8	-1.7 ± 3.4	-3.7	0.3			
DBP indexes									
SD 24h (mmHg)	**ARB+Ex**	9.7 ± 1.6	9.6 ± 1.8	-0.1 ± 2.1	-1.2	1.2	.205	.764	.225
	BB+Ex	10.4 ± 2.8	9.4 ± 1.8	-1.0 ± 1.9	-2.2	0.1			
SD awake (mmHg)	**ARB+Ex**	8.5 ± 0.9	9.0 ± 1.5	0.5 ± 1.9	-0.7	1.6	.250	.768	.018
	BB+Ex	9.6 ± 2.7	8.3 ± 1.6	-1.3 ± 1.6	-2.3	-0.4			
SD asleep (mmHg)	**ARB+Ex**	8.5 ± 1.7	7.5 ± 2.0	-1.0 ± 2.8	-2.6	0.7	.331	.930	.720
	BB+Ex	8.2 ± 2.8	7.8 ± 2.0	-0.4 ± 4.0	-2.8	1.9			
SDdn (mmHg)	**ARB+Ex**	8.5 ± 0.8	8.6 ± 1.2	0.1 ± 1.5	-0.8	1.0	.191	.876	.102
	BB+Ex	9.2 ± 2.3	8.2 ± 1.6	-1.0 ± 1.8	-2.1	0.1			
ARV (mmHg)	**ARB+Ex**	7.4 ± 0.7	7.5 ± 1.5	0.1 ± 1.2	-0.6	0.8	.137	.773	.081
	BB+Ex	8.4 ± 3.1	6.9 ± 1.5	-1.5 ± 2.9	-3.2	0.2			
Another indexes									
SBP Nocturnal Dipping (%)	**ARB+Ex**	9.1 ± 7.5	5.6 ± 10.2	-3.5 ± 8.9	-8.7	1.7	.451	.815	.243
	BB+Ex	7.7 ± 8.4	8.4 ± 7.6	0.8 ± 8.4	-4.2	5.7			
DBP Nocturnal Dipping (%)	**ARB+Ex**	11.8 ± 9.2	8.5 ± 11.0	-3.2 ± 11.4	-10.0	3.5	.564	.638	.457
	BB+Ex	11.7 ± 10.8	12.1 ± 10.7	0.4 ± 11.6	-6.4	7.3			
SBP Morning surge (mmHg)	**ARB+Ex**	22.7 ± 8.1	25.7 ± 10.5	2.9 ± 14.9	-5.9	11.7	.262	.223	.799
	BB+Ex	18.4 ± 13.7	23.0 ± 8.4	4.6 ± 16.6	-5.2	14.4			
DBP Morning surge (mmHg)	**ARB+Ex**	19.9 ± 4.9	21.4 ± 4.8	1.5 ± 5.9	-2.0	4.9	.516	.647	.960
	BB+Ex	18.6 ± 13.6	20.3 ± 7.2	1.7 ± 15.6	-7.4	10.9			
Blood Pressure Load									
SBP 24h > 130 (%)	**ARB+Ex**	25.1 ± 22.1	13.7 ± 16.5	-11.4 ± 14.7	-20.1	-2.7	<.001	.159	.580
	BB+Ex	14.9 ± 14.5	6.5 ± 6.3	-8.4 ± 10.6	-14.7	-2.1			
SBP Awake > 135 (%)	**ARB+Ex**	18.9 ± 17.6	9.3 ± 12.0	-9.7 ± 12.7	-17.2	-2.2	<.001	.120	.652
	BB+Ex	10.6 ± 12.3	3.1 ± 3.8	-7.5 ± 9.5	-13.1	-1.9			
SBP Asleep > 120 (%)	**ARB+Ex**	27.4 ± 36.6	21.3 ± 35.2	-6.1 ± 22.9	-19.6	7.4	.244	.648	.810
	BB+Ex	23.9 ± 27.1	14.6 ± 21.9	-9.3 ± 37.7	-31.5	12.9			
DBP 24h > 80 (%)	**ARB+Ex**	27.5 ± 27.1	25.2 ± 23.0	-2.3 ± 13.4	-10.2	5.6	.261	.786	.576
	BB+Ex	27.2 ± 24.0	20.4 ± 21.1	-6.8 ± 23.2	-20.5	6.9			
DBP Awake > 85 (%)	**ARB+Ex**	20.7 ± 23.6	15.4 ± 19.0	-5.3 ± 12.2	-12.5	1.9	.074	.732	.949
	BB+Ex	18.2 ± 20.3	12.5 ± 15.2	-5.7 ± 16.4	-15.4	4.0			
DBP Asleep > 70 (%)	**ARB+Ex**	34.0 ± 33.7	39.8 ± 36.1	5.8 ± 29.4	-11.5	23.1	.825	.812	.594
	BB+Ex	35.3 ± 29.0	32.9 ± 32.8	-2.4 ± 41.8	-27.0	22.2			

