UNIVERSIDADE FEDERAL DE MINAS GERAIS
FACULDADE DE MEDICINA

INTERAÇÕES MEDICAMENTOSAS DA VARFARINA EM CARDIOPATAS CHAGÁSICOS E NÃO CHAGÁSICOS ATENDIDOS EM AMBULATÓRIOS DO HOSPITAL DAS CLÍNICAS DA UFMG

MARIA AUXILIADORA PARREIRAS MARTINS

BELO HORIZONTE

- 2012 -

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MARIA AUXILIADORA PARREIRAS MARTINS

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais, como requisito parcial para obtenção do título de Doutor.

Área de concentração: Ciências da Saúde: Infectologia e Medicina Tropical

Orientador:
Prof. Dr. Antonio Luiz Pinho Ribeiro

Co-orientadores:
Prof. Dr. Manoel Otávio da Costa Rocha
Profa. Dra. Cibele Comini César

BELO HORIZONTE

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ATA DA DEFESA DE TESE DE DOUTORADO de **MARIA AUXILIADORA PARREIRAS MARTINS,** nº de registro 2009654301. Às quatorze horas do **dia treze do mês de janeiro de dois mil e doze**, reuniu-se na Faculdade de Medicina da UFMG, a Comissão Examinadora de tese indicada pelo Colegiado do Programa, para julgar o trabalho final intitulado: **"INTERAÇÕES MEDICAMENTOSAS DA VARFARINA EM CARDIOPATAS CHAGÁSICOS E NÃO-CHAGÁSICOS ATENDIDOS EM AMBULATÓRIOS DO HOSPITAL DAS CLÍNICAS DA UFMG"**, requisito final para a obtenção do grau de doutora em Medicina, pelo Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical. Abrindo a sessão, o Presidente da Comissão, Prof. Antônio Luiz Pinho Ribeiro, após dar a conhecer aos presentes o teor das normas regulamentares do trabalho final, passou a palavra à candidata, para apresentação de seu trabalho. Seguiu-se a arguição pelos examinadores, com a respectiva defesa da candidata. Logo após, a Comissão se reuniu sem a presença da candidata e do público, para julgamento e expedição do resultado final. Foram atribuídas as seguintes indicações:

Prof. Antônio Luiz Pinho Ribeiro /Orientador	Instituição:UFMG	Indicação: APROVADA
Prof. Adriano Max Moreira Reis	Instituição: UFMG	Indicação: APROVADO
Profa. Suely Meireles Rezende	Instituição: UFMG	Indicação: APROVADA
Prof. Cristiano Soares de Moura	Instituição: UFBA	Indicação: APROVADO
Prof. Alberto Kazuo Fuzikawa	Instituição: Hospital BIOCOR	Indicação: aprovado

Pelas indicações, a candidata foi considerada: APROVADA

O resultado final foi comunicado publicamente à candidata pelo Presidente da Comissão. Nada mais havendo a tratar, o Presidente encerrou a sessão e lavrou a presente ATA, que será assinada por todos os membros participantes da Comissão Examinadora. Belo Horizonte, 13 de janeiro de 2012.

Prof. Antônio Luiz Pinho Ribeiro/Orientador _____

Prof. Adriano Max Moreira Reis _____

Profa. Suely Meireles Rezende _____

Prof. Cristiano Soares de Moura _____

Prof. Alberto Kazuo Fuzikawa _____

Prof. Vandack Alencar Nobre Júnior/Coordenador _____

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Geraldo de Souza Filho

Prof. Vandack Alencar Nobre Jr.
Coordenador do Programa de
Pós-Graduação em Ciências da Saúde:
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DECLARAÇÃO

A Comissão Examinadora abaixo assinada, composta pelos professores doutores: Antônio Luiz Teixeira Júnior, Adriano Max Moreira Reis, Suely Meireles Rezende, Cristiano Soares de Moural e Alberto Kazuo Fuzikawa, aprovou a defesa de tese intitulada: **"INTERAÇÕES MEDICAMENTOSAS DA VARFARINA EM CARDIOPATAS CHAGÁSICOS E NÃO-CHAGÁSICOS ATENDIDOS EM AMBULATÓRIOS DO HOSPITAL DAS CLÍNICAS DA UFMG"** apresentada pela doutoranda **MARIA AUXILIADORA PARREIRAS MARTINS** para obtenção do título de Doutora em Medicina, pelo Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical da Faculdade de Medicina da Universidade Federal de Minas Gerais, realizada em 13 de janeiro de 2012.

Prof. Antônio Luiz Pinho Ribeiro
Orientador

Prof. Adriano Max Moreira Reis

Profa. Suely Meireles Rezende

Prof. Cristiano Soares de Moura

Prof. Alberto Kazuo Fuzikawa

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Antônio Vaz de Macedo – Representante Discente

Ao Mauro, meu grande amor, por me incentivar
e estar sempre ao meu lado.

Aos meus pais, pelos sacrifícios e escolhas
que me ajudaram a construir quem sou.

“Give me the courage to change what should be changed in my life,
But give me the strength to accept what can not be changed,
And give me the wisdom to distinguish between these two.”

Old monastic prayer

“We shall not cease from exploration.
And the end of all our exploring
will be to arrive where we started
and know the place for the first time"

Thomas S. Eliot

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RESUMO

Introdução: As interações medicamentosas (IM) são causa importante de eventos adversos, que podem aumentar a morbimortalidade relacionada a medicamentos e ter impacto social e econômico significativo. A varfarina se destaca como fármaco de alto risco devido ao índice terapêutico estreito, ampla variabilidade dose-reposta e potencial de IM. A identificação precoce das IM com varfarina pode auxiliar na prevenção de eventos adversos, principalmente sangramentos. **Objetivos:** Avaliar as IM potenciais da varfarina comparando diferentes fontes de informação e investigar a ocorrência de IM graves em cardiopatas chagásicos e não chagásicos atendidos no Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG). **Métodos:** As listas de interações da varfarina de três compêndios (*Drug Interaction Facts*, *Drug Interactions: Analysis and Management* e DRUG-REAX), do formulário da Organização Mundial da Saúde (OMS) e da bula do Marevan® foram comparadas considerando: substâncias citadas, classificação de gravidade e nível de evidência científica. Realizou-se, ainda, estudo transversal envolvendo pacientes cardiopatas para avaliar IM da varfarina e sua frequência de acordo com as fontes. O coeficiente kappa foi calculado para avaliar a concordância entre as fontes de informação. **Resultados:** Foi listado um total de 537 interações. Apenas 13 (2,4%) interações da varfarina foram comuns às cinco fontes, sendo que a maioria citada nos compêndios e na lista da OMS não estava presente na bula. O coeficiente kappa Fleiss foi -0.0080. Apenas duas interações foram classificadas como graves coincidentemente nos três compêndios e na lista da OMS. Foram estudados 280 pacientes (84 chagásicos e 196 não chagásicos), sendo a maioria do sexo feminino (54,6%) com média de idade de 56,8 (DP 13,1) anos. Não houve diferenças estatisticamente significantes em suas características sócio-demográficas, embora os não chagásicos tenham apresentado mais co-morbidades. A frequência das interações graves da varfarina nesses pacientes foi variável entre os compêndios, com coeficiente kappa Fleiss de 0,295. A frequência de interações graves da varfarina se mostrou discordante e com ampla variabilidade entre as fontes ao se avaliar o histórico de sangramento e se comparar chagásicos e não chagásicos. **Conclusões:** Houve baixa concordância entre as cinco fontes analisadas sobre interações da varfarina, sendo a bula a fonte mais incompleta de informações. A avaliação das interações da varfarina em pacientes cardiopatas revelou que a discordância encontrada nos compêndios se estende à prática clínica.

Palavras-chave: varfarina, toxicidade de drogas, interações de medicamentos, interações alimento-droga, interações ervas-drogas, bulas de medicamentos, doença de Chagas, *Trypanosoma cruzi*

ABSTRACT

Introduction: Drug interactions (DI) are an important cause of adverse events. They can increase drug related morbi-mortality and result in significant social and economic impact. Warfarin is a high risk drug due to its narrow therapeutic index, variability in dose-response and potential for DI. The early identification of warfarin DI may help to prevent adverse events, especially hemorrhage. **Objectives:** To evaluate potential warfarin DI in different sources of drug information and to investigate the frequency of severe warfarin DI in Chagas and non-Chagas disease patients at the Hospital das Clínicas of the Universidade Federal de Minas Gerais (UFMG). **Methods:** The lists of warfarin interactions provided by three compendia (*Drug Interaction Facts*, *Drug Interactions: Analysis and Management* and DRUG-REAX), the World Health Organization (WHO) Model Formulary and the Marevan® package insert were all compared in terms of: cited substances, severity ratings and documentation levels. A cross-sectional study was carried out enrolling patients with heart diseases to evaluate warfarin DI and its frequency according to the sources. A kappa coefficient was used to calculate the agreement between the sources. **Results:** A total of 537 interactions were listed. Only 13 (2.4%) were common to the five sources. Most critical interactions cited by the compendia were missing from the package insert. The global Fleiss' kappa coefficient was -0.0080. Only two warfarin interactions were reported as critical coincidently by the three compendia and by the WHO. A total of 280 patients were studied (84 Chagas and 196 non-Chagas disease patients). Most patients were female (54.6%) with an average age of 56.8 (SD 13.1) years old. They showed no statistical differences in their sociodemographic characteristics. However, non-Chagas individuals had more comorbidities. The frequency of severe warfarin DI was variable among the sources resulting in a Fleiss' kappa coefficient of 0.295. The frequency of severe warfarin DI showed disagreement with a wide variability between the sources when history of bleeding was assessed and Chagas and non-Chagas disease patients were compared. **Conclusions:** Poor agreement was found among five sources listing warfarin interactions. The package insert was the most incomplete source of drug information. The evaluation of warfarin DI in patients with heart diseases showed that the disagreement found in the compendia extends itself to the clinical practice.

Keywords: warfarin, drug toxicity, drug interactions, food-drug interactions, herb-drug interactions, drug labeling, Chagas disease, *Trypanosoma cruzi*

LISTA DE ABREVIATURAS E SIGLAS

Anvisa – Agência Nacional de Vigilância Sanitária

AO – Anticoagulantes orais

AVEi – Acidente vascular encefálico isquêmico

CA – Clínica de Anticoagulação

CYP –Citocromo P450

CTR – Centro de Tratamento e Referência

DI – *Drug interactions*

DIAM – *Drug Interactions: Analysis and Management*

DIF – *Drug Interaction Facts*

DP – Desvio padrão

EPUB – *Eletronic Publication*

IM – Interações medicamentosas

INR – *International Normalized Ratio*

OMS - Organização Mundial da Saúde

OTC-drugs – *Over-the-counter drugs*

RNI – Relação Normalizada Internacional

SD – *Standard deviation*

SPSS – *Statistical Package for the Social Sciences*

T. cruzi – Trypanosoma cruzi

UFMG – Universidade Federal de Minas Gerais

VKORC1 – *Vitamin K epoxide reductase complex subunit 1*

WHO – *World Health Organization*

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SUMÁRIO

APRESENTAÇÃO

A implantação da clínica de anticoagulação (CA) no Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG) para assistência aos pacientes cardiopatas era uma necessidade antiga da Instituição e com utilidade potencial para aprimorar o cuidado aos pacientes em terapia anticoagulante oral. Frente ao planejamento Institucional, foi possível implantar o Serviço e, ao mesmo tempo, documentar seus resultados clínicos em um projeto de pesquisa intitulado “Avaliação do Impacto da Implantação de Clínica de Anticoagulação na Assistência a Pacientes Chagásicos e Não Chagásicos Atendidos no Hospital das Clínicas da UFMG”, sendo o presente trabalho parte desse projeto.

A CA para assistência aos cardiopatas foi vinculada ao Serviço de Hematologia do Hospital das Clínicas da UFMG, tendo em vista que esse serviço já desenvolvia atividades voltadas para o controle da anticoagulação oral em pacientes hematológicos com trombofilias. As etapas de implantação da CA envolveram reuniões de sensibilização com o corpo clínico, planejamento logístico para organização do serviço e discussão da padronização de condutas, incluindo revisão do protocolo clínico, elaboração da cartilha de orientações e do cartão de usuário de anticoagulante oral (APÊNDICES A e B).

Como farmacêutica, o envolvimento em todas as etapas de implantação do serviço contribuiu para minha formação acadêmica, pessoal e profissional, permitindo-me o desenvolvimento de habilidades clínicas e a capacidade de interagir em ambiente multiprofissional. De maneira mais especial, o foco assistencial é uma importante perspectiva e uma das potencialidades da prática profissional do farmacêutico que, em sua plenitude, vai além das atividades focadas no medicamento, devendo ter o cuidado ao ser humano e o compromisso com a melhoria de sua qualidade de vida, como a base do seu processo de atuação. Essas questões encontram ainda mais ressonância diante do envelhecimento e adoecimento populacionais crescentes, das limitações sócio-econômico-culturais, ainda encontradas na maior parte da população brasileira, e da complexidade dos tratamentos ofertados.

Nesse contexto, as interações medicamentosas representam um elemento que merece atenção especial em pacientes em terapia anticoagulante oral devido ao seu potencial de induzir complicações clínicas. A abordagem das interações medicamentosas da varfarina nesse trabalho poderá trazer subsídios para melhoria das ações voltadas para o cuidado aos pacientes atendidos nas CA.

1 INTRODUÇÃO

O uso de medicamentos é um dos elementos essenciais no processo de assistência à saúde, embora possa oferecer riscos relacionados a reações adversas, interações medicamentosas ou outros problemas desencadeados durante o processo de utilização. Medidas voltadas para a promoção do uso racional de medicamentos são importantes para aumentar a efetividade da farmacoterapia e minimizar a morbi-mortalidade induzida por medicamentos[1]. Nesse sentido, o atendimento ambulatorial oferecido por clínicas multidisciplinares para monitorização do tratamento com anticoagulantes orais (AO) é um exemplo de estratégia útil para aumentar a segurança dos pacientes[2].

Os AO, derivados cumarínicos, são amplamente utilizados na prevenção e no tratamento de distúrbios tromboembólicos, sendo a varfarina o principal representante dessa classe. Suas desvantagens incluem estreita faixa terapêutica e risco aumentado para ocorrência de reações adversas. Em relação à toxicidade, destacam-se como suas principais manifestações: sangramento, em função da exacerbação do seu efeito anticoagulante, potencial efeito teratogênico e, com menor frequência, necrose cutânea[3]. Os sangramentos devem ser diferenciados conforme a gravidade para auxiliar na definição de condutas para seu manejo. Os eventos graves podem envolver sangramento retroperitonial, no sistema nervoso central ou em qualquer outro sítio, tais como os tratos genito-urinário ou gastrintestinal, que resultem em alterações sistêmicas. A presença de sangramentos pode requerer administração de vitamina K, uso de plasma fresco ou complexo protrombínico para reversão do efeito anticoagulante[4]. Vale ressaltar que a anticoagulação insuficiente também pode oferecer risco de complicação grave devido à falta de proteção contra tromboembolismo[5].

Na prática clínica, observa-se ampla variabilidade na dose-resposta à varfarina o que requer monitorização laboratorial frequente para auxiliar nos ajustes de dose e prevenir complicações. O teste laboratorial utilizado é calculado a partir do tempo de protrombina e expresso pela Relação Normalizada Internacional (RNI). Quanto maior o valor do exame RNI, maior o risco de hemorragia. A frequência de monitorização pode variar, sendo as medidas diárias indicadas no início da terapia, para evitar a ocorrência de anticoagulação excessiva no paciente muito sensível. O intervalo entre os testes de RNI pode ser gradualmente aumentado para semanal e, em seguida, mensal, para pacientes submetidos à terapia prolongada, nos quais a faixa terapêutica tenha sido alcançada e se mantido estável. Considera-se o RNI-alvo entre 2 e 3 para a maioria das indicações da varfarina[3].

Muitas substâncias podem interagir com significância clínica com a varfarina, potencializando o risco de complicações do tratamento[6-9]. Ressalta-se que as interações medicamentosas (IM) foram identificadas como um exemplo de evento adverso relacionado a medicamentos com característica previsível e passível de manejo. Na população idosa, comorbidades e polifarmácia apresentam prevalência importante e podem aumentar os riscos de IM potenciais[10]. A relação entre a dose da varfarina e a resposta pode, ainda, ser influenciada por fatores fisiopatológicos, presença de polimorfismos genéticos[11-13], falta de precisão no exame laboratorial utilizado para monitorização, quantidade de vitamina K ingerida na alimentação[3], uso incorreto do medicamento, grau de informação do paciente acerca da doença e do tratamento, impacto da terapia anticoagulante na qualidade de vida, bem como problemas de acesso ao medicamento e ao serviço de saúde[14-17].

A indicação do anticoagulante oral deve ser feita mediante criteriosa avaliação médica para estimar se os benefícios do tratamento suplantam os riscos associados ao uso do medicamento. As indicações principais para as quais há comprovação científica da eficácia de uso crônico da varfarina incluem pacientes com próteses mecânicas valvares, com histórico de trombose venosa profunda, tromboembolismo pulmonar, fibrilação atrial crônica e/ou acidente vascular encefálico isquêmico (AVEi) cardioembólico[3;18]. O número de pacientes com indicação de anticoagulação oral é crescente, especialmente devido ao envelhecimento populacional, que poderá aumentar 2,5 vezes o número de pacientes com fibrilação atrial nos próximos 40 anos[19].

