PONTIFÍCIA UNIVERSIDADE CATÓLICA DO PARANÁ
ESCOLA DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE
**MESTRADO**

CAMILA HARTMANN

# O EFEITO DA IVABRADINA EM PACIENTES COM INSUFICIÊNCIA CARDÍACA COM FRAÇÃO DE EJEÇÃO REDUZIDA: REVISÃO SISTEMÁTICA E METANÁLISE

CURITIBA
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Dissertação apresentada ao programa de Pós-Graduação em Ciências da Saúde da Escola de Medicina da Pontifícia Universidade Católica do Paraná, como parte dos requisitos para obtenção do título de Mestre em Ciências da Saúde.

**Orientadora:** Prof.ª Dra. Cristina Pellegrino Baena.
**Co-orientadora:** Prof.ª Dra. Lidia Ana Zytynski Moura.

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**ATA DA SESSÃO PÚBLICA DE EXAME DE DISSERTAÇÃO DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE EM NÍVEL DE MESTRADO DA PONTIFÍCIA UNIVERSIDADE CATÓLICA DO PARANÁ.**

Aos vinte e oito dias do mês de setembro de 2016, realizou-se a sessão pública de defesa de dissertação, **"O EFEITO DA IVABRADINA EM PACIENTES COM INSUFICIÊNCIA CARDÍACA COM FRAÇÃO DE EJEÇÃO REDUZIDA: REVISÃO SISTEMÁTICA E METANÁLISE"** apresentado por **Camila Hartmann** para obtenção do título de mestre; Área de Concentração: Medicina e áreas afins.

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## DEDICATÓRIA

*Dedico esta conquista a minha família que sempre me apoiou e me incentivou em todos os momentos: minha mãe Denise, meu pai Ricardo, meu irmão Luís Felipe e meu marido Edgar. Amo vocês.*

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## EPÍGRAFE

**“A tarefa não é tanto ver aquilo que ninguém viu, mas pensar o que ninguém ainda pensou sobre aquilo que todo mundo vê. ”**

**(Arthur Schopenhauer)**

## RESUMO

**Objetivos**: Esta meta-análise foi realizada a fim de estudar o efeito adicional da Ivabradina, separadamente do efeito dos betabloqueadores, nos desfechos de morte cardiovascular, morte por qualquer causa, hospitalização por IC e frequência cardíaca na população de pacientes com Insuficiência Cardíaca com Fração de Ejeção Reduzida (ICFER). **Métodos:** Buscas eletrônicas nas bases de dados Embase, MEDLINE, PubMed, Cochrane Library, CINAHL, Web of Science, Scopus, SciELO e LILACS foram conduzidas até junho de 2016, envolvendo estudos controlados randomizados em que a Ivabradina foi comparada a um grupo controle. Os agrupamentos dos riscos relativos RR e intervalos de confiança (95%) foram calculados usando os eventos relatados nos estudos. O efeito *Random* foi utilizado para resumir os resultados, e a qualidade dos estudos foi avaliada com a ferramenta para risco de viés da Cochrane. **Resultados:** Dos 1.790 estudos encontrados, sete preencheram os critérios de inclusão para a revisão sistemática e meta-análise. A população estudada foi de 17.747 pacientes. Na maioria dos estudos, o risco de viés foi alto quando foram usadas doses de betabloqueador mais baixas do que o recomendado. Os agrupamentos dos riscos relativos RR (95%) para morte por qualquer causa, morte cardiovascular e hospitalização por IC foram de 0,98 (0,90 – 1,06); 0,99 (0,91 – 1,08); e 0,86 (0,79 – 0,93) respectivamente. A frequência cardíaca diminuiu em 8,7 (6,37 – 11,03) batimentos por minuto com a Ivabradina comparada ao grupo controle. A análise de subgrupo por dose de betabloqueador mostrou que para pacientes em uso do tratamento recomendado (pelo menos 50% da dose-alvo de betabloqueador), a frequência cardíaca (IC 95%) diminuiu em 4,70 (3,67 – 5,73), enquanto que para pacientes que não estavam em uso do tratamento recomendado ou para os quais não havia referência à dose, a frequência cardíaca diminuiu em 8,60 (8,13 – 9,08). **Conclusão:** A Ivabradina reduziu significativamente frequência cardíaca e hospitalização por IC. O efeito adicional da Ivabradina sobre a frequência cardíaca parece estar inversamente correlacionado com a dose de betabloqueador. Doses de betabloqueadores que não foram reportadas ou que foram mais baixas do que o tratamento recomendado limitaram as conclusões sobre o efeito adicional de Ivabradina.



**Palavras-chave:** Ivabradina; insuficiência cardíaca; disfunção ventricular esquerda; beta-antagonistas adrenérgicos; frequência cardíaca; desfecho de tratamento.

## ABSTRACT

**Aims:** This meta-analysis was performed in order to study the additional effect of Ivabradine, apart from the effect of beta-blockers, on cardiovascular death, all-cause mortality, hospitalization due to HF and heart rate in a Heart Failure with Reduced Ejection Fraction (HFrEF) population. **Methods:** Electronic searches in Embase, Medline, PubMed, Cochrane Library, CINAHL, Web of Science, Scopus, SciELO and LILACS were conducted up to June 2016 involving randomized controlled trials where Ivabradine was compared to a control group. Pooled relative risks RR and CI (95%) were calculated using the events reported in the studies. Random effect was used to summarize the results and quality of studies was evaluated with the Cochrane risk of bias tool. **Results:** Of 1,790 studies found, seven met the inclusion criteria for the systematic review and meta-analysis. The studied population consisted of 17,747 patients. The risk of bias was generally high for beta-blocker doses lower than the recommended. Pooled relative risks RR (95%) for all-cause mortality, cardiovascular death and hospitalization for HF were 0.98 (0.90 – 1.06); 0.99 (0.91 – 1.08); and 0.86 (0.79 – 0.93) respectively. Heart rate (CI 95%) decreased by 8.7 (6.37 – 11.03) beats per minute with Ivabradine compared to the control group. Subgroup analysis by beta-blocker dose showed that for patients on recommended treatment (at least 50% of the beta-blocker target dose), heart rate (CI 95%) decreased by 4.70 (3.67 – 5.73), whereas for patients not on recommended treatment or with unreported dose, heart rate decreased by 8.60 (8.13 – 9.08). **Conclusion:** Ivabradine significantly reduced heart rate and hospitalization due to HF. The additional effect of Ivabradine on hear rate appears to be inversely correlated with the dose of beta-blocker. Unreported beta-blocker doses and beta-blocker doses lower than the recommended treatment limited the conclusions on the additional effect of Ivabradine.



**Keywords:** Ivabradine; heart failure; left ventricular dysfunction; adrenergic beta-antagonists; heart rate; treatment outcome.

## LISTA DE ABREVIATURAS

**CINAHL –** *Cumulative Index to Nursing and Allied Health Liteature*

**FE –** Fração de Ejeção

**GRADE –** *Grading of Recommendations Assessment, Development and Evaluation*

**IC –** Insuficiência Cardíaca

**ICFEP –** Insuficiência Cardíaca com Fração de Ejeção Preservada

**ICFER –** Insuficiência Cardíaca com Fração de Ejeção Reduzida

**LILACS –** Literatura Latino-Americana e do Caribe em Ciências da Saúde

**MEDLINE –** *Medical Literature Analysis and Retrieval System Online*

**MeSH –** *Medical Subject Heading*

**NLM –** *U.S. National Library of Medicine*

**PRISMA –** *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

**PUCPR –** Pontifícia Universidade Católica do Paraná

**SciELO –** *Scientific Electronic Library Online*

**TIAB –** *Title/Abstract*

**TW –** *Text Words*

**SUMÁRIO**

## 1 INTRODUÇÃO

A insuficiência cardíaca (IC) crônica é uma síndrome clínica responsável por grande número de internações e altos gastos públicos[1]. Apesar dos avanços no seu tratamento nos últimos 30 anos, ainda apresenta alta taxa de mortalidade (aproximadamente 50% em 5 anos)[2]. Em países desenvolvidos, 1 a 2% da população apresenta IC[3] e sua prevalência também aumenta com a idade, sendo que esses números passam para 8 a 10% na população acima dos 60 anos[4]. Com o aumento global da população idosa, o risco de desenvolver IC está crescendo proporcionalmente[1]. Assim, faz-se necessária a manutenção da pesquisa para o tratamento dessa população.

Define-se IC como uma síndrome clínica complexa de caráter sistêmico, relacionada ao inadequado suprimento sanguíneo para atender as necessidades metabólicas teciduais na presença de retorno venoso normal (ou fazê-lo somente com elevadas pressões de enchimento)[1]. Assim, os sintomas e sinais clínicos da IC podem ser decorrentes da disfunção ventricular sistólica, diastólica ou ambas. A IC sistólica também é conhecida como IC com fração de ejeção reduzida (ICFER), mais precisamente fração de ejeção menor que 40%[5], e é responsável por 60% dos casos em adultos. Já a IC com fração de ejeção preservada (ICFEP), representada pela disfunção ventricular diastólica, é responsável pelos 40% restantes e possui particularidades fisiopatológicas e de tratamento[6].

O tratamento medicamentoso da ICFER atua nos mediadores responsáveis pelo remodelamento cardíaco e possui três objetivos principais: melhorar os sintomas; reduzir a progressão da doença; e reduzir as internações e a mortalidade[1,5]. A terapia padrão da ICFER inclui inibidores da enzima conversora da angiotensina (IECA), betabloqueadores, antagonistas da aldosterona, hidralazina e nitrato[1,5]. Os betabloqueadores comprovadamente reduzem mortalidade total, mortalidade cardiovascular, morte súbita e progressão da doença[7]. Apesar de sua atuação como antagonista do sistema simpático, parece que em parte seu efeito pode estar relacionado com o controle da frequência cardíaca[8].

