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ANÁLISE ECONÔMICA DE TESTES DIAGNÓSTICOS EM CARDIOPATIA ISQUÊMICA ESTÁVEL SOB A PERSPECTIVA DO SISTEMA ÚNICO DE SAÚDE.

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SUMÁRIO

LISTA DE SIGLAS E ABREVIATURAS

angio-TC: angiotomografia coronária com múltiplos detectores

ATS: avaliação de tecnologia em saúde

Can$: dólares canadenses

CAT: cateterismo cardíaco / angiografia coronariana

DAC: doença arterial coronariana

€: euros

eco-estresse: ecocardiograma de estresse

£: libras esterlinas

NICE: National Institute for Health and Care Excellence

PET: tomografia com emissão de prótons

QALYs: quality adjusted life-years (anos de vida ajustados para qualidade)

RC: Razão de chance

RCEI: Razão de custo-efetividade incremental

RNM-estresse: ressonância nuclear magnética cardíaca de estresse

RR: risco relativo

SPECT: cintilografia de perfusão miocárdica

SUS: sistema único de saúde

US$: dólares americanos

WTP: willingness-to-pay (disposição a pagar)

RESUMO

Introdução e objetivos. O Sistema Único de Saúde (SUS) atualmente disponibiliza ergometria, ecocardiograma de estresse e cintilografia miocárdica como testes não-invasivos para avaliação diagnóstica de doença arterial coronariana (DAC), mas não a angiotomografia computadorizada de coronárias ou a ressonância magnética cardíaca. Esta avaliação econômica avalia estratégias baseadas nos testes atualmente disponíveis, comparando-as entre si, e também com novas potenciais estratégias usando testes atualmente não disponibilizados pelo SUS.

Métodos. Foi desenvolvido um modelo de decisão analítico comparando 11 estratégias de testes diagnósticos para avaliação de pacientes com angina estável possível, com probabilidades baixa, intermediária e alta de DAC. Foi realizada análise do desempenho das estratégias em curto prazo, baseada em árvore de decisão, buscando quantificar o custo por diagnóstico correto. Adicionalmente, realizamos análise do impacto das estratégias no longo prazo, baseada em um modelo de estados transicionais (Markov), quantificando o impacto das estratégias diagnósticas na sobrevida e na qualidade de vida. Todas as análises foram realizadas sob a perspectiva do SUS, e o horizonte temporal, no caso da análise de longo prazo, foi por toda a vida. Foi realizada análise de sensibilidade determinística de todos os parâmetros relevantes, e também análise de sensibilidade probabilística com variação simultânea de todos os parâmetros relevantes.

Resultados. Na análise de curto prazo, observou-se que estratégias baseadas em ergometria como teste inicial tiveram o custo mais baixo, mas geraram um número alto de diagnósticos incorretos. Estratégias baseadas na realização de angiotomografia de

coronárias ou ecocardiograma de estresse mostraram-se as mais atraentes do ponto de vista de custo-efetividade, custando 540 e 576 reais por diagnóstico correto, respectivamente. Na análise de longo prazo, observou-se que a escolha do teste teve um impacto pequeno, mas mensurável na sobrevida ajustada para qualidade. Trocar estratégias baseadas em ergometria por aquelas baseadas em angiotomografia de coronárias aumenta a efetividade, com uma razão de custo-efetividade incremental de 5.800 reais por ano de vida ajustado para qualidade ganho. As estratégias baseadas em ecocardiograma de estresse tiveram desempenho quase idêntico ao das estratégias baseadas em angiotomografia de coronárias. A estratégia baseada na realização de ressonância magnética cardíaca teve alta eficácia diagnóstica, mas o seu custo mais alto resultou em uma razão de custo-efetividade incremental desfavorável, nas análises de curto e longo prazo. As estratégias baseadas em cintilografia miocárdica foram dominadas em todos os cenários, devido ao seu valor de reembolso elevado.

Conclusões. A incorporação da angiotomografia de coronárias ao rol de testes diagnósticos disponíveis no SUS é recomendável, com base nos resultados desta análise econômica. Dentre os testes atualmente disponíveis, o ecocardiograma de estresse se mostrou a opção mais custo-efetiva. A ressonância magnética cardíaca é uma alternativa altamente efetiva, mas sua incorporação ao SUS só se torna atraente do ponto de vista econômico se o seu valor de reembolso se mantiver mais baixo do que a estimativa atual.