Outro grupo importante para o qual poderá estar indicada anticoagulação oral crônica inclui pacientes com doença de Chagas[20]. Essa doença parasitária pode evoluir com acometimento cardíaco, o que aumenta o risco cardioembólico e constitui fator de risco independente para a ocorrência de AVEi. Existem evidências de benefícios da anticoagulação oral em chagásicos com trombo intracardíaco, fibrilação atrial ou histórico de AVEi[20-23]. Essa doença continua sendo grave problema de saúde pública na América Latina, cuja prevalência total da infecção humana por *Trypanosoma cruzi* é estimada em 16 a 18 milhões de casos, sendo que 25% a 35% dos infectados podem evoluir para distúrbios cardiovasculares[24].

Com relação ao tratamento com varfarina, é necessário definir parâmetros para avaliar a qualidade da anticoagulação em serviços especializados[25]. Os principais desfechos de interesse incluem o controle do RNI e a incidência de complicações hemorrágicas e

tromboembólicas. O RNI pode ser analisado por meio da porcentagem de resultados na faixa terapêutica, também chamada de fração RNI, ou utilizando-se o método Rosendaal para calcular a porcentagem de tempo do RNI na faixa terapêutica[26;27]. Esse último é considerado indicador útil, pois se correlaciona adequadamente com desfechos de interesse, tais como AVEi, tromboembolismo venoso e sangramento grave[5].

O nível de controle da anticoagulação oral é um determinante crítico do benefício da varfarina. Embora seja geralmente aceitável que o tempo de estabilidade da anticoagulação na faixa terapêutica superior a 60% confira benefício significativo em relação à terapia com agentes antiplaquetários, observa-se que o controle da anticoagulação pode variar entre 38% a 69% ao comparar-se diferentes serviços de anticoagulação[5] ou entre 46% a 78% para a comparação entre países[28].

Considerando-se que muitos pacientes não atingem controle adequado e permanecem susceptíveis a complicações tromboembólicas ou hemorrágicas, a principal forma de contribuir para o adequado manejo da varfarina é melhorando a qualidade do cuidado prestado. Esforço e habilidade são necessários tanto por parte do profissional de saúde quanto do paciente para estabilizar a anticoagulação na faixa terapêutica. Um dos grandes desafios da prática clínica é individualizar o tratamento, escolhendo a melhor conduta para cada paciente. Para tanto, deve-se considerar, ainda, intervenções mais amplas que possibilitem a aplicação de conhecimentos em farmacologia clínica na prática assistencial objetivando melhorar o controle do RNI, o manejo de eventos adversos e a educação dos pacientes sobre o tratamento com AO derivados cumarínicos. As ações devem ser adaptadas às necessidades de cada serviço[5;29-31].

O manejo de pacientes em uso de anticoagulantes derivados cumarínicos pode ser realizado de diferentes maneiras. É comum que o controle da anticoagulação oral seja feito pelo cardiologista ou clínico que também é responsável pela abordagem integral do paciente. O controle realizado por clínicas de anticoagulação tem sido apontado como estratégia de monitorização superior à prática clínica usual no que diz respeito à efetividade e segurança do tratamento[32-40]. Esse tipo de serviço pode contribuir para aumentar o tempo do RNI em faixa terapêutica e minimizar a incidência de eventos adversos. Nesse contexto, a atuação da equipe multidisciplinar tem papel relevante na orientação dos pacientes quanto aos medicamentos em uso, risco de complicações, cuidados na alimentação e na prevenção de erros laboratoriais pré-analíticos[40].

Uma das estratégias para promoção da segurança do paciente é aumentar os conhecimentos dos profissionais de saúde sobre as IM da varfarina e possibilitar o aprimoramento de condutas para o manejo adequado dos pacientes. Diante do exposto, desenvolveu-se o presente trabalho para analisar a qualidade das informações sobre IM com varfarina disponíveis para consulta pelos profissionais de saúde, bem como investigar a ocorrência de IM com varfarina em cardiopatas chagásicos e não chagásicos recém-admitidos na clínica de anticoagulação do Hospital das Clínicas da UFMG.

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3 OBJETIVOS

OBJETIVO GERAL

Avaliar as interações medicamentosas da varfarina utilizando diferentes fontes de informação e investigar sua frequência em cardiopatas chagásicos e não chagásicos atendidos em ambulatórios do Hospital das Clínicas da UFMG.

OBJETIVOS ESPECÍFICOS

Avaliar qualitativa e quantitativamente, de forma comparativa, as listas de interações da varfarina disponíveis no Formulário da Organização Mundial da Saúde, na bula do Marevan® e em três compêndios reconhecidos internacionalmente;

Investigar, no contexto da prática clínica, a frequência e tipo de fármacos envolvidos em interações potencialmente graves da varfarina em cardiopatas chagásicos e não chagásicos atendidos em ambulatórios do Hospital das Clínicas da UFMG, empregando diferentes fontes de informação (Formulário da Organização Mundial da Saúde e três compêndios).

4 ARTIGOS

4.1 Artigo 1: *Warfarin drug interactions: a comparative evaluation of the lists provided by five information sources*

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Abstract

Purpose: Detecting potential drug interactions can lead to early interventions that protect patients from serious drug-related problems. The aim of this study was to evaluate the agreement among the lists of warfarin interactions provided by five information sources.

Methods: The lists of warfarin interactions, and the corresponding severity ratings and documentation levels presented by the three compendia and by the World Health Organization (WHO) Model Formulary, were all compared, and each list was compared to that provided on the package insert of Marevan, a brand of warfarin. The compendia used were: *Drug Interaction Facts*, *Drug Interactions: Analysis and Management* and DRUG-REAX. A kappa coefficient was used to calculate the agreement among the sources.

Results: A total of 537 interactions were listed. Only 13 (2.4%) were common to the five sources. The global Fleiss' kappa coefficient was -0.0080, which indicated poor agreement. Eleven warfarin interactions appeared only in the Marevan package insert. Importantly, 243 interactions (45.3% of the total) were deemed significant in at least one compendium. Only two warfarin interactions were reported as critical by all the three compendia and by WHO. The most critical interactions cited by the compendia were missing from the package insert.

Conclusions: Poor agreement was found among five sources listing warfarin interactions. Potentially severe clinical consequences might occur due to these discrepant recommendations. Finally, the lack of standard terminology and clinical guidance, as well as the possible inaccuracy of severity ratings and documentation might contribute to heterogeneous procedures in clinical practice.

Keywords: warfarin, drug toxicity, herb-drug interactions, food-drug interactions, drug labeling

Introduction

Adverse events related to health care are a significant problem worldwide. It has been estimated that approximately 98,000 Americans die annually due to medical incidents [1]. In particular, adverse drug events can be responsible for emergency department visits and hospital admissions, with significant social and economic impact [2]. Drug interactions (DIs) have frequently been identified as an example of predictable and manageable adverse drug events. Comorbidities and polypharmacy, which are especially prevalent in elderly populations, are associated with higher risks of potential drug interactions [3].

Treatment with warfarin has been proven to be efficacious in preventing and treating thromboembolic events, but its administration is widely known to be associated with common and potentially severe drug-drug and drug-food interaction risks [4-7]. In a prospective study conducted in the UK, DIs accounted for 16.6% of hospitalizations caused by adverse drug reactions, and warfarin, particularly in combination with other drugs, was implicated in most cases of gastrointestinal bleeding [8]. The management of patients under warfarin therapy is challenging due to the drug's narrow therapeutic index, wide dose response variability, and the need for frequent monitoring of the International Normalized Ratio (INR) [9, 10].

Warfarin acts by inhibiting the vitamin K conversion cycle in the liver, which hinders the biological activation of vitamin K-dependent proteins - factors II, VII, IX and X, as well as the activation of anticoagulant proteins, C and S. Warfarin is a racemic mixture of two active enantiomers (R- and S- forms) [10]. Its oral bioavailability is high and nearly 99% of the racemic warfarin circulates bound to plasma proteins [11], with a half-life of 36 to 42 hours [10]. Combining warfarin and other drugs may lead to competitive displacement of serum protein binding, enhancing its hypoprothrombinemic effect [12]. Warfarin isomers are metabolically transformed in the liver by different pathways: S-isomer is metabolized mainly by the cytochrome P450 2C9 (CYP2C9) and has fivefold the potency of the R-isomer [13]. It has been shown that mutations in the gene coding for CYP2C9 might result in an increase of the warfarin anticoagulant effect [14, 15]. On the other hand, mutations in vitamin K epoxide reductase complex subunit 1 (VKORC1) may induce pharmacodynamic warfarin resistance [15-17]. These genetic polymorphisms not only increase dose- and INR- variability, but they also amplify the

propensity to drug interactions for certain individuals [18]. Besides, there might be ethnic differences interfering in warfarin response [14, 19-24].

Variability in dose response to warfarin may also be attributed to other factors, such as age and body size, estimations of warfarin clearance [15], patient compliance [25], and effects due to interactions with diet and other drugs [7, 10]. The identification of drugs, foods and dietary supplements with potential harmful interactions would enable early interventions at various levels in the healthcare system aimed at protecting patients from serious drug-related problems. Prescription and non-prescription medications should appear in a patient's drug lists in order to help the healthcare provider make a proper assessment of DIs. However, these lists are often incomplete and erroneous, given the complexity of the use of medications and patient's access to over-the-counter drugs (OTC-drugs) [26], drugs sold over the Internet and retail prescription programs [27]. For example, the concomitant intake of herbal medicines with the potential for interacting with warfarin, such as Saint John's Wort, is not usually made known to the physician. Even if drug lists were complete and comprehensive, clinicians may not have a complete overview of all substances in use that have the potential for warfarin interactions. Regarding drug interaction compendia, several authors have pointed out that there is little concordance in the available lists of DIs, and that there are substantial differences in the severity classifications [28-35]. In this study, we sought to compare the list of potential warfarin interactions provided on the package insert of Marevan, the most commonly used warfarin brand in Brazil, with those of three renowned compendia on drug interactions, and the interaction list provided by the World Health Organization (WHO) Model Formulary.

Methods

Selection of Drug Interactions Compendia

Lists of warfarin interactions were identified in the following drug interaction compendia: *Drug Interaction Facts* [36], *Drug Interactions: Analysis and Management* [12] and the Micromedex DRUG-REAX [11]. The selection of these references relates to their renown and their widespread use by healthcare professionals in several countries. The interaction table in the WHO Model Formulary [37], which is regularly peer-reviewed and up-dated, was also included in this analysis.

The lists of warfarin interactions and their corresponding severity ratings and evidence grading reported in these sources were compared. In addition, each of these lists was compared to the list provided on the package insert of Marevan (Farmoquímica, Brazil). The reason for including the package insert of Marevan in this analysis is its frequent use by healthcare professionals and patients alike as a widely available source of understandable information.

Evaluation of Warfarin Interactions

To assess the concordance between warfarin interactions identified in the three compendia, in the WHO Model Formulary and in the Marevan package insert, two authors (MAPM and PPSC) independently reviewed the content of each reference. Any disagreements regarding terms or classifications were discussed until a consensus was reached. All warfarin interactions were listed: drugs (including their classes), foods, herbal products, biological products, such as vaccines and monoclonal antibodies, dietary supplements, tobacco and ethanol. The precise lists obtained from the five sources were compiled into a descriptive table in Microsoft Excel using the following variables: 1) drug terminology, as indicated in the reference; 2) the clinical significance severity rating; 3) the level of documentation of the interaction, when available.

Data Analysis

The consulted sources were compared in terms of similarities and inconsistencies in the listed substances that affect warfarin action (i.e., drugs and foods) and levels of documentation and classification systems used to rate the severity of these interactions. To assess the concordance among the sources, each of the warfarin interactions was transformed into a binary variable, according to its presence or absence in each individual list. The Fleiss' kappa coefficient [38] was calculated to evaluate the overall concordance, and Cohen's kappa coefficient [39] was used to determine the pair-wise concordance among the lists. The concordance was evaluated according to the following degrees of agreement for kappa coefficients proposed by Landis and Koch [40]: <0=poor, 0.00 to 0.20=slight, 0.21 to 0.40=fair, 0.41 to 0.60=moderate, 0.61 to 0.80=substantial and 0.81 to 1.00=almost perfect. Data were analysed using the Statistical Package for the Social Sciences (SPSS for Windows, version 18.0, SPSS Inc, Chicago, IL). Information from these sources was also reviewed in terms of the rating system for the severity of interactions and their supporting documentation.

Results

A total of 537 entries were listed. Specifically, there were 272 entries listed in *Drug Interaction Facts*, 159 in *Drug Interactions: Analysis and Management*, 396 in DRUG-REAX, 69 on the Marevan package insert, and 58 in the interaction table of the WHO Model Formulary. A total of 306 entries (57.0%) were present in only one source, 107 (19.9%) were present in two sources, 75 (14.0%) were present in three sources, and 36 (6.7%) were present in four sources. Only 13 (2.4%) entries were common to the five sources. Among these common entries, 11 corresponded to drugs, one corresponded to drug classes, and one was ethanol (Table 1). Eleven warfarin interactions were exclusively listed in the Marevan package insert; these included generic citations, such as hepatotoxic drugs, corticosteroids, anabolic steroids and broad-spectrum antibiotics, and individual drug names, such as aztreonam, cotrimoxazole, dextropropoxifen, dichloralphenazone, feprazon, phenyramidol and tolbutamide.

Overall, warfarin-interacting substances were listed as individual drugs, drug classes and non-drug substances. The terminology adopted was not standardized. For example, thyroid hormones were listed in all sources as a drug class, though *Drug Interaction Facts* also cited specific drugs from this class, such as dextrothyroxine and levothyroxine. In all sources, drugs were the main chemical entity cited as interacting with warfarin. DRUG-REAX reported the highest proportion of interactions with non-drug substances (22.0%). Overall, 15.9% and 12.9% of drug classes were listed on the warfarin product insert and in *Drug Interaction Facts*, respectively. Table 2 summarizes the frequency of entries according to their classification.

The classification of clinical severity and documentation level showed substantial heterogeneity between the three compendia and the WHO's list, as summarized in Table 3. Likewise, we found significant differences among the lists of substances that potentially interact with warfarin. The same was true for comparison of the compendia with the package insert. In this context, the global Fleiss' kappa coefficient was -0.0080, indicating poor agreement among the five sources. For the classification of substances, Fleiss' kappa coefficient was 0.014, -0.074 and -0.123 for drugs, drug classes and others, respectively. The pair-wise concordance with Cohen's kappa coefficient also showed little concordance among the lists. The highest coefficients were those for *Drug Interaction Facts versus Drug Interactions: Analysis and*

Management (0.270) and for *Drug Interactions: Analysis and Management versus* the Marevan package insert (0.220), both of which showed a fair agreement, as shown in Table 4.

Among the total number of entries, 243 (45.3%) warfarin interactions were judged as "major" or "contraindicated" or "to be avoided" in at least one of the sources, including the three compendia and the WHO's list. A total of 176 warfarin interactions were cited as potentially harmful by only one source, 53 interactions were coincidently cited by two sources, and 12 by three sources. Only two interactions (with aspirin and metronidazole) were reported as critical in the three compendia and in the WHO's list. Interactions considered to be potentially harmful were those classified as 1 and 4 by *Drug Interaction Facts*, as 1 and 2 by *Drug Interactions: Analysis and Management,* as "major" and "contraindicated" by DRUG-REAX and as potentially hazardous interaction in the WHO Model Formulary. The absolute frequency of entries according to the clinical significance for each source is shown in Table 5. As depicted in Table 3, the documentation level and severity classification provided by DRUG-REAX appear in independent categories. In this source, clinical evidence was rated as "fair" for most warfarin interactions (48.7%) and as "excellent" in a minority of cases (4.0%).

In several cases, a certain interaction was not mentioned at all in one of the compendia, while being considered as clinically significant in the two others. For example, 57.9% of interactions classified as 1 and 4 by *Drug Interaction Facts* were not referred to in *Drug Interactions: Analysis and Management*. In addition, the clinical significance ratings for some commonly cited interactions varied greatly among the compendia. For example, the warfarin-levofloxacin interaction was rated as "major" by DRUG-REAX, with excellent supporting documentation, while classified as "moderate" by *Drug Interaction Facts* and as "minor" by *Drug Interactions: Analysis and Management*.

Classification of severity and evidence grading for potential DIs were not provided by the manufacturer. According to the Marevan package insert, warfarin interactions may enhance or reduce the anticoagulant effect, but its clinical significance was not included. A total of 54 entries were listed as interactions with an elevated risk for enhancing the anticoagulation effect, 13 interactions were listed as reducing the anticoagulation effect, and two (phenytoin and corticosteroids) interactions were listed for both effects. In addition, the manufacturer omitted a large number of interactions

mentioned in the other sources. Comparing the package insert with the lists provided by the compendia and the WHO's list the percentage of harmful interactions omitted by the manufacturer was: 94.4% for DRUG-REAX, 86.8% for *Drug Interaction Facts,* 68.8% for WHO Model Formulary and 54.5% for *Drug Interactions: Analysis and Management*.

Discussion

Our findings reveal considerable discrepancies between different sources of information on potential warfarin interactions. We observed a lack of standardization in the terminology used, an absence of homogeneous criteria for severity classification and poor or even absent grading of the clinical evidence. Together, these shortcomings make the use of these sources for clinical judgment problematic. Moreover, the information provided by the manufacturer (Marevan) showed only a poor agreement with that provided by three widely used compendia, and with the interaction table in the WHO Model Formulary.

Our results are in line with those reported previously [29-31] in which concordance rates of 2.2 and 8.9% were found. Most studies have found that more than 50.0% (range 14.0-71.7%) of entries are present in one source but not in the other sources [28, 29, 31]. Some authors have also calculated the agreement among the different compendia. Abarca et al. [29] calculated the intraclass correlation coefficient to be –0.092, indicating poor agreement. In a study performed by Olvey et al. [34], an evaluation of DI pairs deemed to be critical showed a low level of agreement between DRUG-REAX (updated January, 2009) and *Drug Interactions: Analysis and Management* (updated January, 2007), with a correlation of 0.076. Anthony et al. [33] examined warfarin interactions in three drug information compendia (Clinical Pharmacology, ePocrates and Micromedex) and a warfarin product label (Coumadin). They found little agreement among the sources, with a global Fleiss kappa coefficient of -0.026, which is consistent with our result (-0.0080). In our study, we showed that these disagreements are still present in the updated versions of renowned compendia. Additionally, we described discrepancies in the clinical severity ratings and calculated the proportions of entries by clinical significance among the compendia. We also included the interaction table provided in the WHO Model Formulary, which represents an international consensus that has been thoroughly reviewed.

