UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
Programa de Pós-Graduação em Ciências da Saúde:
Cardiologia e Ciências Cardiovasculares

USO DE DIURÉTICOS E DE SILDENAFIL EM PACIENTES COM INSUFICIÊNCIA CARDÍACA CRÔNICA: REVISÃO SISTEMÁTICA, METANÁLISE E DADOS PRELIMINARES DE ENSAIO CLÍNICO RANDOMIZADO MULTICÊNTRICO

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How are we going to win this battle? Surely not with a single magic bullet, wheter it is a gene, device or drug. Most important, as any battle, we must understand the terrain on wich it will be fought.

Eugene Braunwald

ABREVIATURAS E SIGLAS

AAS	Ácido acetilsalicílico
AVE	Acidente vascular encefálico
BRA	Bloqueador do receptor da angiotensina
cGMP	Monofosfato de guanosine cíclica
EAV	Escala análogo visual
ECR	Ensaio clínico randomizado
fe	Fração de ejeção
HAP –	Hipertensão arterial pulmonar
HP	Hipertensão pulmonar
IC	Insuficiência Cardíaca
IECA	Inibidores da enzima conversora de angiotensina
IMC	Índice de massa corporal
NT-proBNP	Porção N-terminal do peptídeo natriurético cerebral
NYHA	*New York Heart Association*
pad	Pressão arterial diastólica
PAPm	Pressão da artéria pulmonar média
PAS	Pressão arterial sistólica
Poap	Pressão de oclusão da artéria pulmonar
PSAP	Pressão sistólica da artéria pulmonar
ReBIC	Rede Brasileira de Insuficiência Cardíaca
RVP	Resistência vascular pulmonar

SUMÁRIO

RESUMO

A necessidade de buscar novos tratamento para a Insuficiência Cardíaca (IC) crônica levanta o questionamento da eficácia e segurança de drogas que não foram adequadamente testadas ou que ainda não tiveram sua eficácia aceita pela comunidade científica. O sildenafil é um vasodilatador com potencial eficácia na redução da pressão sistólica da artéria pulmonar (PSAP), mas com pequenos estudos e sem demonstração de impacto em desfechos duros. Os diuréticos de alça são utilizados rotineiramente em pacientes com IC sem sinais de congestão e tal prática não está recomendada nas diretrizes terapêuticas, desconhecemos sua eficácia e segurança neste cenário. No intuito de elucidar estas questões, foram desenvolvidos I) revisão sistemática com metanálise para estudo uso de sildenafil. II) revisão sistemática com metanálise para estudo uso de diurético de alça, III) Delineamento e execução em andamento de ensaio clínico randomizado multicêntrico testando a retirada de diurético de alça. **I e II) Métodos e resultados**: Ambas revisões sistemáticas foram realizadas no Pubmed, Embase e Cochrane, e termos relacionados à insuficiência cardíaca crônica diurético de alça e sildenafil foram utilizados, respectivamente. Após avaliação de texto completo, apenas estudos em humanos foram incluídos na metanálise. A droga sildenafil foi avaliada em 9 estudos randomizados contra placebo e demonstrou redução de hospitalização (RR 0.29, 95% C.I 0.11 to 0.78) e melhora progressiva em parâmetros funcionais e hemodinâmicos O uso de diurético de alça foi testado em 7 ensaios clínicos e não mostrou significância em piora da função renal, distúrbio eletrolítico e mudança de peso. **III) Métodos e resultados:** Em um estudo duplo-cego randomizado, de não inferioridade, multicêntrico compara-se o a segurança e tolerabilidade da retirada de furosemida de pacientes com IC crônica e estável com disfunção ventricular. Com início da coleta em setembro de 2015, até o momento 96 pacientes foram randomizados. **Conclusão:** Quanto ao sildenafil, já temos evidências que apontam para um efeito benéfico e progressivo na melhora da capacidade funcional, perfil hemodinâmico e redução de hospitalização em pacientes com IC com disfunção ventricular e pressão da artéria pulmonar elevada A recomendação para uso de diurético de alça em pacientes estáveis com IC permanece uma incógnita e o ensaio clínico em andamento nos trará uma resposta de importante impacto clínico na tomada de decisão para manutenção do uso de diurético**.**

Palavras-chave: Insuficiência Cardíaca; Diuréticos; Sildenafil; Inibidores das Fosfodiesterase 5;

ABSTRACT

The challenges and promises of new treatments for chronic heart failure (CHF) raises the question the efficacy and safety of drugs that have not been properly tested or that have not yet had their efficacy accepted by the scientific community. Sildenafil is a vasodilator with potential efficacy in reducing pulmonary artery systolic pressure (PSAP), but with small studies and no demonstration of impact on hard outcomes. Routinely, Loop diuretics are used in patients with HF without signs of congestion and such practice is not recommended in the therapeutic guidelines, we do not know its efficacy and safety in this scenario. In order to elucidate these questions, I) systematic review with meta-analysis were developed to study the use of sildenafil. II) systematic review with meta-analysis to study the use of loop diuretics, III) Design and execution in progress of a multicenter randomized clinical trial testing for loop diuretic withdrawal. I and II) Methods and results: Both systematic reviews were performed in PubMed, Embase and Cochrane, and terms related to chronic diuretic heart failure of the loop and sildenafil were used, respectively. After full-text evaluation, only human studies were included in the meta-analysis. The drug sildenafil was evaluated in 9 randomized placebo-controlled studies and demonstrated a reduction in hospitalization (RR 0.29, 95% CI 0.11 to 0.78) and progressive improvement in functional and hemodynamic parameters. The use of a loop diuretic was tested in 7 clinical trials and did not show significant deterioration in renal function, electrolyte disturbance and weight change. III. METHODS AND RESULTS: In a double-blind randomized, non-inferiority, multicenter study, the safety and tolerability of furosemide withdrawal from patients with chronic and stable HF with ventricular dysfunction were compared. Randomization started at September 2015, to the moment 96 patients were randomized. CONCLUSION: Regarding sildenafil, we already have evidence of a beneficial and time-related effect on the improvement of functional capacity, hemodynamic profile and reduction of hospitalization in patients with HF with ventricular dysfunction and elevated pulmonary artery pressure. The recommendation for the use of a loop diuretic in stable patients with HF remains an unknown and the ongoing clinical trial will provide us with an important clinical impact response in the decision making to maintain the use of diuretics.

Keywords: Heart Failure; Diuretics; Sildenafil Citrate; Phosphodiesterase Inhibitors 5

1. MARCO TEÓRICO

1.1 INSUFICIÊNCIA CARDÍACA

A constante crescente prevalência da insuficiência cardíaca (IC) está atingindo proporções epidêmicas. Com o envelhecimento da população e a melhora no tratamento das doenças cardiovasculares, a tendência é de que os números sigam aumentando. Entre os idosos de países ocidentais, já é a principal causa de admissão hospitalar e atinge cerca de 5% da população mundial(1). No cenário brasileiro, no período de 2004 a 2014, foram registrados 301.136 mortes(2), sendo que a enfermidade é a principal causa de reospitalização, com elevada mortalidade em 5 anos, despendendo cerca de 5% do orçamento destinado aos gastos com saúde(3)

A IC é uma doença crônica e o tratamento envolve diversas medicações. Portanto, a necessidade de um modelo de acompanhamento longitudinal e multidisciplinar é imprescindível e tem se mostrado como uma das intervenções de maior eficácia. O manejo da IC teve enormes avanços nos últimos 30 anos e esses, nos fazem questionar a eficácia de antigas drogas, como furosemida e digoxina. Tais medicações foram implementadas no arsenal terapêutico sem estudos com delineamentos adequados e foram testadas em pacientes virgens de outros tratamentos.

As inovações não apenas nos fazem questionar o velho, o antigo tratamento, mas trazem um melhor entendimento sobre a patofisiologia e isso nos faz reconhecer fatores que podem estar associados com a piora e com a progressão da doença.

1.1.1 HIPERTENSÃO PULMONAR GRUPO 2

A hipertensão arterial pulmonar (HAP) começou a ser estudada devido à sua prevalência entre os pacientes com disfunção ventricular, atingindo entre 49% a 79% dos pacientes com IC com

disfunção ventricular(4). O desenvolvimento da HAP é consequência do prejudicado relaxamento e distensibilidade do ventrículo esquerdo(5). Independentemente da etiologia da disfunção ventricular esquerda, a presença de pressões elevadas na artéria pulmonar está associada com maior gravidade dos sintomas, baixa tolerância ao exercício e pior prognóstico(6).

Define-se hipertensão pulmonar (HP) quando a pressão da artéria pulmonar média (PAPm) atinge valores iguais ou superiores a 25 mmHg em repouso, mensurada por cateterismo da artéria pulmonar. A PAPm pode elevar-se devido ao aumento da pressão de oclusão da artéria pulmonar (Poap), devido ao fenômeno hiperdinâmico, pelo aumento do débito cardíaco ou por hiper-resistência, devido ao aumento da resistência vascular pulmonar (RVP). Estabelece-se hipertensão venosa pulmonar quando a Paop >15mmHg, pós-capilar devido à doença cardíaca esquerda (7). A classificação de Dana Point (8), divide-se em cinco categorias, a HP relacionada com doença cardíaca esquerda é classificada como grupo 2 e tem, na hipertensão venosa pulmonar, o gatilho de sua fisiopatogenia.

O aumento da pressão no átrio esquerdo e de forma retrógrada e passiva eleva a pressão da artéria pulmonar média. Inicialmente a resistência vascular pulmonar está normal, no entanto, o estresse contínuo na vasculatura pulmonar e o componente pós capilar, congestão venosa, levam ao barotrauma da microcirculação. Este fenômeno promove o remodelamento estrutural das artérias da vasculatura pulmonar, com proliferação de miofibroblastos, com deposição de fibrose e matriz extracelular, que passam a formar o componente pré-capilar da hipertensão pulmonar do grupo 2 (6). A disfunção endotelial pode levar ao desequilíbrio das substâncias vasodilatadoras e vasoconstritoras nas artérias da pequena vasculatura pulmonar, desencadeando um aumento de endotelina-1, redução de óxido nítrico circulante, dessensibilização dos receptores de peptídeos natriuréticos e ativação da cadeia inflamatória.

Apesar da hipertensão pulmonar ser um processo multifatorial e progressivo, a observação da redução da pressão sistólica da artéria pulmonar e a manutenção de sua normalização em pacientes submetidos ao implante de dispositivos de assistência ventricular esquerda indicam que essa alteração na circulação pulmonar pode ser reversível (9).

Está claro que alterações na hemodinâmica pulmonar ocorrem desde estágios iniciais da insuficiência cardíaca e que devemos considerar a redução da pressão sistólica da artéria pulmonar e a reversibilidade desse ciclo nocivo como um alvo terapêutico naqueles pacientes com insuficiência crônica e manejo otimizado.

1.1.2 SILDENAFIL E INIBIDORES DA FOSFODIESTERASE-5

Sildenafil é um inibidor seletivo da fosdiesterase-5, a principal isoenzima das fosfodiesterases responsável pela hidrólise intracelular da monofosfato de guanosine cíclica (cGMP) na vasculatura pulmonar. Altas concentrações de fosfodiesterase-5 são encontradas nas células do músculo liso dos vasos pulmonares e na vasculatura sistêmica, tanto venosa, quanto arterial periférica. Inibição da fosfodiesterase-5 prolonga a ação do cGMP, que é o segundo mensageiro na cascata de liberação do óxido nítrico. Isto provoca o aumento da disponibilidade do óxido nítrico no leito vascular, causando relaxamento das células musculares lisas e, consequentemente, vasodilatação (10,11).Tal mecanismo justifica o uso do sildenafil no tratamento da disfunção erétil, distúrbio no qual a droga faz parte da primeira linha de tratamento (12,13)

A indicação de sildenafil na terapêutica da hipertensão arterial pulmonar primária está bem estabelecida, mostrando benefícios na melhora da capacidade funcional e redução da pressão média da artéria pulmonar (14). No entanto, estudos demonstrando a eficácia do sildenafil em pacientes com

IC são limitados e com amostra pequena, com desfechos restritos à avaliação hemodinâmica, sem dados robustos sobre o benefício clínico desta terapia (15), o que tampouco justifica o uso de sildenafil na insuficiência cardíaca, independentemente da fração de ejeção do ventrículo esquerdo e classe funcional (16,17).

O Sildenafil tem se mostrado uma droga promissora quando se almeja a vasodilatação do sistema arterial. Alguns estudos que avaliaram o efeito do sildenafil em pacientes hipertensos com disfunção diastólica mostraram, por avaliação ecocardiográfica, a indução do relaxamento ventricular esquerdo e a redução de NT-proBNP (18).

O estudo RELAX é o maior ensaio clinico randomizado, multicêntrico, realizado com sildenafil em pacientes com fração de ejeção preservada num seguimento de 24 semanas. Embora tenha sido muito esperado, seus resultados não mostraram benefício na melhora da capacidade de exercício ou em desfechos secundários como mortalidade e hospitalização (16). No entanto, estão sendo feitas diversas análises de subgrupos do estudo RELAX, na tentativa de identificar possíveis preditores de resposta ao sildenafil. Recentemente, uma subanálise demonstrou que o grupo de pacientes com fibrilação atrial apresentou pior performance ao exercício físico (19), assim como Borlaug et al. Subanálise do estudo RELAX evidenciou que ocorre uma modesta redução da contratilidade miocárdica agudamente após o uso de sildenafil e sugere que o efeito do sildenafil é benéfico na vasculatura sistêmica, porém questiona seu impacto no remodelamento ventricular (20).

Uma das hipóteses para a ausência de benefício nos pacientes com fração de ejeção preservada estaria relacionada com o grau de disfunção endotelial. Especula-se que pacientes com maior acometimento e doença do endotélio apresentariam maior benefício com o uso do sildenafil, visto que seu principal efeito é na vasodilatação arterial, aumento do óxido nítrico circulante (21).

1.1.3 DIURÉTICOS DE ALÇA

Introduzida no mercado há 45 anos, a furosemida – um potente diurético de alça – alterou a história dos pacientes com insuficiência cardíaca. Desde então, salvou a vida de muitas pessoas em edema agudo de pulmão e eliminou a prática das sangrias. Seu uso intravenoso promove uma rápida diurese e natriurese. Os diuréticos de alça são, até hoje, os mais usados em quadros edematosos. Seu mecanismo de ação consiste na inibição do co-transportador Na^{+}-K^{+}-$2Cl^{-}$ na porção ascendente da alça de henle, onde aproximadamente um terço do sódio é reabsorvido. O diurético de alça inibe a reabsorção de água e sódio e aumenta a excreção do potássio, magnésio e cloreto. Furosemida, bumetanide, torsemide e ácido *ethacrynic* são os representantes dessa classe de diuréticos(22).

Diuréticos aparecem como base do tratamento de pacientes com insuficiência cardíaca crônica ou em episódios de descompensação. No entanto, apesar de seus benefícios na resolução de quadros de congestão com aumento da diurese, estudos apontam que a depleção de eletrólitos e a redução da volemia no intravascular provocam a ativação do Sistema renina angiotensina aldosterona e outros sistemas neuro-hormonais que podem perpetuar o quadro de congestão(23,24).

1.1.4 RECOMENDAÇÕES PARA O USO DE DIURÉTICOS DE ALÇA.

As recomendações da diretrizes terapêuticas atuais são unanimes ao restringir o uso de diuréticos para pacientes (25) com sinais e sintomas de congestão, mas reforçam a falta de evidência para tal recomendação e a necessidade de sólidas evidências científicas que avaliem a eficácia e segurança dos diuréticos de alça (26).

A diretriz brasileira de IC crônica, publicada em 2012, recomenda o uso de diuréticos em pacientes com sinais e sintomas de congestão com grau de recomendação I e nível de evidência C (27). Já o Consenso Europeu de 2016, além de recomendar o uso de diurético de alça para redução

de sintomas em pacientes hipervolêmicos (IB), recomenda o uso de diurético de alça para reduzir hospitalizações com grau de recomendação IIa e nível de evidência B (26). Não diferente, a diretriz da sociedade Americana coloca os diuréticos de alça como tratamento para pacientes com disfunção sistólica e retenção de fluídos com o objetivo de melhorar sintomas (IC) (25).

Ambas diretrizes, da sociedade europeia e da americana, usam como referência para recomendação a metanálise da Cochrane publicada por Faris em 2014, que mostrou redução significativa de mortalidade e hospitalização na análise de 14 estudos com 525 pacientes comparando o uso de diurético de alça versus placebo, digoxina ou inibidores da enzima conversora de angiotensina (IECA) (28). A metanálise de Faris foi retirada do PubMed, em abril de 2016, por questões metodológicas e erros de seleção da população dos estudos incluídos (29). Portanto, os maiores consensos para manejo de IC fazem uma recomendação usando um estudo com erros metodológicos.

1.1.5 ESTUDOS OBSERVACIONAIS COM DIURÉTICOS DE ALÇA

Estudos observacionais apontam para um efeito deletério pelo uso prolongado de diuréticos, provocando perda de função renal e aumento da mortalidade. Acredita-se que o uso de furosemida em doses elevadas resulte em redução do volume intravascular circulante, sinalizando a ativação do sistema renina-angiotensina, junto com uma redução compensatória dos peptídeos natriuréticos (30). Diuréticos também podem contribuir para progressão da doença por provocarem depleção de eletrólitos, distúrbios dos minerais ósseos, hipotensão e fibrose miocárdica. Em subanálise do estudo SOLVD, verificou-se que os pacientes euvolêmicos recebendo furosemida apresentavam um aumento na atividade da renina plasmática (31).

Em estudo com análise de pontuação de tendências com pacientes ambulatoriais NYHA classes I-II, Dini et al. demonstraram que o risco de morte aumenta linearmente com o aumento das doses diárias de furosemida estratificadas por quartis. A dose de 50 mg/dia foi identificada como valor limite para predizer a maior mortalidade em três anos (32). Do mesmo modo, Damman et al. em subanálise do estudo CORONA mostraram que pacientes em uso de furosemida apresentaram piora da função renal, independente da dose utilizada, e que o grupo de pacientes com dose > 80 mg apresentou maior mortalidade e hospitalização (33).

No entanto, especula-se se os diuréticos contribuem para o aumento da mortalidade ou são apenas marcadores de gravidade e instabilidade. Mielniczuk et al. mostraram, em coorte de 183 pacientes ambulatoriais com IC, que pacientes em uso de doses > 80 mg/dia apresentaram mais episódios de instabilidade, hospitalizações e maior mortalidade. Porém, quando ajustada para estabilidade clínica, a associação da mortalidade com o uso de diurético perde sua significância (34). Outra justificativa na tentativa de inocentar a furosemida e sua relação causa-efeito com mortalidade é que a associação entre grave disfunção ventricular e dano crônico à função renal já está bem estabelecida e conhecida como Síndrome cardiorrenal. Pacientes com disfunção renal crônica necessitam de doses maiores de diuréticos para atingir a concentração transglomerular adequada e obter a mesma resposta da droga quando comparados aos pacientes com função renal preservada. A disfunção renal está associada com o aumento da mortalidade de forma independente, tanto em pacientes sintomáticos quanto em pacientes assintomáticos com disfunção do ventrículo esquerdo (35).