Nesse sentido, a Ivabradina é uma droga que também reduz frequência cardíaca por bloquear os canais *If* do nó sinusal, sem reduzir contratilidade miocárdica[9]. Sua eficácia no tratamento da ICFER foi demonstrada com um grande estudo randomizado controlado publicado em 2010[10] o qual demonstrou benefício apenas em desfecho combinado de morte cardiovascular ou internação por insuficiência cardíaca para pacientes com frequência cardíaca basal acima de 70 batimentos por minuto (bpm). Entretanto, esse efeito não ocorreu no subgrupo de pacientes que usavam mais de 50% da dose-alvo de betabloqueador[11]. O efeito da Ivabradina na ICFER separadamente do betabloqueador, portanto, não é claro. Não há síntese de evidência demonstrando que o uso isolado da Ivabradina no manejo da ICFER reduz mortalidade. Apesar disso, a diretriz brasileira[12] e europeia[5] sobre diagnóstico e tratamento da IC, que utilizam o sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) para graduação da qualidade de evidência e força de recomendação[13], recomendam o uso da Ivabradina.

Na diretriz europeia[5] a classe de recomendação é “IIa”, condição para a qual há evidências conflitantes e/ou divergência de opiniões sobre segurança e eficácia do tratamento, mas são favoráveis à sua indicação. O nível de evidência considerado é “B”, quando os dados foram obtidos a partir de metanálise menos robusta, um único estudo randomizado ou de estudos não randomizados (observacionais). Com relação à diretriz brasileira[12], a classe de recomendação também é “IIa”, porém o nível de evidência considerado é “A”, quando os dados foram obtidos a partir de múltiplos estudos randomizados de bom porte, concordantes e/ou de metanálise robusta de estudos clínicos randomizados.

O que se verifica, entretanto, é que não existe evidência forte e estudos robustos concordantes a respeito do uso da Ivabradina na ICFER e fica clara a lacuna na evidência a respeito do seu real efeito nessa população. A prescrição de uma droga sem o suporte científico adequado pode provocar potenciais efeitos deletérios envolvendo custo, dificuldade de aderência, interações medicamentosas, efeitos colaterais, entre outros que devem ser ponderados frente ao real benefício ofertado ao paciente[14,15,16].

## 2 JUSTIFICATIVA

Não está claro na literatura qual é o efeito da Ivabradina na ICFER separadamente do efeito já estabelecido do betabloqueador. Apesar de não existir síntese de evidência demonstrando que o uso isolado da Ivabradina no manejo da ICFER reduz mortalidade, ela é indicada como classe de recomendação “IIa” em diretrizes nacionais e internacionais da especialidade[5,12]. Nesse sentido, a revisão sistemática e metanálise procura preencher a lacuna da literatura sobre o real efeito da Ivabradina em pacientes com ICFER.

## 3 OBJETIVO

### 3.1 Objetivo geral

Avaliar o efeito da terapia com Ivabradina em pacientes com ICFER, separadamente do efeito do betabloqueador, por intermédio de uma revisão sistemática.

### 3.2 Objetivos específicos

1. Analisar por meio de metanálise o risco relativo de hospitalização por insuficiência cardíaca, morte por qualquer causa e morte cardiovascular em pacientes com ICFER que fazem uso da Ivabradina;
2. Analisar o efeito da Ivabradina sobre frequência cardíaca;
3. Analisar os efeitos colaterais da Ivabradina em relação aos efeitos colaterais dos grupos controle dos estudos incluídos.

## 4 DESENVOLVIMENTO

A pergunta principal desta dissertação surgiu em 2014 durante o segundo ano de Especialização em Cardiologia. Durante as atividades práticas, realizadas no ambulatório de Insuficiência Cardíaca da Santa Casa de Misericórdia de Curitiba, existia sempre o questionamento de quando iniciar a Ivabradina e qual seria o real benefício dessa medicação na sobrevida dos pacientes. A partir dessa discussão, a Prof.ª Dra. Lidia Ana Zytynski Moura sugeriu uma revisão sistemática sobre o assunto para esclarecer esta questão e verificar os níveis de evidência da medicação. Sua experiência pessoal durante um Estudo Clínico Randomizado[10] mostrou que não havia cobrança da Indústria em manter os pacientes com dose-alvo de betabloqueador durante a intervenção com Ivabradina ou placebo, um possível viés de confusão.

A Prof.ª Dra. Cristina Pellegrino Baena, que havia acabado de retornar da Holanda onde adquiriu muita experiência em revisão sistemática e metanálise, se interessou pelo projeto e aceitou realizar a orientação do trabalho. A experiência adquirida com metanálise durante o Trabalho de Conclusão de Curso da graduação, com o Prof. Dr. Emilton Lima Junior, assegurou confiança e facilitou o início do projeto pelo conhecimento prévio da metodologia. Assim, o bom início e andamento do trabalho acabou sendo a base para a aprovação no programa de Pós-Graduação em Ciências da Saúde da Pontifícia Universidade Católica do Paraná.

O trabalho teve início com a revisão bibliográfica inicial e montagem da estratégia de busca nas bases de dados. Foi necessário o conhecimento de termos MeSH (*Medical Subject Headings*) e revisão do protocolo PRISMA[17,18], um guia para a realização de revisões sistemáticas e metanálises com informação transparente e que garante qualidade pela exigência metodológica. Após a busca nas bases de dados, as então alunas de medicina (agora já formadas) Natasha Ludmila Bosch e Luara de Aragão Miguita ajudaram na seleção dos títulos e artigos com o programa Endnote. A Prof.ª Dra. Lidia Ana Zytynski Moura esteve presente para decidir a inclusão ou exclusão de artigos duvidosos. A análise estatística foi realizada junto com a Prof.ª Dra. Cristina Pellegrino

Baena utilizando o software STATA, assim como a análise de qualidade dos artigos, que foi realizada utilizando a ferramenta Cochrane para risco de viés[19].

Após todas essas etapas, houve novos encontros com a Prof.ª Dra. Lidia Ana Zytynski Moura para entender os resultados e aprimorar a discussão, a qual se apresentou bastante rica e demonstrou ser o tópico principal do trabalho. Reuniões mensais de Epidemiologia promovidas pela Prof.ª Dra. Cristina Pellegrino Baena também ajudaram a amadurecer o entendimento dos resultados e o desenvolvimento da discussão. Por fim, houve a parte de redação e revisão.

Após todo esse processo de desenvolvimento, entende-se que o objetivo dessa dissertação de mestrado é o de contribuir, com alto nível de evidência, para a decisão profissional de médicos que cuidam de pacientes com Insuficiência Cardíaca. Será apresentado a seguir, a metodologia utilizada e o manuscrito redigido, que visa publicação internacional (o jornal alvo é *o European Journal of Heart Failure* com fator de impacto de 6.526). O resumo foi aceito e o trabalho já foi apresentado como tema-livre oral no XV Congresso Brasileiro de Insuficiência Cardíaca em Campos do Jordão, São Paulo; e também como tema-livre oral em uma Miniconferência no 71º Congresso Brasileiro de Cardiologia em Fortaleza, Ceará.

# 5 MÉTODOS

## 5.1 PRISMA

O protocolo PRISMA[17,18] *(Preferred Reporting Items for Systematic Reviews and Meta-Analyses)* foi utilizado como guia para a revisão sistemática. Trata-se de uma metodologia rígida com um *checklist* de 27 itens e um diagrama de fluxo de quatro fases. O *checklist* descreve todas as etapas de uma revisão sistemática de maneira detalhada, desde a correta apresentação do título, passando pelo resumo, metodologia, resultados e discussão. O diagrama de fluxo de quatro fases deixa clara a evolução da metodologia aplicada e os motivos de exclusão dos artigos. Dessa forma, o protocolo PRISMA[17,18] assegura informação transparente e completa para revisões sistemáticas e metanálises. O *checklist* e o diagrama foram adicionados como anexo ao final da dissertação para conhecimento de todos os critérios exigidos.

## 5.2 Estratégia de busca

Uma revisão sistemática foi realizada nas bases de dados Embase, MEDLINE, PubMed Cochrane Library, CINAHL, Web of Science, Scopus, SciELO e LILACS até junho de 2016 para identificar os artigos que estudaram a eficácia da terapia com Ivabradina em pacientes com ICFER.

Para a construção da busca foi utilizada uma combinação de descritores, incluindo inicialmente os termos MeSH (*Medical Subject Heading*), que controlam o vocabulário de termos biomédicos usados para descrever o tema de cada artigo no MEDLINE, PubMed e outras bases de dados da *U.S. National Library of Medicine* (NLM). Os termos MeSH incluem aproximadamente 26 mil termos organizados hierarquicamente por categorias de assunto, que são atualizados anualmente para refletir as mudanças na medicina e na terminologia médica[20]. Dentro de cada termo MeSH são encontrados outros termos mais específicos que ficam organizados internamente e são acessados após a identificação do termo MeSH. Os termos MeSH utilizados nessa busca, portanto,

foram: insuficiência cardíaca, *benzazepine*, beta-antagonistas adrenérgicos, frequência cardíaca, hospitalização e morte.

Na estratégia final de busca, também foram incluídos outros descritores mais específicos identificados como palavras importantes presentes no título ou resumo (TIAB – *Text/Abstract*) ou palavras livres no texto (TW – *Text Words*). O objetivo da sistematização da busca era o de incluir todos os estudos existentes considerando alvos de população, intervenção e desfecho. A estratégia de busca completa e as palavras-chave foram expostas no material suplementar do artigo. As referências presentes nos artigos identificados pela estratégia de busca também foram procuradas manualmente, a fim de serem somadas ao trabalho e à revisão da literatura.

### 5.3 Critérios de inclusão e exclusão

Foram incluídos no estudo apenas ensaios clínicos randomizados controlados onde Ivabradina foi comparada ao grupo controle (placebo ou betabloqueador). ICFER foi definida como insuficiência cardíaca com uma fração de ejeção (FE) menor ou igual a 40%. Os critérios de inclusão foram estudos que relataram a terapia com Ivabradina em pacientes com ICFER; estudos que avaliaram os efeitos Ivabradina sobre a frequência cardíaca, hospitalização, morte cardiovascular e morte por qualquer causa, antes e depois da terapia no grupo controle e intervenção; e estudos envolvendo apenas adultos.