There are several reasons for the discrepancies among the sources. First, each compendium adopts different criteria for inclusion of DIs. It is important to keep in mind that not all drugs in a class necessarily interact with the same compounds to the same extent in all individuals, given genetic polymorphisms and the related sensitivity to DIs [15]. In most cases, there is not enough available evidence to include or exclude an individual drug as an example of an entire class. Second, as search terms vary greatly, some warfarin interactions may have been overlooked. Third, the references used to guide the classification of severity ratings do not seem to be homogeneous. It is not clear whether the clinical evidence cited by each compendium is based on an independent review of primary or secondary sources, unpublished reports released by drug companies, product labels or reports collected by national post-marketing surveillance systems.

The mere number of possible interactions is not a good measure of the quality of the information and is not useful from a practical point of view. The completeness of DI lists may not be compatible to its user-friendliness. In relation to computer assisted support, over-alerting could make clinicians ignore significant warfarin interactions [41]. DI lists should provide guidance on the clinical relevance of interactions, but the lack of a single “gold standard” or “universal” compendium may be confusing and actually cause wide variations in clinical practice. Given the large number of potential interactions with warfarin, it is almost impossible to decide whether an individual is at danger of DIs. One piece of general advice that may be given is to consult multiple sources of information to search for DIs of clinical significance.

Warfarin treatment is a challenging task in clinical practice. Supra- and subtherapeutic INRs can place patients at increased risk of either bleeding or thromboembolic events. Even patients with a history of a stable INR can present sudden variations in INR-values after changes in concomitant medications. Time aspects of DIs may be relevant in terms of determining a suitable time-point for INR-monitoring and should consider the risks for: displacement of albumin (rapid onset and short-term), CYP-inhibition (intermediate onset and long-term recovery time) and CYP induction (slow onset and long-term recovery time)[42]. It is also important to consider the strength of interaction and pharmacogenetic aspects. Most warfarin interactions can be handled by dose adjustments. Thus, advising clinicians to follow-up INR-values within the first 2 weeks after any change in concomitant drug administration, health status or life styles could be reasonable as a general recommendation.

To the best of our knowledge, this is the first study to evaluate the package insert of Marevan, one of the most commonly used warfarin brands in Brazil. It was surprising to find that a large number of important warfarin interactions were not mentioned at all in the package insert. Some of these (e.g. aspirin) have a high potential for harm. The package insert of Coumadin, a brand commonly used in the USA, shows an extensive list of interactions that is about fourfold longer than the list provided for Marevan. Generic citations of drug classes and the lack of classification of severity and references indicate the low quality of the information supplied with the product. Our findings should alert healthcare professionals that oftentimes the information provided by drug companies should not be used as the sole reference for guiding dose adjustments and determination of INR- monitoring intervals. In addition, our study identified an urgent need for improvement in the content of the Marevan package insert, specifically in the list of potential warfarin interactions with drugs, foods, and herbal supplements.

Some limitations of the present study should be addressed. Due to the variability in terminology, subtle differences in the classification of drugs were taken into account and were not aggregated in cases where the source was not clear about the substances included in the referred classes. This approach may have led to an overestimation of the total number of interactions. For example, the hepatotoxic drugs interaction warnings on the Marevan package insert did not include specific drug names; thus, these warnings were considered as an individual entry, regardless of whether or not they were cited by another source as individual drugs or drug classes under different terms. Other entries were aggregated because they clearly referred to the same substance. For example, entries related to “ethanol” and “alcohol” were considered one entry (named “ethanol”). Finally, DI compendia are updated frequently as new information is discovered. Thus, this study should be considered valid for the compendia evaluated and the brand chosen in 2010.

In conclusion, our assessment of the sources of information on DIs shows that poor agreement persists on the lists of warfarin interactions included in the five drug information sources that we evaluated. The clinical impact of poor consistency among the sources is unknown. Severe clinical consequences might occur due to the differing recommendations for the same warfarin interaction. The possible inaccuracy of severity ratings and the lack of standard terminologies may contribute to heterogeneous procedures in clinical practice and may compromise the detection of potentially life-

threatening interactions. Sources of information should provide a grading system in the medical advice they offer in terms of the risk and expected strength of DIs. Clear references to specific documentation on DIs and explicit recommendations how to prevent and manage warfarin interaction-induced adverse reactions are needed to ensure patient safety. An effort to improve the quality of information provided by Marevan is also urgently required to increase the reliability of the instructions given to patients and healthcare professionals.

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Table 1 Warfarin-interacting substances that are listed in all five sources of information on drug interactions

Acetaminophen	Fluconazole
Allopurinol	Griseofulvin
Carbamazepine	Metronidazole
Ciprofloxacin	Miconazole
Contraceptives	Phenytoin
Erythromycin	Quinidine
Ethanol	

Table 2 Frequency of entries according to the classification of various warfarin-interacting substances in the five studied sources of information on drug interaction

Drug Interaction Source	Substance classification, n (%)			Total entries
	Drug	Drug class	Other[a]	
Drug Interaction Facts	219 (80.5)	35 (12.9)	18 (6.6)	272
Drug Interactions: Analysis and Management	142 (89.3)	4 (2.5)	13 (8.2)	159
DRUG-REAX	302 (76.3)	7 (1.7)	87 (22.0)	396
Marevan package insert	56 (81.2)	11 (15.9)	2 (2.9)	69
WHO Model Formulary	56 (96.6)	1 (1.7)	1 (1.7)	58

[a]Other = foods, biological products, dietary supplements, tobacco and ethanol.

Table 3 Specifics of the classification systems for drug interactions presented by the five studied sources of information

Sources on Drug Interactions	Classification systems
Drug Interaction Facts	Significance rating based on severity and documentation: 1 = major severity (documentation suspected or more); 2 = moderate severity (documentation suspected or more); 3 = minor severity (documentation suspected or more); 4 = major/moderate severity (documentation possible); 5 = minor severity (documentation possible or any severity; documentation unlikely).
Drug Interactions: Analysis and Management	Significance rating based on the recommended clinical management strategy: 1 = avoid combination; 2 = usually avoid combination; 3 = minimise risk; 4 = no action required; 5 = no interaction. The documentation level is not available.
DRUG-REAX	Five severity categories are used to classify DI (contraindicated, major, moderate, minor and unknown). There are six categories used for the documentation level (excellent, good, fair, poor, unlikely and unknown).
Marevan package insert	There is no ranking system. The description of warfarin interactions is based on the expected action (reduction or stimulation of the anticoagulation effect).
WHO Model Formulary	The symbol * indicates a potentially hazardous interaction and the combined administration of the drugs involved should be avoided, or only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

Table 4 Measures of pair-wise concordance of the binary variables for the presence or absence of warfarin interactions among the five sources of information

Sources	Drug Interaction Facts	Drug Interactions: Analysis and Management	DRUG-REAX	WHO formulary
Marevan package insert	0.074	0.220	0.013	0.170
Drug Interaction Facts	-	0.270	-0.102	0.100
Drug Interactions: Analysis and Management	-	-	0.046	0.129
DRUG-REAX	-	-	-	-0.003

Table 5 Warfarin interactions according to the absolute frequency of entries and clinical significance found in four sources of information on drug interactions

Source	Clinical significance	n
Drug Interaction Facts[a]	1	101
	2	60
	3	0
	4	96
	5	15
Drug Interactions: Analysis and Management[a]	1	1
	2	32
	3	64
	4	41
	5	21
DRUG-REAX	Contraindicated	1
	Major	71
	Moderate	322
	Minor	2
	Unknown	0
WHO Model Formulary	Potentially hazardous interacion	48
	Usually without serious consequences	10

[a]See Table 3 “Classification systems” for a description of the rating used by the different sources

4.2 Artigo 2: *Evaluation of warfarin drug interactions using four different sources of information in patients with heart diseases treated at a teaching hospital in Brazil*

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Abstract

Introduction: Previous studies showed poor agreement among compendia and information sources regarding listing and classifying the severity of warfarin drug interactions (DI). Potentially severe clinical consequences might occur due to these discrepant recommendations. The aim of this study was to assess the presence of potentially severe warfarin DI in outpatients with heart diseases in a teaching hospital, using as sources of drug information four renowned interaction lists, evaluating the agreement among these sources.

Methods: A cross-sectional study was carried out enrolling *Trypanosoma cruzi*-infected and non-infected patients to evaluate severe warfarin DI and its frequency according to DI lists provided by three compendia (*Drug Interaction Facts* (DIF), *Drug Interactions: Analysis and Management* (DIAM) and DRUG-REAX) and the World Health Organization (WHO) Model Formulary. A kappa coefficient was used to calculate the agreement among the sources. Descriptive statistical methods were used for the evaluation of data.

Results: A total of 280 patients were studied. Most patients were female (54.6%) with an average age of 56.8 (SD 13.1) years old. *T. cruzi*-infected and non-infected patients showed no statistical differences in their sociodemographic characteristics. However, non-infected individuals had more comorbidities. Regarding the concordance among sources, the global Fleiss' kappa coefficient was 0.295 showing fair agreement. *T. cruzi*-infected individuals are less likely to have severe warfarin DI than non-infected patients ($p<0.05$ for DIAM, DRUG-REAX and the WHO Model Formulary). Patients with history of bleeding showed severe warfarin DI more frequently than patients with no history of bleeding, considering DIF compendium ($p=0.007$).

Conclusions: The evaluation of warfarin DI in patients with heart diseases showed that the disagreement between the compendia is observed in the clinical practice. Discrepancies in the evaluation of DI might contribute to a wide variability in clinical practice and bring significant clinical consequences.

Keywords: warfarin, drug therapy, herb-drug interactions, drug interactions, Chagas disease, *Trypanosoma cruzi*

Introduction

Drug interactions (DI) have frequently been identified as a cause of adverse drug events (1). Rates of potential DI have been investigated in studies performed at different levels of health care such as in the emergency room, outpatient clinics, hospitals and at discharge. Such studies have found rates of potential DIs ranging from 5.4% to 88.8% of patients (2-12) and involved heterogeneous patient populations and study designs. In Brazil, the rates reported for potential DI range from 22% to 72% of patients evaluated (13-18). Patients with cardiovascular diseases are often treated with complex dosing regimens. In addition to the pharmacotherapy for heart failure itself, the treatment of comorbidities (e.g. hypertension, diabetes mellitus, dyslipidemia) frequently increase the number of drugs considered necessary for these patients (11). The use of five or more medications translates into polypharmacy, which is a known risk factor for DI (19). Warfarin is a coumarinic oral anticoagulant widely used by patients with cardiovascular diseases. It shows a high propensity for DI, which may complicate with hemorrhagic or thromboembolic events (20-27).

Trypanosoma cruzi infection, known as Chagas disease, is a prevalent and typical disease from Latin America that may lead to cardiovascular abnormalities and sudden death (28-33). Warfarin is particularly recommended in *T. cruzi*-infected patients with left ventricular apical aneurysms with mural thrombus, atrial fibrillation or previous stroke (34). Information about DI in Brazilian patients with heart disease, infected or non-infected by *T. cruzi,* is scarce. Healthcare professionals should be aware of warfarin DI in order to provide careful monitoring and appropriate dose adjustments (20). Additionally, recent studies have reported that renowned compendia cite warfarin interactions with discrepancies in terms of the drugs listed and the criteria used to classify severity and documentation levels (35-37). From a practical point of view, the effect of poor agreement among sources on drug information has not yet been tested in clinical practice. The objective of this study was to evaluate potentially severe warfarin DI in outpatients with cardiovascular diseases using as sources of drug information four renowned interaction lists and to evaluate the agreement among these sources. Another objective was to evaluate the frequency of warfarin DI according to *T. cruzi*-infection and the frequency of warfarin DI in patients with history of bleeding.

Material and methods

This is a cross-sectional study involving patients recruited from September 2009 to August 2010 at the Ambulatories of Cardiology and Internal Medicine, and also at the Training and Referral Center for Infectious and Parasitic Diseases of a teaching hospital in Belo Horizonte, Southeast Brazil. This is a public hospital which serves as a referral center for the Brazilian Health System in the State of Minas Gerais focusing on diseases of medium and high complexity. The research project was approved by the University Ethics Committee and registered in the National System of Information on Ethics in Research.

Patients in treatment with warfarin aged 18 years or older who met the inclusion criteria were recruited in the process of their admission in an anticoagulation clinic recently established at the hospital to assist outpatients for anticoagulation control. The inclusion criteria involved cardiopathy with history of atrial fibrillation/flutter, stroke/transient ischemic attack (TIA), thrombosis or mechanical heart valves and indication for chronic oral anticoagulation. Informed consent was obtained from each patient. Exclusion criteria were patients using phenprocoumon or those who had initiated warfarin treatment less than 30 days before the interview.

Individuals were considered *T. cruzi*-infected if they presented positive serology for *T. cruzi* in two or more tests using different methods, including reaction to indirect immunofluorescence, indirect hemagglutination, and enzyme-linked immunosorbent assay, conducted at the hospital laboratory (38).

Sociodemographic and clinical data were initially collected by patient interview and then confirmed by prescription and chart review. Sociodemographic data included sex, age, self-declared skin color, marital status, school degree, occupation and month income. Clinical information included number and type of drug/herbal products prescribed for chronic use and any over-the-counter (OTC) drug used continuously by patients, indication for anticoagulation, target for prothrombin time expressed as international normalized ratio (INR) and comorbidities. Chronic use of medications was defined as a treatment of at least 30 days prior to the interview. The researcher was blinded to warfarin DI listed in each source of information during data collection. History of bleeding was collected in the chart and/or deemed as a patient report of past hemorrhage of any type and severity after the beginning of the treatment with warfarin.

The lists of potential warfarin DI and the severity classification were identified in the following drug interaction compendia: *Drug Interaction Facts* (DIF) (39), *Drug Interactions: Analysis and Management* (DIAM) (40) and the Micromedex DRUG-REAX (21) (updated December 2011). The selection of these references relates to their renown and their widespread use in clinical research and practice (5;8;10;14;35;41). DRUG-REAX, one of Micromedex database, is a source of drug information available online and constantly updated by the editorial board. The interaction table in the World Health Organization (WHO) Model Formulary (42), which is also regularly peer-reviewed and up-dated, was also included in this analysis. Interactions considered potentially harmful were those classified as 1 and 4 by DIF, as 1 and 2 by DIAM, as "major" and "contraindicated" by DRUG-REAX and as potentially hazardous interaction in the WHO Model Formulary. The complete classification of clinical severity used by each compendia and the WHO's list is depicted in the Figure 1. Adverse events related to critical warfarin DI were not assessed.

The drugs were listed for each patient and then the presence of potentially severe warfarin DI for the four interaction lists were compiled into a descriptive table in Microsoft Excel. The severity classification of a drug class was considered when the specific drug name was not cited separately. The number of severe warfarin interactions presented by patients was also considered. The mechanism involved in DI and its effect on augmenting or inhibiting the anticoagulant response were also investigated.

To assess the concordance among the sources, the occurrence of at least one warfarin DI of clinical importance by patient was transformed into a binary variable, according to its presence or absence in each individual list. Fleiss' kappa coefficient was calculated to evaluate the overall concordance among interaction lists (43). The concordance was evaluated according to the following degrees of agreement for kappa coefficients proposed by Landis and Koch (44): less than 0=poor, 0.00 to 0.20=slight, 0.21 to 0.40=fair, 0.41 to 0.60=moderate, 0.61 to 0.80=substantial and 0.81 to 1.00=almost perfect.

Baseline characteristics of the patients were registered by double entry using EpiData software (version 3.1, EpiData Assoc, Denmark). All data were analyzed with the Statistical Package for Social Sciences (SPSS for Windows, version 18.0, SPSS Inc, Chicago, IL). Descriptive statistical methods were used for the evaluation of data. The

Kolmogorov-Smirnov test was used to evaluate the normality of the variables. Pearson chi-square test or Fisher exact tests, when indicated, were carried out in order to compare categorical sociodemographic and clinical variables between *T. cruzi*-infected and non-infected individuals. Each quantitative variable was assessed by Student t-test or Mann-Whitney U tests, when indicated. Finally, the associations between *T. cruzi* infection and warfarin DI; and history of bleeding and warfarin DI were calculated by Pearson chi-square tests. A value of $p<0.05$ was considered as statistically significant.

Results

A total of 280 patients were studied. Most patients were female (54.6%) and the average age was 56.8 (standard deviation - SD 13.1) years old. *T. cruzi*-infected and non-infected individuals were not significantly different regarding sociodemographic characteristics, as described in Table 1.

T. cruzi-infected and non-infected individuals had some differences in the indications for anticoagulant therapy and comorbidities. Regarding indications for anticoagulation therapy, stroke, TIA and heart thrombus were more frequent in infected patients. On the other hand, aortic and mitral mechanical valve was the most frequent indication for warfarin use among non-infected patients. In general, non-infected patients showed more comorbidities than infected patients. Heart failure was more common in patients infected with *T. cruzi* than in non-infected individuals (Table 2).

A variety of 100 drugs was listed as being used chronically by the patients studied. The five most commonly used medications were furosemide, enalapril, carvedilol, acetylsalicylic acid and digoxin. The frequency of drugs used by the patients is summarized in Table 3. Among them, 42 (42.0%) drugs were classified as having the potential of critical warfarin interaction in at least one source of drug information.