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3. JUSTIFICATIVA

Pequenos ensaios clínicos demonstraram melhora hemodinâmica com redução da pressão sistólica da artéria pulmonar com o uso de sildenafil em pacientes ambulatoriais com insuficiência cardíaca e disfunção ventricular. Considerando o mecanismo pelo qual se justifica o efeito do sildenafil acredita-se que o benefício da droga está diretamente relacionado com o tempo de uso. Até o presente momento, não existem dados robustos que confirmem esta associação.

Na presença da necessidade de orientações mais específicas e seguras a respeito da prescrição de diuréticos de alça na população de pacientes crônicos com insuficiência cardíaca, torna-se importante a realização de estudos que sumarizem os achados de ensaios clínicos randomizados anteriores na intenção de responder a esta questão.

Considerando-se que o uso de diuréticos de alça está recomendado para a manutenção da volemia, questionar a suspensão de diurético em pacientes euvolêmicos é plausível, especialmente, num cenário que estudos observacionais associam o uso de diuréticos com aumento de mortalidade.

4. HIPÓTESE

O uso de sildenafil em pacientes ambulatoriais com insuficiência cardíaca e com disfunção ventricular tem seu benefício relacionado ao tempo de uso da medicação.

O uso de diurético de alça em pacientes com insuficiência cardíaca crônica não apresenta benefício.

A retirada de diurético de alça em pacientes com insuficiência cardíaca crônica com disfunção ventricular, em classe funcional NYHA I-II não é inferior à manutenção da droga.

5. OBJETIVOS

- Avaliar o efeito do uso de diurético de alça sobre o risco de ocorrência de congestão pulmonar e sistêmica, em estudos de intervenção em humanos (metanálise);
- Avaliar a segurança e tolerabilidade da retirada de diurético furosemida em pacientes com IC classe funcional NYHA I-II e com fração de ejeção $\leq$ 45% (ensaio clínico randomizado protocolo);
- Avaliar o efeito do uso de sildenafil sobre parâmetros de capacidade funcional, hemodinâmicos e incidência de hospitalização, em estudos de intervenção em humanos (metanálise).

6. ARTIGO 1 – Efeito associado ao tempo de uso de Sildenafil em pacientes com Insuficiência Cardíaca: uma revisão sistemática e metanálise de ensaios clínicos randomizados

Time-Dependent Effects of Sildenafil in Heart Failure Patients:

A Systematic Review and Meta-analysis of Randomized Controlled Trials

Running Title: Meta-analysis of sildenafil for heart failure patients

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e-mail: biolo.andreia@gmail.com **Abstract**

Background: Sildenafil is a selective inhibitor of type 5 phosphodiesterase (PDE5) with favorable acute hemodynamic effects in patients with heart failure. However, evidence of time-related benefits is limited to small size studies.

Methods and Results: We conducted a systematic review and meta-analysis of randomized controlled clinical trials (RCTs) of sildenafil therapy in patients with heart failure. A systematic search was realized by two independent reviewers using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (1966-2017), and reports from scientific meetings (2005-2016). Reviewers determined methodological quality of studies and extracted descriptive and outcome data. Studies were classified in 3 groups based on period of treatment: acute: 60 minutes to 24 hours; mid-term: >24hours to 6 months; and long-term: more than 6 months. Nine RCTs enrolling 316 patients with heart failure were included. Compared to placebo, sildenafil therapy resulted in time-dependent improvements in peak VO2: there was no change with acute therapy, and significant step-wise increase with mid-term (+2.55 $ml.kg^{-1}.min^{-1}$, 95% CI 0.20 to 4.91, p=0.03), and long-term therapy (+3.12 $ml.kg^{-1}.min^{-1}$. 95% CI 1.90 to 4.34, p<0.001). Similar results were found for the slope of increase in ventilation over carbon dioxide output (VE/VCO_2 slope), and LV ejection fraction. On the other hand, reduction in systolic pulmonary arterial pressure (PAP) was observed across all time points, and it was also more pronounced with mid and long-term follow-up. Finally, pooled analysis showed a significant reduction in all-cause hospitalizations with sildenafil treatment (RR 0.29, 95% CI 0.11 to 0.78, p=0.01).

Conclusions: Sildenafil use appears to have time-related benefits on reducing pulmonary hypertension and on improving left ventricular and exercise performances in patients with stable heart failure. Pooled data also showed a benefit on reducing hospitalizations. Adequately powered RCTs are needed to evaluate its role on heart failure survival.

Keywords: heart failure, pulmonary hypertension, sildenafil, meta-analysis

Introduction

Pulmonary hypertension is highly prevalent in patients with heart failure, present in 42% to 80% of patients with severe left ventricular (LV) systolic dysfunction (1,2). It has also been increasingly recognized as a consequence of heart failure with preserved left ventricular ejection fraction (LVEF)(3,4). Pulmonary hypertension usually develops as a consequence of impaired LV relaxation and distensibility, and has innumerous adverse anatomical and functional effects on the pulmonary capillaries, arterial and venous circulation, and right ventricular function (3). The presence of pulmonary hypertension is usually associated with worse prognosis in patients with heart failure (2,4,5).

Sildenafil is a selective inhibitor of type 5 phosphodiesterase (PDE5), the main phosphodiesterase isoform responsible for the hydrolysis of intracellular cyclic guanosine mono-phosphate (cGMP) in the pulmonary vasculature, ultimately leading to a selective vasodilatory effect (6,7). It has been successfully used to treat erectile dysfunction and has been shown to improve exercise capacity and decrease pulmonary vascular resistance in patients with either group 1 or group 2 pulmonary arterial hypertension (8-11).

After PDE5 inhibition efficacy was proven in the aforementioned settings, other studies have been published evaluating its safety and acute effects in heart failure patients with different etiologies and ventricular functions(12,13). Further studies were then performed to assess its long-term effects, most of which demonstrated lasting benefit in this subset of patients, even in the absence of significant pulmonary hypertension (14-17) However, studies evaluating sildenafil in patients with heart failure are limited to small sample sizes and results are therefore mostly restricted to hemodynamic findings with no robust data about clinical benefits of this therapy. The aim of the present study was to perform a systematic review and meta-analysis of randomized, controlled trials of sildenafil in patients with

heart failure. We examined the acute and chronic effects of sildenafil on pulmonary arterial pressure (PAP), LVEF, peak oxygen consumption (VO2), the slope of increase in ventilation over carbon dioxide output (VE/VCO2 slope), and its chronic effects on hospitalizations in these patients.

Methods

Search Strategy

We searched MEDLINE (PubMed), EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. All searches were not limited to time-period or languages. Searches were performed between December 2016 and January 2017. The MEDLINE database was searched using MeSH keywords including *sildenafil, heart failure*, and *randomized controlled trials.* The Cochrane Library and Central Register of Controlled Trials were searched using exploding keywords including *sildenafil and 5-phosphodiesterase inhibitors.* The EMBASE database was searched by using exploding keywords *sildenafil* and *heart failure.* We conducted additional searches to identify non-published studies reported only at scientific meetings and at ClinicalTrial.gov. We also performed electronic searches of the annual scientific sessions of the European Society of Cardiology (2005-2016), Heart Failure Society of America (2005-2016), and International Society for Heart and Lung Transplantation (2005-2016). This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement(18).

Eligibility Criteria

Reports of randomized clinical trials (RCT) of sildenafil in patients with heart failure, left ventricle systolic dysfunction and elevated pulmonary arterial pressure were included, with no

restriction about *New York Heart Association* (NYHA) functional classification, or comparison agent (placebo or other vasodilators). We included trials if they reported at least one of the following as outcome data: systolic PAP, either from invasive pulmonary monitoring or echocardiography, peak VO2 and/or VE/VCO_2 slope from cardiopulmonary exercise test, hospitalization, and mortality. Reports of crossover trials were not excluded. Exclusion criteria were as follows: (1) studies of post cardiac transplantation, early post-myocardial infarction patients or on left ventricular assistance device; (2) children or animal studies; (3) RCTs that evaluated different outcomes from those cited above; (4) duplicate publications, where reports with more complete and/or updated data was available from the same trial. A PRISMA flow diagram of the study selection process is illustrated in **FIGURE 1.**

Data extraction and quality assessment

Eligibility assessment and data extraction were both performed independently by two blinded investigators (P.R.R. and E.D.A.). Reviewers were not blinded to authors, institutions, or manuscript journals. Abstracts that did not provide enough information regarding the inclusion and exclusion criteria were retrieved for full-text evaluation. Reviewers independently evaluated titles, abstracts and full-text articles and determined study eligibility. The *GRADE approach* was utilized to verify the quality of reports and the agreement rate between reviewers was = 90% for quality assessment (19) (supplement material). Disagreements were solved by consensus and if disagreement persisted, by a third reviewer (A.B.). To avoid possible double counting of patients included in more than one report by the same working group, patient recruitment periods and baseline characteristics were evaluated. The corresponding author was contacted as needed to obtain data not included in the published report. Detailed search strategy and grade tables are available at supplementary material.

Information on participant characteristics, trial design and duration, sildenafil dose, control,

and outcomes were extracted using a standardized protocol. Main outcomes included systolic PAP, LVEF, peak VO2, VE/VCO2 slope, and number of patients experiencing hospitalization or death. We also evaluated other hemodynamic data including systemic vascular resistance and wedge pulmonary pressure. Adverse effects as hypotension and bradycardia was evaluated by systemic arterial pressure and heart rate.

Studies were classified in 3 groups based on period of treatment with sildenafil: acute response: 60 minutes to 24 hours; mid-term response: >24hours to 6 months; and long-term response: more than 6 months.

Statistical analysis

Experimental and placebo groups were compared using relative risk (for hospitalization) or unstandardized mean differences (systolic PAP, LVEF, peak VO2 and VE/VCO2 slope). Pooled estimates across studies and 95% confidence intervals (CI) were determined by meta-analysis using the log transformation. The studies were grouped by time of evaluation (acute, mid-term and long-term). The log transformation with the Mantel_Haenszel method was used for relative risk estimation and no transformation with the inverse variance method was used for mean differences. Between studies heterogeneity was assessed using the I^2 statistics and the p-value from the Q test. I^2 above 50% was considered high heterogeneity and the random effects model with DerSimonian and Laird estimation method was then used. Comparison among subgroups was carried out using Bonferroni criterion. All analyses were carried out in Stata statistical software version 10.0 (StataCorp LP, College Station, Texas).

Results

We initially identified 2089 potentially relevant reports. Of these, 1913 reports were excluded based on title and abstract. Full-text versions of the remaining 68 reports were then retrieved for detailed evaluation. Of these, 59 reports were excluded for reasons listed in Figure 1. Briefly, 12 presented different outcomes and 12 trials with different population from those studied in this meta-analysis, 6 review and 5 letters were between reports. The remaining 9 randomized controlled trials were included in the meta-analysis.

All included studies were randomized, double-blinded, placebo-controlled trials. A total of 316 patients were randomized. Characteristics of the selected studies are summarized in Table 1. Three trials had a crossover protocol; all employed a placebo or drug-free wash out period (20-22). All trials included only patients with LV dysfunction and mild to moderate secondary pulmonary hypertension. Patients had predominantly chronic stable heart failure and were on optimized treatment. The proportion of patients on NYHA functional class IV across the studies was small (4% to 13%). The mean age of participants ranged between 45 and 72 years. Male subjects comprised 77% to 100% of the enrollees.

On time-dependent analysis, sildenafil therapy resulted in stepwise improvements on peak VO2: no significant acute effects (+1.62 $ml.kg^{-1}.min^{-1}$95% CI -1.62 to 4.87), increase at mid-term therapy (+2.55 $ml.kg^{-1}.min^{-1}$95% CI 0.20 to 4.9), and further increase at long-term (+3.12 $ml.kg^{-1}.min^{-1}$95% CI 1.90 to 4.34) (Figure 2A). Likewise, VE/VCO_2 slope improved at mid and long-term follow-up (mid-term, -6.28, 95% CI -9.07 to -3.49; long-term -7.78, 95% CI -11.06 to -4.51), with no evidence of acute effects (Figure 2B).

As depicted in Figure 3, analyses of functional and hemodynamic parameters showed a stepwise time-dependent improvement on LVEF (acute, + 1.04%, 95% CI -0.48 to 2.55; mid-term + 5.35%, 95% CI 3.40 to 7.30; long-term + 6.0%, 95% CI 3.25 to 8,75) (Figure 3A). On the other hand,

efficacy of sildenafil to reduce systolic PAP was observed early after intervention (reduction of -8.56 mmHg, 95% CI -10.33 to -6.78 in the acute response group compared to -12.05 mmHg, 95% CI-14.00 to -10.10 at mid-term and -13.30 mmHg, 95% CI -16.47 to -10.13 in the long-term group) (Figure 3B). No difference was found for systemic vascular resistance (Figure 3C). Wedge pulmonary pressure values were not changed at acute and mid-term periods, with a subtle reduction at long-term, which was analyzed in only one study (Figure 3D).

All-cause hospitalizations were reported by 3 of the 9 trials for patients with 1, 6 and 12 months of follow-up. In one study, no events were observed at sildenafil group. All-cause hospitalizations were significantly reduced in sildenafil treated patients (RR 0.28, 95% C.I 0.09 to 0.85), as shown in Figure 4.

Heart rate and systolic blood pressure (SBP) were evaluated as changes in these variables could represent adverse effects of sildenafil. No change was observed for heart rate regardless of the time. A small reduction on SBP was observed only in the acute response, and this reduction was not observed in mid- and long-term responses (Figure 5).

Discussion

The present meta-analysis of sildenafil in patients with heart failure has three main findings: 1) sildenafil therapy reduced pulmonary hypertension and improved left ventricular and exercise performances, 2) the detected improvements were not only maintained with long-term use, but also increased in magnitude, as for systolic PAP, ejection fraction, peak VO_2, and VE/VCO2 slope; and 3) pooled analysis showed a significant effect on reducing hospitalizations in sildenafil-treated patients.

Sildenafil, a potent inhibitor of PDE5, produces significant vasodilation mediated by nitric oxide (NO) release and cGMP accumulation. Sildenafil has been shown to produce pulmonary and systemic vasodilatation, decreased LV filling pressure, and increased cardiac index without causing systemic hypotension (26,27). These effects contrast those of most currently used vasodilators, whose use is limited by systemic hypotension and depression of myocardial contractility (28,29). Our secondary outcomes showed no variance of heart rate ate systolic arterial pressure during sildenafil use, suggesting the safety of drug. In addition, the mechanisms for the benefits of sildenafil seem not to be restrict to systolic PAP reduction or to its action in the arterial bed; direct endothelial and myocardium protective effects have been described and are believed to be important, especially in the heart failure scenario (30,31)

Pulmonary hypertension has been extensively studied in the context of heart failure, mostly because of its strong association with mortality in these patients (32,33). The present analysis shows an important reduction of systolic PAP with sildenafil, with a time related response. At this meta-analysis we could only observe the effect of sildenafil on patients presented elevated pulmonary arterial pressure. Hryniewicz et al. (25) was the only study without elevated pulmonary hypertension as inclusion criteria, but it was not evaluated for primary outcomes. To explain how sildenafil could impact on remodeling we need to understand that a pathogenesis of group2 PH is a multistep and multifactorial process developing through the progressive mechanical lung capillary injury, vascular functional impairment with structural remodeling, and subsequent worsening in right ventricular function. Experimental studies and anatomopathological reports have been associated the interstitial and alveolar edema with proliferation of myofibroblasts with fibrosis, extracellular matrix deposition and increased expression of a series of pro-inflammatory cytokines (34). Once sildenafil promotes pulmonary vasodilatation and increases nitric oxide availability, this cascade is interrupted. Nonetheless, the question if the benefit of sildenafil is restricted to patients with elevated pulmonary

hypertension still without answer.

Two measures of cardiorespiratory performance, peak VO2 and VE/VCO2 slope, were both significantly improved after sildenafil treatment. The peak VO2 improvement, of 3.48 $ml.kg^{-1}.min^{-1}$, represents an improvement which is similar or greater than the expected effect size from conventional aerobic or resistance training (34), or from modalities such as cardiac resynchronization therapy (36) . VE/VCO2 slope was also significantly reduced in the treatment group. In fact, ventilatory efficiency, as assessed by the VE/VCO2 slope, has been shown to be a powerful prognostic marker in the heart failure population, superior to peak VO2 in some studies (37,38). Most studies using sildenafil on heart failure adopted ventilatory parameters as primary outcomes.

Another interesting observation from the present meta-analysis is related to the greater improvement in systolic PAP and VE/VCO2 slope with long-term treatment. This time-dependent continued improvement (i.e., the longer the treatment, the greater the improvement) could suggest that the observed findings were not purely related to hemodynamic effects but rather involved arterial and/or myocardial remodeling effects which might take place with long-term use. In fact, decreased LV and septal wall thickness and LV mass have been shown with chronic sildenafil treatment, supportive of direct remodeling and prolusitropic effect on cardiac function(39) and experimental studies have been established reduction on inflammatory cytokines and promoting angiogenesis. However, one should take this as a hypothesis-generating observation rather than a conclusion from the present study. Further studies are needed to better address this issue.

Accumulated data of individual trials cannot confirm benefits of sildenafil in reducing either mortality or hospitalization when compared to placebo in patients with heart failure reduced ejection fraction (HFrEF). The present meta-analysis demonstrates that sildenafil significantly reduced the

risk of all-cause hospitalizations in these patients and the time-dependent effect on hemodynamic parameters (40,41). Our analysis, however, should be seen in a conservative way given the reduced number of trials and the small population enrolled by these trials. To the best of our knowledge, this represents the largest number of analyzed patients.

It is important to consider some published trials with sildenafil on heart failure that were not described on this meta-analysis because they didn't fill up inclusion criteria, although their results corroborate with our findings. Bocchi et al. showed significant improvement at exercise capacity after a 50 mg of sildenafil on 6-minute-walking and cardiopulmonary exercise test on an acute evaluation (42). Curoto-Grasiosi et al. in a 70 patients clinical trial also demonstrated improvement of exercise capacity after 2 hours of 50 mg of sildenafil on 6-minute-walking-test (43). RELAX was the only multicenter double blind trial, with robust sample of heart failure patients with preserved left ventricle function followed by 24 weeks and was not able to reach any significant outcome, including exercise capacity (44). A protocol of a multicenter trial with HFrEF patients has been published on 2012 but this study has suspended participant recruitment recently (45).

The present study has some limitations. The selected trials were small size studies, majority of them comes from a single institution which increase a risk of bias. The GRADE approach was moderate for 5 studies and high for 4 studies. and in general their quality was low, with increased risk of bias in some studies. However, intervention and placebo groups were similar for most studies. Some desired variables, as NYHA functional class, 6-minute-walking test and NT-proBNP was not included in our meta-analysis because missing data on trials. Also, heterogeneity was found for VO_2 peak and VE/VCO_2 slope analyses but only at acute sub analysis; however, these might be explained by the observed relation between effect sizes and duration of therapy. Finally, small number of outcomes limits a more definite conclusion about the effects of sildenafil on prognosis.