1. INTRODUÇÃO

Doenças cardiovasculares estão entre as principais causas de morbimortalidade no Brasil e no mundo (1, 2). Apesar de importantes avanços no tratamento e prevenção da doença aterosclerótica, pacientes com doença arterial coronariana (DAC) estável ainda têm morbidade e mortalidade elevadas (3). Adicionalmente, a ocorrência de sintomas anginosos significativos e persistentes é um problema comum, e traz significativo impacto na qualidade de vida (4-6).

Dada a magnitude do problema, não é surpreendente que os sistemas de saúde invistam valores elevados na investigação diagnóstica de cardiopatia isquêmica. No ano de 2013, o Sistema Único de Saúde (SUS) dispendeu, apenas no âmbito ambulatorial, cerca de 16 milhões de reais com reembolso de ergometrias, e mais de 90 milhões de reais com cintilografia miocárdica de estresse/repouso (7).

Ao longo das últimas décadas, inúmeros estudos descreveram as propriedades diagnósticas desses diferentes métodos para detecção da doença arterial coronariana, sendo estabelecido que acurácia dos mesmos não é perfeita, variando de 60% a próximo de 100%. Nesse cenário, os conceitos clinico-epidemiológicos do Teorema de Bayes norteiam a prática clínica, e a escolha dos métodos deveria seguir os princípios de probabilidades da doença e o desempenho individual de cada método.

No entanto, há pouca organização do sistema de saúde nacional em relação a protocolos de avaliação de pacientes com possível angina estável. A estratégia de investigação, a escolha dos exames complementares, e o momento da sua realização ficam tipicamente a critério do médico que atende o paciente, fazendo com que a preferência individual e a

disponibilidade local sejam os principais fatores considerados na solicitação de um teste provocativo.

Atualmente, estão disponíveis para realização pelo SUS para diagnóstico de cardiopatia isquêmica estável a ergometria, a cintilografia de perfusão miocárdica (SPECT), o ecocardiograma de estresse (eco-estresse), e a cineangiocoronariografia. Métodos mais recentes, como a angiotomografia coronária com múltiplos detectores (angioTC) e a ressonância nuclear magnética cardíaca de estresse (RNM-estresse) ainda não se encontram na tabela de exames disponíveis (1). Há ampla variação do custo desses procedimentos para o SUS e da frequência de sua realização, como mostra a **tabela 1**.

Tabela 1 – Custo dos testes para o SUS e número de exames ambulatoriais realizados em 2013 (7).

Procedimento	**Custo unitário (R$)**	**Exames realizados (2013)**	**Custo total (R$ - 2013)**
Ecocardiograma de estresse	174	18.635	3 milhões
Cintilografia miocárdica (repouso + estresse)	793	114.881	91 milhões
Ergometria	32	500.949	16 milhões
Cinecoronariografia (cateterismo cardíaco)	615	131.412	81 milhões

A avaliação formal da custo-efetividade comparativa dos diferentes testes diagnósticos para cardiopatia isquêmica estável nunca foi realizada para o contexto do sistema público de saúde brasileiro. Essa análise poderia embasar decisões sistemáticas sobre a estratégia a ser abordada em pacientes com suspeita de angina estável, buscando a racionalização dos recursos disponíveis em termos tecnológicos, bem como dos gastos públicos com saúde.

2. REVISÃO DA LITERATURA

2.1. Doença arterial coronariana

A cardiopatia isquêmica é, na maioria dos casos, causada por obstrução ao fluxo de uma ou mais artérias coronarianas por placas ateromatosas, gerando graus variáveis de isquemia e necrose de cardiomiócitos.

Graus menores de obstrução coronariana (até 50 - 70% da luz do vaso) normalmente são bem tolerados, devido à capacidade exibida pelo leito arterial coronariano de variar a resistência e, consequentemente, o fluxo. À medida que progride a obstrução ao fluxo coronariano, a doença aterosclerótica passa a impedir o aumento necessário da perfusão quando há aumento da demanda por fluxo, como acontece durante o esforço ou estresse emocional.