Foram excluídos os estudos realizados em animais; estudos que envolveram crianças ou mulheres grávidas; cartas, resumos, anais de conferências, estudos observacionais, estudos crossover, experimentos de aglomeração e estudos prospectivos de coorte; e estudos envolvendo pacientes com fibrilação atrial devido a ineficácia da Ivabradina nesta população.

### 5.4 Identificação e seleção dos estudos

Após a remoção dos artigos duplicados, dois autores revisaram de maneira independente cada título e resumo pré-selecionado, utilizando o programa *Endnote,* a

fim de identificar somente os estudos que preencheram corretamente os critérios de inclusão. Desacordos sobre qualquer variedade de itens foram resolvidos por meio de discussões e um terceiro autor (e *expert* no assunto) esteve disponível para resolver as divergências. Após a seleção inicial, os artigos foram selecionados com base em seu texto completo.

As listas de referências dos artigos selecionados foram pesquisadas para analisar publicações adicionais. Os autores foram contatados diretamente para estudos e dados adicionais e/ou não publicados.

### 5.5 Extração de dados

Dois autores coletaram os dados, através de um formulário de coleta pré-definido. Um terceiro autor, independente, revisou os dados extraídos. As características extraídas dos estudos incluíram: data de publicação, título, definição do estudo, duração da intervenção, tipo de intervenção, supervisão, entre outras. Registraram-se dados sobre os participantes de cada trabalho, número de participantes, inclusive o número total incluído na análise, sexo, idade, uso de medicamentos, comorbidades. E por fim, com relação aos resultados, foram coletados aqueles referentes aos desfechos avaliados, como morte por qualquer causa, morte cardiovascular e hospitalização por insuficiência cardíaca nos pacientes submetidos à intervenção, além de frequência cardíaca e eventos adversos.

### 5.6 Qualidade dos estudos

A qualidade de cada estudo foi avaliada pela ferramenta Cochrane para risco de viés[19], que contém os seguintes critérios: geração de sequência aleatória; ocultação da alocação; cegamento dos participantes; cegamento da avaliação dos resultados e dos avaliadores do desfecho; integridade dos resultados e dados incompletos; relatórios seletivos dos resultados; e outras fontes de viés (por exemplo: número de participantes). Nessa ferramenta, para cada um dos critérios de qualidade descritos, é realizada a qualificação do estudo em: alto risco para viés, baixo risco ou risco incerto.

Esse processo foi realizado por dois autores de maneira independente e, depois, verificou-se a concordância entre as avaliações. Desacordos sobre qualquer variedade de itens foram resolvidos por meio de discussões. A partir dessa avaliação qualitativa de cada estudo, foi verificado, ao final, qual qualidade (alto risco, baixo risco ou risco incerto) estava mais prevalente em cada critério. Dessa forma, foi possível obter um panorama geral do risco de viés de cada critério, o qual pode ser transferido para os resultados da revisão sistemática. Essa ferramenta também foi adicionada como anexo ao final da dissertação para conhecimento geral.

### 5.7 Análise estatística

As características dos pacientes nos diversos estudos foram resumidas por meio de média ponderada. Para metanálise dos resultados foram calculados os agrupamentos dos riscos relativos com os respectivos intervalos de confiança de 95% (95% IC) em cada grupo nos estudos. Estas estimativas foram reunidas pelo método aleatório *(random)* com os respectivos 95% IC. Foi realizada uma análise de subgrupo a fim de comparar os estudos que relataram todos os pacientes tratados com pelo menos 50% das doses alvo betabloqueador, como definido pelo *Guideline* da Sociedade Europeia de Cardiologia (ESC)[12], aos estudos que relataram menos pacientes que receberam esta dose ou que não relataram tais dados. Para análise da heterogeneidade entre os artigos foi empregado o *I-squared* ($I^2$). As análises foram conduzidas com software estatístico STATA versão 12.0 (StataCorpLp, Texas, United States).

## 6 RESULTADOS - ARTIGO

# THE EFFECT OF IVABRADINE THERAPY ON HEART FAILURE PATIENTS WITH REDUCED EJECTION FRACTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**KEY WORDS**
Ivabradine; heart failure; left ventricular dysfunction; adrenergic beta-antagonists; heart rate; treatment outcome

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## ABSTRACT

**Aims:** This meta-analysis was performed in order to study the additional effect of Ivabradine, apart from the effect of beta-blockers, on cardiovascular death, all-cause mortality, hospitalization due to HF and heart rate in a Heart Failure with Reduced Ejection Fraction (HFrEF) population.

**Methods and results:** Extensive electronic searches were conducted up to June 2016 to include randomized controlled trials where Ivabradine was compared to a control group. Of 1,790 studies found, seven met the inclusion criteria for the systematic review and meta-analysis. The studied population consisted of 17,747 patients. The risk of bias was generally high for beta-blocker doses lower than the recommended. Interventions lasted 1.5-22.9 months and pooled relative risks RR (95%) for all-cause mortality, cardiovascular death and hospitalization for HF were 0.98 (0.90 – 1.06); 0.99 (0.91 – 1.08); and 0.86 (0.79 – 0.93) respectively. Heart rate (CI 95%) decreased by 8.7 (6.37 – 11.03) beats per minute with Ivabradine compared to the control group. Subgroup analysis by beta-blocker dose showed that for patients on recommended treatment (at least 50% of the beta-blocker target dose), heart rate (CI 95%) decreased by 4.70 (3.67 – 5.73), whereas for patients not on recommended treatment or with unreported dose, heart rate decreased by 8.60 (8.13 – 9.08).

**Conclusion:** Ivabradine significantly reduced heart rate and hospitalization due to HF. The additional effect of Ivabradine on hear rate appears to be inversely correlated with the dose of beta-blocker. Unreported beta-blocker doses and beta-blocker doses lower than the recommended treatment limited the conclusions on the additional effect of Ivabradine.

**Keywords:** Ivabradine; heart failure; left ventricular dysfunction; adrenergic beta-antagonists; heart rate; treatment outcome.

## INTRODUCTION

Chronic heart failure (HF) is a complex systemic clinical syndrome characterized by inadequate blood supply to meet tissue metabolic needs[1]. It is responsible for many hospitalizations and high public spending[1]. Despite advances in treatment over the past 30 years, HF still has a high mortality rate (approximately 50% at 5 years)[2]. In developed countries, 1-2% of the population suffer from HF[3] and its prevalence also increases with age, reaching 8 to 10% in the population over 60 years[4]. With the global increase of the elderly population, the risk of developing HF is growing proportionally[1]. Therefore, it is necessary to maintain the research for the treatment of the HF population.

Heart failure with reduced ejection fraction (HFrEF) is defined by HF symptoms and signs in addition to an ejection fraction less than 40%[5], and accounts for 60% of HF cases in adults. The HFrEF symptoms are due to compensatory mechanisms in an attempt to maintain adequate cardiac output[6]. Treatment of HF targets mediators responsible for cardiac remodeling while aiming at three goals: improvement in symptoms; slowing of disease progression; fewer hospital visits and decreasing mortality[1,5]. Standard treatment in HFrEF includes angiotensin-converting enzyme inhibitor antagonists, beta-blockers, aldosterone antagonists, hydralazine and nitrate[1,5].

Another treatment alternative for HFrEF is Ivabradine, a specific inhibitor of the $I_f$ current in the sinoatrial node[7,8] which has been undergoing testing for HFrEF in the past decade. It is a pure heart-rate-lowering drug, which was studied in two large randomized controlled trials with different objectives and populations and a small improvement in outcomes. In these studies, Ivabradine was used simultaneously with a beta-blocker, for ethical reasons, as the recommended treatment for HFrEF patients is at least 50% of the beta-blocker target dose[1,5]. However, beta-blockers are a class of drugs which also reduce heart rate, so they may have been a confounder. Therefore, the additional effect of Ivabradine in HFrEF populations, apart from the effect of beta-blockers, is still not clear.

To clarify and summarize the available literature on intervention studies of Ivabradine in the management of HFrEF a systematic review was conducted. The objective of this systematic review and meta-analysis was to study the additional effect of therapy with Ivabradine in terms of cardiovascular death, all-cause mortality,

hospitalization due to HF, heart rate and functional status in studies reporting those effects in HFrEF populations.

## METHODS

### Search strategy and study selection

In order to identify articles that study the effect of Ivabradine therapy on HFrEF patients, a systematic electronic search was performed in the Embase, Medline, Pubmed, Cochrane Library, CINAHL, Web of Science, Scopus, SciELO and LILACS databases for studies published up to June 2016. In order to perform a thorough search of the databases, the following Medical Subject Heading (MeSH) terms were used: *heart failure, adrenergic beta-antagonists, benzazepines, heart rate, hospitalization* and *death*. Full search strategies and keywords are summarized in the supplementary material.

A pre-defined protocol in accordance with The PRISMA guidelines[9] was followed. The selection criteria were followed to include randomized controlled trials with parallel design where Ivabradine was compared to a control group. HFrEF was defined as HF with an ejection fraction (EF) less than 40%[5]. The inclusion criteria were studies reporting Ivabradine therapy in patients with chronic HFrEF and optimized or sub-optimized beta-blocker treatment. The included studies looked at Ivabradine effects on cardiovascular death, all-cause mortality, hospitalization due to HF, heart rate and functional status before and after therapy in the control group and intervention group. Only publications on adults were included and studies performed on animals and pregnant women were excluded. Letters, abstracts, conference proceedings, clinical trials, cluster trials and prospective cohort studies were excluded. There were also excluded studies involving patients with acute heart failure and, and due to the specific effect of Ivabradine in the sinoatrial node, studies involving patients with atrial fibrillation.

After removal of duplicates, two authors independently reviewed each title and abstract to determine whether the study met the inclusion criteria. Disagreements about any selection of items were resolved through discussions and by a third author if needed. After the initial screening, the articles were selected based on their complete text.

Reference lists of the selected articles were searched for additional publications. The authors were contacted directly for any additional and/or unpublished studies.

**Data extraction and analysis**

Data extraction from these articles was performed independently by two authors through a data collection form which was designed prior to the database searches. Study and participant characteristics, comparison groups, results, analyses and conclusions were recorded. The main study characteristics recorded were date of publication, geographic origin, population size, definition of the source of study design and population inclusion criteria. The type of statistical analysis, heart rate at baseline, dose of beta-blocker, results and subgroups results and conclusions were extracted. If data has been published in multiple articles, the study with the more complete set of data was included in the analysis.