Conclusions

Sildenafil improves exercise performance, PAP, and LV function in patients with heart failure, and the effect on peak VO2, VE/VCO2 slope and systolic PAP were not only sustained but greater with long-term use. Also, there is evidence for a significant effect on reducing hospitalizations in this group of patients. Properly powered RCTs should further address its effects on long-term prognosis in heart failure.

Disclosures

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Figure Legends

Figure 1. Flowchart of the search strategy of studies.

Figure 2. Mean difference in functional parameters at acute, mid-term and long-term in the trials considering sildenafil compared to placebo therapy on EFrHF patients. A: peak of oxygen consumption VO_2 and B: VE/VO_2 slope.

Figure 3. Mean difference in functional and hemodynamics parameters at acute, mid and long term in the trials considering sildenafil compared to placebo therapy on EFrHF patients. A: ejection fraction (%); B: pulmonary artery systolic pressure (mmHg); C: systemic vascular resistance ($dyn \cdot s/cm^{-5}$) and D: wedge pulmonary pressure (mmHg).

Figure 4. Relative risk of hospitalizion at mid and long term in the studies considering sildenafil compared to placebo therapy on EFrHF patients.

Figure 5. Control of adverse effects represented by mean difference in heart rate in beats per minute (A) and systolic blood pressure in mmHg (B) at acute, mid and long term in the trials considering sildenafil compared to placebo therapy on EFrHF patients.

Table 1- Baseline characteristics of trials included in the meta-analysis.

Source	Design	Dose mg	Follow up	Group	N	Age mean (SD), y	Functional Class, NYHA	Ejection Fraction,%	Pulmonary Systolic Arterial Pressure, mmHg*	Etiology Ischemic,%	Drugs,% ACE or ARB/BB/DIU†
Guazzi 2004(21)	Crossover	50	60 minutes	Sildenafil/Placebo	16	55.1±8.2	II-III	30.2±3.2	34.7±3.2*	68	87/68/100
Guazzi 2004(22)	Crossover	50	60 minutes	Sildenafil/Placebo	10	57.9±4.5	II-III	≤40	32.9±2.7*	60	80/60/100
Hryniewicz 2005(25)	Parallel	50	60 minutes	Sildenafil	16	57±3	II-III	27±3	--	25	100/87/75
				Placebo	16	54±2	II-III	23±2		50	100/100/81
Lewis 2007(24)	Parallel	225¶	90 days	Sildenafil	17	54±4	II-IV	19±2	30±2.0§	47	77/100/100
Guazzi 2008(20)	Crossover	150	60 minutes	Sildenafil/Placebo	16	56.6±4.3	II-III	31.8±2.2	35.3±2.2*	62	93/75/81
	Parallel	150	30 days	Sildenafil	11	45±12	I-III	27±5	56±13*	36	100/91/100

Behling 2008(23)				Placebo	8	53±11	I-III	30±7	62±23*	25	100/88/100
Guazzi 2007(14)	Parallel	150	180 days	Sildenafil	23	62±3	II-III	30.6±3.0	33.7±3.1*	47	82/60/69
				Placebo	23	63±4	II-III	31.9±3.3	31.9±2.7*	43	78/69/65
Guazzi 2012(15)	Parallel	150	365 days	Sildenafil	16	66±8	III-IV	29.0±8.0	34.8±4.0§	31	81/81/-
				Placebo	16	68±6	III-IV	28.0±7.0	34.0±3.0§	43	69/75/-
Guazzi 2011(17)	Parallel	150	365 days	Sildenafil	23	60±4	II-III	29.5±3.0	37.1±4.3*	47	83/78/-
				Placebo	22	61±4	II-III	30.2±4.0	37.7±3.9*	54	90/90/-

* Pulmonary arterial pressure denotes pulmonar systolic arterial pressure.

† ACE – angiotensin-converting-enzyme inhibitor, ARB - angiotensin receptor blockers, BB – beta-bloquers, DIU – diuretics.

‡ Age expressed by mean and maximum and minimum age.

§ Pulmonary arterial pressure expressed by mean pulmonar arterial pressure.

¶ The initial dose of study medication was 75 mg daily and was up-titrated every 2 weeks to 250 mg daily as tolerated. N/A – not available data

Figure 1. Flowchart of the search strategy of studies.

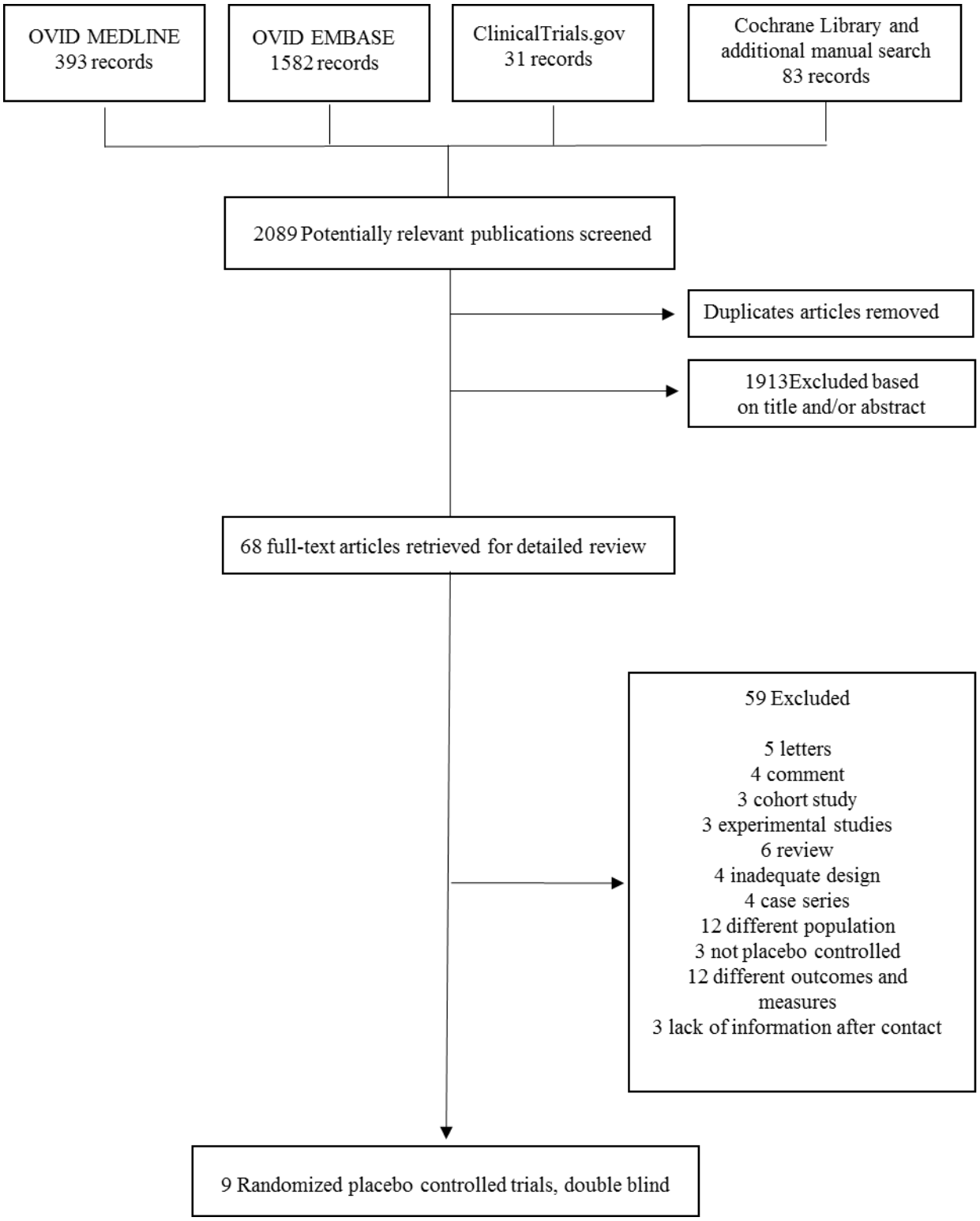


Figure 2.

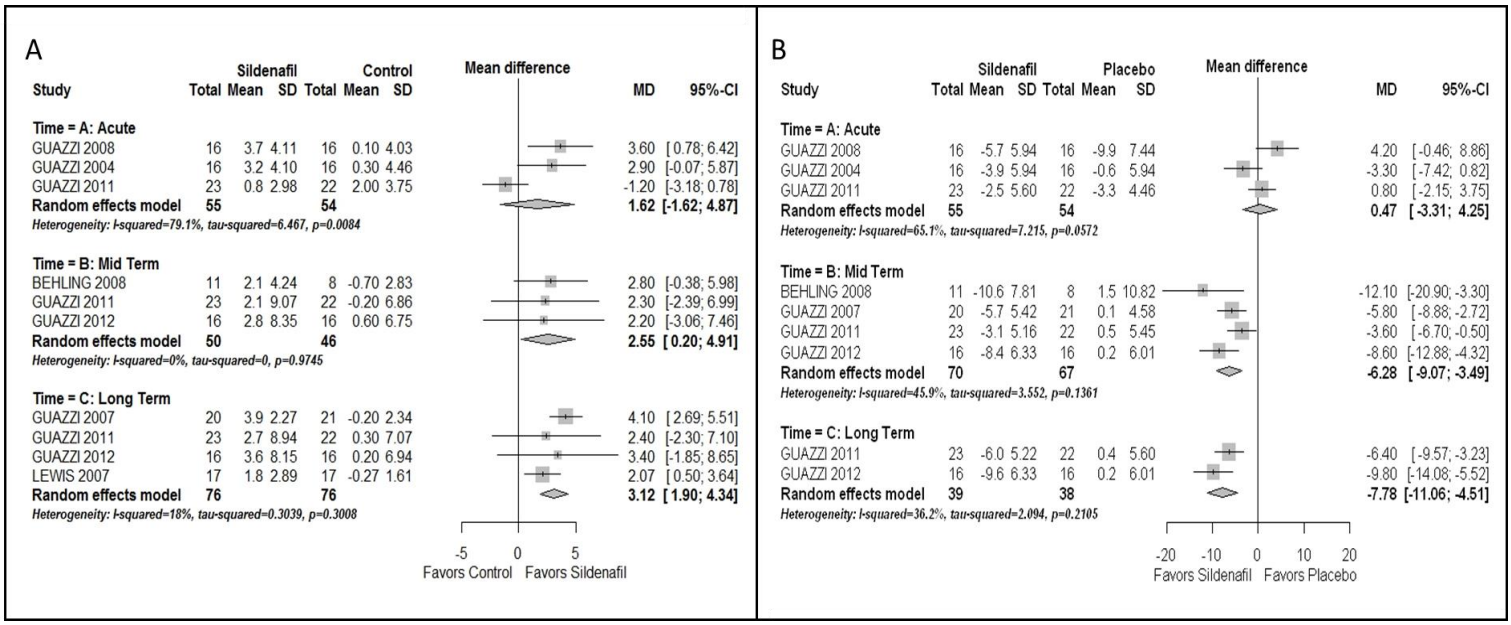

A
Sildenafil
Control
Study
Total Mean SD Total Mean SD
MD 95%-CI
Time = A: Acute
GUAZZI 2008 16 3.7 4.11 16 0.10 4.03 3.60 [0.78; 6.42]
GUAZZI 2004 16 3.2 4.10 16 0.30 4.46 2.90 [-0.07; 5.87]
GUAZZI 2011 23 0.8 2.98 22 2.00 3.75 -1.20 [-3.18; 0.78]
Random effects model 55 54 1.62 [-1.62; 4.87]
Heterogeneity: I-squared=79.1%, tau-squared=6.467, p=0.0084
Time = B: Mid Term
BEHLING 2008 11 2.1 4.24 8 -0.70 2.83 2.80 [-0.38; 5.98]
GUAZZI 2011 23 2.1 9.07 22 -0.20 6.86 2.30 [-2.39; 6.99]
GUAZZI 2012 16 2.8 8.35 16 0.60 6.75 2.20 [-3.06; 7.46]
Random effects model 50 46 2.55 [0.20; 4.91]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9745
Time = C: Long Term
GUAZZI 2007 20 3.9 2.27 21 -0.20 2.34 4.10 [2.69; 5.51]
GUAZZI 2011 23 2.7 8.94 22 0.30 7.07 2.40 [-2.30; 7.10]
GUAZZI 2012 16 3.6 8.15 16 0.20 6.94 3.40 [-1.85; 8.65]
LEWIS 2007 17 1.8 2.89 17 -0.27 1.61 2.07 [0.50; 3.64]
Random effects model 76 76 3.12 [1.90; 4.34]
Heterogeneity: I-squared=18%, tau-squared=0.3039, p=0.3008
Mean difference
-5 0 5
Favors Control Favors Sildenafil
B
Sildenafil
Placebo
Study
Total Mean SD Total Mean SD
MD 95%-CI
Time = A: Acute
GUAZZI 2008 16 -5.7 5.94 16 -9.9 7.44 4.20 [-0.46; 8.86]
GUAZZI 2004 16 -3.9 5.94 16 -0.6 5.94 -3.30 [-7.42; 0.82]
GUAZZI 2011 23 -2.5 5.60 22 -3.3 4.46 0.80 [-2.15; 3.75]
Random effects model 55 54 0.47 [-3.31; 4.25]
Heterogeneity: I-squared=65.1%, tau-squared=7.215, p=0.0572
Time = B: Mid Term
BEHLING 2008 11 -10.6 7.81 8 1.5 10.82 -12.10 [-20.90; -3.30]
GUAZZI 2007 20 -5.7 5.42 21 0.1 4.58 -5.80 [-8.88; -2.72]
GUAZZI 2011 23 -3.1 5.16 22 0.5 5.45 -3.60 [-6.70; -0.50]
GUAZZI 2012 16 -8.4 6.33 16 0.2 6.01 -8.60 [-12.88; -4.32]
Random effects model 70 67 -6.28 [-9.07; -3.49]
Heterogeneity: I-squared=45.9%, tau-squared=3.552, p=0.1361
Time = C: Long Term
GUAZZI 2011 23 -6.0 5.22 22 0.4 5.60 -6.40 [-9.57; -3.23]
GUAZZI 2012 16 -9.6 6.33 16 0.2 6.01 -9.80 [-14.08; -5.52]
Random effects model 39 38 -7.78 [-11.06; -4.51]
Heterogeneity: I-squared=36.2%, tau-squared=2.094, p=0.2105
Mean difference
-20 -10 0 10 20
Favors Sildenafil Favors Placebo

Figure 3.