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SD: Standard deviation; SDdn: SD day and night; ARV: Average real variability; Blood pressure Load: percentage of measures above standard; CI: Confidence interval; Inter.: Interaction; ARB+Ex: Angiotensin AT1 receptor blockers users and exercise; BB+Ex: β-blockers users and exercise.

Figure 4 represents 24-hour blood pressure curves used for the calculation of 24h SBP (Panel A) and DBP (Panel B) areas under the curves (AUC), as well as their respective AUC values (Panels C and D). There were no interaction or group effects but rather reduction (time effect p=0.005) in 24h SBP AUC (ΔARB+Ex = -136.8 ± 175.8; ΔBB+Ex = -72.1 ± 176.5 mmHg.24h). No changes were found in DBP (ΔARB+Ex = -49.8 ± 99.18; ΔBB+Ex = -2.4 ± 140.15 mmHg.24h).

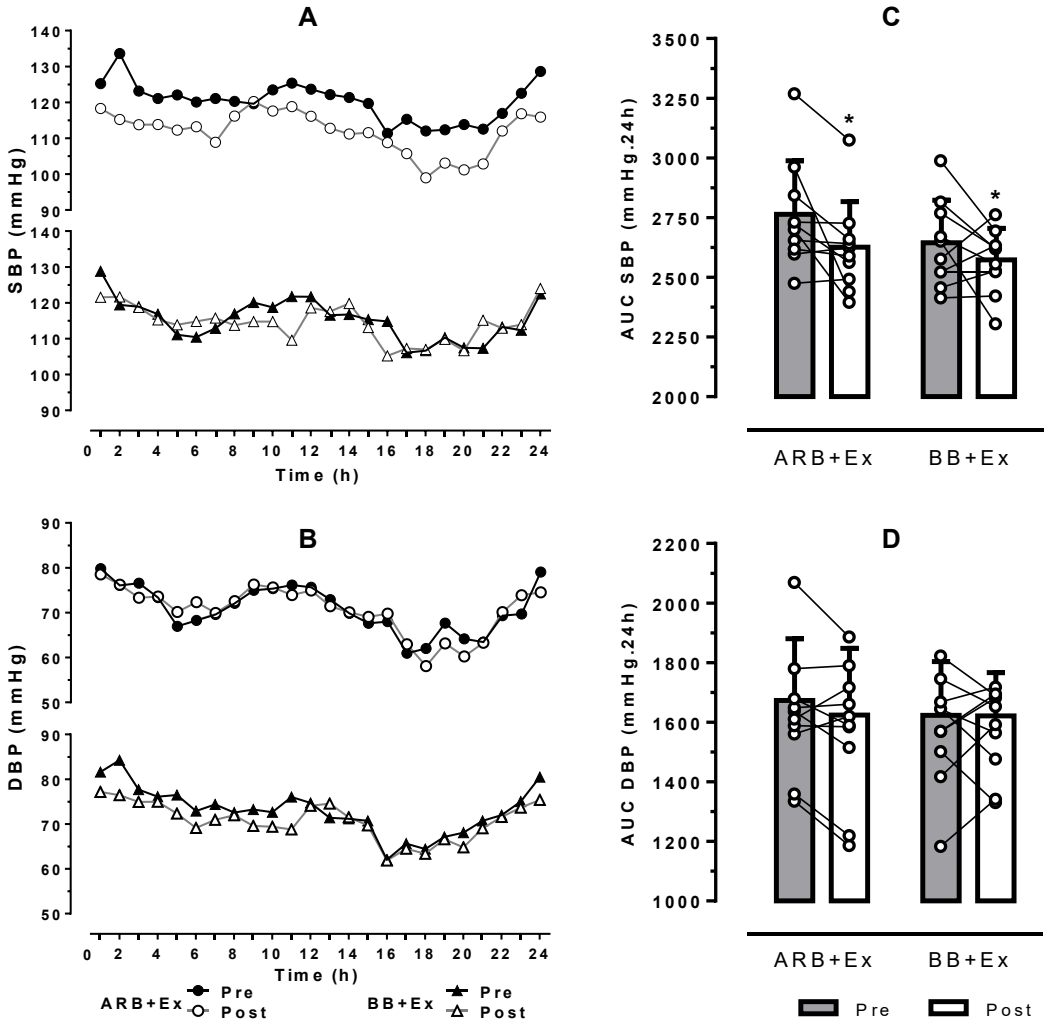

Figure 4 – 24h blood pressure and correspondent area under the curve. Panels A and B represents hourly mean values of systolic and diastolic BP respectively. Panels C and D represents values of 24h area under the curve of systolic and diastolic BP respectively, in these panels the circles connected by lines represents individual values. AUC: Area under the curve; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; *: Time Effect; ARB+Ex: Angiotensin AT1 receptor blockers users and exercise; BB+Ex: β-blockers users and exercise.

Discussion

This study aimed to evaluate cardiovascular effects of combined aerobic and resistance exercise training in hypertensive postmenopausal women under effect of β-adrenergic blockers and angiotensin receptor blockers antihypertensive-drugs. Our main finding was that both groups had similar responses in resting and ambulatory blood pressure after combined exercise training but BPV in BB+Ex (SBP and DBP awake SD) were greater than in ARB+Ex group. Furthermore, 12 weeks of combined moderate intensity training are enough to reduce resting, awake and 24h SBP and DP, SD of 24h and awake SBP (BPV), as well as reductions in SBP loads of 24h and awake in both groups of postmenopausal women with hypertension.