The frequency of patients with warfarin DI of clinical importance showed substantial heterogeneity between the three compendia and the WHO list. According to the source of information, 34.3% of patients showed clinical significant drug interactions using DIAM, 61.8% using the WHO Model Formulary, 64.6% according to DRUG-REAX and 93.2% according to DIF. The overall concordance measured by Fleiss' kappa

coefficient was 0.295 (CI 95%; 0.247-0.343; p<0.001) showing fair agreement among the four sources.

Low agreement was found among the sources in respect to the type of warfarin interacting drugs cited and its severity classification. Acetylsalicylic acid was the only drug with agreement among the four sources of drug information. Glucosamine was included in the list because it is regulated as a drug product in Brazil. Most suspected or proven mechanisms for those warfarin DI detected in this study involved pharmacokinetics and may lead to a hyperprothrombinemic effect. The substances mentioned in at least one source with the rating of severity and the possible effect on anticoagulation are shown in the Figure 2.

The number of potentially severe interactions for each patient according to each of the four sources of drug information is depicted in Table 4. The highest number of drugs classified as warfarin interacting with the potential of severe significance by DIF is reflected in a higher frequency of patients with multiple warfarin interactions at the same time, ranging from two to six interactions, when compared to the other sources. DIAM was the source with the lowest frequency of warfarin interactions of clinical importance.

T. cruzi-infected patients are less likely to have potentially severe warfarin interactions than those who are non-infected non-infected (p<0.05) for DIAM, DRUG-REAX and WHO Model Formulary (Table 5). Patients with history of bleeding presented severe warfarin interactions more frequently than patients with no history of bleeding, considering the DIF compendium (p=0.007) (Table 6).

Discussion

In these 280 patients with cardiovascular diseases treated with warfarin, the frequency of critical warfarin drug interactions ranged from 34.3% to 93.2% of patients depending on the source of information used. The number of severe interactions presented by patients individually also varied significantly when using the different drug interaction lists. For instance, according to DIAM, most individuals showed no potentially interacting co-medications. On the other hand, using DIF, most patients had at least one severe warfarin DI and nearly 40% showed from three to six interactions

simultaneously. In general, discrepancies among sources were found both in *T. cruzi*-infected and non-infected individuals. However, it seemed to be more problematic in infected patients due to the wider variation found. For example, DIAM and DIF showed 9.5% and 89.3% of patients with potentially severe warfarin DI, respectively. In addition, history of bleeding was associated with the presence of critical warfarin DI only when DIF was used as a source of drug information. The decision of the sources to include drug classes instead of individual drugs as warfarin interactors may have contributed to the discrepancies found.

Despite previous studies (35;36) evaluating theoretical agreement among lists of warfarin interacting substances have shown negative results, a better agreement was found in our study when they were compared to the global Fleiss' kappa coefficient for the list of patients presenting at least one critical warfarin DI using four sources on drug information (0.295). This may be explained by the fact that a small number of drugs is used by patients with heart diseases and these drugs are prescribed routinely, whereas the comparison of the complete lists provided by different compendia showed substances of uncommon use in patients with heart diseases and the drug information about them may be even more erratic.

Regarding the frequency of warfarin DI when using DIF, DRUG-REAX and WHO Model Formulary, our results are in line with other studies in which at least 54% of the patients evaluated were exposed to potentially interacting substances concomitantly with long-term warfarin (20;23;24). The clinical effect of choosing a source despite the others suggests a wide spectrum of discrepancies in detecting patients at higher risk for warfarin-related events and a possible heterogeneity in clinical guidance. Recognizing the complexity of drug therapy and the large number of potential warfarin DI, Martins et al. (35) considered to be reasonable to follow-up INR values within the first two weeks after any change in concomitant drug use, health status or life styles. However, without a "gold standard" to assess DI, we could assume that if a healthcare provider adopts a sole compendium with a longer list of warfarin DI, such as DIF, patients with changes in the current medication would need more frequent appointments than those evaluated using DIAM, for example. In that case, healthcare settings should be structurally prepared to deliver proper care for a larger demand from patients.

Warfarin DI have been associated with increased bleeding risk in some studies (22;24-26). Co-medication has been recently added to a novel prediction model for bleeding risk in anticoagulated patients with atrial fibrillation (45). In a study performed in Sweden in 2000-2002, Jonsson et al. (25) demonstrated that warfarin DI contributed to 41% of warfarin-associated cerebral hemorrhages. Narum et al. (26) showed that more than 50% of the warfarin-associated bleeding events reported to the Norwegian reporting system were associated with the use of potentially interacting medicines. In another study carried out by Vitry et al. (22), bleeding-related hospitalization rates significantly increased when warfarin was co-prescribed with low-dose acetylsalicylic acid, clopidogrel, clopidogrel and acetylsalicylic acid, amiodarone and antibiotics. Even though the incidence of warfarin-related bleeding has not been assessed in our study, information about past hemorrhagic events may help to provide better clinical evaluation once previous studies have reported that patients with a history of bleeding may have higher risk for future hemorrhage (45-47). The discrepancies among sources of information hindered the assessment of the association between history of bleeding and potentially severe warfarin DI. Additionally, memory bias and incomplete information represented some difficulties in collecting retrospective data on history of bleeding and the drugs used concomitantly with warfarin at the time of the bleeding episode.

There are various mechanisms through which warfarin can interact with other substances. The majority of warfarin interactions are characterized by pharmacokinetic and pharmacodynamic mechanisms resulting in either hyper- or hypoprothrombinemia. Pharmacokinetic interactions may lead to changes in the half-life and clearance of warfarin secondary to modifications in absorption, distribution, metabolism or excretion. Increased anticoagulant effect expressed by higher levels of INR could be associated to the use of concomitant drugs that may induce warfarin displacement from protein binding or inhibit hepatic metabolism performed by cytochrome P450 enzymes (26;48). INR values above 4.0 have been considered a risk factor for intracranial hemorrhage (49). On the other hand, pharmacodynamic interactions may occur without changes in kinetic parameters (48). Warfarin DI that could increase bleeding risk are manifested clinically not by rising INR, but due to synergistic pharmacological effects that inhibit hemostasis (23). The information on pharmacological mechanisms involved in warfarin DI and its effect on the anticoagulation are not consensual in the literature, oftentimes are also not well established, and suggest multiple and complex mechanisms. In this study, most potentially severe warfarin DI seemed to involve pharmacokinetic

mechanisms and to be associated with the increase of anticoagulant effect (Figure 2). These findings are in line with the results showed by Narum et al. (26).

Our results showed that nearly 30% of the patients were using low dose acetylsalicylic acid in combination with warfarin and it was the only warfarin DI with agreement among the sources of drug information. There are multiple and alternative mechanisms that have been reported for acetylsalicylic acid-warfarin interaction, such as the transient displacement of warfarin from the protein binding (50), the direct suppression of the synthesis of vitamin k-dependent clotting factor and the additive effect on the hemostasis reached by acetylating irreversibly platelets for up to 7-10 days (23). The latter is supposed to be the main mechanism for the effect of low dose acetylsalicylic acid and may lead to little influence on INR values. Low dose acetylsalicylic acid (80–100 mg daily) in addition to warfarin in patients with mechanical heart valves reduces all-cause mortality, with significant reductions in thromboembolism but with more bleeding complications (51). These patients should have their INR levels carefully monitored and watched for signs of bleeding.

In our study, 17.5% of patients received concomitant therapy with the antiarrhytmic agent amiodarone which presents a well documented interaction with warfarin. This interaction may lead to the prolongation of INR. The inhibition of cytochrome P450 is the mechanism proposed and this phenomenon may be observed in the first 3-4 days after starting amiodarone and may be delayed for up to 3 weeks. After discontinuation of amiodarone, the recovery time may take weeks to months (52). Another example of interacting drug with the potential of increasing INR levels also by inhibiting liver metabolism is simvastatin which was prescribed to 28.2% of patients (21). Though few patients were taking rifampicin and barbiturates, it is important to draw attention to their interacting mechanisms which involve the induction of warfarin's metabolism thus decreasing the INR and requiring higher warfarin doses. When these agents are discontinued without appropriate warfarin dose adjustments, rebound increases in INR may occur (53;54). Other substances with the potential for warfarin DI, such as trimetoprim-sulfamethoxazole and *Ginkgo biloba* (42), were prescribed less frequently. When the concomitant use of warfarin and interacting drugs is unavoidable, INR levels should be monitored frequently to provide proper warfarin dose adjustments.

In respect to patients' characteristics, socioeconomic aspects were not expected to be similar when *T. cruzi*-infected were compared to non-infected patients, once infected individuals usually belong to social groups with lower levels of literacy and income (55). However, the homogeneity observed between the groups studied may be explained by the origin of most of the patients treated at that public institution who mainly and indistinctly proceed from the poorest population segments of the state of Minas Gerais. *T. cruzi*-infected patients showed more frequency of heart failure and heart thrombus. In these patients, low left ventricular ejection fraction has been reported to be independently associated with ischemic cerebrovascular events, even though thrombus was not associated with long-term risk for these events in a study performed by Nunes et al. (56). Besides, the higher frequency of stroke and TIA is commonly found in *T. cruzi*-infected patients (34). The use of larger number of drugs was supposed to be true among non-infected patients due to the higher frequency of general comorbidities when compared to *T. cruzi*-infected individuals. However, there was no quantitative difference in the chronic medications used by both groups.

Conversely, the type of drugs used varied among groups. For instance acetylsalicylic acid was used only by non-infected patients. This finding may have contributed to increase the frequency of potentially severe warfarin DI among non-infected patients when using DIAM, DRUG-REAX and WHO Model Formulary as sources of drug information. DIF showed a tendency to classify a large number of drugs as warfarin interacting, including beta-blockers and thiazide diuretics differently from the other sources. As *T. cruzi*-infected patients frequently were treated with these drugs, this criterion may explain why DIF was the only source for which no difference in the frequency of potentially severe warfarin DI was found between *T. cruzi*-infected and non-infected patients.

Discrepancies among sources could be also considered as a public health problem due to the high number of patients taking warfarin and its possible influence on clinical procedures. The lack of criteria in ranking the sources of drug information and the heterogeneity in detecting potentially severe warfarin DI may interfere on the logistic of healthcare services and could lead to higher warfarin-related hospitalizations, emergency department visits and costs. Surveillance on warfarin DI remains a challenge in clinical practice, especially for patients with heart disease, due to the complexity of the drug therapy, variable effect of comorbidities on the clinical manifestations of DI, constant changes in prescription, the use of nonprescription

substances and the dynamism of the introduction of new therapeutic agents for which DI profiles are often incompletely characterized. Even if the physician is aware of the main DI related to the drugs prescribed routinely in this setting, it is very difficult to have a complete overview of the critical DI spectrum presented by a patient with many comorbidities and for whom care is often delivered also by other specialists. Anticoagulation clinics may represent a suitable strategy in detecting DI and patients at risk for clinical complications. Multidisciplinary teams, including pharmacists among others healthcare professionals, may be of relevance to help handling warfarin DI.

One of the strengths of our study is the evaluation of potentially severe warfarin DI in a real-world setting comparing its frequency in patients with cardiovascular diseases according to four renowned sources of drug information. Moreover, considering the epidemiologic importance of *T. cruzi*-infection in Latin America and the lack of DI studies in infected patients, our results contributed to improve knowledge on warfarin DI in these patients. In addition, we characterized its frequency, using different sources on drug information in comparison with non-infected individuals. Further studies on DI involving other high risk medications would be useful to evaluate the agreement among compendia once that probably the discrepancies could not be restrict to warfarin interactions.

Some limitations of our study should be pointed out. Cross-sectional studies do not allow evaluating causality, but only associations. In addition, information about compliance and the use of herbal products and OTC-drugs may have been omitted by patients and they were not taken into account to calculate the frequency of warfarin DI. Due to usual complexity of the dose regimen, there may be other potential non-warfarin interactions which would increase the frequency of DI and the risk for drug related problems. Finally, we evaluated potential warfarin interactions, and there was no attempt herein to investigate if they resulted in adverse drug events.

In conclusion, the evaluation of potential warfarin DI in patients with heart disease showed that the disagreement among the sources is observed in a real context of healthcare. Discrepancies in detecting potentially severe warfarin DI showed a wider range of variation in *T. cruzi*-infected than in non-infected individuals for the most sources of drug information. Variability among sources was also found when the association between history of bleeding and severe warfarin DI was investigated. The

mentioned discrepancies in the evaluation of DI might contribute to a heterogeneity in the clinical procedures and bring significant consequences to those patients.

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Figure 1 Specificities of the classification systems for drug interactions presented by four drug information sources

Sources on Drug Interactions	Classification systems
Drug Interaction Facts	Significance rating based on severity and documentation: 1 (major severity; documentation suspected or more); 2 (moderate severity; documentation suspected or more); 3 (minor severity; documentation suspected or more); 4 (major/moderate severity; documentation possible); 5 (minor severity; documentation possible or any severity; documentation unlikely)
Drug Interactions: Analysis and Management	Significance rating based on the recommended clinical management strategy: 1 (avoid combination); 2 (usually avoid combination); 3 (minimise risk); 4 (no action required); 5 (no interaction).
DRUG-REAX	Five severity categories are used to classify DI Contraindicated (the drug combination is not recommended) Major (the interaction may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects) Moderate (the interaction may result in an exacerbation of the patient's condition and/or require an alteration in therapy) Minor (the interaction would have limited clinical effects. Clinical effects may include an increase in the frequency or severity of side effects but generally would not require a major alteration in therapy) Unknown (not determined)
WHO Model Formulary	The symbol * indicates a potentially hazardous interaction and the combined administration of the drugs involved should be avoided, or only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

Table 1 Sociodemographic characteristics of total and *Trypanosoma cruzi*-infected and non-infected participants in warfarin use

Characteristcs	Total (n=280)	*Trypanosoma cruzi* infection		*p*-Value
		Yes (n = 84)	No (n = 196)	
Female sex, n (%)	153 (54.6)	40 (47.6)	113 (57.7)	0.122*
Age, mean (SD)	56.8 (13.1)	58.2 (12.8)	56.2 (13.3)	0.238†
Skin color, n (%)				
White	62 (22.1)	14 (16.7)	48 (24.5)	0.279*
Non-White	218 (77.8)	70 (83.3)	148 (75.5)	
Marital status, n (%)				
Single	41 (14.6)	10 (11.9)	31 (15.8)	
Married	185 (66.1)	56 (66.7)	129 (65.8)	0.671*
Divorced	23 (8.2)	9 (10.7)	14 (7.1)	
Widowed	31 (11.1)	9 (10.7)	22 (11.2)	
School degree, n (%)				
No literacy	27 (9.6)	11 (13.1)	16 (8.2)	
Incomplete elementary school	166 (59.3)	58 (69.0)	108 (55.1)	
Elementary school	34 (12.1)	5 (6.0)	29 (14.8)	0.058‡
Incomplete high school	15 (5.4)	3 (3.6)	12 (6.1)	
High school	35 (12.5)	7 (8.3)	28 (14.3)	
Incomplete college	3 (1.1)	0 (0.0)	3 (1.5)	
Occupation, n (%)				
Employed	45 (16.1)	9 (10.7)	36 (18.4)	
Unemployed	18 (6.4)	5 (6.0)	13 (6.6)	0.258*
Retired	217 (77.5)	70 (83.3)	147 (75.0)	
Monthly income – US dollars (Percentiles 25; 50; 75)	279.00;464.00; 710.00	279.00;437.00; 749.00	279.00;470.00; 710.00	0.924§

* Pearson Chi-square tests; † Student t test; ‡Fisher exact test; §U Mann-Whitney test.

Table 2 Clinical characteristics of total and *Trypanosoma cruzi*-infected and non-infected participants in warfarin use

Clinical information	Total (n=280)	*Trypanosoma cruzi* infection		*p*-Value
		Yes (n = 84)	No (n = 196)	
Number of drugs in chronic use (Percentiles 25; 50; 75)	4.0; 6.0; 7.0	4.0; 5.0; 7.0	4.0; 6.0; 7.0	0.219*
Target-INR†, n (%)				
2.0-3.0	198 (70.7)	84.0 (100)	114 (58.2)	<0.001‡
2.5-3.5	82 (29.3)	0 (0)	82 (41.8)	
Indications for anticoagulation therapy				
Stroke, n (%)	65 (23.2)	29 (34.5)	36 (18.4)	0.003‡
Transient isquemic attack, n (%)	12 (4.3)	7 (8.3)	5 (2.6)	0.048§
Atrial fibrillation or Flutter, n (%)	178 (63.6)	49 (58.3)	129 (65.8)	0.233‡
Lung hypertension, n (%)	5 (1.8)	1 (1.2)	4 (2.0)	1.0§
Heart thrombus, n (%)	35 (12.5)	21 (25.0)	14 (7.1)	<0.001‡
Pulmonary thromboembolism, n (%)	8 (2.9)	2 (2.4)	6 (3.1)	1.0§
Other systemic thromboembolism, n (%)	2 (0.7)	1 (1.2)	1 (0.5)	0.511§
Deep venous thrombosis, n (%)	16 (5.7)	5 (6.0)	11 (5.6)	1.0§
Aortic mechanical valve, n (%)	42 (15.0)	0 (0.0)	42 (21.4)	<0.001‡
Mitral mechanical valve, n (%)	62 (22.1)	0 (0.0)	62 (31.6)	<0.001‡
Tricuspid mechanical valve, n (%)	1 (0.4)	0 (0.0)	1 (0.5)	1.0§
Comorbidities, n (%)	273 (97.5)	78 (92.9)	195 (99.5)	0.003§
Dyslipidemia, n (%)	103 (36.8)	26 (31.0)	77 (39.3)	0.185‡
Coronary artery disease, n (%)	33 (11.8)	5 (6.0)	28 (14.3)	0.048‡
Gastrointestinal disease, n (%)	18 (6.4)	6 (7.1)	12 (6.1)	0.750‡
Hematological disease, n (%)	42 (15.0)	11 (13.1)	31 (15.8)	0.559‡
Neuropsychiatric disorders, n (%)	36 (12.9)	6 (7.1)	30 (15.3)	0.061‡
Valve diseases, n (%)	55 (19.6)	2 (2.4)	53 (27.0)	<0.001‡
Peripheral vascular disease, n (%)	8 (2.9)	4 (4.8)	4 (2.0)	0.246§
Osteoarticular diseases, n (%)	24 (8.6)	10 (11.9)	14 (7.1)	0.192‡
Respiratory diseases, n (%)	42 (15.0)	6 (7.1)	36 (18.4)	0.016‡
Rheumatic diseases, n (%)	27 (9.6)	2 (2.4)	25 (12.8)	0.007‡
Systemic arterial hypertension, n (%)	168 (60.0)	41 (48.8)	127 (64.8)	0.012‡
Hypothyroidism, n (%)	38 (13.6)	11 (13.1)	27 (13.8)	0.879‡
Heart failure, n (%)	168 (60.0)	60 (71.4)	108 (55.1)	0.011‡
Liver disfunction, n (%)	6 (2.1)	2 (2.4)	4 (2.0)	1.0§
Kidney disfunction, n (%)	55 (19.6)	20 (23.8)	35 (17.9)	0.251‡
Neoplasias, n (%)	12 (4.3)	2 (2.4)	10 (5.1)	0.520§
Risk of falls, n (%)	148 (52.9)	51 (60.7)	97 (49.5)	0.085‡
History of bleeding, n (%)	195 (69.6)	56 (66.7)	139 (70.9)	0.478‡

* U Mann-Whitney test; † International Normalized Ratio; ‡ Pearson Chi-square tests; § Fisher exact tests.