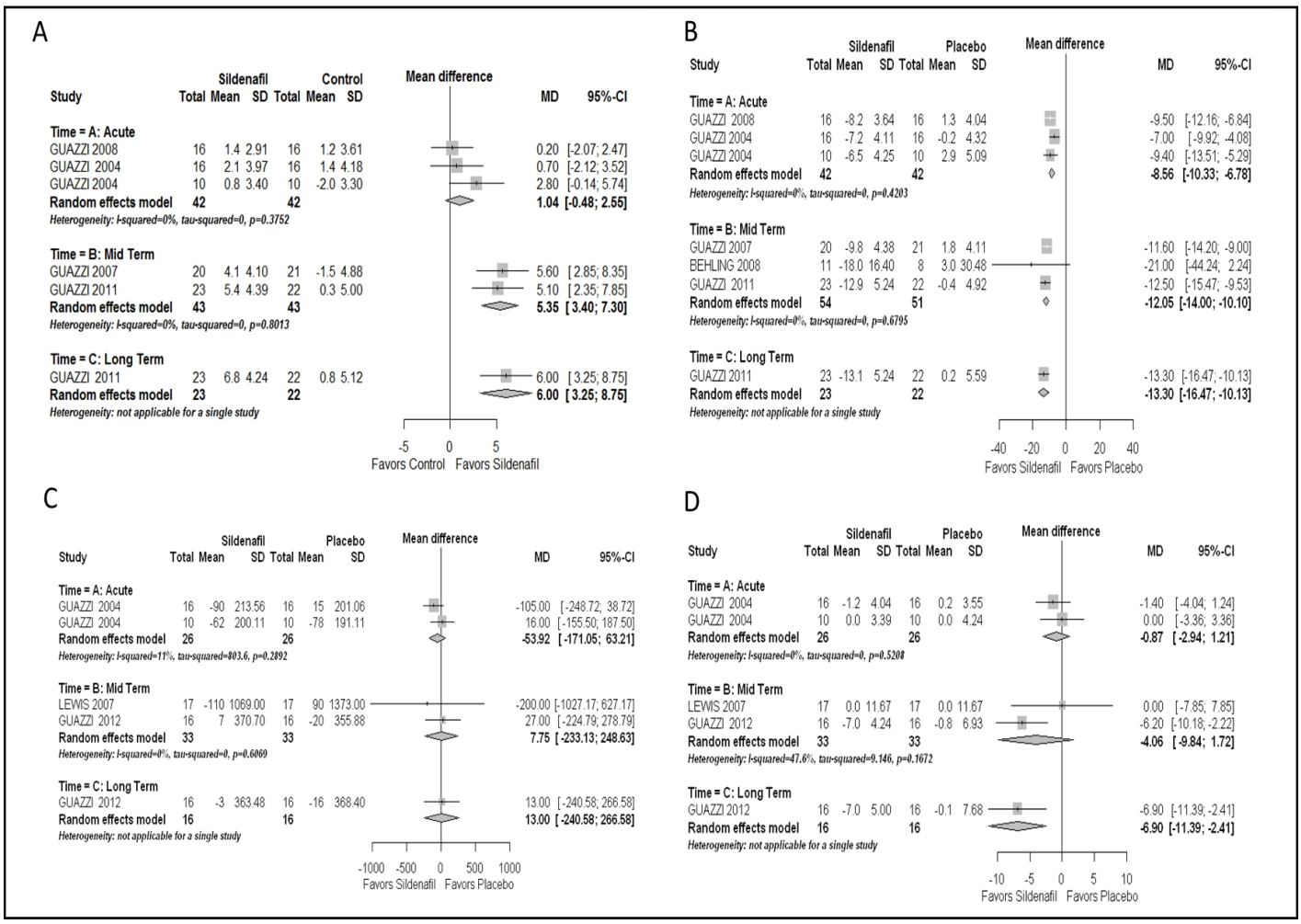

A
Sildenafil
Control
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Time = A: Acute
GUAZZI 2008 16 1.4 2.91 16 1.2 3.61 0.20 [-2.07; 2.47]
GUAZZI 2004 16 2.1 3.97 16 1.4 4.18 0.70 [-2.12; 3.52]
GUAZZI 2004 10 0.8 3.40 10 -2.0 3.30 2.80 [-0.14; 5.74]
Random effects model 42 42 1.04 [-0.48; 2.55]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.3752
Time = B: Mid Term
GUAZZI 2007 20 4.1 4.10 21 -1.5 4.88 5.60 [2.85; 8.35]
GUAZZI 2011 23 5.4 4.39 22 0.3 5.00 5.10 [2.35; 7.85]
Random effects model 43 43 5.35 [3.40; 7.30]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.8013
Time = C: Long Term
GUAZZI 2011 23 6.8 4.24 22 0.8 5.12 6.00 [3.25; 8.75]
Random effects model 23 22 6.00 [3.25; 8.75]
Heterogeneity: not applicable for a single study
-5 0 5
Favors Control Favors Sildenafil
B
Sildenafil
Placebo
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Time = A: Acute
GUAZZI 2008 16 -8.2 3.64 16 1.3 4.04 -9.50 [-12.16; -6.84]
GUAZZI 2004 16 -7.2 4.11 16 -0.2 4.32 -7.00 [-9.92; -4.08]
GUAZZI 2004 10 -6.5 4.25 10 2.9 5.09 -9.40 [-13.51; -5.29]
Random effects model 42 42 -8.56 [-10.33; -6.78]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.4203
Time = B: Mid Term
GUAZZI 2007 20 -9.8 4.38 21 1.8 4.11 -11.60 [-14.20; -9.00]
BEHLING 2008 11 -18.0 16.40 8 3.0 30.48 -21.00 [-44.24; 2.24]
GUAZZI 2011 23 -12.9 5.24 22 -0.4 4.92 -12.50 [-15.47; -9.53]
Random effects model 54 51 -12.05 [-14.00; -10.10]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.6795
Time = C: Long Term
GUAZZI 2011 23 -13.1 5.24 22 0.2 5.59 -13.30 [-16.47; -10.13]
Random effects model 23 22 -13.30 [-16.47; -10.13]
Heterogeneity: not applicable for a single study
-40 -20 0 20 40
Favors Sildenafil Favors Placebo
C
Sildenafil
Placebo
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Time = A: Acute
GUAZZI 2004 16 -90 213.56 16 15 201.06 -105.00 [-248.72; 38.72]
GUAZZI 2004 10 -62 200.11 10 -78 191.11 16.00 [-155.50; 187.50]
Random effects model 26 26 -53.92 [-171.05; 63.21]
Heterogeneity: I-squared=11%, tau-squared=803.6, p=0.2892
Time = B: Mid Term
LEWIS 2007 17 -110 1069.00 17 90 1373.00 -200.00 [-1027.17; 627.17]
GUAZZI 2012 16 7 370.70 16 -20 355.88 27.00 [-224.79; 278.79]
Random effects model 33 33 7.75 [-233.13; 248.63]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.6069
Time = C: Long Term
GUAZZI 2012 16 -3 363.48 16 -16 368.40 13.00 [-240.58; 266.58]
Random effects model 16 16 13.00 [-240.58; 266.58]
Heterogeneity: not applicable for a single study
-1000 -500 0 500 1000
Favors Sildenafil Favors Placebo
D
Sildenafil
Placebo
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Time = A: Acute
GUAZZI 2004 16 -1.2 4.04 16 0.2 3.55 -1.40 [-4.04; 1.24]
GUAZZI 2004 10 0.0 3.39 10 0.0 4.24 0.00 [-3.36; 3.36]
Random effects model 26 26 -0.87 [-2.94; 1.21]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.5208
Time = B: Mid Term
LEWIS 2007 17 0.0 11.67 17 0.0 11.67 0.00 [-7.85; 7.85]
GUAZZI 2012 16 -7.0 4.24 16 -0.8 6.93 -6.20 [-10.18; -2.22]
Random effects model 33 33 -4.06 [-9.84; 1.72]
Heterogeneity: I-squared=47.6%, tau-squared=9.146, p=0.1672
Time = C: Long Term
GUAZZI 2012 16 -7.0 5.00 16 -0.1 7.68 -6.90 [-11.39; -2.41]
Random effects model 16 16 -6.90 [-11.39; -2.41]
Heterogeneity: not applicable for a single study
-10 -5 0 5 10
Favors Sildenafil Favors Placebo

Figure 4.

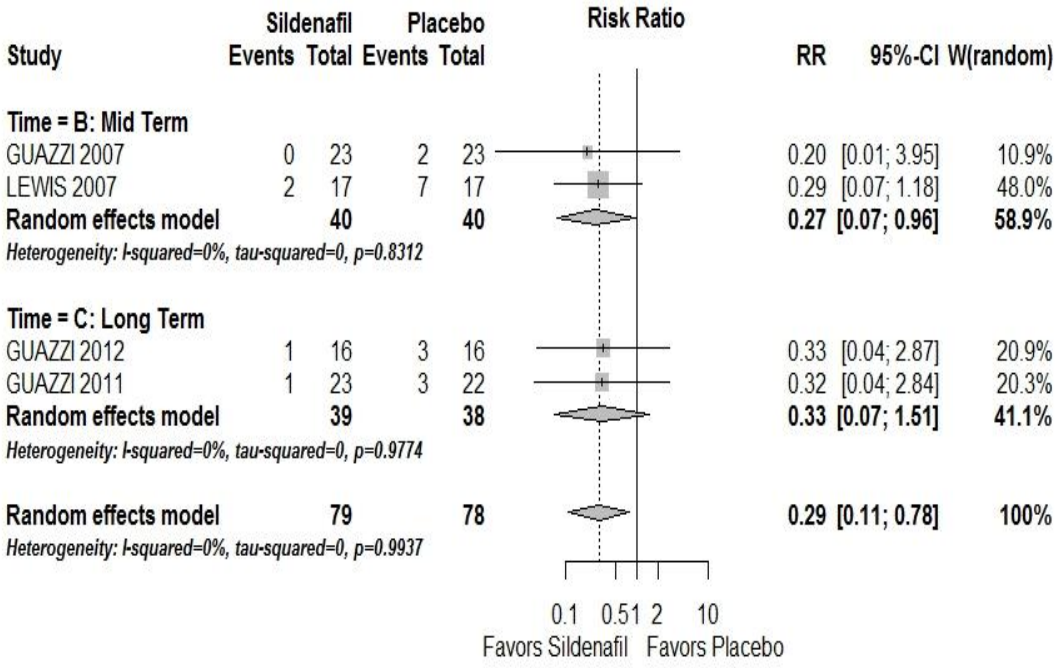
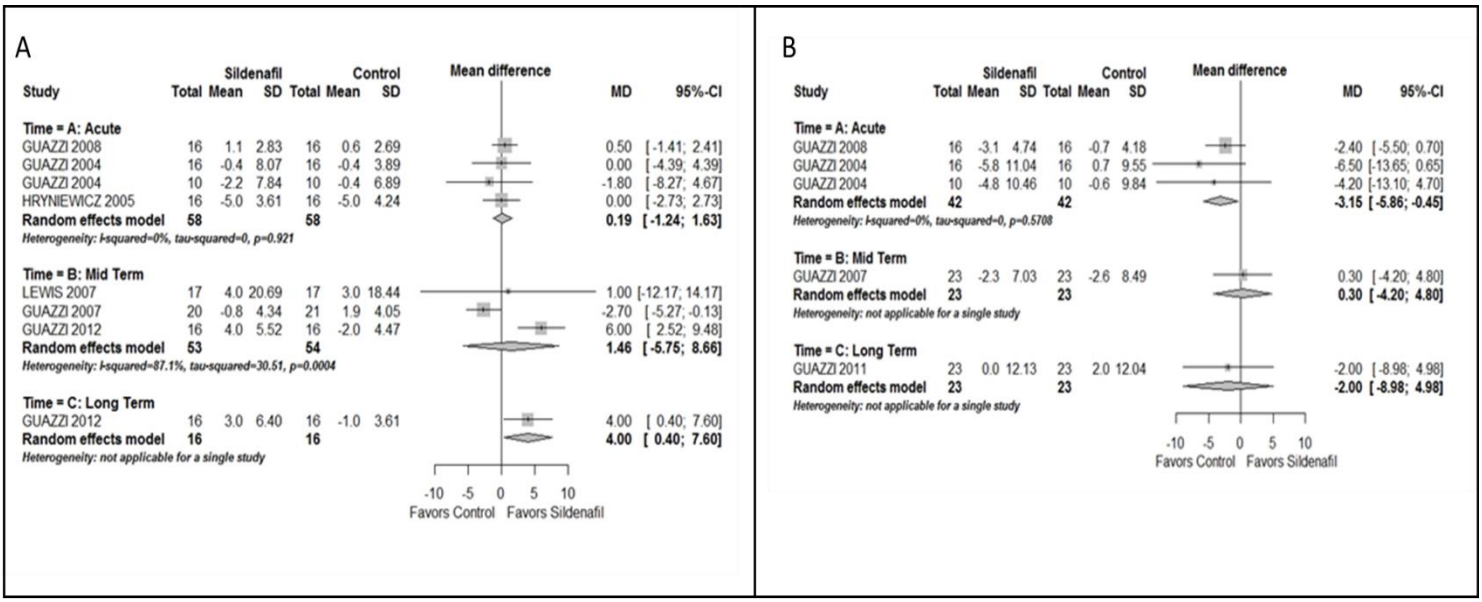

Study
Sildenafil Events Total
Placebo Events Total
Risk Ratio
RR 95%-CI W(random)
Time = B: Mid Term
GUAZZI 2007 0 23 2 23 0.20 [0.01; 3.95] 10.9%
LEWIS 2007 2 17 7 17 0.29 [0.07; 1.18] 48.0%
Random effects model 40 40 0.27 [0.07; 0.96] 58.9%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.8312
Time = C: Long Term
GUAZZI 2012 1 16 3 16 0.33 [0.04; 2.87] 20.9%
GUAZZI 2011 1 23 3 22 0.32 [0.04; 2.84] 20.3%
Random effects model 39 38 0.33 [0.07; 1.51] 41.1%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9774
Random effects model 79 78 0.29 [0.11; 0.78] 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9937
0.1 0.51 2 10
Favors Sildenafil Favors Placebo

Figure 5.


A
Sildenafil
Control
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Time = A: Acute
GUAZZI 2008 16 1.1 2.83 16 0.6 2.69 0.50 [-1.41; 2.41]
GUAZZI 2004 16 -0.4 8.07 16 -0.4 3.89 0.00 [-4.39; 4.39]
GUAZZI 2004 10 -2.2 7.84 10 -0.4 6.89 -1.80 [-8.27; 4.67]
HRYNIEWICZ 2005 16 -5.0 3.61 16 -5.0 4.24 0.00 [-2.73; 2.73]
Random effects model 58 58 0.19 [-1.24; 1.63]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.921
Time = B: Mid Term
LEWIS 2007 17 4.0 20.69 17 3.0 18.44 1.00 [-12.17; 14.17]
GUAZZI 2007 20 -0.8 4.34 21 1.9 4.05 -2.70 [-5.27; -0.13]
GUAZZI 2012 16 4.0 5.52 16 -2.0 4.47 6.00 [2.52; 9.48]
Random effects model 53 54 1.46 [-5.75; 8.66]
Heterogeneity: I-squared=87.1%, tau-squared=30.51, p=0.0004
Time = C: Long Term
GUAZZI 2012 16 3.0 6.40 16 -1.0 3.61 4.00 [0.40; 7.60]
Random effects model 16 16 4.00 [0.40; 7.60]
Heterogeneity: not applicable for a single study
-10 -5 0 5 10
Favors Control Favors Sildenafil
B
Sildenafil
Control
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Time = A: Acute
GUAZZI 2008 16 -3.1 4.74 16 -0.7 4.18 -2.40 [-5.50; 0.70]
GUAZZI 2004 16 -5.8 11.04 16 0.7 9.55 -6.50 [-13.65; 0.65]
GUAZZI 2004 10 -4.8 10.46 10 -0.6 9.84 -4.20 [-13.10; 4.70]
Random effects model 42 42 -3.15 [-5.86; -0.45]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.5708
Time = B: Mid Term
GUAZZI 2007 23 -2.3 7.03 23 -2.6 8.49 0.30 [-4.20; 4.80]
Random effects model 23 23 0.30 [-4.20; 4.80]
Heterogeneity: not applicable for a single study
Time = C: Long Term
GUAZZI 2011 23 0.0 12.13 23 2.0 12.04 -2.00 [-8.98; 4.98]
Random effects model 23 23 -2.00 [-8.98; 4.98]
Heterogeneity: not applicable for a single study
-10 -5 0 5 10
Favors Control Favors Sildenafil

Supplements

Structured search.

"sildenafil" [Supplementary Concept] OR "desmethyl sildenafil" OR"desmethylsildenafil" OR "homosildenafil" OR "Viagra" OR "Pfizer brand 1 of sildenafil citrate" OR "Abbott brand of sildenafil citrate" OR "Revatio" OR "Pfizer brand 2 of sildenafil citrate" OR "sildenafil citrate" OR "UK 92480-10" OR "UK-92,480-10" OR "acetildenafil" OR "hydroxyhomosildenafil" AND "Heart Failure"[Mesh] OR "Cardiac Failure" OR "Myocardial Failure" OR "Heart Failure, Left-Sided" OR "Heart Failure, Left Sided" OR "Left-Sided Heart Failure" OR "Left Sided Heart Failure" OR "Heart Failure, Right-Sided" OR "Heart Failure, Right Sided" OR "Right-Sided Heart Failure" OR "Right Sided Heart Failure" OR "Congestive Heart Failure" OR "Heart Failure, Congestive" OR "Heart Decompensation" OR "Decompensation, Heart" AND (randomized controlled Trial[pt] OR controlled clinical Trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR Double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR (“clinical trial”[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw]) OR (“latin square”[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh])

Table 1: Grade summary of evidence for outcomes hospitalization, left ventricule

ejection fraction and pulmonary systolic arterial pressure.

Sildenafil compared to Placebo in heart failure patients

Patient or population: heart failure patients

Setting: Ambulatorial patients

Intervention: Sildenafil

Comparison: Placebo

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with Placebo	**Risk with Sildenafil**				
Hospitalization (Hospitalization) follow up: range 3 months to 12 months	225 per 1.000	**61 per 1.000** (16 to 216)	**RR 0.27** (0.07 to 0.96)	80 (2 RCTs)	⨁⨁⨁⨁ HIGH [a]	NNT = 6
Left Ventricule Ejection Fraction (LVEF) assessed with: % follow up: mean 6 months	The mean left Ventricule Ejection Fraction was **30.5** %	The mean left Ventricule Ejection Fraction in the intervention group was 5,35 % more (3,4 more to 7,3 more)	-	86 (2 RCTs)	⨁⨁⨁⨁ HIGH [a]	
Pulmonary Systolic Arterial Pressure (PSAP) assessed with: mmHg follow up: mean 6 months	The mean pulmonary Systolic Arterial Pressure was **37.3** mmHg	The mean pulmonary Systolic Arterial Pressure in the intervention group was 12,05 mmHg fewer (14 fewer to 10,1 fewer)	-	105 (3 RCTs)	⨁⨁⨁⨁ HIGH	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

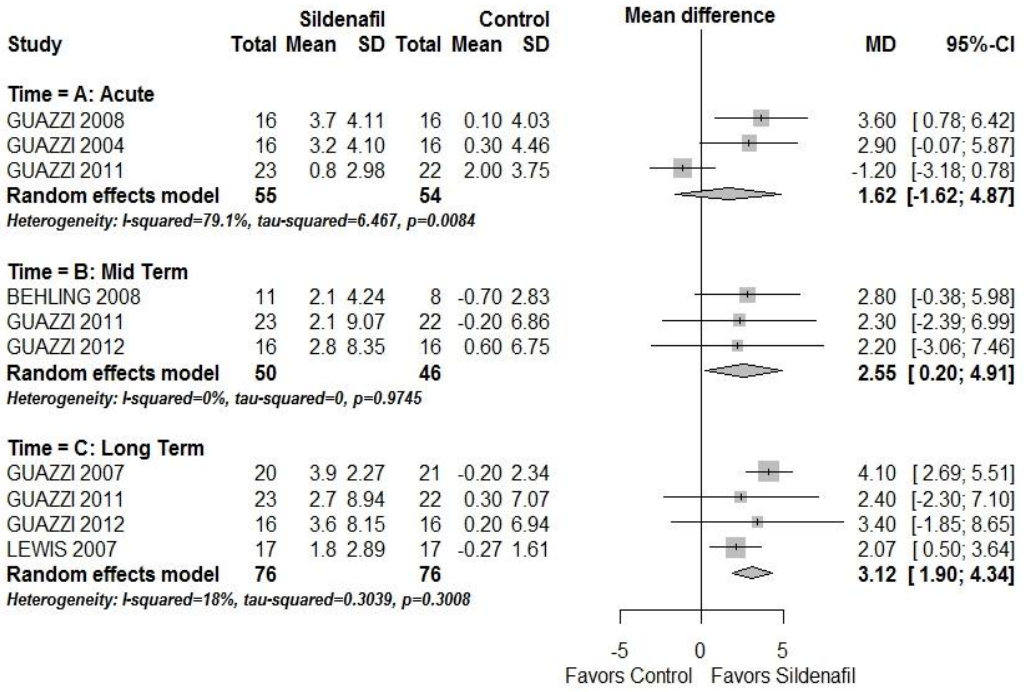


Figure 1. Mean difference in the outcome of peak of oxygen consumption VO_2 at acute, mid and long term in the trials considering sildenafil compared to placebo therapy on EFrHF patients.

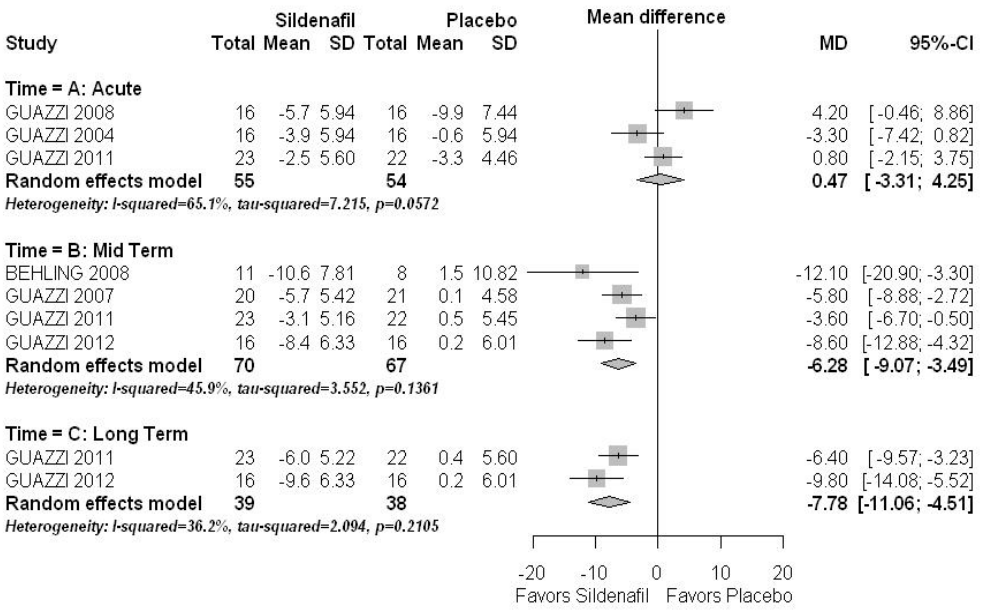


Figure 2. Mean difference in the outcome of VE/VO_2 slope at acute, mid and long term in the trials considering sildenafil compared to placebo therapy on EFrHF patients.