Regarding the characteristics of exercise, this training volume (60 minutes/day) was chosen because at moderate intensity it can provide significant changes in BP (Cornelissen and Smart, 2013). Despite the hypothesis that BB+Ex would perform the aerobic exercises with lower absolute load, this was not confirmed (Maximum load on pre-training treadmill test: ARB+Ex = 8.42 ± 3.35; BB+Ex= 7.42 ± 3.33 % of inclination) even with the difference in the maximum HR reached in the same test (Maximum HR on pre-training treadmill test: ARB+Ex = 157.40 ± 12.34; BB+Ex = 128.10 ± 16.17 bpm). Moreover, exercise may act attenuating several risk factors associated with HT such as: lower lean mass (Butcher *et al*., 2018), high fat mass percentage (Das *et al*., 2018), besides the diverse cardiovascular benefits in postmenopausal women (Lin and Lee, 2018). Another important point of exercise in relation to HT, and which further emphasizes the need for exercise in this population is the low adherence to drug treatment (Peacock and Krousel-Wood, 2017). This not only requires the use of non-pharmacological strategies as a form of treatment, but has also become one of the main demands of patients, caregivers and health professionals (Khan *et al*., 2017).

In this sense, an important evidence is that exercise training may decrease resting BP (Cornelissen and Smart, 2013), including in hypertensive postmenopausal women (Lin and Lee, 2018; Son *et al*., 2017). Furthermore, we emphasize the importance of ambulatory measurement in hypertensive patients (Whelton *et al*., 2017), since it provides monitoring information and BP behavior over 24 hours. In general, high BP values and their variability during 24 hours are associated with a higher cardiovascular risk, becoming an important parameter for the monitoring of cardiovascular health (Zawadzki *et al*., 2017). With respect to exercise characteristics, the Cornelissen and Smart meta-analysis (2013) showed more pronounced

results in SBP and DBP after isometric training, in addition to positive and fairly consistent evidences about aerobic and resisted exercises, but combined training seems to reduce only DBP. Moreover, this study showed better results in moderate to high intensity exercises, with sessions of at least 30 minutes, supervised, in male participants and especially in hypertensive patients. In contrast, the present study demonstrated more significant falls in SBP even with moderate intensity supervised combined training in hypertensive women, in consonance with another meta-analysis (Naci *et al*., 2018) that found combined exercise training as the main strategy for SBP control.