Table 3 Chronic drug use in patients with cardiovascular diseases treated with warfarin*

Drugs in chronic use	n	%
furosemide	131	46.8
enalapril	97	34.6
carvedilol	96	34.3
acetylsalicylic acid	89	31.8
digoxin	87	31.1
captopril	83	29.6
simvastatin	79	28.2
spironolactone	70	25.0
hydrochlorothiazide	54	19.3
amiodarone	49	17.5
losartan	49	17.5
propranolol	36	12.9
omeprazole	34	12.1
levothyroxine	32	11.4
atenolol	30	10.7
metformin	22	7.9
amlodipine	21	7.5
penicillin G	20	7.1
clonazepam	13	4.6
fluoxetine	13	4.6
ferrous sulfate	10	3.6
metoprolol	10	3.6
glibenclamide	9	3.2
allopurinol	6	2.1
amitriptyline	6	2.1
carbamazepine	6	2,1
diltiazem	6	2.1
insulin	6	2.1
others†	<6	<2.0

*n=280

†Includes cardiovascular drugs, psychotropics, hormones, antiinfectives and analgesics for systemic use, antineoplastic drugs and drugs for respiratory diseases

Table 4 Frequency of potentially severe interactions for patients with cardiovascular diseases treated with warfarin*

Drug Interaction Source	Number of potential severe warfarin interactions by patient						
	Absence	Presence					
		1	2	3	4	5	6
Drug Interaction Facts, n (%)	19 (6.8)	56 (20.0)	90 (32.1)	69 (24.6)	37 (13.2)	8 (2.9)	1 (0.4)
Drug Interactions: Analysis and Management, n (%)	184 (65.7)	95 (33.9)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
DRUG-REAX, n (%)	99 (35.3)	128 (45.7)	50 (17.9)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
WHO Model Formulary, n (%)	107 (38.2)	111 (39.6)	49 (17.5)	11 (3.9)	1 (0.4)	1 (0.4)	0 (0.0)

* n=280

Figure 2 Occurrence of potentially severe drug interactions with warfarin according to four drug information sources

Drug	Mechanism of action*	Influence on anticoagulant effect†	*Drug Interaction Facts*	*Drug Interactions: Analysis and Management*	DRUG-REAX	WHO Model Formulary
acetylsalicylic acid	PK/PD	↑	■	■	■	■
allopurinol	PK	↑	■			
amiodarone	PK/PD	↑	■		■	
amitriptyline	PK	↑				■
atazanavir	PK	↑	■			
atenolol	NE	unknown	■			
azathioprine	PK	↓				■
azithromycin	PK	↑	■	■		■
carbamazepine	PK	↓				■
carvedilol	NE	unknown	■			
citalopram	NE	↑	■			
desogestrel	NE	unknown		■		■
diethylstilbestrol	PD	↓	■			
efavirenz	PK	↑	■			
erythromycin	PK	↑	■			■
fluoxetine	PD	↑	■		■	■
gemfibrozil	PK	↑	■	■		
Ginkgo biloba	PD	↑	■	■	■	
glibenclamide	NE	unknown				■
glimepiride	NE	unknown			■	
glucosamine	PD	↑	■			
hydrochlorothiazide	PK/PD	↓	■			
isoniazid	NE	↑	■	■		
levothyroxine	PK/PD	↑	■			■
lovastatin	PK	↑	■			
medroxyprogesterone	NE	↑ / ↓	■			■
methimazole	PK/PD	↓	■			
metoprolol	NE	unknown	■			
omeprazole	PK	↑	■			
paroxetine	NE	↑	■		■	
phenobarbital	PK	↓		■		■
phenytoin	PK	↓				■
propranolol	PK	↑	■			
ranitidine	PK	↑	■			
rifampicin	PK	↓		■		■
ritonavir	PK	↓	■			■
sertraline	NE	↑	■		■	
simvastatin	PK	↑	■		■	■
sotalol	NE	unknown	■			
sulfadiazine	NE	↑				■
sulfasalazine	NE	↑	■			
trimethoprim-sulfamethoxazole	PK/PD	↑ / ↓	■		■	■

* PD: Pharmacodynamics; PK: Pharmacokinetics; NE: not established; † ↓: decrease; ↑: increase

Table 5 Association between potentially severe warfarin interactions and *Trypanosoma cruzi* infection, according to four sources of drug information

Presence of severe warfarin interaction	Total	*Trypanosoma cruzi* infection		*p*-Value*
		Yes (n = 84)	No (n = 196)	
Drug Interaction Facts, n (%)	261 (93.2)	75 (89.3)	186 (94.9)	0.087
Drug Interactions: Analysis and Management , n (%)	96 (34.3)	8 (9.5)	88 (44.9)	<0.001
DRUG-REAX, n (%)	181 (64.6)	46 (54.8)	135 (68.9)	0.024
WHO Model Formulary, n (%)	173 (61.8)	32 (38.1)	141 (71.9)	<0.001

*Pearson chi-square tests

Table 6 Association between potentially severe warfarin interactions and history of bleeding, according to four sources of drug information

Presence of severe warfarin interaction	Total	History of bleeding		*p*-Value*
		Yes (n = 195)	No (n=85)	
Drug Interaction Facts, n (%)	261 (93.2)	187 (95.9)	74 (87.1)	0.007
Drug Interactions: Analysis and Management, n (%)	96 (34.3)	67 (34.4)	29 (34.1)	0.969
DRUG-REAX, n (%)	181 (64.6)	133 (68.2)	48 (56.5)	0.059
WHO Model Formulary, n (%)	173 (61.8)	127 (65.1)	46 (54.1)	0.081

*Pearson chi-square tests

5 CONSIDERAÇÕES FINAIS

No presente estudo, foram encontradas discrepâncias significativas na qualidade e quantidade das informações sobre interações da varfarina disponíveis em duas referências bibliográficas (*Drug Interaction Facts* e *Drug Interactions: Analysis and Management*), uma base de dados (DRUG-REAX) e no formulário da OMS, bem como na bula de uma das marcas de varfarina comumente utilizada no Brasil (Marevan®). A concordância global entre as fontes foi muito baixa, sendo a bula do fabricante a fonte de informação mais incompleta. Observou-se falta de padronização nos termos utilizados, nos critérios de classificação de gravidade e falhas na identificação do nível de evidência científica que fundamenta as interações.

A elaboração das listas de informação sobre medicamentos sugere, ainda, falta de padronização nos critérios de seleção dos trabalhos científicos que evidenciam as interações medicamentosas. Diferenças no processo de atualização das fontes podem influenciar a incorporação de novas informações. Os livros (DIF e DIAM) tendem a incorporar mais lentamente novos conhecimentos, enquanto a base de dados (DRUG-REAX) pode apresentar maior frequência e agilidade na atualização *online* das informações. A elaboração da lista da OMS conta, ainda, com a colaboração de uma equipe de especialistas para auxiliar na seleção e interpretação das evidências científicas. Esses fatores podem contribuir para as discrepâncias observadas entre os compêndios.

Em relação à bula do Marevan®, há necessidade de revisão na lista de interações disponível, citando, de forma mais detalhada, as interações potenciais da varfarina com medicamentos, alimentos, suplementos dietéticos, fitoterápicos, álcool e tabaco. Ressalta-se o papel importante da Agência Nacional de Vigilância Sanitária (Anvisa) na definição de padrões mínimos para elaboração das bulas brasileiras e avaliação da qualidade de suas informações, já que essa é uma fonte de consulta rápida frequentemente utilizada pelos profissionais de saúde. A adoção do Formulário Terapêutico Nacional como fonte alternativa de consulta, sendo esse um documento nacional elaborado por comissão técnica e multidisciplinar e baseado em evidências científicas, poderá contribuir para a obtenção de informação de melhor qualidade do que as bulas[1].

Sobre a investigação da frequência de interações potencialmente graves da varfarina em pacientes cardiopatas, utilizando de forma comparativa quatro referências internacionalmente reconhecidas (*Drug Interaction Facts, Drug Interactions: Analysis and Management,* DRUG-REAX e formulário da OMS), observou-se que as

discrepâncias teóricas se estendem ao contexto da prática assistencial. A discordância na lista de interações e as divergências na classificação de gravidade levaram a uma grande variabilidade no tipo de substâncias envolvidas e na frequência de interações graves, de acordo com a fonte consultada.

A comparação das interações graves da varfarina entre pacientes chagásicos e não chagásicos também evidenciou variações entre as fontes de informações, cujas discrepâncias apresentaram maior amplitude nos chagásicos em relação aos não chagásicos. Considerando a importância epidemiológica da doença de Chagas em nosso meio e a utilidade potencial da varfarina para prevenção de eventos cardioembólicos, destaca-se a relevância da avaliação das interações nos chagásicos de forma a determinar o comportamento desse grupo em relação aos não chagásicos e ampliar os conhecimentos sobre a farmacoterapia empregada na doença de Chagas.

Sobre as interações medicamentosas, não existe critério para hierarquização das fontes de informação e padronização de recomendações clínicas para o manejo dos eventos adversos relacionados. As consequências mais preocupantes das variações na identificação das interações graves da varfarina, de acordo com o método utilizado, estariam relacionadas com a heterogeneidade de condutas na prática assistencial e possíveis efeitos clínicos negativos para o paciente.

A vigilância das interações medicamentosas permanece um desafio na prática clínica, especialmente no cuidado ao paciente cardiopata, tendo em vista a complexidade da farmacoterapia, o efeito variável das comorbidades sobre a manifestação clínica das interações, as modificações constantes na prescrição médica, a utilização de medicamentos sem prescrição médica e o dinamismo da introdução de novos fármacos no mercado, os quais ainda não apresentam seu perfil de interações caracterizado. Nesse contexto, destaca-se a relevância das clínicas de anticoagulação na assistência aos pacientes em uso de varfarina, a necessidade de aprimoramento dos conhecimentos sobre terapêutica e a importância da atuação da equipe multidisciplinar que pode incluir, além do médico, outros profissionais de saúde, tais como farmacêuticos e enfermeiros, contribuindo para o adequado manejo dos pacientes. Esses elementos, em conjunto, podem ter papel importante na promoção da segurança do paciente e para melhoria da qualidade assistencial, o que é atual objeto de investigação do grupo de pesquisadores envolvidos no projeto que aborda a avaliação do impacto da implantação da CA do Hospital das Clínicas da UFMG.

Na atualidade, há esforços na busca de novos fármacos com eficácia comparável ou superior aos AO derivados cumarínicos, especialmente para tratamento de pacientes portadores de fibrilação atrial. Busca-se nesses novos agentes, maior segurança relacionada com melhor dose-resposta sem a necessidade de monitorização constante, além de menor incidência de reações adversas graves como, por exemplo, sangramento intracraniano[2]. Resultados satisfatórios têm sido apontados para fármacos com propriedades farmacocinéticas e farmacodinâmicas diferentes dos antagonistas da vitamina K, tais como a dabigatrana, um potente inibidor competitivo da trombina[3], e os inibidores diretos do fator Xa, apixaban[4] e rivaroxaban[5]. Embora tais opções já tenham sido aprovadas pela Anvisa para comercialização no Brasil, seu custo elevado é fator que limita o acesso da maioria dos pacientes com indicação de anticoagulação oral a esses agentes. É possível que nos próximos anos, co-existam duas realidades nas quais se poderá observar pacientes em uso de AO derivados cumarínicos e pacientes já em tratamento com os novos AO.

A realização do presente estudo traz perspectivas para um melhor entendimento sobre as interações da varfarina e aprimoramento do cuidado ao paciente em tratamento com AO. A avaliação do impacto da implantação da CA voltada para o atendimento aos cardiopatas no Hospital das Clínicas da UFMG encontra-se em andamento e está sendo realizada por meio da análise do controle da anticoagulação e da incidência de complicações apresentados pelos pacientes em estudo. Futuramente, há perspectivas de realização de um estudo prospectivo, objetivando traçar o perfil de risco da população atendida pelo serviço e derivar um modelo de predição e estratificação de risco para complicação hemorrágicas e tromboembólicas decorrentes do tratamento anticoagulante oral. A validação desse modelo preditivo ajustado para a população brasileira possibilitaria seu uso em nosso meio, individualizando o tratamento e melhorando a assistência oferecida aos pacientes.

6 REFERÊNCIAS

(1) Brasil. Formulário Terapêutico Nacional 2010, Rename 2010, Brasília: Ministério da Saúde. 1-1135. 2010.

(2) Mega JL. A new era for anticoagulation in atrial fibrillation. *N Engl J Med* 2011;365:1052-1054.

(3) Connolly SJ, Ezekowitz MD, Yusuf S et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-1151.

(4) Granger CB, Alexander JH, McMurray JJ et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-992.

(5) Patel MR, Mahaffey KW, Garg J et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-891.

ANEXO A

Aprovação COEP 2009 (2208x2736x16M jpeg)

UNIVERSIDADE FEDERAL DE MINAS GERAIS
COMITÊ DE ÉTICA EM PESQUISA - COEP

Parecer nº. ETIC 376/09

Interessado(a): Prof. Antonio Luiz Pinho Ribeiro
Departamento de Clínica Médica
Faculdade de Medicina - UFMG

DECISÃO

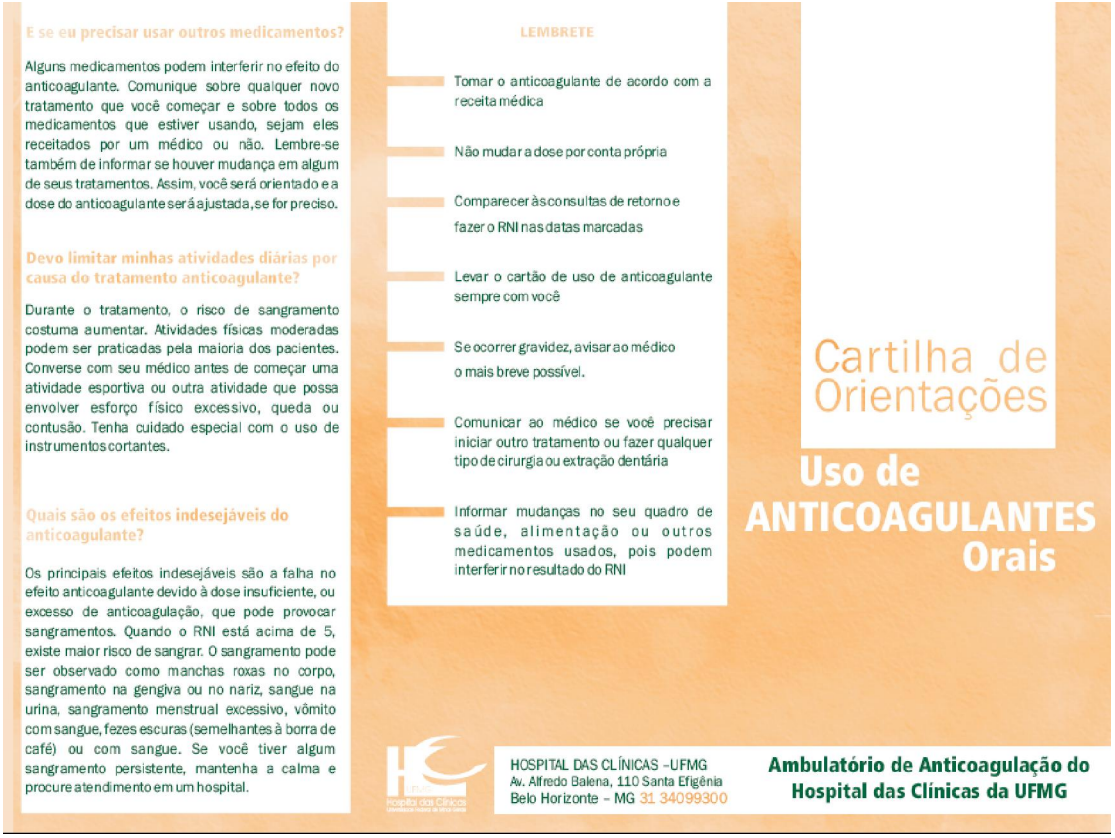
O Comitê de Ética em Pesquisa da UFMG – COEP aprovou, no dia 02 de setembro de 2009, o projeto de pesquisa intitulado **"Avaliação do impacto da implantação de clínica de anticoagulação na assistência a pacientes chagásicos e não-chagásicos atendidos no Hospital das Clínicas da UFMG"** bem como o Termo de Consentimento Livre e Esclarecido.