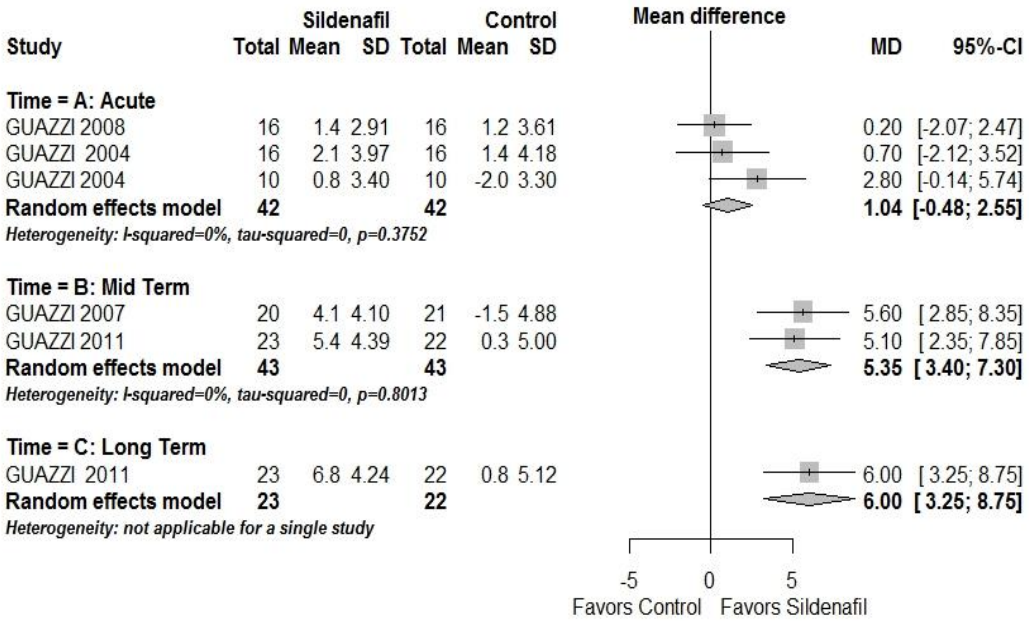


Figure 3. Mean difference in ejection fraction (%) at acute, mid and long term in the trials considering sildenafil compared to placebo therapy on EFrHF patients.

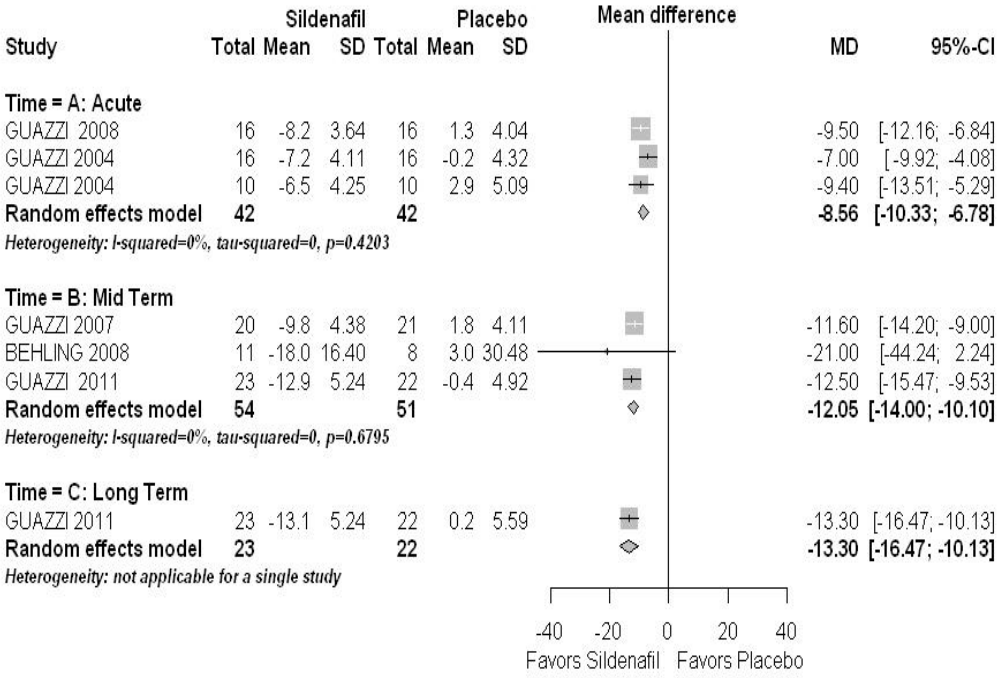


Figure 4. Mean difference in pulmonary artery systolic pressure (mmHg) at acute, mid and long term in the studies considering sildenafil compared to placebo therapy on EFrHF patients.

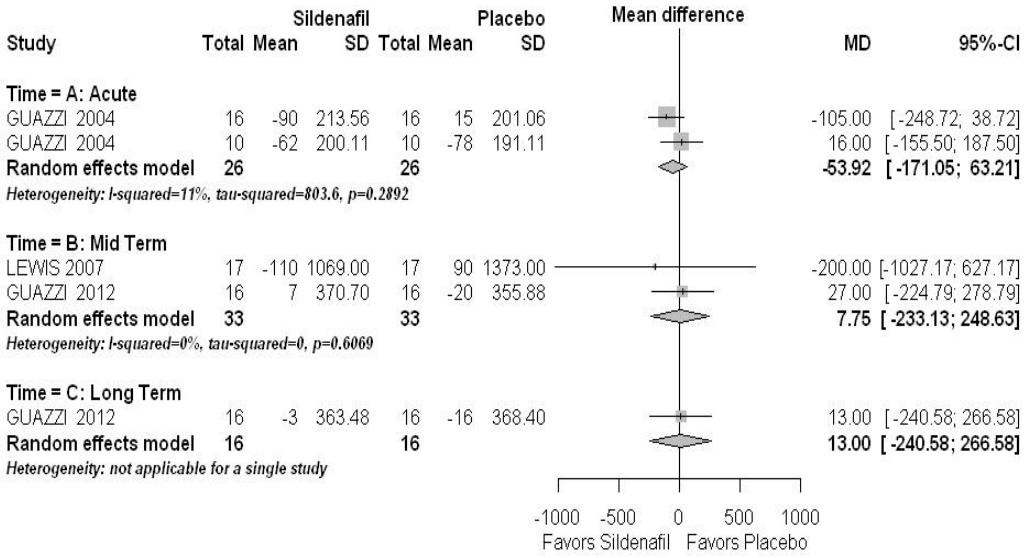


Figure 5. Mean difference in systemic vascular resistance (dyn·s/cm^{-5}) at acute, mid and long term in the studies considering sildenafil compared to placebo therapy on EFrHF patients.

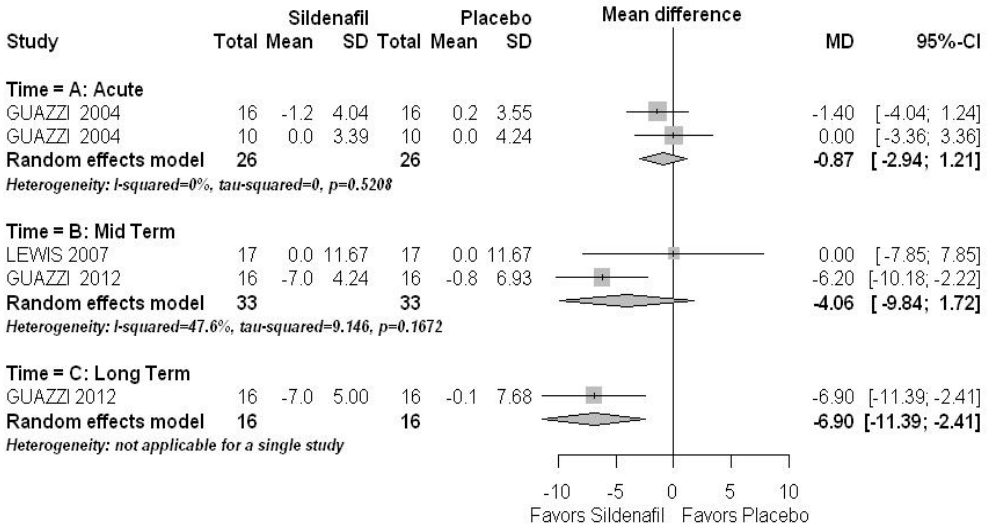


Figure 6. Mean difference in wedge pulmonary pressure (mmHg) at acute, mid and long term in the studies considering sildenafil compared to placebo therapy on EFrHF patients.

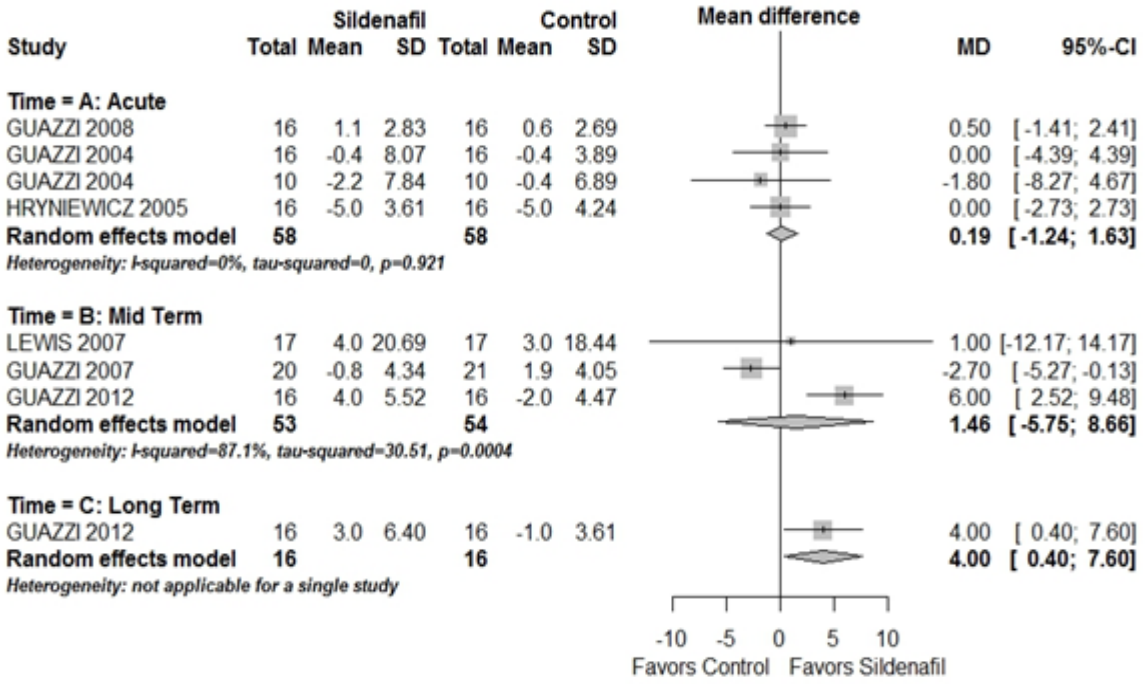


Figure 7. Mean difference in heart rate (beats/minute) at acute, mid and long term in the studies considering sildenafil compared to placebo therapy on EFrHF patients.

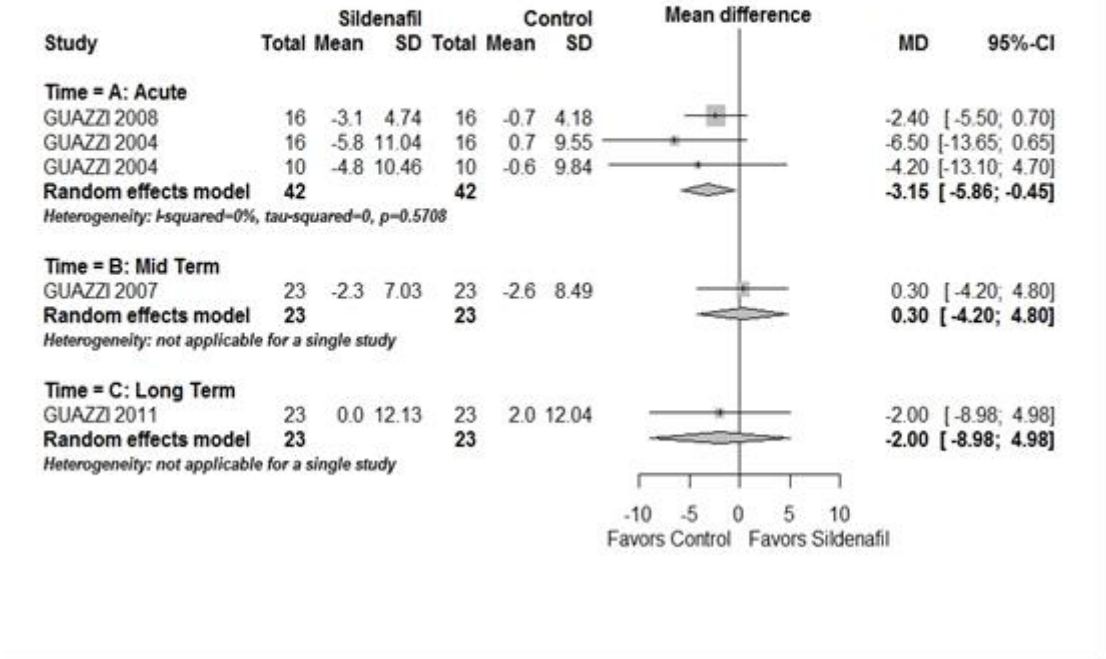


Figure 8. Mean difference in systolic arterial pressure (mmHg) at acute, mid and long term in the studies considering sildenafil compared to placebo therapy on EFrHF patients.

7. ARTIGO 2 – Diurético de alça na Insuficiência Cardíaca crônica: uma revisão sistemática e metanálise de ensaios clínicos randomizados

Henle Loop Diuretics on Chronic Heart Failure: A Systematic Review and Meta-analysis of Randomized Controlled Trials

Running Title: Meta-analysis of diuretics for heart failure patients

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Abstract

Background: The use of diuretics is an important tool for the treatment of both chronic and acute decompensated heart failure. Despite the undeniable beneficial effects improving peripheral and central congestion, the chronic maintenance of diuretics in HF patients may be unnecessary and may even compete with other, life-saving, therapies. We therefore sought to investigate the evidence for or against diuretic use in chronic HF patients.

Methods and Results: We conducted a systematic review and meta-analysis of randomized controlled trials of henle loop diuretic compared to usual care, placebo or dose reduction. A systematic search was realized by two independent reviewers using MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (1966-2017). Keywords were "*randomized controlled trial", "heart failure"*and *"diuretics"*. Data extraction was standardized according to the inclusion and exclusion criteria and GRADE Pro software was used to qualify the evidence. Eight RCTs enrolling 246 patients with heart failure were included. Follow-up ranged from 7 days to 12 months. Compared to control group, patients receiving henle loop diuretic had no difference in weight, systolic blood pressure or serum levels of potassium. Analysis of the outcome worsening congestion, showed benefits of diuretic use when compared to no/reduction of diuretic (RR 0.20, 95% CI 0.06 to 0.65, $p<0.01$), without difference when compared to thiazide diuretic (RR0.80, 95% CI 0.19 to 3.37, $p=0.95$).

Conclusions: Despite common use, the evidence supporting either to maintain or withdraw loop diuretics in patients with chronic HF without congestion is poor. Adequately powered trials are needed to evaluate the efficacy of henle loop diuretics on chronic heart failure as well as the safety of diuretics withdraw in this scenario.

Introduction

Chronic heart failure (HF) patients require lifelong treatment with multiple medications. Drug therapy for HF has greatly improved in the last 30 years, impacting in HF-related morbidity and mortality. Since these unquestionable advances were reached, the efficacy of old drugs as furosemide and digoxin have been questioned (1). The idea that diuretics are the mainstay of treatment in chronic HF should be reviewed. Considering that benefits are related to the control of hypervolemia resulting in reducing ventricular filling pressures and pulmonary venous congestion, there is no biological plausibility to use furosemide on euvolemic patients with stable HF. Following this precept, current clinical guidelines suggest the use of diuretics in HF patients with clinical signs and symptoms of congestion, but reinforce the lack of solid clinical scientific evidence for this recommendation, and the potential risks that might be involved (2,3).

The discussion about the role of diuretics on worsening renal failure, electrolyte disturbs and even in the potential increase of mortality is ongoing. Long-term use of loop agents has been associated with mortality in a dose-dependent manner in observational studies, is believed that overuse of diuretics promotes neurohormonal activation (4,5). However, higher doses might represent an indirect measure of severity of disease that justifies higher mortality, Mielnickzuk et al. shows that high-dose diuretics may be more of a marker than a cause of instability, high-dose of diuretics were a strong univariate predictor of subsequent HF events, however, after adjustment for clinical stability diuretic dose no longer remained significant (6).

Based on these uncertainties about diuretic use in HF, this meta-analysis was designed to evaluate the randomized controlled trials that have tested the effects of henle loop diuretics use in stable, chronic HF outpatients.

Methods

Study design

The present systematic review and meta-analysis included studies

evaluating chronic HF patients using henle loop diuretics.

Search strategy

Randomized controlled trials of several classes of diuretics compared to usual care, placebo, withdrawn/dose reduction were eligible to be included in this analysis if they were published in full in a peer-reviewed journal. These studies were found through a literature search in the PubMed and EMBASE database from 1950 to February 2017. Keywords were "*randomized controlled trial", "heart failure"* and *"diuretics". **A search in*** Cochrane Library was also performed. For use in the sensitivity analysis, additional meta-analyses that met the previously mentioned criteria were analyzed. Search was realized between November 2016 and February 2017. Detailed search strategy is available at the supplementary material.

Eligibility criteria

Randomized controlled trials (RCT) with henle loop diuretic with no restrictions for a control group were included in the meta-analyses. Studies published in languages other than English were excluded. Studies had to examine the effects henle loop diuretic on outpatients with HF with no limits regarding left ventricle ejection fraction (LVEF) or *New York Heart Association* (NYHA) functional class. Studies on combination therapy were excluded.

Data extraction and quality assessment

Two reviewers (L.M and S.A) independently reviewed the results of each search according to the inclusion and exclusion criteria, with a standardized data extraction tool and also applied standard scales to judge study quality and risk of bias. A third reviewer (M.B) adjudicated in cases of doubt.

The primary outcome collected from the studies was number of patients that presented worsening of clinical status because of progression of congestion. Because HF hospitalization can be defined as worsening of congestion in most cases, and in order to ensure sufficient data for a meaningful analysis, HF hospitalization was included in the worsening of congestion outcome. This systematic review and meta-analysis is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (7). A PRISMA flow diagram of the study selection process is illustrated in **FIGURE 1.** Tables with grade assessment of evidence quality are available as supplementary material.