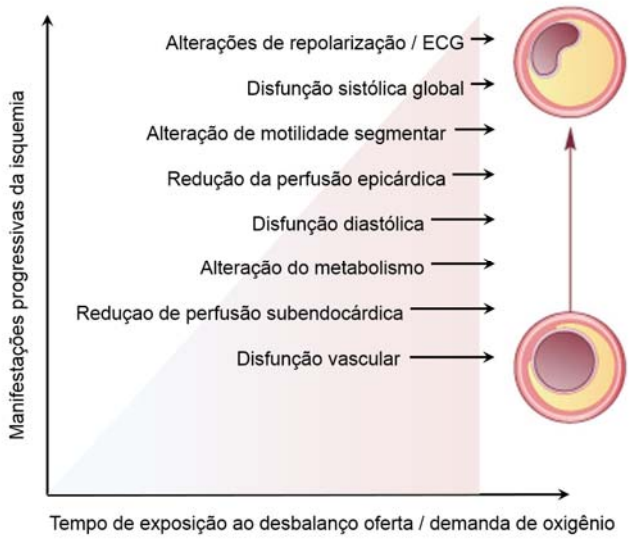
Estes episódios transitórios de perfusão miocárdica inadequada, em momentos de aumento da demanda de oxigênio, caracterizam a doença arterial coronariana estável, que se manifesta tipicamente com dor torácica anginosa (angina estável).

Obstruções graves e abruptas das coronárias, geralmente relacionadas a ruptura e trombose da placa de ateroma, causam repercussões miocárdicas e clínicas mais graves e imediatas, geralmente apresentando-se clinicamente na forma de angina instável ou infarto do miocárdio. Essas condições clínicas têm mecanismos fisiopatológico, prognóstico e manejo completamente diferentes da doença arterial coronariana estável, e não são o objeto de estudo deste trabalho.

Na avaliação diagnóstica de pacientes com suspeita de angina estável, a história clínica é a ferramenta mais útil e importante. É possível, em muitos casos, definir ou excluir o diagnóstico, ao levar em conta características demográficas, faixa etária e características da dor. Nos casos em que este diagnóstico não pode ser estabelecido de forma definitiva através da avaliação clínica, métodos diagnósticos complementares funcionais ou anatômicos podem ser utilizados.

Os testes funcionais são baseados na realização de exercício ou na injeção de fármacos, visando aumentar a demanda ou reduzir a oferta de oxigênio ao miocárdio, ou ainda induzir heterogeneidade no fluxo coronariano através da vasodilatação. Estes testes se baseiam no princípio da cascata isquêmica, que define que a isquemia miocárdica progressivamente mais grave e/ou prolongada produz anormalidades sequenciais de perfusão, contração, repolarização e sintomas (Figura 1).

Figura 1. A cascata isquêmica. Adaptado de Shaw et al. J Am Coll Cardiol. Oct 20, 2009; 54(17): 1561–1575



Além dos testes funcionais, métodos diagnósticos que permitem estimar diretamente o grau de estenose coronariana também estão disponíveis, representados pela cineangiocoronariografia e, mais recentemente, pela angiotomografia computadorizada de coronárias.

2.2. Desempenho dos testes diagnósticos

Como muitos dos testes avaliados estão disponíveis há muito tempo, há um número enorme de estudos de avaliação do seu desempenho diagnóstico. Sendo assim, sempre que possível, esta revisão foca nas revisões sistemáticas e metanálises, que agrupam e sumarizam os achados dos estudos individuais, fornecendo resultados globais mais robustos.

2.2.1. Ergometria

A ergometria, baseada na realização de atividade física graduada sob monitorização eletrocardiográfica, foi um componente-chave do diagnóstico da doença arterial coronariana durante várias décadas. A presença de isquemia miocárdica pode ser detectada pela presença de dor anginosa desencadeada pelo esforço, ou por alterações eletrocardiográficas características, particularmente o desvio do segmento ST. O desempenho diagnóstico da ergometria já foi exaustivamente testado em estudos clínicos e metanálises.