O relatório final ou parcial deverá ser encaminhado ao COEP um ano após o início do projeto.

Profa. Maria Teresa Marques Amaral
Coordenadora do COEP-UFMG

APÊNDICES

APÊNDICE A



E se eu precisar usar outros medicamentos?

Alguns medicamentos podem interferir no efeito do anticoagulante. Comunique sobre qualquer novo tratamento que você começar e sobre todos os medicamentos que estiver usando, sejam eles receitados por um médico ou não. Lembre-se também de informar se houver mudança em algum de seus tratamentos. Assim, você será orientado e a dose do anticoagulante será ajustada, se for preciso.

Devo limitar minhas atividades diárias por causa do tratamento anticoagulante?

Durante o tratamento, o risco de sangramento costuma aumentar. Atividades físicas moderadas podem ser praticadas pela maioria dos pacientes. Converse com seu médico antes de começar uma atividade esportiva ou outra atividade que possa envolver esforço físico excessivo, queda ou contusão. Tenha cuidado especial com o uso de instrumentos cortantes.

Quais são os efeitos indesejáveis do anticoagulante?

Os principais efeitos indesejáveis são a falha no efeito anticoagulante devido à dose insuficiente, ou excesso de anticoagulação, que pode provocar sangramentos. Quando o RNI está acima de 5, existe maior risco de sangrar. O sangramento pode ser observado como manchas roxas no corpo, sangramento na gengiva ou no nariz, sangue na urina, sangramento menstrual excessivo, vômito com sangue, fezes escuras (semelhantes à borra de café) ou com sangue. Se você tiver algum sangramento persistente, mantenha a calma e procure atendimento em um hospital.

LEMBRETE

- Tomar o anticoagulante de acordo com a receita médica
- Não mudar a dose por conta própria
- Comparecer às consultas de retorno e fazer o RNI nas datas marcadas
- Levar o cartão de uso de anticoagulante sempre com você
- Se ocorrer gravidez, avisar ao médico o mais breve possível.
- Comunicar ao médico se você precisar iniciar outro tratamento ou fazer qualquer tipo de cirurgia ou extração dentária
- Informar mudanças no seu quadro de saúde, alimentação ou outros medicamentos usados, pois podem interferir no resultado do RNI

Cartilha de Orientações

Uso de ANTICOAGULANTES Orais

HOSPITAL DAS CLÍNICAS - UFMG
Av. Alfredo Balena, 110 Santa Efigênia
Belo Horizonte – MG 31 34099300

Ambulatório de Anticoagulação do Hospital das Clínicas da UFMG

APÊNDICE B

USO ANTICOAGULANTE

MANTENHA ESSE CARTÃO SEMPRE COM VOCÊ

Ambulatório de Anticoagulação do Hospital das Clínicas da UFMG

Av Alfredo Balena nº110 (Anexo Borges da Costa) (31) 3409-9207
- Santa Efigênia - Belo Horizonte - Minas Gerais (31) 3409-9237

Nome do Médico:

Este cartão contém informações sobre o tratamento com anticoagulante. Elas serão importantes em caso de emergências ou para informar os profissionais de saúde antes que você inicie qualquer outro tratamento.

DADOS PESSOAIS

MANTENHA ESSE CARTÃO SEMPRE COM VOCÊ

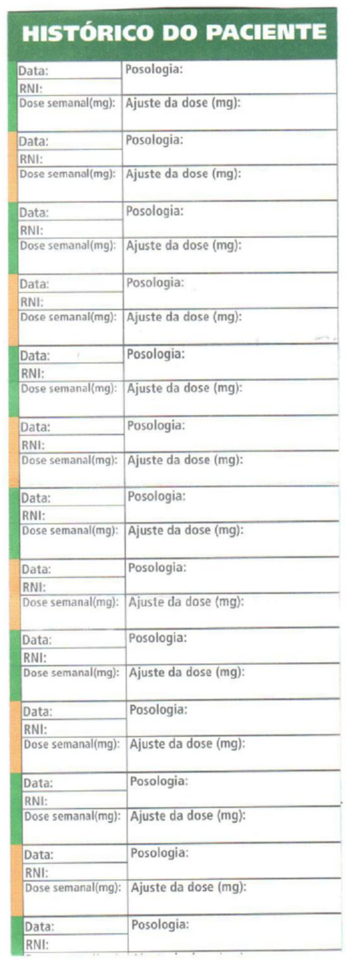
Nome do paciente:

Endereço:

Telefone residencial: Telefone comercial:

Telefone celular:

Em caso de dúvidas, converse com o profissional de saúde do Ambulatório de Anticoagulação do HC/UFMG



HISTÓRICO DO PACIENTE

Data: RNI:	Posologia:
Dose semanal(mg):	Ajuste da dose (mg):
Data: RNI:	Posologia:
Dose semanal(mg):	Ajuste da dose (mg):
Data: RNI:	Posologia:
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Dose semanal(mg):	Ajuste da dose (mg):
Data: RNI:	Posologia:
Dose semanal(mg):	Ajuste da dose (mg):
Data: RNI:	Posologia:

APÊNDICE C

CARTA DE ESCLARECIMENTO AOS PACIENTES

Universidade Federal de Minas Gerais – Hospital das Clínicas

Algumas pessoas com doenças que aumentam a coagulação do sangue precisam usar remédio anticoagulante regularmente para evitar trombose e derrame. O excesso de efeito desse remédio pode causar sangramento. Por isso, o uso do anticoagulante precisa ser acompanhado por um exame chamado RNI (Relação Normalizada Internacional) que ajuda na escolha da dose certa.

Estamos realizando uma pesquisa para avaliar a implantação de um novo serviço de acompanhamento de pacientes que usam varfarina (Marevan®) que é um remédio anticoagulante. Esse novo serviço será comparado com o serviço atualmente oferecido pelo Hospital das Clínicas da UFMG. O novo serviço irá centralizar e padronizar os procedimentos de acompanhamento e orientação dos pacientes.

Gostaríamos de convidá-lo para participar dessa pesquisa que terá a duração de um ano. Nos primeiros seis meses, você poderá receber o acompanhamento feito pelo serviço disponível atualmente no hospital ou o acompanhamento pelo novo serviço de anticoagulação. Nos últimos seis meses, você receberá o atendimento pelo novo serviço.

Se você concordar em participar da pesquisa, seu prontuário será revisado para procurarmos informações sobre sua doença e os resultados de RNI. Quando você vier fazer sua consulta de rotina, precisaremos entrevistá-lo durante cerca de 20 minutos. A entrevista será uma vez por mês se o tratamento anticoagulante estiver controlado, sendo no mínimo 12 entrevistas durante a pesquisa. Caso o RNI esteja alterado, as consultas serão mais frequentes e as entrevistas acontecerão mais vezes por mês no dia que você vier consultar. O atendimento será feito no Hospital das Clínicas da UFMG. Se necessário, serão fornecidos atestados de presença para justificar ausência no trabalho ou na escola.

Este estudo poderá contribuir para que seu tratamento anticoagulante funcione melhor e seja mais seguro. Além disso, sua participação poderá contribuir para que possamos melhorar a assistência aos pacientes que usam anticoagulantes e que são atendidos nos ambulatórios do Hospital das Clínicas da UFMG.

Os registros de sua participação neste estudo serão mantidos confidenciais. No entanto, os pesquisadores e, algumas vezes, o Comitê de Ética em Pesquisa da UFMG, poderão ter acesso aos dados. Os resultados desse estudo serão publicados e/ou apresentados em encontros científicos, sendo que, em qualquer publicação, seu nome não será revelado.

Sua participação neste estudo é voluntária e sua recusa em participar dele, ou seu desligamento, não envolverá penalidade ou perda de benefícios aos quais você tem direito. Você poderá desistir de participar em qualquer momento da pesquisa.

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Universidade Federal de Minas Gerais – Hospital das Clínicas

Acredito ter sido suficientemente informado(a) a respeito das informações que li ou que foram lidas para mim, explicando a respeito do estudo sobre "Avaliação do Impacto da Implantação de Clínica de Anticoagulação na Assistência a Pacientes Chagásicos e Não-Chagásicos Atendidos no Hospital das Clínicas da UFMG".

Eu conversei com a farmacêutica Maria Auxiliadora Parreiras Martins sobre minha decisão em participar desse estudo. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, seus desconfortos, as garantias de confidencialidade e de esclarecimentos permanentes. Ficou claro também que tenho garantia do acesso ao meu tratamento. Concordo voluntariamente em participar deste estudo e poderei retirar o meu consentimento a qualquer momento, sem prejuízo ou perda de qualquer benefício que eu possa ter adquirido, ou do meu atendimento neste serviço.

Eu, _____, abaixo assinado, RG-HC/UFMG_____, dou meu consentimento em participar do estudo sobre "Avaliação do Impacto da Implantação de Clínica de Anticoagulação na Assistência a Pacientes Chagásicos e Não-Chagásicos Atendidos no Hospital das Clínicas da UFMG", após ser informado(a) sobre a pesquisa, ter entendido todos os procedimentos e tirado todas as minhas dúvidas sobre a carta de informação.

_____
Paciente

_____
Testemunha

_____
Pesquisador

Belo Horizonte, _____de _____ de 20_____.

Durante o estudo, caso você tenha alguma dúvida a respeito de seus direitos como participante da pesquisa, ou apresentar qualquer problema médico, você poderá entrar em contato conosco:
Universidade Federal de Minas Gerais (UFMG), Faculdade de Medicina, Departamento de Clínica Médica. Endereço: Av. Alfredo Balena, 190, B. Santa Efigênia, Belo Horizonte-MG CEP 30130-100.
(31) 9643-8625 (Maria Auxiliadora) / (31) 3409-9379 (Dr. Antônio)
(31) 9977-6773 (Dr. Manoel) / (31) 9831-0004 (Dr. Vandack)
(31) 9611-6427 (Dra. Cibele)

Se preferir, você pode entrar em contato com o Comitê de Ética em Pesquisa da UFMG:
Endereço: Av. Antônio Carlos, 6627, Unidade Administrativa II – 2º. Andar – sala 2005, Campus Pampulha, Belo Horizonte, MG – Brasil, CEP 31270-901.
Telefone: (31) 3409-4592

APÊNDICE D

PROTOCOLO DE PESQUISA – Entrevista

IDENTIFICAÇÃO
O significado das abreviaturas é: NA = não se aplica; NS = não sabe; SI=sem informação.

1- Nome: _____

2- Número de registro: __ __ __ __ __ __ 3- Código na pesquisa: __ __ __ __ __

4- Data de entrada no estudo: __ __ / __ __ / __ __ __ __ 5- Data de nascimento: __ __ / __ __ / __ __ __ __

6- Sexo: (1) Feminino (2) Masculino

7- Cor da pele (auto-declarada): (1) Amarela (2) Branca (3) Indígena (4) Parda (5) Preta (9) NS

8- Estado civil:
(1) Solteiro(a)
(2) Casado(a) / União estável (convive maritalmente)
(3) Separado(a) / Divorciado(a)
(4) Viúvo(a)
(9) NS

9- Profissão: _____

10- Nome da mãe: _____

11- Endereço atual:
Rua/Avenida:_____
Número: __ __ __ __ __ Complemento: __ __ __ __ Bairro:_____
Cidade: _____ Estado: __ __ CEP: __ __ __ __ __ - __ __ __

12- Número de pessoas residentes no domicílio: __ __

13- Telefone residencial: (__ __ __) __ __ __ __ - __ __ __ __ Telefone celular: __ __ __ __ - __ __ __ __

14- E-mail: _____

15- Outro contato: (__ __ __) __ __ __ __ - __ __ __ __ Telefone celular: __ __ __ __ - __ __ __ __
Nome: _____ Vínculo:_____
Rua/Avenida:_____
Número: __ __ __ __ __ Complemento: __ __ __ __ Bairro:_____
Cidade: _____ Estado: __ __ CEP: __ __ __ __ __ - __ __ __

16- Outro contato: (__ __ __) __ __ __ __ - __ __ __ __ Telefone celular: __ __ __ __ - __ __ __ __
Nome: _____ Vínculo:_____
Rua/Avenida:_____
Número: __ __ __ __ __ Complemento: __ __ __ __ Bairro:_____
Cidade: _____ Estado: __ __ CEP: __ __ __ __ __ - __ __ __

17- Grau de escolaridade:
(0) Nunca estudou
(1) Ensino fundamental incompleto
(2) Ensino fundamental completo
(3) Ensino médio incompleto
(4) Ensino médio completo
(5) Graduação incompleta
(6) Graduação completa
(7) Pós-Graduação incompleta
(8) Pós-Graduação completa
(9) SI

18- Renda familiar: R$_____

Responsável pelo registro de dados:_____ (nome legível) **Data: ___ / ___ / ___**

Código na pesquisa: ___ ___ ___ ___ ___

PROTOCOLO DE PESQUISA – Entrevista

As questões numeradas de 19 a 53 referem-se ao uso de medicamentos, histórico de doenças e hábitos de vida do paciente.

USO DE MEDICAMENTOS

O significado das abreviaturas é: NA = não se aplica; NS = não sabe; SI=sem informação.

19- Quando você iniciou o tratamento com varfarina? __ __ / __ __ __ __
Mês Ano

20- Onde você consegue o medicamento para o tratamento?
(1) Posto de saúde
(2) Aquisição em farmácia/drogaria
(3) Doação
(4) Outra origem. Especificar: _____

21- Qual marca de varfarina você usa?
(verificar a prescrição médica; mostrar o recordatório nas questões 21 a 23)
(1) Coumadin®
(2) varfarina sódica (medicamento genérico)
(3) Marevan®
(4) Warfarin®
(5) Outro. Especificar: _____
(8) NS

22- Você já trocou a marca da varfarina? (1) Não (2) Sim (8) NS
Em caso negativo, ir à questão 24.

23- Quantas marcas já foram usadas? (1) 2 (2) 3 (3) 4 (4) 5 (7) NA (8) NS

24- Você já deixou de tomar o medicamento alguma vez por dificuldade de comprá-lo ou consegui-lo no posto de saúde? (1) Não (2) Sim (8) NS

25- Seu médico já receitou o comprimido de varfarina partido? (1) Não (2) Sim (8) NS
Em caso negativo, ir à questão 28.

26- Em quantas partes, você já precisou partir o comprimido? (1) 2 (2) 4 (3) 8 (8) NS
Outro. Especificar: _____

27- O que você usa para partir o comprimido?
(1) Boca / dentes
(2) Faca
(3) Mão
(4) Partidor de comprimido
(5) Outro. Especificar: _____

28- Você faz o exame de sangue RNI sempre no mesmo laboratório? (1) Não (2) Sim (8) NS

29- Você faz o exame de sangue RNI no laboratório do HC/UFMG? (1) Não (2) Sim (8) NS

Responsável pelo registro de dados:_____ **(nome legível)** **Data:** ___ / ___ / ___

Código na pesquisa: ___ ___ ___ ___ ___

PROTOCOLO DE PESQUISA – Entrevista

USO DE MEDICAMENTOS (continuação)
O significado das abreviaturas é: NA = não se aplica; NS = não sabe; SI=sem informação.

30- Você está usando algum medicamento, além da varfarina? (1) Não (2) Sim (8) NS
Em caso afirmativo, preencher o quadro abaixo:

Nome comercial	Princípio ativo	Posologia	Via de administração	Prescrição médica	Padrão de uso
1-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
2-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
3-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
4-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
5-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
6-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
7-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
8-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
9-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico
10-				(1) Não (2) Sim	(1) Contínuo (2) Esporádico

31- Total de medicamentos usados de modo contínuo, incluindo a varfarina: _____

HISTÓRICO DE DOENÇAS

Quais doenças você tem ou já teve?
Assinalar as doenças mencionadas pelo paciente:

32- Angina ou infarto	(1) Não	(2) Sim	(8) NS
33- Arritmia	(1) Não	(2) Sim	(8) NS
34- Câncer	(1) Não	(2) Sim	(8) NS
35- Cirrose	(1) Não	(2) Sim	(8) NS
36- Colesterol/triglicérides alto	(1) Não	(2) Sim	(8) NS
37- Derrame	(1) Não	(2) Sim	(8) NS
38-Doença de Chagas	(1) Não	(2) Sim	(8) NS
39-Doença psiquiátrica	(1) Não	(2) Sim	(8) NS
40-Diabetes	(1) Não	(2) Sim	(8) NS
41-Embolia pulmonar	(1) Não	(2) Sim	(8) NS
42-Insuficiência cardíaca	(1) Não	(2) Sim	(8) NS
43-Insuficiência renal	(1) Não	(2) Sim	(8) NS
44-Pressão alta	(1) Não	(2) Sim	(8) NS
45-Problema na tireóide	(1) Não	(2) Sim	(8) NS
46-Trombose	(1) Não	(2) Sim	(8) NS
47-Outra(s)	(1) Não	(2) Sim	

Especificar:_____

HÁBITOS DE VIDA

HÁBITOS ALIMENTARES
48- Você come verduras, pelo menos três vezes por semana? (1) Não (2) Sim (8) NS
(Exemplificar: couve, espinafre, mostarda, brócolis, alface)

49- Você toma chá, pelo menos três vezes por semana? (1) Não (2) Sim (8) NS
(Exemplificar: chá preto, hortelã, boldo, chá verde, "sete folhas")

Responsável pelo registro de dados:_____ (nome legível) **Data: ___ / ___ / ___**

Código na pesquisa: ___ ___ ___ ___ ___

PROTOCOLO DE PESQUISA – Entrevista/Exames

HÁBITOS DE VIDA (continuação)
O significado das abreviaturas é: NA = não se aplica; NS = não sabe; SI=sem informação.