Statistical analysis

Meta-analyses of progression of congestion with the need to initiate furosemide were performed using a fixed effects model, risk ratios (RRs). Experimental and control groups were compared using unstandardized mean differences (creatinine and potassium serum levels, systolic blood pressure and weight). Pooled estimates across studies and 95% confidence intervals (CI) were determined by meta-analysis using the log transformation. The studies were grouped by control category (thiazide o no/reduction diuretic dose). The log transformation with the Mantel_Haenszel method was used for relative risk estimation and no transformation with the inverse variance method was used for mean differences. Between studies heterogeneity

was assessed using the I^2 statistics and the p-value from the Q test. I^2 above 50% was considered high heterogeneity and the random effects model with DerSimonian and Laird estimation method was then used. All analyses were carried out in Stata statistical software version 10.0 (StataCorp LP, College Station, Texas).

Results

We initially identified 5212 potentially relevant reports. Of these, 632 reports were duplicates or not in English. While 246 studies were selected by abstracts, 73 full-text versions of the remaining reports were then retrieved for detailed evaluation. Of these, 65 studies were excluded for reasons listed in Figure 1. The remaining 8 RCT were included in the meta-analysis with moderate evidence quality assessment.

Most included studies were randomized, double-blind controlled trials, except for one open label design and one single blinded study. One trial had a crossover protocol; and one trial had an open label design (15,14). Four trials included patients with LV dysfunction, 2 trials included patients with preserved LVEF and 2 trials did not report on ventricular function. Patients had chronic HF and were on different drugs; only 3 studies included patients on optimized HF treatment. All patients were on NYHA functional class I to III across the studies. The studies varied in size from 24 to 97 patients, totalizing 342 patients. Patients were on average 64.1 years old, and male patients were overrepresented in all studies, making up 81% of the sample. Follow-up ranged from 7 days to 12 months. Table 1 shows baseline characteristics of the study populations.

Compared to control group, henle loop diuretic therapy resulted in significant better control of volemia, resulting in less events of worsening of congestion (RR 0.20, 95% CI 0.06

to 0.65, p<0.01) (Figure 2). On the other hand, efficacy of henle loop diuretic versus thiazide diuretic at the same outcome was similar (RR0.80, 95% CI 0.19 to 3.37, p=0.95) (Figure 3).

As depicted in Figure 4, analyses of serum creatinine levels did not reach statistical difference (0.00, 95% CI -0.07 to 0.07, p=0.97), as well as serum potassium levels (-0.31, 95% CI -0.71 to 0.10, p=0.13).

Evaluation of body weight was presented in only two trials and there was no difference between groups when followed by 6 to 12 weeks (-0.22, 95% CI -7.39 to 6.96, p=0.76). Systolic blood pressure shows a tendency to reduction with henle loop diuretic, but the difference was not significant (-2.91, 95% CI -13.66 to 7.84, p=0.59).

Discussion

The present meta-analysis of henle loop diuretics in patients with HF highlights the lack of evidence either to maintain or withdraw this therapy in this population. Pooled analysis totaling only xx events resulted in a significant effect of maintaining loop diuretics on reducing worsening of congestion as compared to withdraw, but not when compared to the use of thiazide diuretic. No effects were observed on renal function, potassium serum levels, weight and systolic blood pressure. Importantly, in most studies patients were not on optimized HF therapies and therefore these results must be seen with caution.

Besides a number of titles related with the theme, just a small proportion were randomized trials, most of them from 80’ decade when the knowledge and the treatment about HF were far from the nowadays clinical practice. Recently, the only meta-analysis published about this subject was withdrawn from Cochrane database, the author claims misinformation about studies population (16,17). Both American and European guidelines quote the Cochrane

meta-analysis (2,4). In face of this scenario we believe that our biggest contribution is to present a strictly delineated systematic review, that reveals no data about mortality, and scarce data on clinical outcomes, on clinical trials with henle loop diuretic.

Accumulated data of individual trials shows benefits of henle loop agents in reducing congestion when compared to placebo, diuretic withdrawn or 1/3 reduction dose in outpatients with HF. Otherwise the significant benefit on controlling congestion was demonstrated only in two trials. In the study by Haerer et al. (9) patients were treated only with nitrate as background therapy and in Patterson et al. (10) therapy included digoxin and angiotensin-converter-enzyme inhibitors. Both studies included patients with left ventricular dysfunction and mostly on functional class NYHA III. Moreover, at Haerer et al. patients needed to present an elevated pulmonary wedge pressure as inclusion criteria. In fact, the better performance of henle loop agents on these studies could be expected as patients presented hypervolemia and were not on optimized HF therapy.

Another interesting observation from the present meta-analysis is related to the comparison of furosemide and thiazide diuretics on worsening of congestion. The similar response with both diuretics suggests that thiazide diuretics may be an option to treat chronic HF beyond its use associates with furosemide on diuretic resistant patients at decompensation (18).

Contradicting previous observational studies (19,20), the meta-analysis did not show worsening of renal function or hypokalemia with diuretic use. We could speculate that trials that tested creatinine serum levels compared 2 diuretics already associated with creatinine elevation. Potassium pooled analysis were not statistically significant, nevertheless, Vermeleun et al. (12) showed an important reduction of serum potassium levels in the furosemide group comparing to hydrochlorothiazide, but background therapy did not include ACE-inhibitors or mineralocorticoids. With a bigger sample Pehrsson et al. (13), that also compared furosemide

to thiazide diuretic on poorly treated patients, did not find difference on potassium levels. Ogino et al. (15) demonstrated a reduction of potassium comparing furosemide with spironolactone, a known potassium –sparing-diuretic.

No difference on body weight in patients treated with furosemide or thiazide diuretic could suggest similar performance on volemia control with both diuretics. Systolic blood pressure responded equally to furosemide, hydrochlorothiazide or spironolactone.

Limitations

The literature search showed most of articles from 80 and 90 decades and the standard therapy of HF has changed over the last decades. Many of those studies brought furosemide as a control group for phase II-III clinical trials of drugs that were not approved. As well, several studies could not be included because of methodological issues at old studies, and eleven antique studies were not available after many attempts to reach them. Finally, we initially intended to evaluate only trials with HF with reduced EF, but changed to include any EF range as many studies did not report LVEF and that would make the meta-analysis not performable,

Conclusions

The evidence either to maintain or withdraw therapy with loop diuretics in patients with chronic HF is scarce. Although pooled data suggest benefit of loop diuretics on worsening congestion, in several studies patients were not on optimized HF therapy. Well design trials evaluating the use of diuretics on patients with optimized background HF therapy must be performed in order to elucidate their role in this context.

Conflict of interest

None declared.

Funding

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Figure Legends

Figure 1. Flowchart of the search strategy of studies.

Figure 2. Relative risk of worsening of congestion in the studies considering henle loop diuretic compared to no/reduction of diuretic on HF patients.

Figure 3. Relative risk of worsening of congestion in the studies considering furosemide diuretic compared to thiazide diuretic on HF patients.

Figure 4. Mean difference in serum level of creatinine, serum level of potassium, systolic blood pressure and weight in the trials considering henle loop diuretic compared to active control therapy on HF patients.

Table 1- Baseline characteristics of trials included in the meta-analysis.

Study, year	Drug	Control	N drug/control	Age (mean)	NYHA functional class	EF (mean)%	Background Therapy	Study Design	Follow-up
Kraaij 2000 (8)	Furosemide	Placebo Withdraw	21/11	75	I-III	60	BB/ACE/DIG/NIT	ECR, doble-blind	3 months
Haerer 1990 (9)	Piretanide	Placebo	46/14	52.4	II-III	HFrEF	NIT	ECR, single-blind	3 weeks
Patterson 1994 (10)	Torsemide	Placebo	10/14	60.2	II-III	27.2	ACE/DIG	ECR, doble-blind	7 days
Kapelios 2014 (11)	Furosemide	Placebo Decrease 1/3	20/20	62.2	1.9	27.3	BB/ACE/ARAII/DIG	ECR, doble-blind	12 months
Vermeulen 1982 (12)	Furosemide	Hydroclorothiazide	14/12	60.5	I-III	-	DIG/BB/NIT/CCB	ECR, doble-blind	6 weeks
Pehrsson 1985 (13)	Furosemide	Bendroflumethiazide	24/23	65	II-III	-	DIG	ECR, doble-blind	12 weeks

Miyata 2012 (14)	Furosemide	Azosemida	49/48	75	I-III	58.9	BB/ACE NIT/DIG/MRA	ECR, open-label	12 weeks
Ogino 2014 (15)	Furosemide	Espironolactona	16	63	I-III	34.4	ACE/ARAII/BB	ECR, doble blind, crossover	16 weeks

Figure 1.

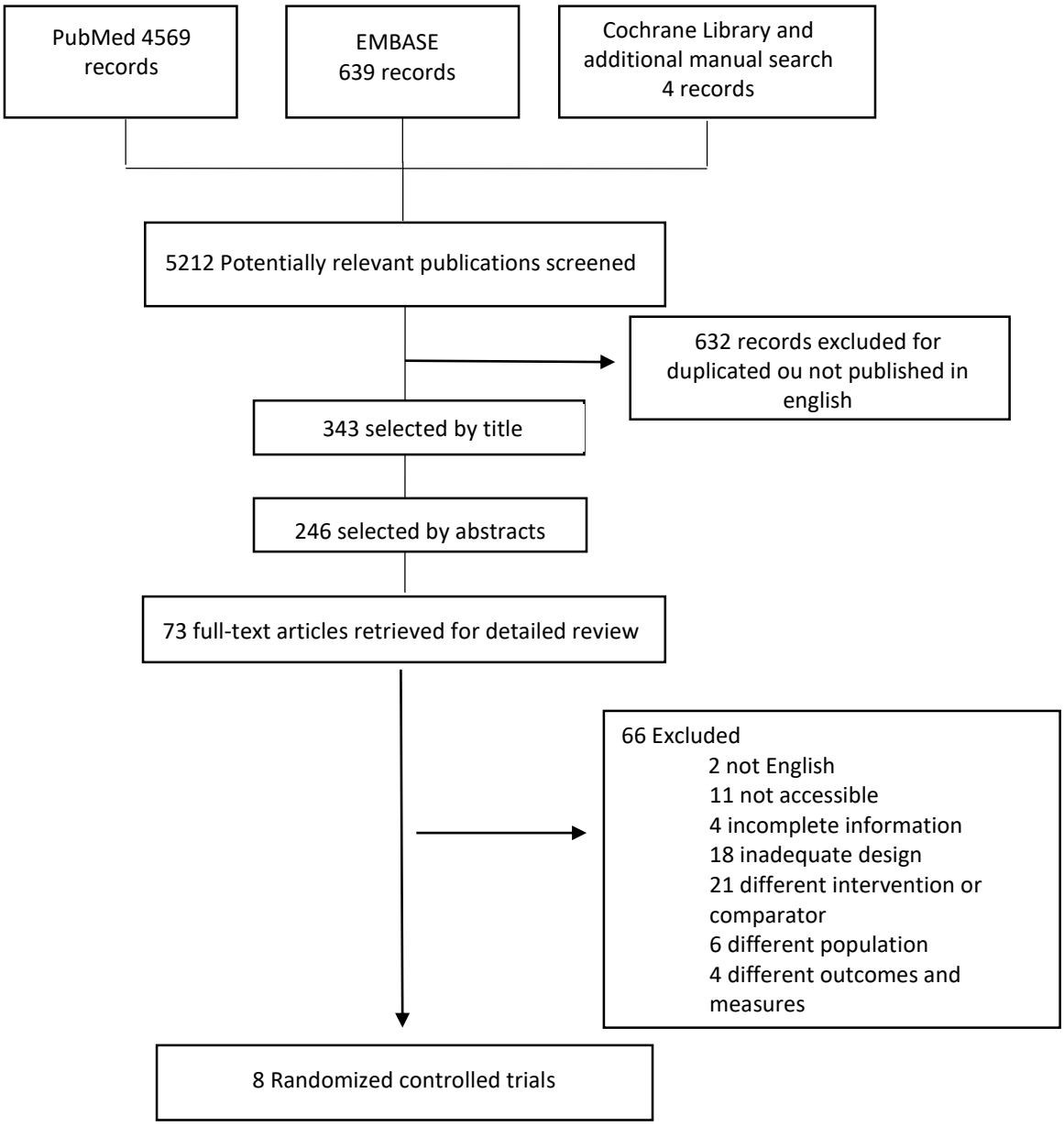

PubMed 4569 records
EMBASE 639 records
Cochrane Library and additional manual search 4 records
5212 Potentially relevant publications screened
632 records excluded for duplicated ou not published in english
343 selected by title
246 selected by abstracts
73 full-text articles retrieved for detailed review
66 Excluded
2 not English
11 not accessible
4 incomplete information
18 inadequate design
21 different intervention or comparator
6 different population
4 different outcomes and measures
8 Randomized controlled trials

Figure 2.

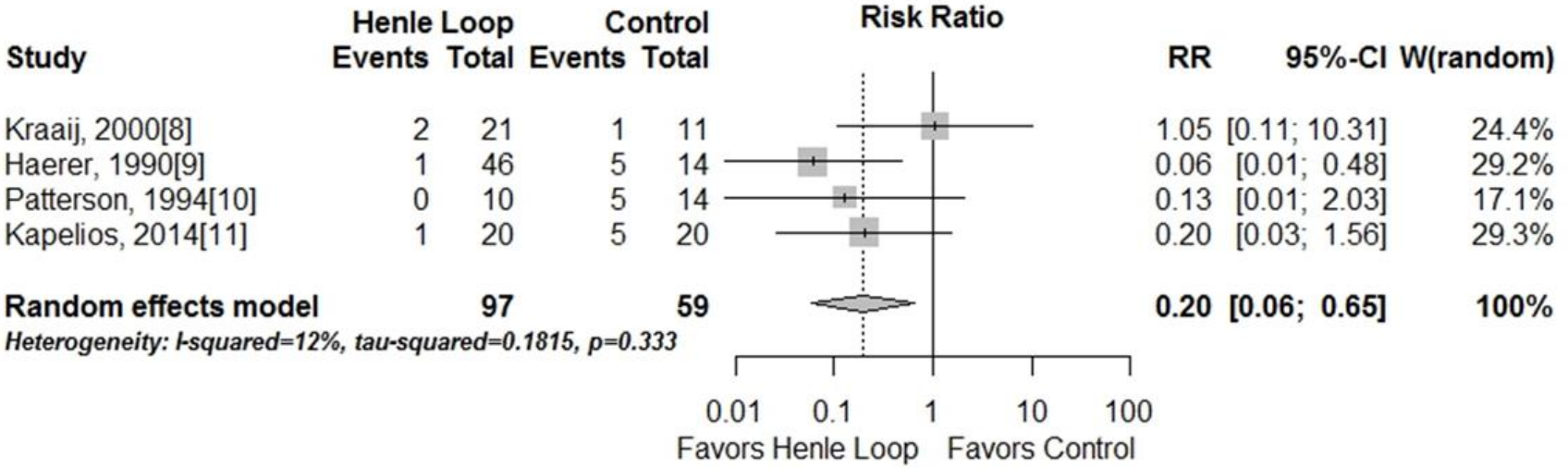

Study
Henle Loop Events Total
Control Events Total
Risk Ratio
RR 95%-CI W(random)
Kraaij, 2000[8] 2 21 1 11 1.05 [0.11; 10.31] 24.4%
Haerer, 1990[9] 1 46 5 14 0.06 [0.01; 0.48] 29.2%
Patterson, 1994[10] 0 10 5 14 0.13 [0.01; 2.03] 17.1%
Kapelios, 2014[11] 1 20 5 20 0.20 [0.03; 1.56] 29.3%
Random effects model 97 59 0.20 [0.06; 0.65] 100%
Heterogeneity: I-squared=12%, tau-squared=0.1815, p=0.333
0.01 0.1 1 10 100
Favors Henle Loop
Favors Control

Figure 3.

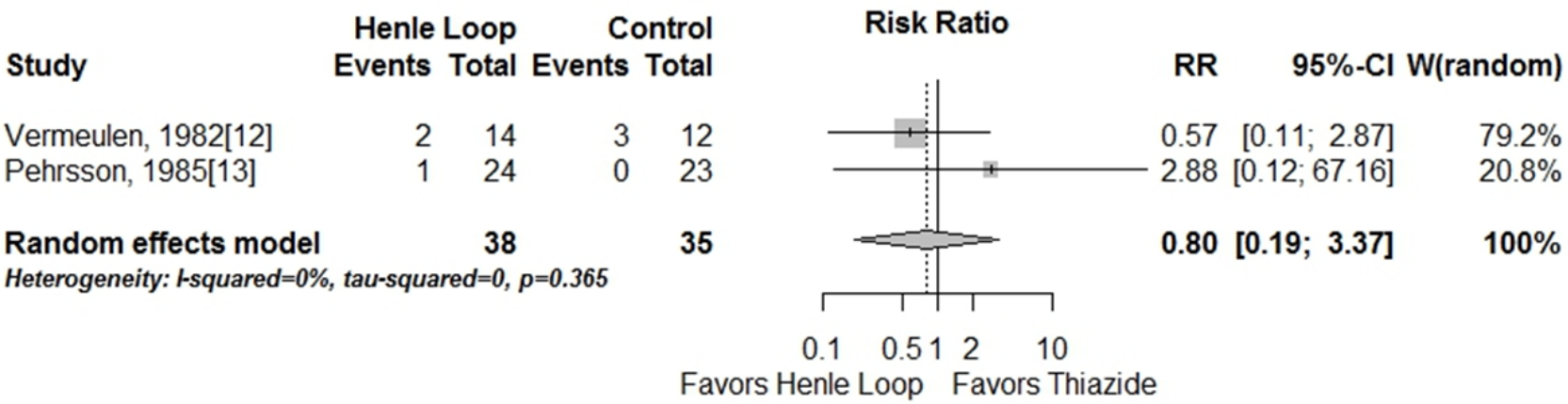
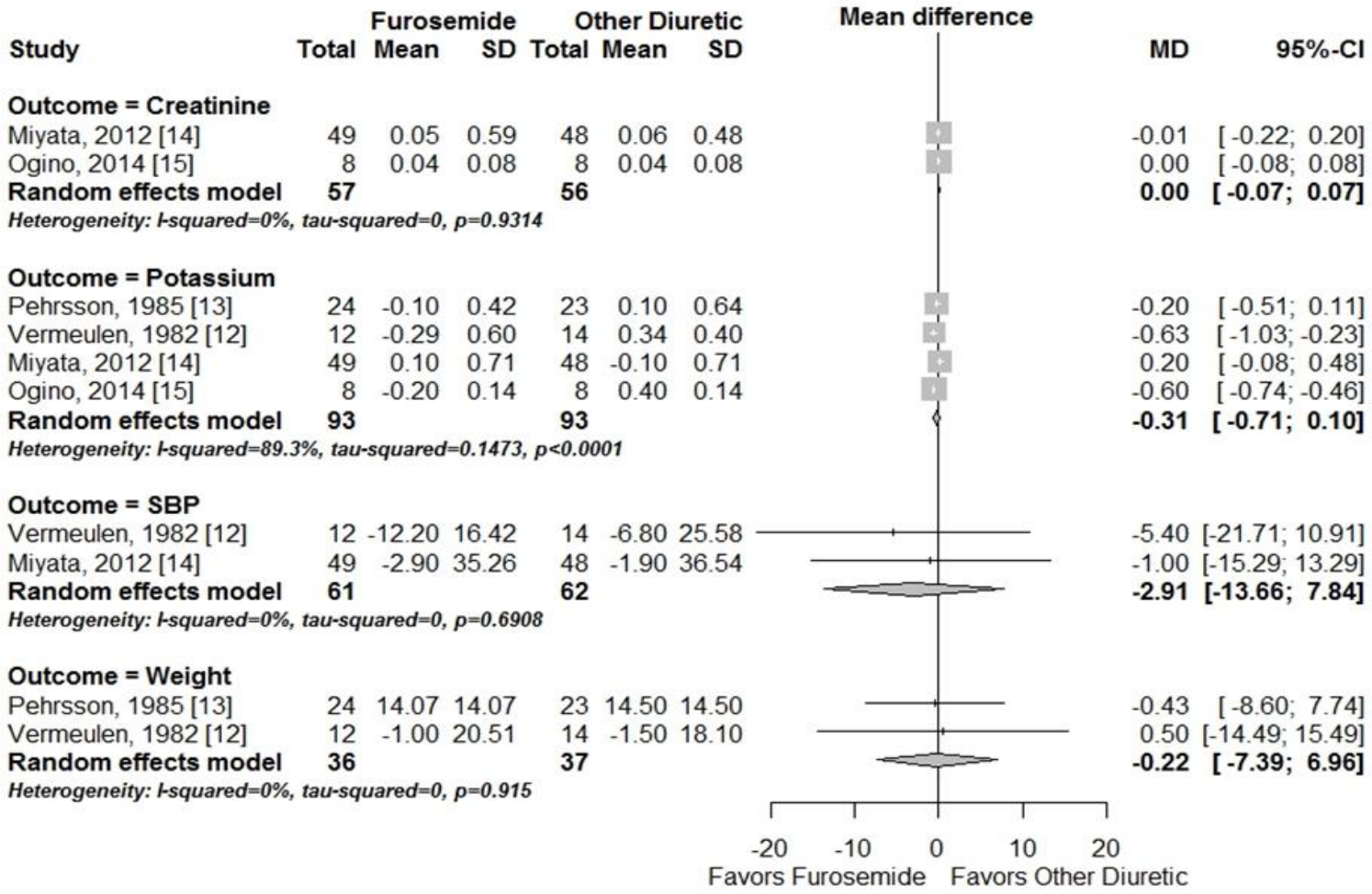