No final da década de 1980, Gianrossi *et al* realizaram revisão sistemática que incluiu 147 estudos, com um total de mais de 24.000 pacientes (8). A variação de desempenho foi bastante ampla, com sensibilidade variando entre 23 e 100% nos estudos, sendo a média global 68%, com desvio padrão 16%. A especificidade variou entre 17 e 100%, com média 77% e desvio padrão 17%. Vários fatores foram identificados pelos autores que influenciam o desempenho, incluindo a conduta com exames equívocos, o uso de exames de imagem como comparador, e o tratamento de resultados com segmento ST ascendente lento. Adicionalmente, foram incluídos na análise estudos com qualidade variável e, em muitos casos, diferenças metodológicas que poderiam comprometer a capacidade de combinar os resultados em metanálise.

Posteriormente, Kwok *et al* analisaram apenas estudos do desempenho da ergometria em mulheres (9), e encontraram sensibilidade de 61% (IC 95% 54 – 68%), e especificidade de 70% (IC 95% 64 – 77%). Novamente, houve ampla variação da acurácia e da qualidade dos estudos incluídos.

Mant *et al* (10) realizaram metanálise dos estudos publicados até 1999 , encontrando razão de verossimilhança positiva de 2,79 (IC 95% 2,53 – 3,07) para infradesnível de ST de 1mm, e de 3,85 (IC 95% 2,49 – 5,98) para infradesnível de ST de 2mm. A razão de verossimilhança negativa foi 0,44 (IC 95% 0,4 – 0,47), e 0,72 (IC 95% 0,65 – 0,81) para infradesnível de ST de 1mm e de 2mm, respectivamente.

Mais recentemente, Mowatt *et al* (11) conduziram nova revisão sistemática e metanálise a respeito da acurácia da ergometria. A busca, desta vez mais restritiva em relação ao tipo e qualidade dos estudos, resultou na inclusão de 70 estudos, dos quais 21 foram

combinados para obter medidas de acurácia, resultando em sensibilidade mediana de 65% (IC 95% 42 – 92%) e especificidade mediana 67% (IC 95% 43 – 83%).

Em relação ao percentual de exames não-diagnósticos, os dados são mais escassos. Avaliações econômicas prévias usaram, na maioria dos casos, pressupostos a respeito desse valor, com estimativas como 15% (12), 18% (13-15), 24% (16) ou 30% (17).

2.2.2. SPECT

A cintilografia miocárdica envolve a administração intravenosa de fármacos radioativos com captação característica no tecido miocárdico. A concentração do radiofármaco é então detectada em situações de repouso e de estresse (físico ou farmacológico), permitindo delimitar as estruturas cardíacas e detectar o padrão de perfusão miocárdica. Quando há isquemia miocárdica, tipicamente observa-se um defeito de captação do radiofármaco durante o estresse, com normalização da captação em repouso.

Em 1998, Fleischmann *et al* (18) publicaram revisão sistemática a respeito da acurácia de SPECT e eco-estresse, considerando cineangiocoronariografia (CAT) como padrão-ouro. A sensibilidade combinada foi 87% (IC 95% 86 – 88%) e a especificidade combinada 64% (IC 95% 60 – 68%), desempenho ligeiramente inferior ao do eco-estresse. Esta análise foi criticada por Kymes *et al* pela potencial heterogeneidade dos estudos incluídos; no entanto, quando os próprios autores da crítica refizeram a análise, encontraram estimativas-ponto semelhantes para sensibilidade e especificidade (19).

A revisão previamente citada de Mowatt (11) encontrou para SPECT sensibilidade 83%, especificidade 59% e 9% de testes indeterminados.

Uma metanálise mais recente, produzida pela agência oficial de Avaliação de Tecnologia em Saúde (ATS) de Ontario, Canadá (20), encontrou sensibilidade 84% (IC 95% 79 – 88%), e especificidade 78% (IC 95% 71 – 85%) com 6,9% de testes indeterminados.

2.2.3. Eco-estresse

A ecocardiografia permite a visualização da estrutura e da função cardíacas, através de imagens formadas com base na geração de ultrassom, que é refletido pelas estruturas intratorácicas. Na presença de doença arterial coronariana, a realização de exercício ou a infusão de fármacos como dobutamina ou dipiridamol podem desencadear anormalidades na função contrátil global ou regional do ventrículo esquerdo, que são detectadas em tempo real pelo examinador.

Na metanálise de Fleischmann *et al* previamente citada (18), a sensibilidade do eco-estresse foi 85% (IC 95% 86 – 88%), e a especificidade 77% (IC 95% 74 – 80%). A metanálise da agência de ATS de Ontario (20) descreveu 79% de sensibilidade (IC 95% 77 – 82%) e 84% de especificidade (IC 95% 82 – 86%), com 4,3% de exames indeterminados.