ETILISMO

50- Você costuma, ou costumava, beber diariamente alguma bebida alcoólica? (1) Não (2) Sim (8) NS
Em caso negativo, ir à questão 53.

51- Você já teve algum problema de saúde por causa do uso de bebida alcoólica? (1) Não (2) Sim (8) NS

52- Qual a quantidade ingerida de bebida alcoólica por dia? (7) NA
Cerveja: __ __ latas/dia (1360mL ~ 4 latas/dia ou ~ 2 garrafas)
Vinho: __ __ copos/dia (568mL ~ 5 taças/dia)
Destilado: __ __ doses/dia (172mL ~ 3 doses/dia)
_____:__ __ doses/dia

TABAGISMO

53- Você fumou no último mês? (quantidade ≥ 1 cigarro) (1) Não (2) Sim (8) NS
(Considerar cigarro, charuto, cachimbo ou o ato de mascar tabaco ou administração de nicotina por adesivo transdérmico ou goma de mascar)

HISTÓRICO DE SANGRAMENTO

54- Depois do início do tratamento com varfarina, você já teve algum tipo de sangramento? (1) Não (2) Sim (8) NS
Em caso negativo, ir à questão 66.

Tipo de sangramento:

55- anemia crônica	(1) Não	(2) Sim
56- epistaxe	(1) Não	(2) Sim
57- hemartrose	(1) Não	(2) Sim
58- hematoma	(1) Não	(2) Sim
59- hematêmese	(1) Não	(2) Sim
60- hematúria	(1) Não	(2) Sim
61- hemoptise	(1) Não	(2) Sim
62- menstruação aumentada	(1) Não	(2) Sim
63- sangramento gastrintestinal	(1) Não	(2) Sim
64- sangramento retal	(1) Não	(2) Sim

65- Outro. Especificar: _____

EXAME FÍSICO

66- Peso: __ __ __kg 67- Altura: __, __ __m 68- IMC=__ __, __

PRESSÃO ARTERIAL

69- Frequência cardíaca: __ __batimentos/minuto

70- Primeira aferição (paciente sentado, em repouso): __ __ __ / __ __ __ mmHg

71- Paciente normotenso(a)? (1) Não (2) Sim (9) SI
Considerar hipertensão quando pressão arterial ≥ 140/90mmHg.
Em caso de alteração, realizar outra aferição na próxima consulta.

72- Segunda aferição: __ __ __ / __ __ __ mmHg (7) NA

73- Se paciente em uso de anti-hipertensivo, a pressão está controlada? (1) Não (2) Sim (7) NA

Responsável pelo registro de dados:_____ (nome legível) **Data: ___ / ___ / ___**

Código na pesquisa: ___ ___ ___ ___ ___

PROTOCOLO DE PESQUISA – Exames

EXAMES LABORATORIAIS

VR = Valores de referência adotados para os exames realizados no laboratório de Análises Clínicas do Hospital das Clínicas da UFMG.
O significado das abreviaturas é: NA = não se aplica; NS = não sabe; SI=sem informação.

SOROLOGIA

74- Sorologia doença Chagas: (1) Não realizado (2) Realizado Data: __ __ / __ __ / __ __ __ __

75- Estado sorológico doença Chagas: (1) Negativo (2) Positiva

76- HEMOGRAMA (1) Não realizado (2) Realizado Data: __ __ / __ __ / __ __ __ __
77- Hemácias __ __ __ __ __ __ __/mm^3 (VR - Homem: 4.300.000-5.700.000hm/mm^3; Mulher: 3.800.000-5.100.000hm/mm^3)
78- Hemoglobina __ __, __ g/dL (VR - Homem: 13,5-17,5g/dL; Mulher: 12-16g/dL)
79- Hematócrito __ __, __% (VR - Homem: 39-49%; Mulher: 35-45%)
80- Contagem plaquetas __ __ __ __ __ __/mm^3 (VR – 140.000-450.000pq/mm^3)
81- Leucócitos – global (1) Normal (2) Alterado (VR – 3.500-10.500/mm^3)
Caso alterado, especificar:_____

82- BIOQUÍMICA (1) Não realizado (2) Realizado Data: __ __ / __ __ / __ __ __ __
83- Albumina __ __,__ mg/dL (VR – 3,5-5,0g/dL)
84- Creatinina __ __, __ mg/dL (VR - Homem: 0,66-1,25mg/dL; Mulher: 0,52-1,04mg/dL)
85- Uréia __ __ mg/dL (VR - Homem: 19-43mg/dL; Mulher: 15-36mg/dL)
86- AST (TGO) __ __ U/L (VR – 14-46U/L)
87- ALT (TGP) __ __ U/L (VR – 13-69U/L)
88- Relação AST/ALT

Complementação:
Colesterol total e frações:
89- Colesterol HDL __ __ __ __ mg/dL (VR - <40mg/dL-baixo; >60mg/dL -alto)
90- Colesterol VLDL __ __ __ __ mg/dL
91- Colesterol LDL __ __ __ __ mg/dL (VR - <100mg/dL-ótimo; 100-129mg/dL-desejável; 130-159mg/dL-limítrofe; 160-189mg/dL-alto;≥190mg/dL- muito alto)
92- Colesterol Total __ __ __ __ mg/dL (VR - <200mg/dL-ótimo; 200-239mg/dL-limítrofe; >240mg/dL-alto)
93- Triglicérides __ __ __ __ mg/dL(VR-<150mg/dL-ótimo;150-200mg/dL-limítrofe;200-499mg/dL-alto;≥500mg/dL-muito alto)

94- TSH __ __ __ micro UI/mL (VR - 0,47-4,64micro UI/mL)

95- Glicemia __ __ __ mg/dL (1°. exame) Data: __ __ / __ __ / __ __ __ __ (VR – 55-99mg/dL)
(1) Jejum (2) Sem jejum

96- Glicemia normal? (1) Não (2) Sim (9) SI
Caso alterado, realizar outra glicemia

97- Glicemia __ __ __ mg/dL (2º. exame) Data: __ __ / __ __ / __ __ __ __ (VR – 55-99mg/dL)
(1) Jejum (2) Sem jejum (7) NA

Responsável pelo registro de dados:_____ (nome legível) **Data: ___ / ___ / ___**

Código na pesquisa: ___ ___ ___ ___ ___

PROTOCOLO DE PESQUISA – Avaliação Clínica

HISTÓRIA CLÍNICA

98- Sorologia positiva para doença de Chagas: (1) Não (2) Sim

99- RNI-alvo (1) 2,0 a 3,0 (2) 2,5 a 3,5

Indicação da varfarina:

100- Acidente vascular cerebral	(1) Não	(2) Sim
101- Fibrilação atrial crônica	(1) Não	(2) Sim
102- Fratura de quadril	(1) Não	(2) Sim
103- Hipertensão pulmonar	(1) Não	(2) Sim
104- Prótese de joelho	(1) Não	(2) Sim
105- Prótese de quadril	(1) Não	(2) Sim
106- Síndrome antifosfolipídica	(1) Não	(2) Sim
107- Tromboembolismo intracardíaco	(1) Não	(2) Sim
108- Tromboembolismo pulmonar	(1) Não	(2) Sim
109- Tromboembolismo sistêmico	(1) Não	(2) Sim
110- Trombose venosa profunda	(1) Não	(2) Sim
111- Válvula mecânica aórtica	(1) Não	(2) Sim
112- Válvula mecânica mitral	(1) Não	(2) Sim

113-Outra. Especificar:_____

114- Presença de co-morbidades: (1) Não (2) Sim
Em caso negativo, ir à questão 135.

CO-MORBIDADES

115- Anemia	(1) Não	(2) Sim
116- Artrite reumatóide	(1) Não	(2) Sim
117- Artrose/Osteoartrose	(1) Não	(2) Sim
118- Câncer	(1) Não	(2) Sim
119- Diabetes	(1) Não	(2) Sim
120- Dislipidemia	(1) Não	(2) Sim
121- Evento coronariano prévio	(1) Não	(2) Sim
122- Hipertensão arterial sistêmica	(1) Não	(2) Sim
123- Hipotireoidismo	(1) Não	(2) Sim
124- HIV	(1) Não	(2) Sim
125- Insuficiência cardíaca	(1) Não	(2) Sim
126- Insuficiência hepática	(1) Não	(2) Sim
127- Insuficiência renal	(1) Não	(2) Sim
128- Lúpus eritematoso sistêmico	(1) Não	(2) Sim

129-Outra. Especificar:_____

DOENÇAS NEUROPSIQUIÁTRICAS

130- Depressão	(1) Não	(2) Sim
131- Doença de Alzheimer	(1) Não	(2) Sim
132- Doença de Parkinson	(1) Não	(2) Sim
133- Esquizofrenia	(1) Não	(2) Sim

134-Outra. Especificar:_____

135- Risco excessivo de queda: (1) Não (2) Sim
Considerar idade superior a 60 anos, presença de doenças neuropsiquiátricas, limitações físicas ou outro fator predisponente a quedas.

HISTÓRICO DE SANGRAMENTO

136- Sangramento menor (1) Não (2) Sim
Evento que não implicou na realização de exames, encaminhamento ou consulta médica específica para seu tratamento

137- Sangramento maior (1) Não (2) Sim
Sangramento que levou à hospitalização ou atendimento médico específico para seu tratamento ou transfusão sanguínea de, pelo menos, 2U de sangue ou queda da hemoglobina (H: <13g/dL; M: <11,5g/dL)

138- Sangramento com risco de morte (1) Não (2)Sim
Hemorragia intracraniana ou retroperitonial ou que provocou parada cardíaca, intervenção cirúrgica ou angiográfica ou sequela irreversível

Responsável pelo registro de dados:_____ (nome legível) **Data: ___ / ___ / ___**

APÊNDICE E

Classification for the drugs used chronically by patients with cardiovascular diseases*, according to the Anatomical Therapeutic Chemical (ATC) system 1/2

Anatomical classification	Pharmacological subgroup	Chemical denomination
Alimentary tract and metabolism	Antacids	calcium carbonate
	Blood glucose lowering drugs, excl. Insulins	glibenclamide, glimepiride, metformin
	Calcium	vitamin d3 + calcium carbonate
	Drugs for peptic ulcer and gastro-oesophageal reflux disease (gord)	omeprazole, ranitidine
	Intestinal antiinflammatory agents	sulfasalazine
	Insulins and analogues	insulin
	Laxatives	lactulose
Antiinfectives for systemic use	Beta-lactam antibacterials, penicillins	benzylpenicillin
	Direct acting antivirals	atazanavir, efavirenz, lamivudine + zidovudine, ritonavir
	Drugs for treatment of tuberculosis	isoniazid + rifampicin, pyrazinamide
	Macrolides, lincosamides and streptogramins	azithromycin, erythromycin
	Sulfonamides and trimethoprim	sulfadiazine, trimethoprim-sulfamethoxazole
Antineoplastic and immunomodulating agents	Hormone antagonists and related agents	fulvestrant
Antiparasitic products, insecticides and repellents	Antimalarials	chloroquine
Antineoplastic and immunomodulating agents	Immunosuppressants	azathioprine
Blood and blood forming organs	Antithrombotic agents	acetylsalicylic acid, cilostazol
	Iron preparations	ferrous sulfate
	Vitamin b12 and folic acid	folic acid, vitamin b12
Cardiovascular system	Ace inhibitors, plain	captopril, enalapril
	Angiotensin II antagonists, plain	losartan
	Antiadrenergic agents, peripherally acting	doxazosin
	Antiarrhythmics, class i and iii	amiodarone
	Arteriolar smooth muscle, agents acting on	hydralazine
	Beta blocking agents	atenolol, carvedilol, metoprolol, propranolol, sotalol
	Cardiac glycosides	digoxin
	High-ceiling diuretics	furosemide
	Lipid modifying agents, plain	atorvastatin, gemfibrozil, lovastatin, simvastatin
	Low-ceiling diuretics, thiazides	hydrochlorothiazide, hydrochlorothiazide + amiloride
	Potassium-sparing agents	spironolactone
	Selective calcium channel blockers with direct cardiac effects	diltiazem, verapamil
	Selective calcium channel blockers with mainly vascular effects	amlodipine, nifedipine
	Vasodilators used in cardiac diseases	isosorbide dinitrate
Genito urinary system and sex hormones	Drugs used in benign prostatic hypertrophy	finasteride
	Estrogens	diethylstilbestrol
	Hormonal contraceptives for systemic use	desogestrel, medroxyprogesterone
	Other urologicals, incl. Antispasmodics	yohimbine
Musculo-skeletal system	Antigout preparations	allopurinol, colchicine
	Antiinflammatory and antirheumatic products, non-steroids	glucosamine, glucosamine + chondroitin, nimesulide
	Drugs affecting bone structure and mineralization	alendronic acid

* n=280

Classification for the drugs used chronically by patients with cardiovascular diseases*, according to the Anatomical Therapeutic Chemical (ATC) system† 2/2

Anatomical classification	Pharmacological subgroup	Chemical denomination
Nervous system	Antiepileptics	carbamazepine, clonazepam, phenobarbital, phenytoin
	Antidepressants	amitriptyline, citalopram, fluoxetine, nortriptyline, paroxetine, sertraline, trazodone
	Antipsychotics	haloperidol, levomepromazine, risperidone
	Antivertigo preparations	betahistine
	Anxiolytics	alprazolam, bromazepam, clobazam, diazepam
	Opioids	tramadol
	Other analgesics and antipyretics	paracetamol, dipyrone
Respiratory system	Adrenergics, inhalants	fenoterol, formoterol
	Decongestants and other nasal preparations for topical use	budesonide, ipratropium bromide
Systemic hormonal preparations, excl. Sex hormones and insulins	Antithyroid preparations	methimazole
	Corticosteroids for systemic use, plain	prednisone
	Thyroid preparations	levothyroxine sodium
Sensory organs	Antiglaucoma preparations and miotics	brinzolamide, timolol, travoprost, latanoprost

* n=280

† Substances non-defined by ATC classification system: cocomel; *Ginkgo biloba*

APÊNDICE F

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Warfarin drug interactions: a comparative evaluation of the lists provided by five information sources

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Abstract
Purpose Detecting potential drug interactions can lead to early interventions that protect patients from serious drug-related problems. The aim of this study was to evaluate the agreement among the lists of warfarin interactions provided by five information sources.
Methods The lists of warfarin interactions and the corresponding severity ratings and documentation levels presented by the three compendia and by the World Health Organization (WHO) Model Formulary were all compared, and each list was compared to that provided on the package insert of Marevan, a brand of warfarin. The compendia used were: *Drug Interaction Facts*, *Drug Interactions: Analysis and Management* and DRUG–REAX. A kappa coefficient was used to calculate the agreement among the sources.
Results A total of 537 interactions were listed. Only 13 (2.4%) were common to the five sources. The global Fleiss' kappa coefficient was −0.0080, which indicated poor agreement. Eleven warfarin interactions appeared only in the Marevan package insert. Importantly, 243 interactions (45.3% of the total) were deemed significant in at least one compendium. Only two warfarin interactions were reported as critical by all three compendia and by WHO. The most critical interactions cited by the compendia were missing from the package insert.
Conclusions Poor agreement was found among five sources listing warfarin interactions. Potentially severe clinical consequences might occur due to these discrepant recommendations. Finally, the lack of standard terminology and clinical guidance, as well as the possible inaccuracy of severity ratings and documentation might contribute to heterogeneous procedures in clinical practice.

Keywords Warfarin · Drug toxicity · Herb–drug interactions · Food–drug interactions · Drug labeling

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Introduction

Adverse events related to health care are a significant problem worldwide. It has been estimated that approximately 98,000 Americans die annually due to medical incidents [1]. Adverse drug events in particular can be responsible for emergency department visits and hospital admissions, with significant social and economic impact [2]. Drug interactions (DIs) have frequently been identified as an example of predictable and manageable adverse drug events. Co-morbidities and polypharmacy, which are especially prevalent in elderly populations, are associated with higher risks of potential drug interactions [3].

Treatment with warfarin has been proven to be efficacious in preventing and treating thromboembolic events, but its administration is widely known to be associated with common and potentially severe drug–drug and drug–food interaction risks [4–7]. In a prospective study conducted in the UK, DIs accounted for 16.6% of hospitalizations caused by adverse drug reactions, and warfarin, particularly in combination with other drugs, was implicated in most cases of gastrointestinal bleeding [8]. The management of patients under warfarin therapy is challenging due to the drug's narrow therapeutic index, wide variability in dose response, and the need for frequent monitoring of the international normalized ratio (INR) [9, 10].

Warfarin acts by inhibiting the vitamin K conversion cycle in the liver, which hinders the biological activation of the vitamin K-dependent proteins factors II, VII, IX, and X, as well as the activation of anticoagulant proteins C and S. Warfarin is a racemic mixture of two active enantiomers (R- and S- forms) [10]. Its oral bioavailability is high, and nearly 99% of the racemic warfarin circulates bound to plasma proteins [11], with a half-life of 36–42 h [10]. Combining warfarin and other drugs may lead to competitive displacement of serum protein binding, enhancing its hypoprothrombinemic effect [12]. Warfarin isomers are metabolically transformed in the liver by different pathways: the S-isomer is metabolized mainly by the cytochrome P450 2C9 (CYP2C9) and has fivefold the potency of the R-isomer [13]. It has been shown that mutations in the gene coding for CYP2C9 might result in an increase of the warfarin anticoagulant effect [14, 15]. On the other hand, mutations in vitamin K epoxide reductase complex subunit 1 (VKORC1) may induce pharmacodynamic warfarin resistance [15–17]. These genetic polymorphisms not only increase dose and INR variability, but they also amplify the propensity to drug interactions in certain individuals [18]. There may also be ethnic differences interfering in warfarin response [14, 19–24].