Patient characteristics in the various studies were summarized using weighted average. Relative risks (RR) and their 95% confidence intervals (CI95%) were calculated using the events reported in each group in the studies. Study RRs were pooled and the random effect was used to summarize the results. Heterogeneity among studies was measured by the I-squared statistic. Quality of studies was evaluated with the Cochrane risk of bias tool[10]. Subgroup analysis was performed in order to compare the studies which reported all patients treated with at least 50% of beta-blocker target doses, as defined by the *European Society of Cardiology* (ESC) Guidelines[5], to the studies which reported fewer patients receiving these doses or studies which did not report such data. All analyses were conducted using Stata version 12.0 (StataCorp LP, College Station, Texas, United States).

## RESULTS

### Studies included

The search resulted in 1,790 abstracts and, after the initial selection based on title and abstract, 59 articles were selected for full reading. Based on the full text and the inclusion criteria, a total number of seven articles were included in the systematic review (**Figure 1**). On data extraction, there were only two studies that reported major outcomes of interest[7,8] such as cardiovascular death, all-cause mortality and hospitalization due to HF. The other 05 studies[11,12,13,14,15] did not report these data, but did report the heart rate before and after intervention with Ivabradine as well as other variables that measure the functional status of patients.

Quality of studies was assessed using the Cochrane risk of bias tool (**Figure 2**). The risk of bias was generally low for: random sequence generation; allocation concealment; blinding of outcome assessment; incomplete outcome data; selective reporting; and results which are not presented as *intention to treat*. The risk of bias was generally unclear for: blinding of participants. Finally, the risk of bias was generally high for: patients using < 50% of beta-blocker target dose; and other sources of bias.

### Population enrolled

The main characteristics of the population included in the systematic review are shown in **Table 1**. The studies involved 17,747 participants, and the two largest studies were responsible for 98.2% of the population (17,422 patients). The mean age of the population was between 49 and 66.8 years, with a weighted average of 63.2 (SD 9.5) years. Most of the population were men, and 87.5% of the population had myocardial ischemia as the primary cause of heart failure. The duration of the studies ranged from 1.5 to 22.9 months, and the 02 largest studies had the longest follow-up.

Reported beta-blocker use weighted average was 87.8% and only three studies[8,11,15] reported the percentage of patients on the target dose of beta-blockers during the intervention. In all three of these studies, less than 50% of patients were on

full-dose beta-blocker treatment. It was not possible to ascertain from the reported methods and results whether the target dose was achieved in other studies. Most studies reported only the percentage of patients using at least 50% of beta-blocker target doses as shown in **Table 1.**

**Main outcomes and meta-analysis**

There were seven studies included in the meta-analysis of heart rate and two studies in the meta-analysis of binary outcomes (all-cause mortality; cardiovascular death; and hospitalization due to HF). Additionally, the reported adverse effects (cardiac, respiratory, renal and neurological disorders) were pooled and meta-analyzed.

Pooled relative risks RR (95%) for all-cause mortality, cardiovascular death and hospitalization for HF were 0.98 (0.90 – 1.06); 0.99 (0.91 – 1.08); and 0.86 (0.79 – 0.93), respectively, as shown in **Figure 3**. Heart rate analysis (CI95%) showed a decrease of 8.7 (6.37 – 11.03) beats/min with Ivabradine compared to control group (**Figure 4**). However there is a high heterogeneity between the studies (I-squared = 95.1%, $p<0.001$).

In order to point out which studies were causing this heterogeneity, analyses were run separately for large and small studies. The decrease in heart rate was respectively 8.25 (7.75 – 8.75) and 6.94 (6.08 – 7.80), but heterogeneity was still high in both analyses (>90%). Heart rate analysis was also run separately for the control group (placebo or beta-blocker) and decrease in heart rate was respectively 8.61 (8.14 – 9.09) and 4.69 (3.66 – 5.72), but it still did not justify the heterogeneity.

Subgroup analysis by beta-blocker dose (**Figure 5**) showed that in studies reporting all the studied population on recommended treatment (at least 50% of the beta-blocker target dose), heart rate (IC95%) decreased by 4.70 (3.67 – 5.73), whereas within groups or studies which reported less than 100% of the studied population on recommended treatment or which did not report the dose, heart rate decreased by 8.60 (8.13 – 9.08). This indicates a significantly lesser effect size when beta-blocker dose was optimum. Meta-regression by beta-blocker target dose was prevented by the lack of sufficient beta-blocker usage information in the included studies.

## Secondary outcomes

Pooled relative risks RR (95%) were 0.86 (0.67 – 1.11) for cardiac disorders; 0.80 (0.66 – 0.97) for respiratory disorders; 0.84 (0.73 – 0.97) for neurological disorders; and 1.24 (0.95 – 1.63) for renal disorders, as shown in **Figure 6.**

Other outcomes reported in some included studies were 6-minute walking test, metabolic equivalent (MET), oxygen uptake (VO2) and brain natriuretic peptide (BNP). Each of these outcomes of functional status were cited by at most two small studies, with data presented differently in each study. In addition, the two largest studies[7,8] did not cite variables of functional status. Therefore, analyses on these outcomes could not be done.

# DISCUSSION

## Discussion of results

This systematic review and meta-analysis of the effect of Ivabradine on patients with HFrEF showed a significant decrease in heart rate compared to the control group. Another finding was the significant effect of Ivabradine on hospitalization due to HF. In contrast, there was no significant effect for cardiovascular death and all-cause mortality.

Our findings reinforce current discussion about the effect of heart rate control in HF prognosis since Ivabradine is a pure heart-rate-lowering drug with no effect in myocardial contractility[7] or other HF pathophysiological systems. It was shown that in patients with stable coronary artery disease and left-ventricular systolic dysfunction Ivabradine can reduce only coronary endpoints, such as hospitalization due to myocardial infarction and coronary revascularization, without a statistically significant reduction in mortality[7]. In the *Systolic Heart Failure Treatment with the $I_f$ inhibitor Ivabradine (SHIFT) trial*[8], Ivabradine was shown to reduce the composite outcome of *cardiovascular death or hospitalization for worsening HF*. Our meta-analysis now clarifies that the result of the previous composite outcome was pushed up by the hospitalization, and that Ivabradine did not reduce mortality. Moreover, beta-blocker target doses of these primary patients seem to have played a crucial role on results[16]. A post-hoc analysis of SHIFT published

in 2012 suggested that, in the subgroup of patients receiving at least 50% of the target dose of beta-blockers, Ivabradine caused no changes in all outcomes analyzed[16].

Beta-blockers are a chronotropic negative class of drugs which also reduce heart rate. They are currently one of the main drugs for the treatment of HFrEF[1,5,6]. However, the effect of beta-blockers in HF relies on a different pathophysiological basis, i.e. by inhibiting the sympathetic nervous system, which is one of the main pathways involved in HF[6]. Therefore, beta-blockers are proven to improve left-ventricular remodeling and reduce total mortality, cardiovascular mortality, sudden deaths and worsening HF[17,18,19]. These effects, however, were also shown to be related at least in part with heart rate control[20].

A meta-analysis published in 2009 evaluated all randomized, placebo-controlled heart failure trials that reported the effect of beta-blockers on all-cause mortality[20]. A meta-regression revealed that for every 5 beats/min reduction in heart rate with beta-blocker treatment, the relative risk for death decreased by 18% (CI 95%, 6% to 29%). Interestingly, differently from what has been reported previously[16], no statistically significant difference in the magnitude of all-cause mortality reduction was found between patients which received high doses of beta-blockers (at least 50% of the target dose) and patients which received low doses. The meta-regression also demonstrated that the magnitude of the survival benefit seen with beta-blockers was significantly associated with the magnitude of heart rate reduction achieved, but not with the dose of beta-blocker administered[20].

Our meta-analysis showed a decrease in heart rate of 8.7 beats/min with Ivabradine compared to the control group. Differently from the effect seen with beta-blockers mentioned above[17,18,19], Ivabradine generally did not reduce the all-cause mortality outcome. However, baseline heart rates could have pushed down the results. Another post-hoc analysis of SHIFT published in 2010 suggested that, in the subgroup of patients with baseline heart rate higher than 80 beats/min, Ivabradine significantly reduced all-cause mortality[21]. This demonstrates that heart rate alone might have an important effect on the prognosis of chronic HFrEF patients, and several pathophysiological mechanisms have been proposed which may explain this effect. First, the increase in heart rate shortens left-ventricular diastolic time and worsens left-

ventricular diastolic filling as well as cardiac output[22,23]. Second, high heart rates could be related with myocardial ischemia, precipitation of rhythm disturbances, and acceleration of atherosclerosis[23]. The second mechanisms are mainly related to ischemic heart failure and, in our meta-analysis, 87.5% of the population had myocardial ischemia as the primary cause of heart failure.

The magnitude of the effect with Ivabradine in HFrEF cannot be known with certainty since the beta-blocker dose was not achieved or not reported in all studies. Therefore, it remains unclear whether Ivabradine has an isolated effect or if the effects reported in the included studies could be attributed to the beta-blocker target doses and their primary reduction in heart rate. The subgroup analysis in our meta-analysis also supports this idea. The studies reporting all the studied population on at least 50% of the target dose during the intervention had a statistically significantly lower reduction in heart rate, indicating a lesser effect size when beta-blocker dose was optimum.

The benefits of lowering heart rate during hospital admission for acute HFrEF have recently been described[24]. The early coadministration of Ivabradine and beta-blockers produced a significant decrease in heart rate compared with beta-blockers alone. It also seemed to improve systolic function and functional and clinical parameters of HFrEF patients in the short-term, but no differences in the clinical events evaluated, i.e. rehospitalisation and death, were reported after four months[24]. It has also been demonstrated that long-term exposure to Ivabradine reduced the incidence of all-cause hospitalizations during the vulnerable phase after a hospitalization due to heart failure [25].