Os resultados dessas metanálises vão ao encontro do conceito geralmente aceito de que SPECT teria sensibilidade ligeiramente superior ao eco-estresse, que por sua vez teria

uma pequena vantagem de especificidade, com acurácia global semelhante entre os dois métodos (21).

2.2.4. Angio-TC

Nos últimos anos, o desenvolvimento de tomógrafos com múltiplos detectores passou a permitir a geração de imagens com resolução temporal e espacial elevadas, suficientes para fornecer informações detalhadas sobre a árvore coronariana. Dessa forma, a angio-TC de coronárias informa sobre a presença e o grau de estenose coronariana, de forma semelhante aos dados obtidas por cineangiocoronariografia.

Em um estudo realizado em um único centro na Holanda, Meijboom et al (22) avaliaram angio-TC em 254 pacientes agendados para realização de cinecoronariografia, e encontraram sensibilidade 93% (IC 95% 94 – 100%), e especificidade 86% (IC 95% 78 – 91%). Outro estudo unicêntrico, desta vez realizado na Suíça com 88 pacientes (23), relatou sensibilidade de 93% (IC 95% 81 – 98%), e especificidade 82% (IC 95% 68 – 92%).

Uma revisão sistemática realizada em 2007 (24) combinou os resultados dos estudos publicados até então a respeito da acurácia da angio-TC, encontrando sensibilidade 98% (IC 95% 96 – 98%), e especificidade 88% (IC 95% 90 – 93%). No entanto, esta análise excluiu segmentos indeterminados dos cálculos de desempenho do teste, o que pode superestimar a acurácia. Adicionalmente, apesar de haver poucos detalhes sobre os

métodos estatísticos usados, o texto sugere a possibilidade de heterogeneidade entre os estudos incluídos.

Mais recentemente, foi publicado o CORE-64, um estudo prospectivo e multicêntrico de maior porte, avaliando o desempenho da angio-TC em um espectro amplo de probabilidades pré-teste (25). Ao avaliar o desempenho global do teste – sem excluir pacientes com escore de cálcio alto – os investigadores relataram sensibilidade 88% (IC 95% 83 – 92%) e especificidade 87% (IC 95% 80 – 92%).

2.2.5. RNM-estresse

A RNM cardíaca, através da geração de campo magnético intenso e observação da transição entre níveis de energia rotacionais dos núcleos atômicos, produz imagens altamente detalhadas das estruturas cardíacas, sendo via de regra mais precisa e reprodutível do que os métodos de imagem previamente disponíveis. Adicionalmente, a presença de necrose ou viabilidade miocárdicas pode ser avaliada de forma confiável através da injeção de gadolíneo, e a infusão de fármacos inotrópicos ou vasodilatadores permite a pesquisa de alterações de contratilidade desencadeadas pelo estresse farmacológico.

Em 2007, Nandalur et al (26) realizaram revisão sistemática e metanálise dos estudos disponíveis, incluindo 37 estudos, e encontrando sensibilidade combinada 83% (IC 95% 79 – 88%) e especificidade 86% (IC 95% 81 – 91%).

Mais recentemente, outra revisão sistemática (27), que incluiu alguns estudos de porte relativamente grande, não disponíveis na ocasião da análise de Nandalur, obteve sensibilidade de 89% (IC 95% 88 – 91%), e especificidade de 80% (IC 95% 78 – 83%). A proporção de testes excluídos (indeterminados) foi de 5%.

2.3. Estratificação de risco

Há várias décadas há interesse na capacidade de testes provocativos identificar pacientes sob maior risco de eventos cardiovasculares. Diversos componentes da ergometria, como capacidade funcional, desvio do segmento ST, e comportamento de variáveis fisiológicas, podem ser usados isoladamente ou em conjunto para fornecer estimativas confiáveis do risco cardiovascular em médio e longo prazo (28-31).

No caso da SPECT, há dados bastante robustos sobre a capacidade de prever prognóstico. A taxa anual de morte ou infarto em pacientes com testes normais foi de menos de 1% ao analisar conjuntamente múltiplos estudos com mais de 3.500 pacientes e seguimento médio de 28 meses, com aumento progressivo do risco de acordo com a presença e extensão de anormalidades (32). Essa capacidade preditiva é independente da presença de doença coronariana no CAT (33).