Variability in dose response to warfarin may also be attributed to other factors, such as age and body size, estimations of warfarin clearance [15], patient compliance [25], and effects due to interactions with diet and other drugs [7, 10]. The identification of drugs, foods, and dietary supplements with potential harmful interactions would enable early interventions at various levels in the healthcare system aimed at protecting patients from serious drug-related problems. Prescription and non-prescription medications should appear in a patient's drug lists in order to help the healthcare provider make a proper assessment of DIs. However, these lists are often incomplete and erroneous, given the complexity of the use of medications and patients' access to over-the-counter drugs (OTC-drugs) [26], drugs sold over the Internet, and retail prescription programs [27]. For example, the concomitant intake of herbal medicines with the potential for interacting with warfarin, such as Saint John's Wort, is not usually made known to the physician. Even if drug lists were to be complete and comprehensive, clinicians may not have a complete overview of all substances in use that have the potential for warfarin interactions. With respect to drug interaction compendia, several authors have pointed out that there is little concordance in the available lists of DIs and that there are substantial differences in the severity classifications [28–35]. In the study reported here, we sought to compare the list of potential warfarin interactions provided on the package insert of Marevan, the most commonly used warfarin brand in Brazil, with those of three renowned compendia on drug interactions and with the interaction list provided by the World Health Organization (WHO) Model Formulary.

Methods

Selection of drug interactions compendia

Lists of warfarin interactions were identified in the following drug interaction compendia: *Drug Interaction Facts* [36], *Drug Interactions: Analysis and Management* [12], and the Micromedex DRUG–REAX [11]. The selection of these references relates to their renown and their widespread use by healthcare professionals in several countries. The interaction table in the WHO Model Formulary [37], which is regularly peer reviewed and updated, was also included in this analysis.

The lists of warfarin interactions and the corresponding severity ratings and evidence grading reported in these sources were compared. In addition, each of these lists was compared to the list provided on the package insert of Marevan (Farmoquímica, Rio de Janeiro, Brazil). The reason for including the package insert of Marevan in this analysis is its frequent use by healthcare professionals and patients alike as a widely available source of understandable information.

Evaluation of warfarin interactions

To assess the concordance between warfarin interactions identified in the three compendia, in the WHO Model Formulary, and in the Marevan package insert, two authors (MAPM and PPSC) independently reviewed the content of each reference. Any disagreements regarding terms or classifications were discussed until a consensus was reached. All warfarin interactions were listed: drugs (including their classes), foods, herbal products, biological products, such as vaccines and monoclonal antibodies, dietary supplements, tobacco, and ethanol. The precise lists obtained from the five sources were compiled into a descriptive table in Microsoft Excel using the following variables: (1) drug terminology, as

indicated in the reference; (2) the clinical significance severity rating; (3) the level of documentation of the interaction, when available.

Data analysis

The consulted sources were compared in terms of similarities and inconsistencies in the listed substances that affect warfarin action (i.e., drugs and foods) and levels of documentation and classification systems used to rate the severity of these interactions. To assess the concordance among the sources, each of the warfarin interactions was transformed into a binary variable, according to its presence or absence in each individual list. The Fleiss' kappa coefficient [38] was calculated to evaluate the overall concordance, and Cohen's kappa coefficient [39] was used to determine the pair-wise concordance among the lists. The concordance was evaluated according to the following degrees of agreement for kappa coefficients proposed by Landis and Koch [40]: <0 = poor; 0.00–0.20 = slight; 0.21–0.40 = fair; 0.41–0.60 = moderate; 0.61–0.80 = substantial; 0.81–1.00 = almost perfect. Data were analyzed using the Statistical Package for the Social Sciences (SPSS for Windows, ver 18.0; SPSS, Chicago, IL). Information from these sources was also reviewed in terms of the rating system for the severity of interactions and their supporting documentation.

Results

A total of 537 entries were listed. Specifically, there were 272 entries listed in *Drug Interaction Facts*, 159 in *Drug Interactions: Analysis and Management*, 396 in DRUG–REAX, 69 on the Marevan package insert, and 58 in the interaction table of the WHO Model Formulary. A total of 306 entries (57.0%) were present in only one source, 107 (19.9%) were present in two sources, 75 (14.0%) were present in three sources, and 36 (6.7%) were present in four sources. Only 13 (2.4%) entries were common to the five sources. Among these common entries, 11 corresponded to drugs, one corresponded to drug classes, and one was ethanol (Table 1). Eleven warfarin interactions were exclusively listed in the Marevan package insert; these included generic citations, such as hepatotoxic drugs, corticosteroids, anabolic steroids, and broad-spectrum antibiotics, and individual drug names, such as aztreonam, cotrimoxazole, dextropropoxifen, dichloralphenazone, feprazon, phenyramidol, and tolbutamine.

Overall, warfarin-interacting substances were listed as individual drugs, drug classes, and non-drug substances. The terminology adopted was not standardized. For example, thyroid hormones were listed in all sources as a drug class, although *Drug Interaction Facts* also cited specific drugs from this class, such as dextrothyroxine and levothyroxine. In all sources, drugs were the main chemical entity cited as interacting with warfarin. DRUG–REAX reported the highest proportion of interactions with non-drug substances (22.0%). Overall, 15.9% and 12.9% of drug classes were listed on the warfarin product insert and in *Drug Interaction Facts*, respectively. Table 2 summarizes the frequency of entries according to their classification.

Table 1 Warfarin-interacting substances common to the five sources used as reference

Acetaminophen	Fluconazole
Allopurinol	Griseofulvin
Carbamazepine	Metronidazole
Oprofloxacin	Miconazole
Contraceptives	Phenytoin
Erythromycin	Quinidine
Ethanol	

The classification of clinical severity and documentation level showed substantial heterogeneity between the three compendia and the WHO's list, as summarized in Table 3. Likewise, we found significant differences among the lists of substances that potentially interact with warfarin. The same was true for our comparison of the compendia with the package insert. In this context, the global Fleiss' kappa coefficient was −0.0080, indicating poor agreement among the five sources. For the classification of substances, the Fleiss' kappa coefficient was 0.014, −0.074 and −0.123 for drugs, drug classes, and others, respectively. The pair-wise concordance with Cohen's kappa coefficient also showed little concordance among the lists. The highest coefficients were those for *Drug Interaction Facts* versus *Drug Interactions: Analysis and Management* (0.270) and for *Drug Interactions: Analysis and Management* versus the Marevan package insert (0.220), both of which showed a fair agreement, as shown in Table 4.

Among the total number of entries, 243 (45.3%) warfarin interactions were judged as "major" or "contraindicated" or "to be avoided" in at least one of the sources, including the three compendia and the WHO's list. A total of 176 warfarin interactions were cited as potentially harmful by only one source, 53 interactions were coincidently cited by two sources, and 12 by three sources. Only two interactions (with aspirin and metronidazole) were reported as critical in the three compendia and in the WHO's list. Interactions considered to be potentially harmful were those classified as 1 and 4 by *Drug Interaction Facts*, as 1 and 2 by *Drug Interactions:*

Table 2 Frequency of entries according to the classification of various warfarin-interacting substances in the five studied sources of drug interaction information

Drug interaction source	Substance classification, *n* (%)			Total entries
	Drug	Drug class	Other[a]	
Drug Interaction Facts	219 (80.5)	35 (12.9)	18 (6.6)	272
Drug Interactions: Analysis and Management	142 (89.3)	4 (2.5)	13 (8.2)	159
DRUG–REAX	302 (76.3)	7 (1.7)	87 (22.0)	396
Marevan package insert	56 (81.2)	11 (15.9)	2 (2.9)	69
WHO Model Formulary	56 (96.6)	1 (1.7)	1 (1.7)	58

[a] Other = foods, biological products, dietary supplements, tobacco, and ethanol

Analysis and Management, as "major" and "contraindicated" by DRUG–REAX, and as potentially hazardous interaction in the WHO Model Formulary. The absolute frequency of entries according to the clinical significance for each source is shown in Table 5. As depicted in Table 3, the documentation level and severity classification provided by DRUG–REAX appear in independent categories. In this source, clinical evidence was rated as "fair" for most warfarin interactions (48.7%) and as "excellent" in a minority of cases (4.0%).

In several cases, a certain interaction was not mentioned at all in one of the compendia, while being considered as clinically significant in the two others. For example, 57.9% of interactions classified as 1 and 4 by *Drug Interaction Facts* were not referred to in *Drug Interactions: Analysis and Management*. In addition, the clinical significance ratings for some commonly cited interactions varied greatly among the compendia. For example, the warfarin–levofloxacin interaction was rated as "major" by DRUG–REAX, with excellent supporting documentation, while classified as "moderate" by *Drug Interaction Facts* and as "minor" by *Drug Interactions: Analysis and Management*.

Classification of severity and evidence grading for potential DIs was not provided by the manufacturer. According to the Marevan package insert, warfarin interactions may enhance or reduce the anticoagulant effect, but its clinical significance was not included. A total of 54 entries were listed as interactions with an elevated risk for enhancing the anticoagulation effect, 13 interactions were listed as reducing the anticoagulation effect, and two (phenytoin and corticosteroids) interactions were listed for both effects. In addition, the manufacturer omitted a large number of interactions mentioned in the other sources. Comparing the package insert with the lists provided by the compendia and the WHO's list the percentage of harmful interactions omitted by the manufacturer was 94.4% for DRUG–REAX, 86.8% for *Drug Interaction Facts*, 68.8% for the WHO Model Formulary, and 54.5% for *Drug Interactions: Analysis and Management*.

Discussion

Our findings reveal considerable discrepancies between different sources of information on potential warfarin interactions. We observed a lack of standardization in the terminology used, an absence of homogeneous criteria for severity classification, and poor or even absent grading of

Table 3 Specifics on the classification systems for drug interactions present in the five sources of information

Sources on drug interactions	Classification systems
Drug Interaction Facts	Significance rating based on severity and documentation: 1 = major severity (documentation suspected or more); 2 = moderate severity (documentation suspected or more); 3 = minor severity (documentation suspected or more); 4 = major/moderate severity (documentation possible); 5 = minor severity (documentation possible or any severity; documentation unlikely)
Drug Interactions: Analysis and Management	Significance rating based on the recommended clinical management strategy: 1 = avoid combination; 2 = usually avoid combination; 3 = minimize risk; 4 = no action required; 5 = no interaction. The documentation level is not available.
DRUG–REAX	Five severity categories are used to classify DI (contraindicated, major, moderate, minor, and unknown). There are six categories used for the documentation level (excellent, good, fair, poor, unlikely, and unknown).
Marevan package insert	There is no ranking system. The description of warfarin interactions is based on the expected action (reduction or stimulation of the anticoagulation effect)
WHO Model Formulary	The symbol * indicates a potentially hazardous interaction, and the combined administration of the drugs involved should be avoided, or only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

DI, Drug interaction; WHO, World Health Organization

Table 4 Measures of pair-wise concordance of the binary variables for the presence or absence of warfarin interactions among the five sources of information

Sources	*Drug Interaction Facts*	*Drug Interactions: Analysis and Management*	DRUG–REAX	WHO formulary
Marevan package insert	0.074	0.220	0.013	0.170
Drug Interaction Facts	-	0.270	−0.102	0.100
Drug Interactions: Analysis and Management	-	-	0.046	0.129
DRUG–REAX	-	-	-	-0.003

the clinical evidence. Together, these shortcomings make the use of these sources for clinical judgment problematic. Moreover, the information provided by the manufacturer (Marevan) showed only a poor agreement with that provided by three widely used compendia and with the interaction table in the WHO Model Formulary.

Our results are in line with those reported previously [29–31] in which concordance rates of 2.2 and 8.9% were found. Most studies have found that more than 50.0% (range 14.0–71.7%) of entries are present in one source but not in the other sources [28, 29, 31]. Some authors have also calculated the agreement among the different compendia. Abarca et al. [29] calculated the intraclass correlation coefficient to be −0.092, indicating poor agreement. In a study performed by Olvey et al. [34], an evaluation of DI pairs deemed to be critical showed a low level of agreement between DRUG–REAX (updated January, 2009) and *Drug Interactions: Analysis and Management* (updated January, 2007), with a correlation of 0.076. Anthony et al. [33] examined warfarin interactions in three drug information compendia (Clinical Pharmacology, ePocrates, and Micromedex) and a warfarin product label (Coumadin). They found little agreement among the sources, with a global Fleiss kappa coefficient of −0.026, which is consistent with our result (−0.0080). In our study, we showed that these disagreements are still present in the updated versions of renowned compendia. Additionally, we described discrepancies in the clinical severity ratings and calculated the proportions of entries by clinical significance among the compendia. We also included the interaction table provided in the WHO Model Formulary, which represents an international consensus that has been thoroughly reviewed.

There are several reasons for the discrepancies among the sources. First, each compendium adopts different criteria for inclusion of DIs. It is important to keep in mind that not all drugs in a class necessarily interact with the same compounds to the same extent in all individuals, given genetic polymorphisms and the related sensitivity to DIs [15]. In most cases, there is not enough available evidence to include or exclude an individual drug as an example of an entire class. Second, as search terms vary greatly, some warfarin interactions may have been over-

Table 5 Warfarin interactions according to the absolute frequency of entries and clinical significance found in four sources of information on drug interactions

Source	Clinical significance	*n*
Drug Interaction Facts[a]	1	101
	2	60
	3	0
	4	96
	5	15
Drug Interactions: Analysis and Management[a]	1	1
	2	32
	3	64
	4	41
	5	21
DRUG–REAX	Contraindicated	1
	Major	71
	Moderate	322
	Minor	2
	Unknown	0
WHO Model Formulary	Potentially hazardous interaction	48
	Usually without serious consequences	10

[a] See Table 3 "Classification systems" for a description of the rating used by the different sources

looked. Third, the references used to guide the classification of severity ratings do not seem to be homogeneous. It is not clear whether the clinical evidence cited by each compendium is based on an independent review of primary or secondary sources, unpublished reports released by drug companies, product labels, or reports collected by national post-marketing surveillance systems.

The mere number of possible interactions is not a good measure of the quality of the information and is not useful from a practical point of view. The completeness of DI lists may not be compatible to its user-friendliness. In relation to computer-assisted support, over-alerting could make clinicians ignore significant warfarin interactions [41]. DI lists should provide guidance on the clinical relevance of interactions, but the lack of a single "gold standard" or "universal" compendium may be confusing and actually cause wide variations in clinical practice. Given the large number of potential interactions with warfarin, it is almost impossible to decide whether an individual is at danger of DIs. One piece of general advice that may be given is to consult multiple sources of information to search for DIs of clinical significance.

Warfarin treatment is a challenging task in clinical practice. Supra- and subtherapeutic INRs can place patients at increased risk of either bleeding or thromboembolic events. Even patients with a history of a stable INR can present sudden variations in INR values after changes in concomitant medications. Time aspects of DIs may be relevant in terms of determining a suitable time-point for INR monitoring and should consider the risks for displacement of albumin (rapid onset and short term), CYP inhibition (intermediate onset and long-term recovery time), and CYP induction (slow onset and long-term recovery time) [42]. It is also important to consider the strength of the interaction and the pharmacogenetic aspects. Most warfarin interactions can be handled by dose adjustments. Thus, advising clinicians to follow-up INR values within the first 2 weeks after any change in concomitant drug administration, health status, or life styles could be reasonable as a general recommendation.

To the best of our knowledge, this is the first study to evaluate the package insert of Marevan, one of the most commonly used warfarin brands in Brazil. It was surprising to find that a large number of important warfarin interactions were not mentioned at all in the package insert. Some of these (e.g., aspirin) have a high potential for harm. The package insert of Coumadin, a brand commonly used in the USA, shows an extensive list of interactions that is about fourfold longer than the list provided for Marevan. Generic citations of drug classes and the lack of classification of severity and references indicate the low quality of the information supplied with the product. Our findings should alert healthcare professionals that oftentimes the information provided by drug companies should not be used as the sole reference for guiding dose adjustments and determining of INR monitoring intervals. In addition, our study identified an urgent need for improvement in the content of the Marevan package insert, specifically in the list of potential warfarin interactions with drugs, foods, and herbal supplements.

Some limitations of our study should be addressed. Due to the variability in terminology, subtle differences in the classification of drugs were taken into account and were not aggregated in cases where the source was not clear about the substances included in the referred classes. This approach may have led to an overestimation of the total number of interactions. For example, the hepatotoxic drugs interaction warnings on the Marevan package insert did not include specific drug names; thus, these warnings were considered as an individual entry, regardless of whether or not they were cited by another source as individual drugs or drug classes under different terms. Other entries were aggregated because they clearly referred to the same substance. For example, entries related to "ethanol" and "alcohol" were considered one entry (named "ethanol"). Finally, DI compendia are updated frequently as new information is discovered. Thus, this study should be considered valid only for the compendia evaluated and the brand chosen in 2010.

In conclusion, our assessment of the sources of information on DIs shows that poor agreement persists on the lists of warfarin interactions included in the five drug information sources that we evaluated. The clinical impact of poor consistency among the sources is unknown. Severe clinical consequences might occur due to the differing recommendations for the same warfarin interaction. The possible inaccuracy of severity ratings and the lack of standard terminologies may contribute to heterogeneous procedures in clinical practice and may compromise the detection of potentially life-threatening interactions. Sources of information should provide a grading system in the medical advice they offer in terms of the risk and expected strength of DIs. Clear references to specific documentation on DIs and explicit recommendations on how to prevent and manage warfarin interaction-induced adverse reactions are needed to ensure patient safety. An effort to improve the quality of information provided by Marevan is also urgently required to increase the reliability of the instructions given to patients and healthcare professionals.

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