Henle Loop
Control
Risk Ratio
Study
Events Total Events Total
RR 95%-CI W(random)
Vermeulen, 1982[12] 2 14 3 12 0.57 [0.11; 2.87] 79.2%
Pehrsson, 1985[13] 1 24 0 23 2.88 [0.12; 67.16] 20.8%
Random effects model 38 35 0.80 [0.19; 3.37] 100%
Heterogeneity: I-squared=0%, tau-squared=0, p=0.365
0.1 0.5 1 2 10
Favors Henle Loop
Favors Thiazide

Figure 4.

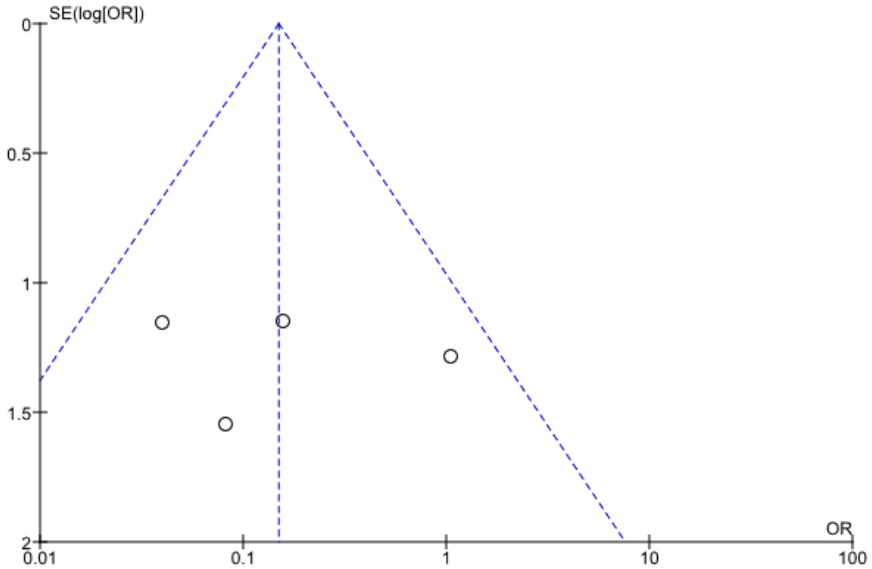

Furosemide
Other Diuretic
Mean difference
Study Total Mean SD Total Mean SD MD 95%-CI
Outcome = Creatinine
Miyata, 2012 [14] 49 0.05 0.59 48 0.06 0.48 -0.01 [-0.22; 0.20]
Ogino, 2014 [15] 8 0.04 0.08 8 0.04 0.08 0.00 [-0.08; 0.08]
Random effects model 57 56 0.00 [-0.07; 0.07]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.9314
Outcome = Potassium
Pehrsson, 1985 [13] 24 -0.10 0.42 23 0.10 0.64 -0.20 [-0.51; 0.11]
Vermeulen, 1982 [12] 12 -0.29 0.60 14 0.34 0.40 -0.63 [-1.03; -0.23]
Miyata, 2012 [14] 49 0.10 0.71 48 -0.10 0.71 0.20 [-0.08; 0.48]
Ogino, 2014 [15] 8 -0.20 0.14 8 0.40 0.14 -0.60 [-0.74; -0.46]
Random effects model 93 93 -0.31 [-0.71; 0.10]
Heterogeneity: I-squared=89.3%, tau-squared=0.1473, p<0.0001
Outcome = SBP
Vermeulen, 1982 [12] 12 -12.20 16.42 14 -6.80 25.58 -5.40 [-21.71; 10.91]
Miyata, 2012 [14] 49 -2.90 35.26 48 -1.90 36.54 -1.00 [-15.29; 13.29]
Random effects model 61 62 -2.91 [-13.66; 7.84]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.6908
Outcome = Weight
Pehrsson, 1985 [13] 24 14.07 14.07 23 14.50 14.50 -0.43 [-8.60; 7.74]
Vermeulen, 1982 [12] 12 -1.00 20.51 14 -1.50 18.10 0.50 [-14.49; 15.49]
Random effects model 36 37 -0.22 [-7.39; 6.96]
Heterogeneity: I-squared=0%, tau-squared=0, p=0.915
-20 -10 0 10 20
Favors Furosemide
Favors Other Diuretic

Supplement Material

Structured search.

((("Heart Failure"[Mesh:NoExp]OR "Cardiac Failure" OR "Heart Decompensation" OR "Decompensation, Heart" OR "Heart Failure, Right-Sided" OR "Heart Failure, Right Sided" OR "Right-Sided Heart Failure" OR "Right Sided Heart Failure" OR "Myocardial Failure" OR "Congestive Heart Failure" OR "Heart Failure, Congestive" OR "Heart Failure, Left-Sided" OR "Heart Failure, Left Sided" OR "Left-Sided Heart Failure" OR "Left Sided Heart Failure")) AND ("Diuretics"[Mesh] OR "Diuretic Effect" OR "Effect, Diuretic" OR "Diuretic Effects" OR "Effects, Diuretic")) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]))

Figure 1: Funnel plot for the studies that evaluates the outcome worse of congestion considering henle loop diuretic compared to no/reduction dose of diuretic.



Quality assessment						
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**
Creatinine serum level mg/dL (follow up: range 12 weeks to 16 weeks; assessed with: mg/dL)						
145 (3 RCTs)	not serious	not serious	serious [a]	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	⊕⊕⊕⊕ HIGH
Potassium serum level mEq/dL (follow up: range 6 weeks to 16 weeks; assessed with: mEq/dL)						
238 (5 RCTs)	not serious	not serious	serious [b]	not serious	all plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕⊕ HIGH
Systolic blood pressure mmHg (follow up: range 6 weeks to 12 weeks; assessed with: mmHg)						

170 (3 RCTs)	not serious	not serious	serious [c]	not serious	all plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕⊕ HIGH
Body weight kg (follow up: range 6 weeks to 12 weeks; assessed with: kg)						
73 (2 RCTs)	not serious	not serious	not serious	not serious	all plausible residual confounding would reduce the demonstrated effect	⊕⊕⊕⊕ HIGH

Table 1: Grade summary of evidence for outcomes creatinine, potassium, systolic blood pressure and weight.

CI: Confidence interval

a. Control drug are not from the same class, Ogino 2014 - espironolactone, Nordrehaug 1992 - benazepril and at Miyata 2012 - azosemida. As the diuretic group were treated with furosemide at Ogino 2014 e Miyata 2012 and with hydroclorotiazide at Nordrehaug 1992.

b. No explanation was provided

c. Control drug are not from the same class, Ogino 2014 - espironolactone, Nordrehaug 1992 - benazepril, Vermeulen 1982-hydroclorothiazide and at Miyata 2012 - azosemida. As the diuretic group were treated with furosemide, except for Nordrehaug 1992 treated with hydroclorotiazide.

Table 1: Grade summary of evidence for outcomes worse of congestion.

Henle loop diuretic compared to no/reduction dose of diuretic for chronic heart failure Bibliography:											
Quality assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no/reduction dose of diuretic	**With Henle loop diuretic**		**Risk with no/reduction dose of diuretic**	**Risk difference with Henle loop diuretic**
Progression of congestion with need to reintroduce henle loop diuretic (follow up: range 3 months to 12 months; assessed with: number of patients)											
156 (4 RCTs)	not serious	not serious	not serious	very serious [a]	all plausible residual confounding would reduce the demonstrated effect	⨁⨁⨁◯ MODERATE	16/59 (27.1%)	4/97 (4.1%)	not estimable	271 per 1.000	**271 fewer per 1.000** (271 fewer to 271 fewer)

a. Small number of patients

8. ARTIGO 3 – Racional e delineamento de um ensaio clínico randomizado, duplo-cego, estudo multicêntrico para avaliar a segurança e tolerabilidade da retirada de furosemida em pacientes ambulatoriais com Insuficiência Cardíaca crônica estável: estudo ReBIC-1

Rational and Design of a Randomized, Double-blind, Multicenter Trial to Evaluate the Safety and Tolerability of Furosemide Withdrawal in Stable Chronic Outpatients with Heart Failure: The ReBIC-1 Trial

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Jose A. Figueiredo Neto, MD ScD; Ilmar Kohler, MD ScD (*in memoriam*);
Luis Beck- da-Silva, MD ScD; Luiz C. Danzmann, MD ScD;
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ABSTRACT

Aims. Furosemide is commonly prescribed for symptom relief in heart failure (HF) patients. Although few data support the continuous use of loop diuretics in apparently euvolemic HF patients with mild symptoms, there are concerns about safety of diuretic withdraw in these patients. The ReBIC-1 trial was designed to evaluate the safety and tolerability of withdrawing furosemide in stable, euvolemic, chronic HF outpatients. This multicenter initiative is part of a Brazilian Research Network in Heart Failure (ReBIC) created to develop clinical studies in HF and composed predominantly by university tertiary care hospitals.

Methods. The ReBIC-1 trial is currently enrolling HF patients in NYHA functional class I-II, left ventricular ejection fraction ≤ 45%, without a HF-related hospital admission within the last 6 months, receiving a stable dose of furosemide (40 or 80 mg per day) for at least 6 months. Eligible patients will be randomized to maintain or withdraw furosemide in a double-blinded protocol. The trial has two co-primary outcomes: (1) dyspnea assessment using a visual-analogue scale evaluated at 4 time points and (2) the proportion of patients maintained without diuretics at the final visit. Enrolled patients will be followed up to 90 days after randomization, and diuretic will be restarted if clinical deterioration or signs of congestion are detected. Pre-defined sub-group analysis based on NT-pro-BNP levels at baseline is planned.

Perspective. Evidence-based strategies aiming to simplify HF pharmacotherapy are needed in clinical practice. The ReBIC-1 trial will determine the safety of withdrawing furosemide in stable chronic HF patients.

INTRODUCTION

Drug therapy for heart failure (HF) has greatly improved in the last 4 decades, impacting in HF-related morbidity and mortality (1). These unquestionable advances, however, were coupled with the hurdles of polypharmacy, the complexity of multiple therapeutic regimens and the inconvenience of potential side effects. Strategies aiming to simplify HF pharmacotherapy are currently the focus of clinical research (2).

Diuretics play a central role in HF treatment, mainly during episodes of acute decompensation (3). Furosemide is the prototype of loop diuretics, acting through the inhibition of the $Na^{+}K^{+}2Cl^{-}$ pump at the thick ascending limb of the Henle loop. According to the ADHERE, the EuroHeart Failure Survey and the BREATHE registries, most patients receive a loop diuretic during a hospital stay for acute decompensated HF and the majority is discharged taking a "maintenance dose" (4-6). Despite the undeniable beneficial hemodynamic effects leading to improvement of peripheral and central congestion, the net clinical effect of the chronic use of diuretics on HF prognosis is controversial.

Observational studies suggest that use of high doses of diuretics might be related to unfavorable clinical consequences, with a dose dependent association with impaired survival (7,8). Few prospective clinical studies, however, directly evaluated the clinical risks and benefits of diuretic use (9,10). Recently, a meta-analysis, published in 2012, of 14 small randomized controlled trials suggesting that diuretics might reduce the risk of death and HF worsening has been withdrawn due to methodological problems (11).

Current clinical guidelines are unanimous to recommend use of diuretics in HF patients with clinical signs and symptoms of congestion, but reinforce the lack of solid clinical scientific evidence for its use, and the potential risks that might be involved (12-14). The European Society of Cardiology proposes the administration of the lowest dose necessary to achieve

euvolemia, avoiding the unnecessary delay in the use of drugs that modify the natural history of the disease (14). However, in clinical practice, concerns about worsening symptoms and congestion limit furosemide withdrawing.

Based on these uncertainties about diuretic use in HF, the ReBIC-1 trial was designed to evaluate the safety and tolerability of withdrawing furosemide use in stable, euvolemic, chronic HF outpatients in a multicenter double-blinded randomized clinical trial.

METHODS

Methods

ReBIC is a Brazilian research network created to develop clinical studies in heart failure and composed predominantly by university tertiary care hospitals. Data collection, management, and analysis will be performed at the network's data coordinating center at Hospital de Clínicas de Porto Alegre. All the authors reviewed and approved the manuscript and assume full responsibility for the accuracy and completeness of the data and for the fidelity of this report of the study protocol.

Study design

ReBIC-1 is a randomized, double-blinded, parallel group, placebo-controlled, two-arm trial comparing the short-term safety and tolerabitlity of discontinuation of furosemide in apparently euvolemic outpatients with chronic stable HF and reduced left ventricular ejection fraction.

Recruitment and enrollment

Eligible patients on the clinics of Heart Failure from tertiary hospitals in Brazil are phone contacted to evaluation at a screening visit. Patients are men and women between the ages of 18 and 80 years.

The ReBIC-1 trial is enrolling HF outpatients that fulfill the following criteria:

(1) NYHA functional class I or II;

(2) LVEF ≤ 45% by transthoracic two-dimensional echocardiography performed within12 months before the screening visit;

(3) no previous HF related hospitalization or visit to emergency room within 6 months before the screening visit;

(4) treatment with a stable dose of furosemide (40 or 80 mg per day) for at least 6 months before the screening visit;

(5) serum potassium < 5 mEq/L;

(6) optimal HF treatment with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) and beta-blockers, unless contraindicated or not tolerated. Patients receiving mineralocorticoids receptors antagonist or thyazides were included at study. We do not relate patients receiving Angiotensin II Receptor Blocker Neprilysin Inhibitor (ARNI) because that is not avaliable in Brasil.

Factors that would have resulted in exclusion include: (1) clinical congestion score (CCS) > 5 points (supplementary Table 1); (2) prior acute coronary syndrome, stroke or myocardial revascularization within 3 months before the screening visit; (3) any severe valve heart disease (aortic, mitral or tricuspid); (4) severe pulmonary disease (asthma, emphysema or fibrosis); (5) severe hepatic failure or cirrhosis; (6) end-stage acute or chronic renal disease (on hemodialysis); (7) malignancy on active treatment; (8) congenital heart disease; (9) participation on any other interventional clinical research; (10) inability to understand and sign the informed consent. During follow-up up titration of cardiovascular drugs was discouraged.

Sample size on study power

On the basis of our initial power calculation we estimate that 230 patients would need to undergo randomization to have 80% power to detect a 600 points difference between groups in the AUC of dyspnea visual analogue scale and a power of 80% to detect a difference of 15% in the need to furosemide during the 90 days follow-up. We considered a 600 points difference to be a reasonable estimate of the minimum clinically important variation to this scale.

All analyses will be performed according to the intention-to-treat principle. Owing to the use of two coprimary end points (an efficacy, the feasibility of furosemide withdraw, and a safety end point measured by dyspnea VAS), the prespecified threshold for significance for each end point is a p value of less than 0.05.

For secondary end points, a p value of less than 0.05 will be considered to indicate statistical significance. The discontinuation furosemide group will compare with the use of a linear model (for continuous end points, logistic regression for binary end points, or a Cox model and Kaplan-Meier curves for time-to-event end points). In the case of end points for which a relevant baseline value was measured (6 minute walking test and NT-proBNP) the analysis will also be adjusted for the baseline value of that measure.

The change in the Clinical Congestion Score will be evaluated with a repeated measures analysis. Adverse events will be compared with the use of Fisher's exact test; prospectively defined adverse events of interest included weight gain, renal impairment and hyperkalemia. All P values are two-sided.

Ethics and informed consent

Approval of the study protocol was provided by the medical ethics committee of the coordinating center Hospital de Clínicas de Porto Alegre and approved at each participating center. Patients give written informed consent after receiving detailed written and oral information about the study.

Random and allocation

Participants will be randomly allocated in a 1:1 ratio to either an intervention (withdrawal of furosemide) or control (maintenance of furosemide) arm. Randomization will be computer generated and stratified by center and diuretic dose to facilitate balance between the two treatment arms. We estimate that approximate 30% of the sample will be using 80 mg of furosemide, according to our clinics patients.

Intervention

After the initial clinical and laboratory assessment to evaluate inclusion and exclusion criteria, HF outpatients will be randomized to receive placebo or to continue receiving furosemide at their usual dose (40 or 80mg/day) for three months, while the background HF therapy will remain unchanged. Both patients and researchers will be blinded to group allocation. Patients will receive 2 identical bottles of research pills at each visit: a bottle of morning pills to be ingested at 8:00 AM and a bottle of afternoon pills to be ingested at 2:00 PM. Therefore, subjects previously taking 40 mg of furosemide will receive two bottles of placebo (withdrawal group) or one bottle of furosemide and one bottle of placebo (maintenance group). Subjects previously taking 80 mg of furosemide will receive two bottles of placebo (withdrawal group) or two bottles of furosemide (maintenance group).