Concerning the possible physiological mechanisms responsible for these BP falls, in a recent review of cardiovascular benefits of physical training in hypertensive postmenopausal women, Lin and Lee (2018) describe various of these mechanisms, as: 1) increased baroreflex sensitivity; 2) reduction of autonomic dysfunction, with increase vagal tonus and reduction of sympathetic tone; 3) improvement of endothelial function induced by serum increase of vasodilators such as acetylcholine and bradykinin, being that the responses appear to be more evident in macrovasculature in relation to microvasculature with rapid improvements in mediated flow dilation even after combined exercises (Vinet *et al*., 2018); 4) Improvements in nitric oxide metabolism due to increased enzymatic activity and phosphorylation of nitric oxide synthase enzyme, as well as increases in nitrite/nitrate and nitrogen oxide serum concentrations that cause endothelium-dependent vasodilation, reduced vascular resistance and improved arterial stiffness in peripheral arteries, even after combined exercises in this population (Son *et al*., 2017).

Considering drug classes, we could not find studies comparing its influence on chronic exercise effects, but acutely, Angiotensin converting enzyme inhibitors do not seem to potentiate the hypotensive effects of exercises (Queiroz *et al*., 2017) and an intense exercise session seems to have independent but additive effects with ARB (Ramirez-Jimenez *et al*., 2018a), being greater than the isolated exercise (Ramirez-Jimenez *et al*., 2018b, 2018a). No studies in our knowledge described these responses using BB drugs. In this sense, the present study showed that moderate intensity combined exercise training can improve resting, awake, 24-hour and 24-hour AUC SBP of hypertensive women after menopause, independent of the use of ARB or BB drugs, and do not altered DBP. Since exercise acts by many different mechanisms as above mentioned, the differences between ARB and BB may be blunted, so that one mechanism overlaps another that is saturated or blocked. Worth highlighting that reductions

around 5 mmHg of SBP and 2 mmHg of DBP are sufficient to reduce the risk of stroke in 13 and 11.5% respectively (Reboldi *et al*., 2011). Moreover theses BP reductions can avoid myocardial infarction, stroke and mortality caused by cardiovascular diseases (Bundy *et al*., 2017).

Besides that, reductions of BPV over time after exercise training in populations with cardiovascular dysfunctions also appear to be promising (Izdebska *et al*., 2004; Marcus *et al*., 2016) and their results can be independent of BP control (Marcus *et al*., 2016). Thus, decreases found in SD of SBP and DBP in the present study are consistent with literature. However, it should be noted that the majority of BPV studies use aerobic training (Izdebska *et al*., 2004; Pagonas *et al*., 2014), only few use dynamic resistance training (Alex *et al*., 2013) or isometric (Taylor *et al*., 2003) and studies with combined exercise training are even rarer (Marcus *et al*., 2016). Besides that, not just the type, but the exercise intensity seems to be related to the BPV variations, in a bell-shaped relationship with the best results in moderate intensities (Iwasaki *et al*., 2003). Its effect pathway seems to be more influenced by endothelium and vascular smooth muscle adaptations to training than of sympathetic vasomotor activity variations (Iwasaki *et al*., 2003). The primary role of vessels is also reaffirmed by the consistent results of improvements by pharmacological interventions on BPV after the use of calcium channel blockers (Eguchi, 2016; Vishram *et al*., 2015; Webb *et al*., 2010) for causing significant improvements in vascular compliance by vasodilation (Eguchi, 2016).

In this sense, we did not find any study relating classes of medication with exercise in BPV, but in an isolated way, drugs present quite diversified results among classes. In a robust meta-analysis, Webb and collaborators (2010) evaluated the effects of different antihypertensive classes on visit to visit analysis and showed superior results of calcium channel blockers compared to any other class of drugs in decreasing interindividual BPV. Although these results were more evident in SBP, the pattern of DBP responses was similar, but milder. Regarding ambulatory BPV, calcium channel blockers appear to have greater influence on ambulatorial BPV than ARB (Eguchi *et al*., 2016; Frattola *et al*., 2000), even if they also show favorable results (Mitsuhashi *et al*., 2009). Although less consistent, the less promising results seem to be related to the use of BB (Eguchi, 2016; Webb *et al*., 2010), but it is worth emphasizing that a smaller number of studies of ambulatory variability are performed with this type of drug in relation to ARB or calcium channel blockers (Eguchi, 2016). Another detail

worth mentioning is that pharmacological improvements in ambulatory BPV also appear to be independent of BP reductions (Eguchi, 2016).