In our meta-analysis, Ivabradine showed to be a secure drug in terms of adverse events. There was no difference between Ivabradine and the control group for renal and cardiac disorders. In terms of respiratory end neurological disorders, Ivabradine had a small but significant protector effect. This effect could perhaps be explained at least in part by the heart rate lowering caused by Ivabradine. High heart rate was significantly associated with mortality from respiratory disease in men and women even after adjustment for age and smoking[26]. In patients with high heart rates, increased mortalities were also observed from gastrointestinal, neurological and nephrogenic causes[26].

## Limitations

Some limitations of this study should be considered at this point. The first limitation was the number of studies included in the meta-analysis. Even though a comprehensive search strategy was used which applied searches to a wide variety of databases, a surprisingly small number of studies was found given the attention that Ivabradine has received lately. After filtering for inclusion and exclusion criteria, up to 07 studies were included, depending on the outcomes analyzed. For the major outcomes, only 02 studies were included. Still, these 02 studies had a large number of patients and did fit the required criteria. The second limitation was the high heterogeneity. However, heterogeneity was high only with the heart rate outcome, and it did not prevent the analysis since this variable is continuous[27]. Despite our various subgroup analysis, we were not able to explain the high heterogeneity across included studies. Meta-regression on baseline heart rate and beta blocker dosage were prevented due to lack of variability across studies and lack of information in included studies, respectively. Even though we reached out to primary authors for information on beta-blocker dosage, we did not receive the requested data.

Regarding quality of the included studies, we found a high risk of bias for *patients using < 50% of beta-blocker target dose* and *other sources of bias*. Since beta-blockers are heart-rate-lowering drugs, this may have caused interference with heart rate values, leading to high risk of bias for heart rate and possibly to high heterogeneity as well.

## Clinical implications

This study also has important clinical implications. Ivabradine has been shown to be an appropriate treatment alternative when the patient truly cannot tolerate the increase in beta-blocker doses and continues to be symptomatic with high heart rates. Still, it remains unclear whether the effect of Ivabradine plus suboptimum beta-blocker dose versus beta-blocker optimum dose alone could present benefits in terms of clinical outcomes given the difficulty in establishing the effect of Ivabradine without confounders.

Finally, two important questions must be raised concerning treatment and its impact on the prognosis of chronic HFrEF patients. The first is whether applying beta-blocker optimum dose or lowering heart rate to about 60 beats/min should be prioritized when treating chronic HFrEF patients. The second is whether heart rate control is simply a consequence of correct treatment, or instead a target that physicians should strive to achieve. Despite our efforts in this systematic review, these questions will require further prospective studies to be answered.

## CONCLUSION

Ivabradine significantly reduced heart rate and hospitalization due to HF. The heart rate effect size was smaller when beta-blocker dose was optimum. Therefore, the additional effect of Ivabradine on hear rate appears to be inversely correlated with the dose of beta-blocker. Associations regarding hospitalization and other outcomes could not be determined due to the lack of beta-blocker dose reporting in the studies. As a result, unreported beta-blocker doses and beta-blocker doses lower than the recommended treatment limited the conclusions on the additional effect of Ivabradine. Further well-designed prospective studies are warranted to investigate these effects.

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**Figure 1.** PRISMA flow diagram of systematic searches and selection process.

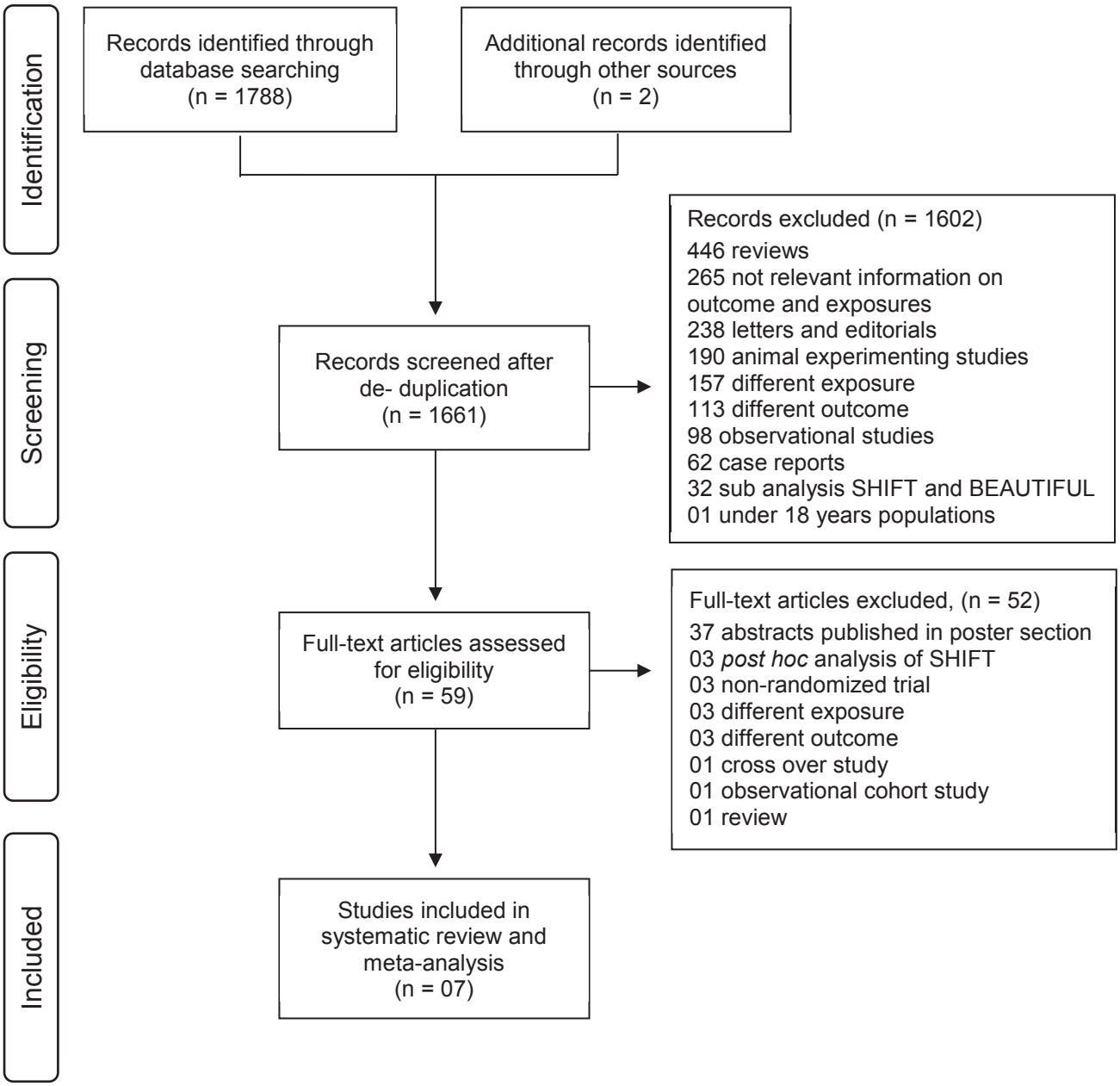


**Table 1.** Characteristics of included studies.

| Study, year | Reference Number | Location | N | Male | Age (years) | Population | LVEF (%) | Ischemic HF | Baseline HR (beats/min) | Beta-blocker use | ≥ 50% beta-blocker target dose |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Tsutsui et al, 2016 | 15 | Japan | 103 | 85.7 | 59.0 (13.1) | Chronic HF, LVEF≤35% and HR≥75 beats/min | 28.4 (5.1) | 42.9 | 82.7 (7.4) | 92.9 | 63.3 |
| Volterrani et al, 2011 | 14 | Italy | 80 | 68 | 66.8 (9.5) | Chronic HF and NYHA II and III | 27 (4.9) | 81 | 76.7 (12.8) | 100 | 100 |
| Amosova et al, 2011 | 11 | Italy | 29 | 89.7 | 59.0 (5.4) | Ischemic HF and LVEF<45% | 39.1 (5.5) | 100 | 75.9 (2.97) | 100 | 100 |
| Mansour et al, 2011 | 12 | Egypt | 53 | 60 | 49.0 (13) | Idiopathic dilated cardiomyopathy, LVEF<40% and HR>70 beats/min | 30.2 (5.6) | 0 | 84 (10) | 100 | 19 |
| Sarullo et al, 2010 | 13 | Italy | 60 | 75 | 52.7 (5.3) | Chronic HF, LVEF≤40% and HR>70 beats/min | 29.8 (6.0) | 100 | 75 (3) | 60 | Not reported |
| Swedberg et al, 2010 | 8 | 37 countries | 6505 | 76 | 60.4 (11.4) | Chronic HF, LVEF≤35% and HR≥70 beats/min | 29 (5.1) | 68 | 79.9 (9.6) | 89 | 56 |
| Fox et al, 2008 | 7 | 33 countries | 10917 | 83 | 65 (8.4) | Stable coronary artery disease and LVEF<40% | 32.4 (5.5) | 100 | 71.6 (9.9) | 87 | Not reported |

Data are shown as n (%) or mean ± SD. HF = Heart failure; LVEF = Left ventricular ejection fraction; NYHA = New York Heart Association; HR = Heart rate; BID = Twi