Follow-up period

Visit 1

At visit 1, patient eligibility will be assessed according to the above-mentioned criteria. Data regarding HF diagnosis, clinical comorbidities, physical examination (to assess the clinical congestion score [CCS]) (15), and laboratory results will be reviewed by a clinical cardiologist. Once eligibility is confirmed and the informed consent form is signed, subjects will undergo a

standard 6 minute-walk test (16) and will be asked to self-assess their level of dyspnea using a visual analog scale (VAS) method (see below - study objectives). At visit 1, blood will also be drawn to measure NT-pro-BNP levels using total heparinized venous blood and a point-of-care equipment (*COBAS* h 232, measuring range from 60-9000 pg/mL; F. Hoffmann-La Roche Ltd, Basel, Swiss). After randomization, patients will then receive 2 bottles (20-25 pills per bottle) of the study drug (morning [8AM] and afternoon [14PM] pills) in a blinded fashion.

Visit 2

Patients will be assessed 15 days after randomization to assure safety and tolerability of study drugs. During visit 2, research personnel will (1) review data regarding signs and symptoms of HF worsening, (2) calculate the CCS, (3) apply the VAS to reassess the dyspnea level, and (4) count the remaining pills in the supplied bottles. Adverse events, tolerability and need of additional furosemide will be evaluated, according to pre-defined criteria. Clinical events (emergency department visits or hospital admissions) will be evaluated for future adjudication. Patients will receive 2 additional bottles (35-40 pills per bottle) of the study drug (morning [8AM] and afternoon [14PM] pills) in a blinded fashion.

Visit 3

Visit 3 will be performed approximately 45 days after randomization. In addition to all procedures executed during visit 2, subjects will also reassess routine laboratory exams and NT-pro-BNP levels. Patients will receive 2 additional bottles (50-55 pills per bottle) of the study drug (morning [8AM] and afternoon [14PM] pills) in a blinded fashion.

Visit 4

Visit 4 will be performed approximately 90 days after randomization. In addition to all procedures executed during visit 3, subjects will also undergo a final 6 minute-walk test. At the final visit, patients will be oriented to reassume their baseline furosemide regimen, irrespective of the clinical outcome during the protocol.

Study Objectives – Primary and secondary endpoints

The trial will have two co-primary endpoints to evaluate the feasibility of furosemide withdrawal. First, dyspnea will be assessed using a visual-analogue scale (VAS). Patients will be asked to mark their level of dyspnea on a horizontal line based on their sensation of shortness of breath during the last week. The left side of the line will indicate "*I am not breathless at all*" and the right side will indicate "severe breathless". The VAS will be scored from 0 to 100 (subjects will be unaware of the numerical value of their response), and applied at baseline, day 15, day 45 and day 90 after randomization. The area under the curve (AUC) of serial assessments of the dyspnea VAS from baseline to the end of follow-up will be the first co-primary efficacy endpoint. The second co-primary endpoint will be the percentage of patients maintained without loop diuretics by the end of follow-up (90 days).

The ReBIC-1 will have 5 secondary endpoints:

(1) the variation on NT pro-BNP levels measured at baseline, day 45 and final visit;

(2) the variation in meters in the 6-minute walk test (baseline to final visit);

(3) the variation in the glomerular filtration rate (ml/min/1.73 m^2) estimated by the Modification of Diet in Renal Disease equation (MDRD) at baseline, day 45 and final visit;

(4) the percentage of patients with a CCS > 5 points at the final visit;

(5) a composite clinical endpoint of heart failure-related death, hospitalization, or emergency room visit during follow-up.

(6) Six-minute-walking test at baseline at final visit.

The ReBIC-1 trial will have only one pre-specified sub-group analysis based on the baseline levels of NT pro-BNP (median and a pre-specified value of 600 pg/mL).

Criteria for initiation of loop diuretic during follow-up

Use of loop diuretics during study visits will be decided by a physician blinded to group allocation, according to pre-defined clinical criteria. It will be recommended the reuse of loop diuretics if a patient has a clear clinical evidence of worsening of congestion (increases in the CCS > 5 points and increases in weight > 2 Kg along with new symptoms or increase in NYHA functional class). The patients with worse of clinical status will be oriented to stop study medication and returned to your usual dose of furosemide. All patients will be followed until the end of 90 days' follow-up, besides need to stop study intervention and reintroduce furosemide. The attendant physician judge to enhance diuretic dose after reintroduce furosemide that will be allowed. Variations in NT pro-BNP levels will not be used as an index of clinical congestion.

Endpoints adjudication

Classification of clinical outcomes will be performed by an independent committee (composed of 3 researchers separately and blinded for group allocation), based on review of data and forms collected by research personnel, hospital charts and death certificate (when appropriate). Eventual discordant cases will be defined by consensus.

Data analysis

Current Status

In order to recruit the 238 patients, all tertiary hospitals and HF clinics invited to this study, have agreed to participate in this research. The first patient was included in September 2015 and on March 24th 2017, the study has randomized 94 patients at 6 centers in Brazil. Recruitment is expected to be completed by December 2017 and the study should close at the beginning of 2018. To guide this study, a scientific advisory board was established with the main goal to advise the participants centres with regard to issues on data collection and follow-up vistis. Members included in the scientific advisory board are the principle investigator and 2 cardiologists and one nurse. The study is being conducted in accordance with the "Good Clinical Practice" recommendations, based on the Declaration of Helsinki (2002). The trial has been registered on Clinicaltrials.gov, NCT02689180

DISCUSSION

REBIC-1 is a randomized, double-blinded, multicenter trial that will provide important information about the safety and tolerability of diuretic withdrawing in euvolemic outpatients with HF. Physicians that treat chronic HF are frequently faced with the clinical dilemma of maintaining furosemide, a drug that has been associated with serious side effects and a worse prognosis, or withdrawing it, at the risk of worsen congestive symptoms and overall morbidity. So far, data has been conflicting and methodologically limited to help in this decision.

Observational studies have consistently suggested that chronic use of diuretics might be deleterious. A cohort study of HF patients with left ventricular systolic dysfunction observed a dose-dependent association between loop diuretic use and impaired survival, after extensive covariate adjustment, particularly for patients using high-dose furosemide (7). In 813 consecutive outpatients with chronic HF, the risk of death increased linearly across quartiles of furosemide daily dose after stratification for a propensity score. A threshold dose of 50 mg/day was related with worse clinical outcomes (8). Domanski et al demonstrated that the risk of hospitalization or death due to worsening HF in patients taking non-potassium sparing diuretics

was significantly increased by 31% compared with patients not taking any diuretic in a sub-analysis of the SOLVD trial (17). Undesirable side effects of loop diuretics are also not trivial and involve activation of the renin-angiotensin-aldosterone system, elevation of norepinephrine levels, increases in heart rate, detrimental effects on renal function and several electrolyte disturbances (3-7).

Few interventional studies have been conducted to evaluate the effects of adjusting diuretic doses in HF patients. The Dose Trial (3) shed some light in the strategies of diuretic adjustment in the scenario of acute decompensated HF, but there is scarce data in the outpatient setting. Three decades ago, Cowley et al suggested that a strategy based on increasing furosemide dose might have more favorable effects on exercise tolerance in symptomatic HF patients than an approach based on adding captopril (9). Richardson et al directly tested the substitution of furosemide by captopril in 14 symptomatic HF patients in a randomized crossover clinical trial. Most patients tolerated the switch, but some developed severe pulmonary congestion (10). In an uncontrolled study, McKie et al (18) evaluated the effects of furosemide reduction in 32 patients with stable symptomatic HF (NYHA class II-III) with and without underlying renal dysfunction. They concluded it was safe to reduce diuretics, a strategy that improved renal function in some subjects, without changes in volume or functional status. Recently, 40 chronic HF patients using ≥ 120 mg of furosemide/day were randomized to either continuation or reduction of furosemide doses in tertiary university medical center in Greece. Decrease of diuretic dose was tolerated in most patients without further cardiac decompensation and was associated with a tendency towards a better prognosis (19). Although provocative, both studies that assessed strategies of diuretic reduction evaluated patients taking higher doses of furosemide than those that will be enrolled in the ReBIC-1 trial. This subgroup might not be representative of most HF outpatients, as stable patients usually take lower doses of furosemide

(20). In addition, most available data on diuretic adjustment in HF outpatients is derived from small single center reports, without an adequate control group or blinding of interventions, and most protocols are not adequately powered to allow conclusions with broad clinical applicability.

Recent HF guidelines from the European Society of Cardiology state that diuretics might be discontinued in selected asymptomatic euvolemic or hypovolemic patients (14). However, identification of this scenario is challenging in clinical practice and the safety of this strategy is uncertain. In this regard, the pre-specified stratified analysis based on natriuretic peptide levels planned by the ReBIC-1 trial may help to identify patients that might not be eligible to diuretic discontinuation. Evaluation of dyspnea, clinical congestion, functional status, and natriuretic peptide levels will be performed in order to assure clinical stability during follow-up visits. The ReBIC-1 trial will be the first multicenter, double-blind, randomized study to address different diuretic adjustment strategies in outpatients with stable HF due to left ventricular dysfunction.

Limitations

Bias was carefully avoided throughout the trial. Selection bias was avoided by having an independent researcher randomize the participants after the baseline data had been collected. Detection bias was avoided by having the follow-up data collected by a researcher who was not involved in randomization. Conclusions

If proven safe and feasible in the present study, diuretic withdraw might be considered as part of the evidence-based approaches in the context of chronic HF, potentially simplifying HF therapy and reducing adverse effects in euvolemic ambulatory patients.

Disclosures

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper, and its final contents.

Funding

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Figure Legends

Figure 1. Flow diagram

Table Legends

Table1. Recruitment centers and respective principal investigator.

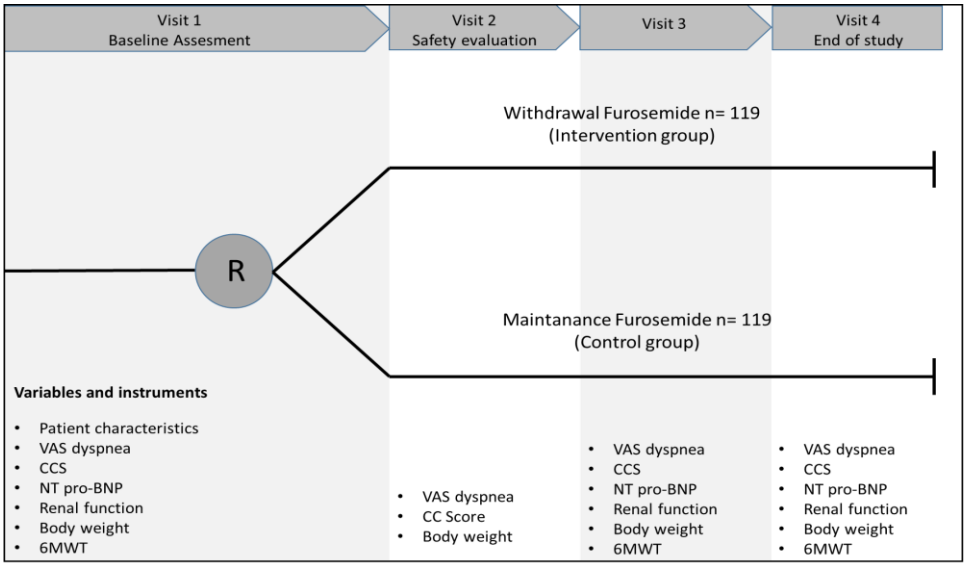

Figure 1.

Institution	Primary Investigators	Status	Initiation of Randomization
The ReBIC Coordinator Center: Hospital de Clinicas de Porto Alegre **Principal Investigators**: Luis E. Rohde, MD and Andréia Biolo, MD **Research Coordinators**: Priscila Raupp da Rosa, MD and Madeni Doebber, RN			
Hospital de Clinicas de Porto Alegre	Andréia Biolo, MD	Recruiting	Yes
Hospital Universitário da ULBRA/RS	Luiz Cláudio Danzmann, MD	Recruiting	Yes
Instituto de Cardiologia – IC/FUC RS	Marciane Rover, MD	Recruiting	Yes
Hospital Universitário da UFPEL/RS	Eduardo Gehling Bertoldi, MD	Recruiting	Yes
Hospital São Lucas da PUC/RS	Priscila Raupp da Rosa, MD	Recruiting	Yes
Hospital Moinhos de Vento – RS	Luis Beck-da-Silva, MD	Approved	No
Hospital da PUC/PR	Lidia Moura Zytynski, MD	Recruiting	Yes
Hospital Universitário UFMA	Jose Albuquerque Figueiredo Neto, MD	Recruiting	Yes
Hospital de Clinicas da UFMG	Antonio Luiz Pinho Ribeiro, MD	Recruiting	Yes
Hospital IGESP da UNIFESP	Dirceu Rodrigues de Almeida, MD	Submitted	No

Table 1.

Supplementary

Table 1. Clinical congestion Score.

CLINICAL CONGESTION SCORE	
FUNCTIONAL CLASS	
NYHA I	**1 point**
NYHA II	**2points**
NYHA III	**3points**
NYHA IV	**4points**
ORTHOPNEIA and PAROXYSMAL NOCTURNAL DYSPNEA (PND)	
One pillow to sleep	**0 points**
> 1 pillow to sleep	**1 point**
At least 1 episode of PND last week	**2 points**
Several episodes of PND last week	**3 points**
Slept sitting at least once last week	**4 points**
EDEMA	
No edema	**0 points**
Edema 1/4+	**1 point**
Edema 2/4+	**2 points**
Edema 3/4+	**3 points**
Edema 4/4+	**4 points**
RALES	
No rales	**0 points**
Basal rales (< ¼ of posterior lungs)	**1 point**
Rales from ¼ to ½ of posterior lungs	**2 points**
Rales> ½ of posterior lungs	**3 points**
Rales in all lung fields (anterior and posterior)	**4 points**
S3	
YES	**1 point**
HEPATOJUGULAR REFLUX	
YES	**1 point**

ESTIMATED CENTRAL VENOUS PRESSURE (CVP)	
CVP:not measureable	**0 points**
CVP between 5-8 cm H_2O	**1 point**
CVP between 8-12 cm H_2O	**2 points**
CVP between 12-15 cm H_2O	**3 points**
CVP between > 15 cm H_2O	**4 points**
FINAL SCORE	

8.1 REBIC 1 – DADOS PRELIMINARES

O estudo está em andamento em 9 hospitais terciários, com o primeiro paciente randomizado em novembro de 2015, totalizando 94 pacientes incluídos e 62 pacientes com seguimento completo. Dados preliminares de 87 pacientes mostram, dentre as características da amostra, o predomínio de homens caucasianos com idade média 60,1 anos, hipertensos na sua maioria e diabéticos. As etiologias isquêmica e idiopática são as principais nesses pacientes (32% e 28%, respectivamente) com fração de ejeção média 32,5%. Dentre as medicações, todos estavam em uso de betabloqueador e 95% em uso inibidor da ECA ou bloqueador do receptor da angiotensina (BRA). A creatinina média foi de 1,12 mg/dL e apenas 16 pacientes possuíam algum tipo de dispositivo cardíaco (Tabela 1).

Com perspectiva de término do estudo, em 2017, com 230 pacientes randomizados pretende-se esclarecer se a retirada de diurético em pacientes crônicos é factível e avaliar quais são os preditores de sucesso desta conduta.

Tabela 1

CARACTERÍSTICAS DA AMOSTRA	
Sexo masculino (n,%)	63 (73)
Etnia caucasiana (n,%)	61 (70)
Idade, anos (média)	60,1
IMC (média)	28,3
PAS, mmHg (média)	124
PAD, mmHg (média)	76
Frequência cardíaca, bpm (média)	69
FE, %	32
Teste de caminhada, m	367
EAV da dispneia, mm	36
NT-proBNP ng/dL	1.118
Creatinina, mg/dL	1,12

COMORBIDADES	
Hipertensão arterial (n,%)	51 (62)
Diabetes mellitus (n,%)	28 (34)
História de tabagismo (n,%)	35 (40)
Fibrilação/flutter atrial (n,%)	13 (15)
AVE prévio	6 (7)
Hipotireoidismo (n,%)	5 (6)
Dispositivos (n,%)	11 (18)
CLASSE FUNCIONAL	
NYHA I (n,%)	64 (73)
NYHA II (n,%)	23 (26)
ETIOLOGIA	
Isquêmica (n,%)	28 (32)
Idiopática (n,%)	25 (28)
Hipertensiva (n,%)	19 (21)
Valvular (n,%)	3 (3,4)
Peri parto (n,%)	2 (2,3)
Chagásica (n,%)	2 (2,3)
Pós-quimioterapia (n,%)	1 (1,4)
Alcoólica (n,%)	2 (2,3)
TRATAMENTO	
Betabloqueadores (n,%)	86 (100)
Tartarato de metoprolol (n,%)	39 (44)
Carvedilol (n,%)	32 (36)
Succinato de metoprolol (n,%)	10 (11)
Bisoprolol (n,%)	4 (4,5)
BRA (n,%)	29 (33)
IECA (n,%)	54 (62)
Enalapril (n,%)	47 (54)
Captopril (n,%)	31 (35)
Lisinopril (n,%)	3 (3,4)
Espironolactona (n,%)	64 (73)
Digoxina (n,%)	38 (43)
AAS (n,%)	37 (42)
Hidralazina (n,%)	16 (18)
Nitrato(n,%)	15 (17)
Tiazídicos (n,%)	7 (8)

9. CONCLUSÕES E CONSIDERAÇÕES FINAIS

A realização dos projetos descritos nesta tese agrega resultados de grande importância para o conhecimento da insuficiência cardíaca. Nossa metanálise sobre o efeito do sildenafil relacionado com o tempo demonstra que os dados de estudos de intervenção em humanos mostram um significante benefício hemodinâmico em remodelamento e, principalmente, na redução do número de hospitalizações. Embora um estudo de metanálise tenha um elevado nível de evidência, sugere-se a realização de ensaio clínico multicêntrico com pacientes com disfunção ventricular para confirmar o benefício da droga e acrescentá-la nas diretrizes de insuficiência cardíaca.

Quanto às conclusões dos estudos com diuréticos, podemos afirmar que as evidências disponíveis para indicação de diurético de alça em pacientes com insuficiência cardíaca crônica em classes funcionais NYHA I-III são fracas e insuficientes para embasamento de uma recomendação. Sendo assim, a prática atual relacionadas à prescrição de diurético de alça deve ser revista à luz de novas evidências.

Confiamos que os resultados do estudo ReBIC 1 contribuirá para a construção do conhecimento nesta área. O estudo REBIC-1 está com aproximadamente 100 pacientes randomizados até o momento e temos a pretensão de finalizar as inclusões até dezembro de 2017.

Independentemente dos futuros resultados do estudo ReBIC 1, a iniciativa para a implementação da Rede Brasileira de Insuficiência Cardíaca, integrando clínicas especializadas em IC de hospitais terciários é a principal meta e legado deste estudo. Pela primeira vez no Brasil, temos um projeto que integra cardiologistas, que são expoentes no tratamento de ponta de IC num esforço voltado para o cuidado do paciente crônico ambulatorial ou manejado na atenção primária.