Regarding the BPV comparison between ARB and BB, our study shows smoothly reductions in awake SBP and DBP SD in ARB+Ex even if the initial values were similar between groups. The non-existence of baseline differences between groups is in accordance to the above-mentioned meta-analysis (Webb *et al*., 2010), that demonstrates similar effects of these classes of drugs. Complementary, Vishram *et al*. study (2015) compared ARB and BB based treatment groups for 24 months (without exercise intervention) and did not find any differences between them. However, it is worth mentioning that in this study, both intervention arms were associated with calcium channel blockers and has a visit-to-visit and non-ambulatory analysis. Concerning the different response patterns, the SD decreases in BB+Ex are as expected in population with cardio-metabolic diseases after the exercise training (Marcus *et al*., 2016). On the other hand, the vasodilator action of ARB+Ex may have saturated the mechanism of action of exercise training, given BPV apparent vessel-dependent response to exercise (Iwasaki *et al*., 2003). Moreover, the worse vascular health of postmenopausal women (Lin and Lee, 2018) could mitigate BPV response, preventing more pronounced responses even in BB+Ex.

The present study presents some limitations, such as: few volunteers, there is no untreated group, existence of polytherapies and the non-standardization of doses and active principles. In this sense, although there are no 3rd generation BB users for having additional vasodilatory effects, BB+Ex has 3 propranolol users, and since it is non-selective drug, could induce more systemic responses than atenolol users, although, we did not detect differences in their response patterns in relation to the rest of the group. On the other hand, some characteristics minimized these limitations, such as: there were no differences in physical activity levels, number of polytherapies or anthropometric and pressure characteristics between groups at baseline, training intensities corresponded to the same relative effort and they all took the same drug and dosage for at least 1 year to be adapted to the drug effects. Thus, the results cannot be generalized to other exercise types, other drugs classes or other populations. But they suggest that moderate intensity combined exercise may be a good strategy to maintain cardiovascular health in hypertensive postmenopausal women, and it appears that BPV responses can be more pronounced in BB+Ex. However, this is an incipient response and further

studies are needed to elucidate the influence of various classes of antihypertensive-drugs on exercise responses.

Conclusion

Resting and ambulatory blood pressure responses after combining aerobic and resistance moderate intensity exercise training are similar between postmenopausal hypertensive women using both β-adrenergic blockers and angiotensin receptor blockers antihypertensive-drugs. This exercise training can reduce SBP and DP during awake and 24h values and reduce SBP variability in both groups, but it seems that BPV responses are greater in β-adrenergic blockers users.