**Figure 2.** Quality of included studies by the Cochrane risk of bias tool.

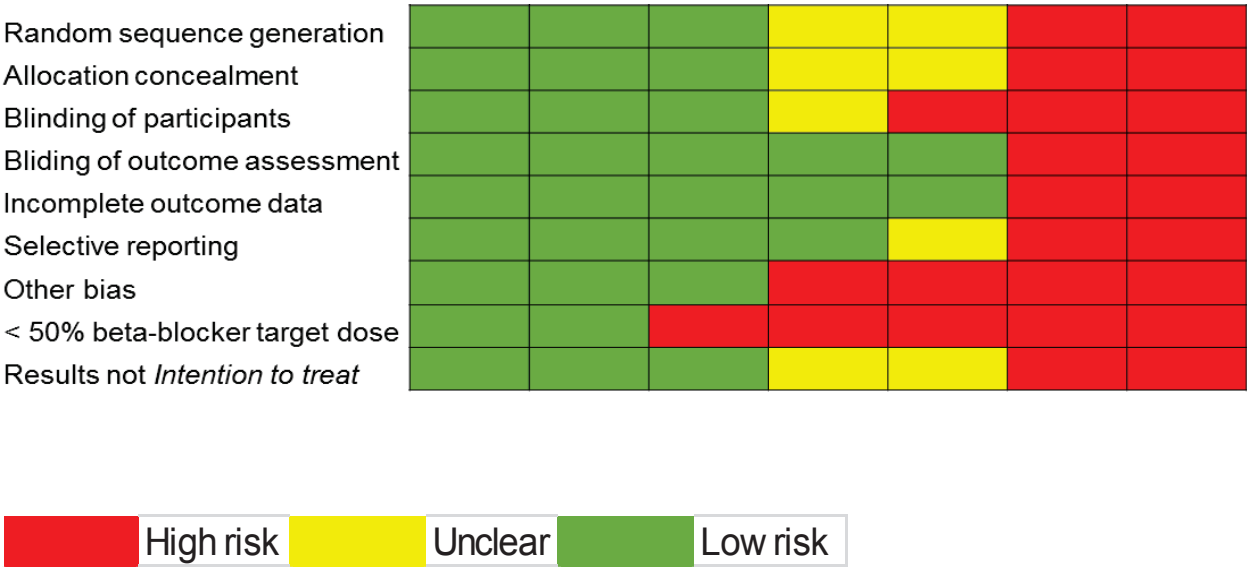


**Figure 3.** Pooled relative risks RR (95%) for binary outcomes.

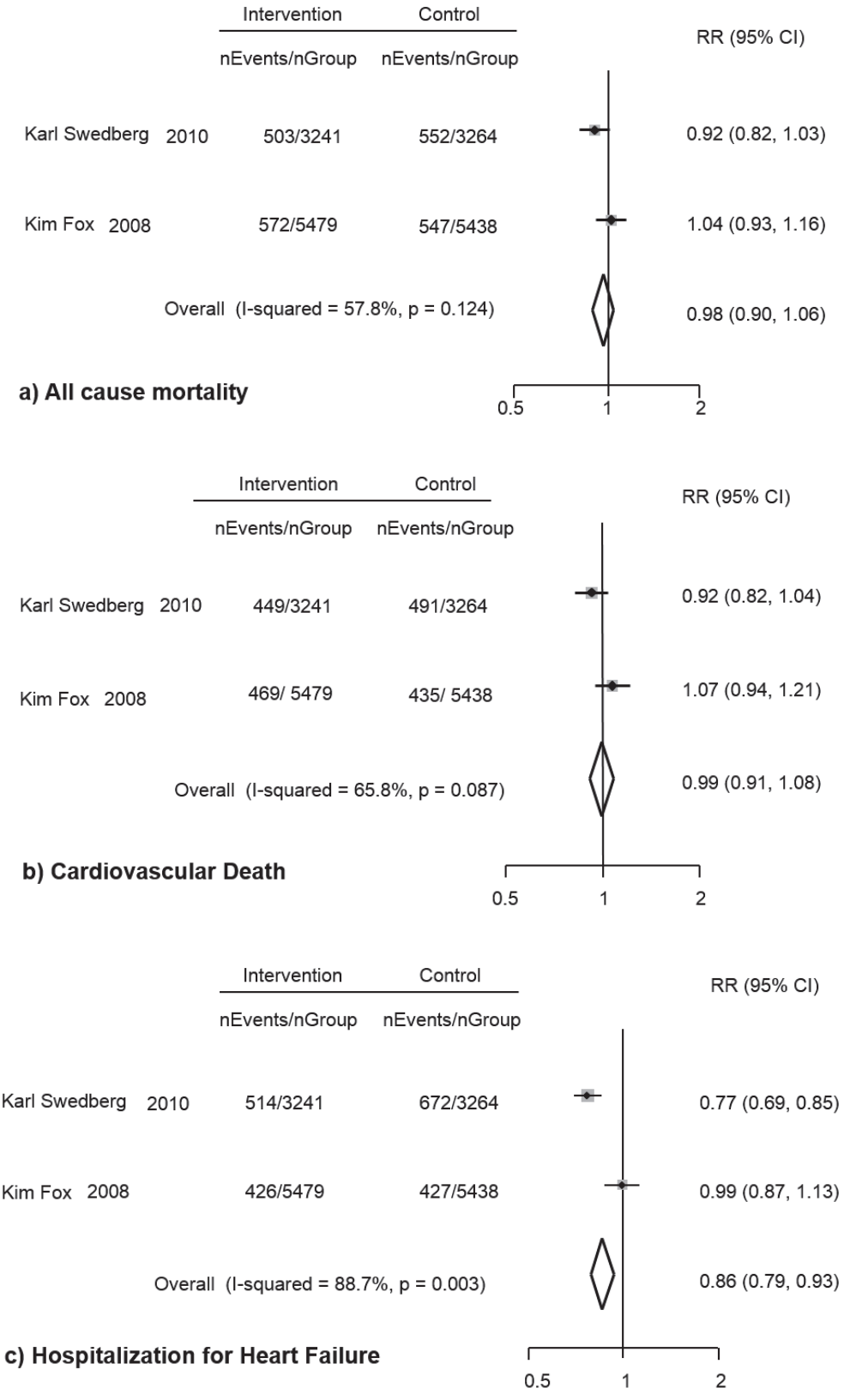


**Figure 4.** Effect of Ivabradine on heart rate outcome.

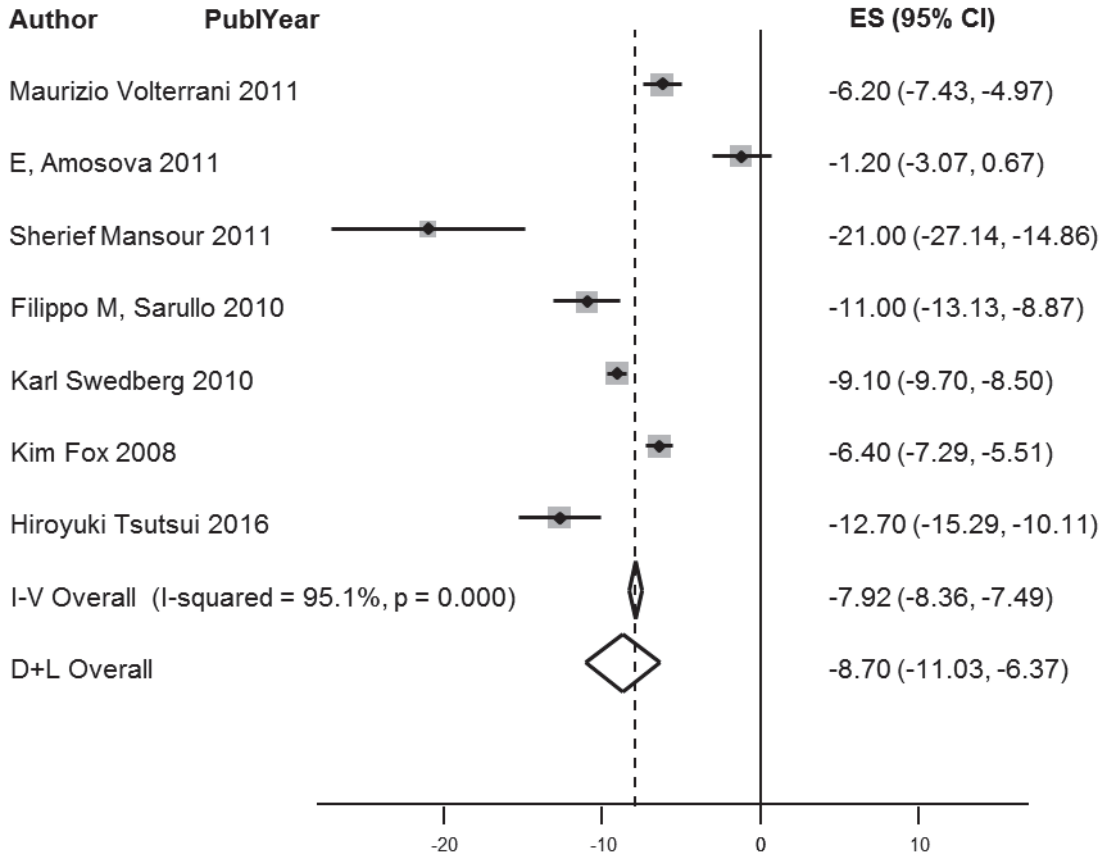


**Figure 5.** Subgroup analysis by beta-blocker dose.

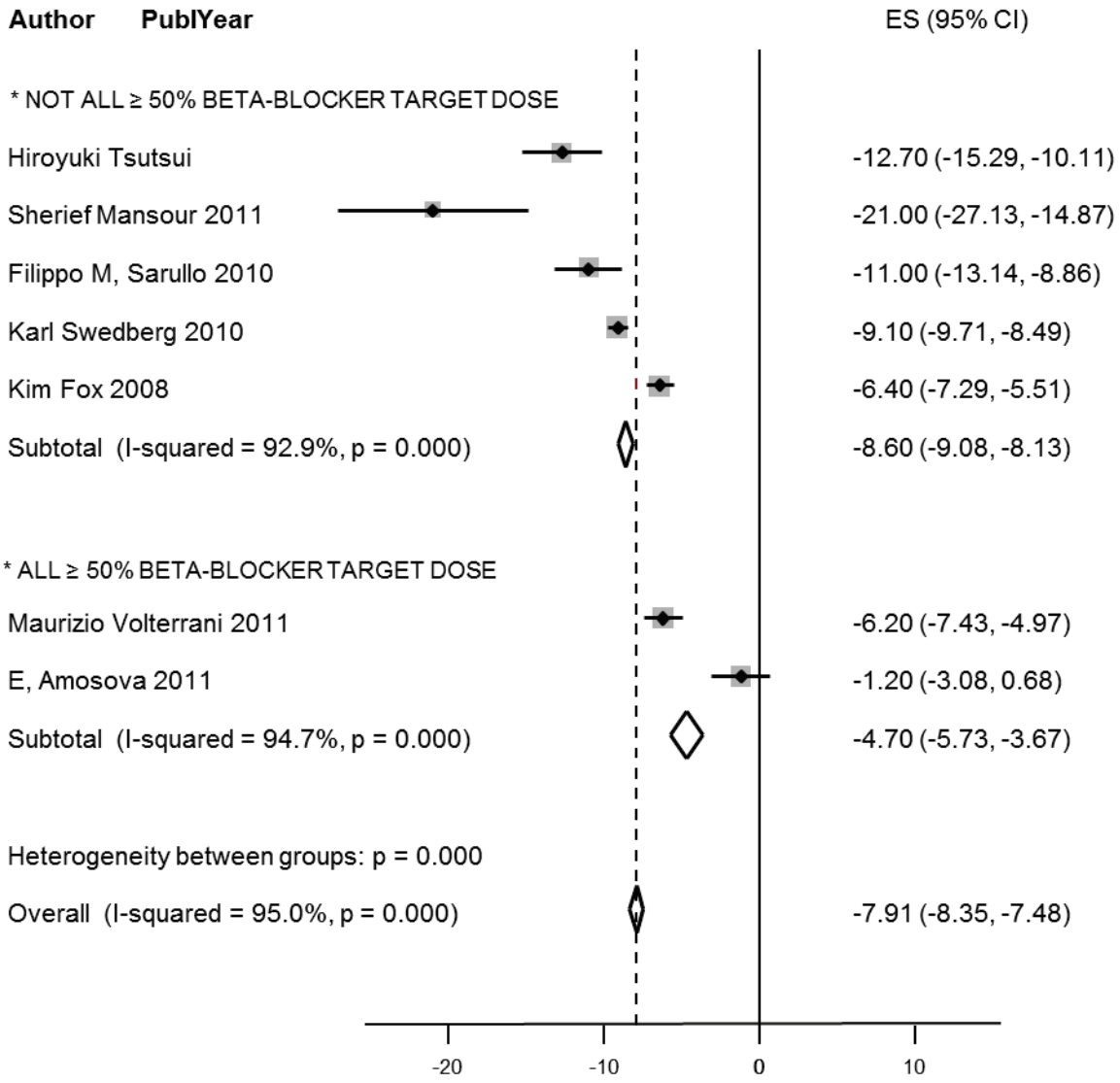
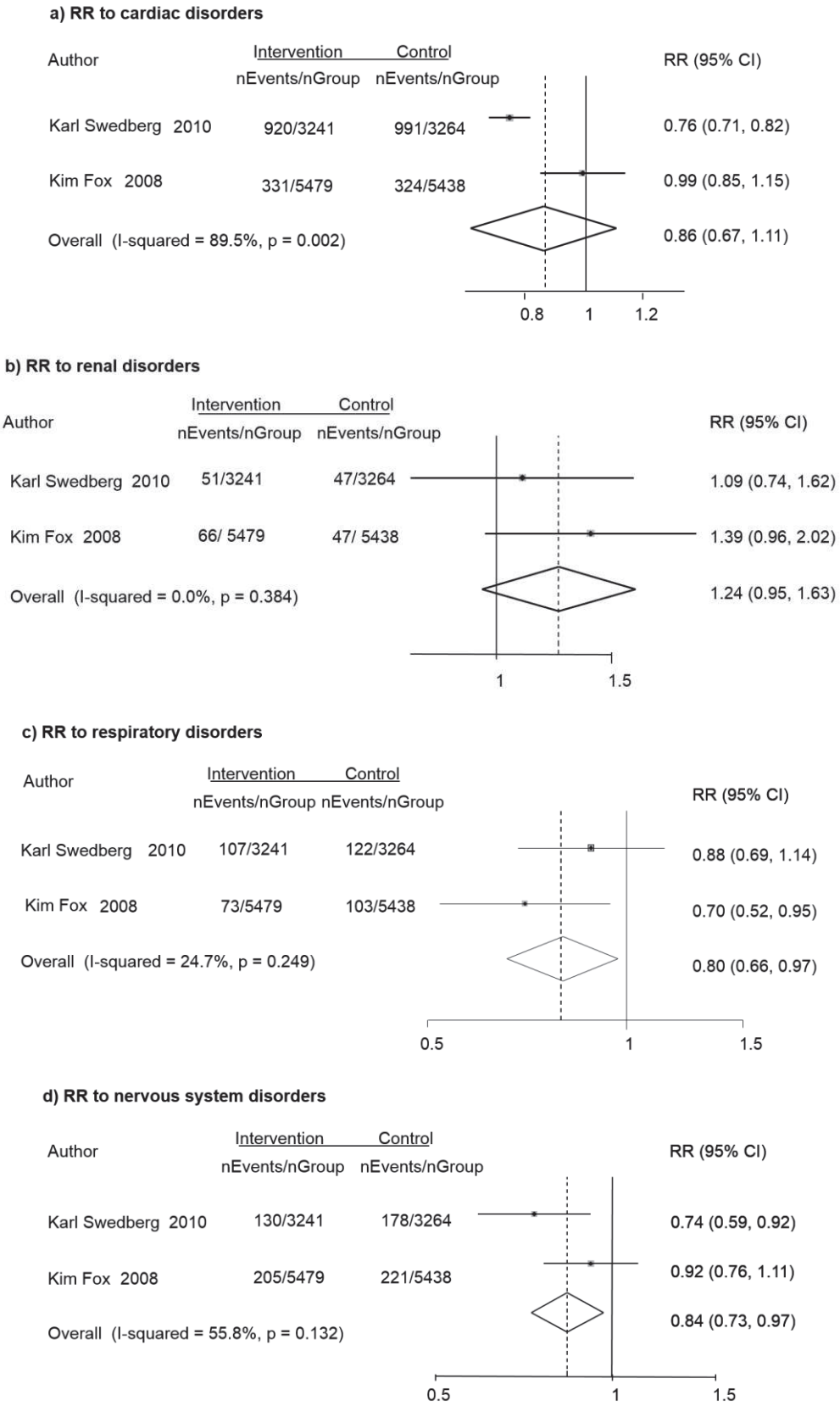


**Figure 6.** Pooled relative risks RR (95%) for adverse events.



## Supplementary information

*Appendix – Methodological Supplement – PubMed search strategy*

| | |
|---|---|
| **P**articipants | ((((((((((((("Heart Failure"[Mesh] OR "Congestive Heart Failure"[tiab] OR "Congestive Heart Failure"[tw]) OR "Myocardial Failure"[tiab]) OR "Left-Sided Heart Failure"[tiab]) OR "Right-Sided Heart Failure"[tiab] OR "Cardiac Failure"[tiab] OR "Heart Failure, systolic"[Mesh] OR "Heart Failure, systolic"[tw] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Diastolic"[tw]) OR "Ventricular Dysfunction, Left"[Mesh] OR "Ventricular Dysfunction, Left"[tw] OR "Ventricular Dysfunction, Right"[Mesh] OR "Ventricular Dysfunction, Right"[tw]) |
| **I**ntervention | AND “Benzazepines”[MeSH]) AND “Ivabradine”[tiab) OR “Ivabradine”[tw]) |
| **C**omparator | AND "Adrenergic Beta-antagonists"[Mesh] OR "Adrenergic Beta-antagonists"[tw] OR "adrenergic beta blockers"[tw] OR "Beta-adrenergic blocking agents"[tw] OR "Beta-blockers"[tw]) |
| **O**utcomes | (("heart rate"[Mesh] OR "heart rate"[tw] OR "heart rates "[tw] OR "pulse rate"[tw]) OR "dyspnea"[tw]) OR "cardiac chronotropy"[tw] OR "cardiac chronotropism"[tw] AND "heart rate control "[tw]) OR "hospitalization"[Mesh] OR "hospitalizations"[tiab]) OR "patient readmission"[tw] OR "Tachycardia, Ventricular"[All Fields] OR ("stroke"[Mesh] OR "cerebrovascular accident"[tw]) OR "myocardial infarction"[Mesh] OR "myocardial infarcts"[tw]) OR "death, sudden, cardiac"[Mesh] OR "sudden cardiac arrest"[tw] OR "Cardiac death"[tw] OR "death"[Mesh])))) |

## 7 CONSIDERAÇÕES FINAIS

Conclui-se que a Ivabradina reduziu significativamente hospitalização por insuficiência cardíaca e frequência cardíaca, sem apresentar efeito em morte por qualquer causa ou morte cardiovascular. No entanto, o risco de viés para dose-alvo de betabloqueador foi alto e ficou clara a existência de possíveis fatores de confusão como: dose de betabloqueador durante o andamento dos estudos, frequência cardíaca inicial e resposta individual ao betabloqueador. Dessa forma, o efeito da Ivabradina separadamente do betabloqueador ainda não é claro. A dose-alvo de betabloqueador deve ser priorizada nos estudos que testam os efeitos da Ivabradina em pacientes com ICFER para anular fatores de confusão e reduzir o risco de viés.

Após a realização desse trabalho, fica evidente que os médicos devem investir ao máximo no tratamento com o betabloqueador antes de procurar tratamento alternativo. Os motivos principais são dois: a diferença de magnitude do efeito entre betabloqueador e Ivabradina; e a dificuldade dos estudos em estabelecer o efeito real da Ivabradina sem fatores de confusão. Entretanto, a Ivabradina demonstrou ser uma alternativa de tratamento quando o paciente realmente não consegue tolerar o aumento gradual da dose de betabloqueador e mantém-se sintomático com frequência cardíaca alta.