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Supplementary data

Ambulatorial blood pressure, Heart rate and Double Product

		M±DP Pre	M±DP Post	Δ	Δ95% CI		p Time	p Group	p Inter.
SBP									
24h (mmHg)	**ARB+Ex**	121 ± 9	115 ± 8	-6 ± 8	-10	1	,006	,172	,428
	BB+Ex	116 ± 7	113 ± 5	-3 ± 7	-7	1			
Awake (mmHg)	**ARB+Ex**	124 ± 9	117 ± 9	-67 ± 9	-12	-1	,002	,149	,304
	BB+Ex	118 ± 7	114 ± 6	-3 ± 5	-7	0			
Asleep (mmHg)	**ARB+Ex**	112 ± 13	110 ± 11	-2 ± 9	-8	3	,173	,288	,711
	BB+Ex	108 ± 12	105 ± 9	-4 ± 13	-12	3			
DBP									
24h (mmHg)	**ARB+Ex**	73 ± 9	71 ± 10	-2 ± 4	-4	0	,339	,761	,344
	BB+Ex	71 ± 8	71 ± 6	0 ± 6	-3	3			
Awake (mmHg)	**ARB+Ex**	75 ± 9	73 ± 10	-2 ± 4	-5	0	,195	,779	,252
	BB+Ex	73 ± 8	73 ± 6	0 ± 5	-3	3			
Asleep (mmHg)	**ARB+Ex**	66 ± 11	66 ± 11	0 ± 8	-5	4	,882	,563	,951
	BB+Ex	64 ± 10	64 ± 8	0 ± 10	-6	6			
MBP									
24h (mmHg)	**ARB+Ex**	90 ± 7	90 ± 8	-1 ± 6	-4	3	,606	,710	,940
	BB+Ex	89 ± 8	89 ± 7	-1 ± 7	-5	3			
Awake (mmHg)	**ARB+Ex**	93 ± 7	91 ± 8	-1 ± 6	-5	2	,367	,710	,904
	BB+Ex	91 ± 8	90 ± 7	-1 ± 6	-4	2			
Asleep (mmHg)	**ARB+Ex**	83 ± 10	85 ± 11	2 ± 9	-3	7	,900	,550	,496
	BB+Ex	82 ± 9	81 ± 9	-1 ± 12	-8	6			
PP									
24h (mmHg)	**ARB+Ex**	48 ± 10	44 ± 6	-4 ± 7	-8	0	,002	,319	,795
	BB+Ex	44 ± 6	41 ± 5	-3 ± 3	-5	-1			
Awake (mmHg)	**ARB+Ex**	48 ± 10	44 ± 6	-4 ± 7	-8	0	,002	,289	,692
	BB+Ex	45 ± 7	41 ± 6	-3 ± 4	-5	-1			
Asleep (mmHg)	**ARB+Ex**	46 ± 11	44 ± 7	-2 ± 7	-6	2	,009	,427	,497
	BB+Ex	44 ± 5	41 ± 4	-4 ± 3	-5	-2			
HR									
24h (mmHg)	**ARB+Ex**	75 ± 7	74 ± 8	-1 ± 6	-5	3	,291	,004	,731
	BB+Ex	67 ± 7	65 ± 8	-2 ± 6	-5	2			
Awake (mmHg)	**ARB+Ex**	78 ± 8	75 ± 9	-2 ± 7	-6	1	,096	,005	,955
	BB+Ex	69 ± 8	66 ± 9	-2 ± 6	-6	2			
Asleep (mmHg)	**ARB+Ex**	65 ± 5	66 ± 5	1 ± 7	-2	5	,748	,003	,145
	BB+Ex	61 ± 6	59 ± 4	-2 ± 3	-4	0			
DP									
24h (mmHg.bpm)	**ARB+Ex**	9085 ± 1055	8527 ± 969	-558 ± 979	-1133	18	,008	,001	,704
	BB+Ex	7777 ± 957	7360 ± 1040	-417 ± 748	-857	22			
Awake (mmHg.bpm)	**ARB+Ex**	9634 ± 1171	8824 ± 1125	-810 ± 960	-1375	-246	,000	,002	,413
	BB+Ex	8127 ± 1097	7625 ± 1162	-502 ± 809	-978	-26			
Asleep (mmHg.bpm)	**ARB+Ex**	7257 ± 1004	7222 ± 634	-35 ± 943	-589	519	,168	,001	,238
	BB+Ex	6572 ± 744	6130 ± 551	-442 ± 662	-831	-53			

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MBP: Mean Blood Pressure; PP: Pulse Pressure; CI: Confidence interval; Inter.: Interaction; ARB+Ex: Angiotensin AT1 receptor blockers users and exercise; BB+Ex: β-blockers users and exercise.

CONSORT checklist

Section/Topic	Item Nº	Checklist item	Reported on page Nº
Title and abstract			
	1a	Identification as a randomised trial in the title	-
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	-
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	20
	2b	Specific objectives or hypotheses	21
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	22
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	21
	4b	Settings and locations where the data were collected	22
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	22-24
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	22-24
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	-
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	-
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	-
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	-
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	-
	11b	If relevant, description of the similarity of interventions	-
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	25
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-

Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	22
	13b	For each group, losses and exclusions after randomisation, together with reasons	22
Recruitment	14a	Dates defining the periods of recruitment and follow-up	23
	14b	Why the trial ended or was stopped	-
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	25
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	22
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	25-29
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	33
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	33
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	29-33
Other information			
Registration	23	Registration number and name of trial registry	22
Protocol	24	Where the full trial protocol can be accessed, if available	22
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	34

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