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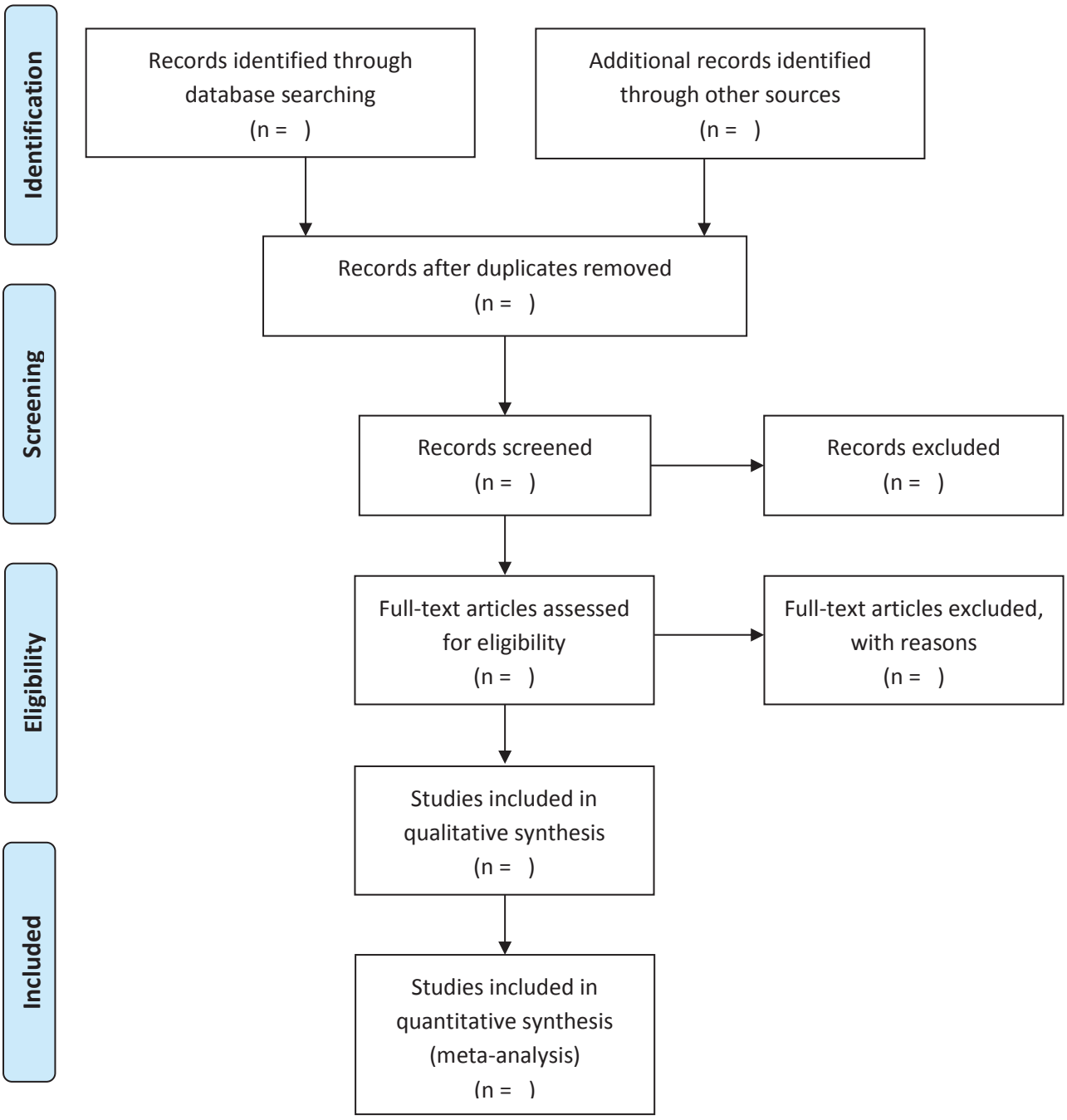
## ANEXO A – PRISMA checklist for systematic review and meta-analysis

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 23 |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 24 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known. | 25 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 25 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. | 26 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | 26 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 26 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | 26 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 26, 27 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 27 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 26, 27 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 27 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). | 27 |

| Section/topic | # | Checklist item | Reported on page # |
|---|---|---|---|
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^2$) for each meta-analysis. | 27 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | 27 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | 27 |
| **RESULTS** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 28 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | 28, 29 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). | 28 |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. | 28, 29 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | 29 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | 28 |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | 29 |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). | 30, 31, 32 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). | 33 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 33, 34 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | 34 |

## ANEXO B – PRISMA Flow Diagram



## ANEXO C – Cochrane risk of bias tool

<table>
<tr><td colspan="2">RANDOM SEQUENCE GENERATION<br>Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.</td></tr>
<tr><td>Criteria for a judgement of ‘Low risk’ of bias.</td><td>The investigators describe a random component in the sequence generation process such as:<ul><li>Referring to a random number table;</li><li>Using a computer random number generator;</li><li>Coin tossing;</li><li>Shuffling cards or envelopes;</li><li>Throwing dice;</li><li>Drawing of lots;</li><li>Minimization*.</li></ul>*Minimization may be implemented without a random element, and this is considered to be equivalent to being random.</td></tr>
<tr><td>Criteria for the judgement of ‘High risk’ of bias.</td><td>The investigators describe a non-random component in the sequence generation process. Usually, the description would involve some systematic, non-random approach, for example:<ul><li>Sequence generated by odd or even date of birth;</li><li>Sequence generated by some rule based on date (or day) of admission;</li><li>Sequence generated by some rule based on hospital or clinic record number.</li></ul>Other non-random approaches happen much less frequently than the systematic approaches mentioned above and tend to be obvious. They usually involve judgement or some method of non-random categorization of participants, for example:<ul><li>Allocation by judgement of the clinician;</li><li>Allocation by preference of the participant;</li><li>Allocation based on the results of a laboratory test or a series of tests;</li><li>Allocation by availability of the intervention.</li></ul></td></tr>
<tr><td>Criteria for the judgement of ‘Unclear risk’ of bias.</td><td>Insufficient information about the sequence generation process to permit judgement of ‘Low risk’ or ‘High risk’.</td></tr>
<tr><td colspan="2">ALLOCATION CONCEALMENT<br>Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.</td></tr>
</table>

| | |
|---|---|
| Criteria for a judgement of 'Low risk' of bias. | Participants and investigators enrolling participants could not foresee assignment because one of the following, or an equivalent method, was used to conceal allocation:<br>• Central allocation (including telephone, web-based and pharmacy-controlled randomization);<br>• Sequentially numbered drug containers of identical appearance;<br>• Sequentially numbered, opaque, sealed envelopes. |
| Criteria for the judgement of 'High risk' of bias. | Participants or investigators enrolling participants could possibly foresee assignments and thus introduce selection bias, such as allocation based on:<br>• Using an open random allocation schedule (e.g. a list of random numbers);<br>• Assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or nonopaque or not sequentially numbered);<br>• Alternation or rotation;<br>• Date of birth;<br>• Case record number;<br>• Any other explicitly unconcealed procedure. |
| Criteria for the judgement of 'Unclear risk' of bias. | Insufficient information to permit judgement of 'Low risk' or 'High risk'. This is usually the case if the method of concealment is not described or not described in sufficient detail to allow a definite judgement – for example if the use of assignment envelopes is described, but it remains unclear whether envelopes were sequentially numbered, opaque and sealed. |
| **BLINDING OF PARTICIPANTS AND PERSONNEL**<br>**Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.** | |
| Criteria for a judgement of 'Low risk' of bias. | Any one of the following:<br>• No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding;<br>• Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken. |
| Criteria for the judgement of 'High risk' of bias. | Any one of the following:<br>• No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding;<br>• Blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding. |
| Criteria for the judgement of 'Unclear risk' of bias. | Any one of the following:<br>• Insufficient information to permit judgement of 'Low risk' or 'High risk';<br>• The study did not address this outcome. |
| **BLINDING OF OUTCOME ASSESSMENT** | |

| **Detection bias due to knowledge of the allocated interventions by outcome assessors.** | |
|---|---|
| Criteria for a judgement of 'Low risk' of bias. | Any one of the following:<br>• No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding;<br>• Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken. |
| Criteria for the judgement of 'High risk' of bias. | Any one of the following:<br>• No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding;<br>• Blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding. |
| Criteria for the judgement of 'Unclear risk' of bias. | Any one of the following:<br>• Insufficient information to permit judgement of 'Low risk' or 'High risk';<br>• The study did not address this outcome. |

## INCOMPLETE OUTCOME DATA

**Attrition bias due to amount, nature or handling of incomplete outcome data.**

| | |
|---|---|
| Criteria for a judgement of 'Low risk' of bias. | Any one of the following:<br>• No missing outcome data;<br>• Reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias);<br>• Missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups;<br>• For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate;<br>• For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size;<br>• Missing data have been imputed using appropriate methods. |
| Criteria for the judgement of 'High risk' of bias. | Any one of the following:<br>• Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups;<br>• For dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate;<br>• For continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; |

| | |
|---|---|
| | • 'As-treated' analysis done with substantial departure of the intervention received from that assigned at randomization;<br>• Potentially inappropriate application of simple imputation. |
| Criteria for the judgement of 'Unclear risk' of bias. | Any one of the following:<br>• Insufficient reporting of attrition/exclusions to permit judgement of 'Low risk' or 'High risk' (e.g. number randomized not stated, no reasons for missing data provided);<br>• The study did not address this outcome. |

## SELECTIVE REPORTING

**Reporting bias due to selective outcome reporting.**

| | |
|---|---|
| Criteria for a judgement of 'Low risk' of bias. | Any of the following:<br>• The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way;<br>• The study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon). |
| Criteria for the judgement of 'High risk' of bias. | Any one of the following:<br>• Not all of the study's pre-specified primary outcomes have been reported;<br>• One or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified;<br>• One or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect);<br>• One or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis;<br>• The study report fails to include results for a key outcome that would be expected to have been reported for such a study. |
| Criteria for the judgement of 'Unclear risk' of bias. | Insufficient information to permit judgement of 'Low risk' or 'High risk'. It is likely that the majority of studies will fall into this category. |

## OTHER BIAS

**Bias due to problems not covered elsewhere in the table.**

| | |
|---|---|
| Criteria for a judgement of 'Low risk' of bias. | The study appears to be free of other sources of bias. |
| Criteria for the judgement of 'High risk' of bias. | There is at least one important risk of bias. For example, the study:<br>• Had a potential source of bias related to the specific study design used; or<br>• Has been claimed to have been fraudulent; or<br>• Had some other problem. |

| | |
|---|---|
| Criteria for the judgement of ‘Unclear risk’ of bias. | There may be a risk of bias, but there is either:<br>• Insufficient information to assess whether an important risk of bias exists; or<br>• Insufficient rationale or evidence that an identified problem will introduce bias. |