O eco-estresse também tem boa capacidade de prever eventos cardiovasculares. Embora taxas de eventos um pouco maiores (3,8%) do que as encontradas com SPECT normal já tenham sido relatadas após eco-estresse sem isquemia (34), é importante levar em conta que as taxas extremamente baixas citadas são encontradas em pacientes com SPECT

normal tanto em repouso como no esforço; levando em conta esse subgrupo de pacientes, fica claro que o desempenho preditivo do eco-estresse é semelhante ao da SPECT (35), com cerca de 1,5% de morte ou reinfarto anuais (36).

A detecção de lesões coronarianas na angio-TC também fornece informações prognósticas, tanto para lesões obstrutivas como não-obstrutivas. Em um estudo observacional de cerca de 1.400 pacientes, com seguimento mediano de 5,6 anos, observou-se que a taxa de eventos variou de 0,2% a 1,2% de acordo com a extensão das lesões coronarianas na angio-TC (37). Mais recentemente, foi publicada análise do estudo multisítio CONFIRM, com informações sobre mais de 15.000 pacientes. Observou-se, em comparação com pacientes sem lesões pela angio-TC, hazard ratio para eventos cardiovasculares maiores de 2,5 para lesões não-obstrutivas, 9,1 para lesões obstrutivas de um único vaso, e até 24,5 para lesões em 3 coronárias (38).

A RNM-estresse é capaz de fornecer importantes informações prognósticas, com a avaliação de perfusão e motilidade segmentar durante o estresse. De modo semelhante ao observado com cintilografia miocárdica e eco-estresse, pacientes com exames normais têm prognóstico excelente, e a presença de isquemia esteve associada com uma chance de risco de 12,51 para eventos cardíacos maiores (39). Além disso, a pesquisa de realce tardio com gadolíneo parece fornecer informações prognósticas significativas, e que são independentes dos achados de isquemia (40).

O desempenho das diferentes modalidades na predição de eventos cardiovasculares futuros parece, portanto, ser semelhante, observando-se taxas anuais de eventos menores

do que 1% após exames totalmente normais, com aumento progressivo do risco de acordo com a extensão das anormalidades.

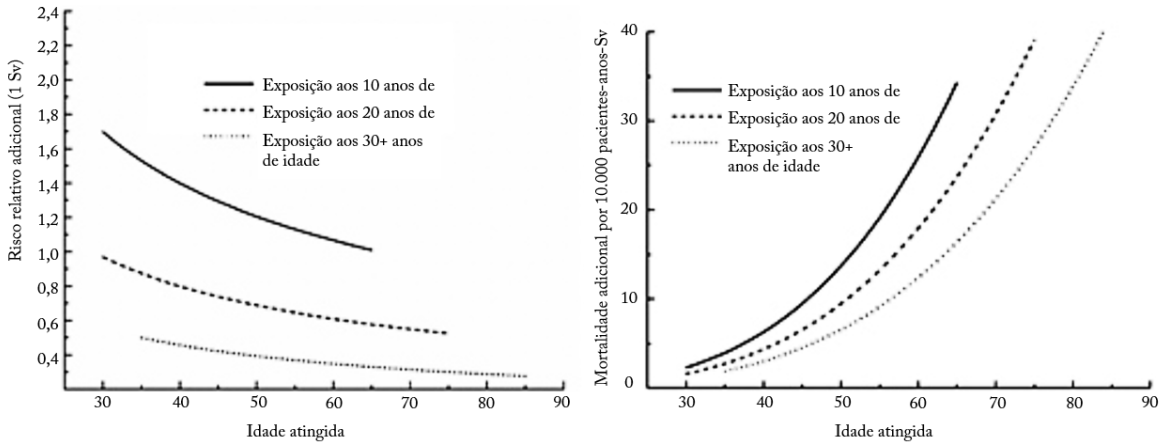
2.4. Exposição a radiação e risco de câncer

No caso da SPECT, da angio-TC e da cineangiocoronariografia, a visualização das estruturas é obtida através de radiação ionizante. Há considerável debate quanto ao impacto dessa exposição no risco de câncer durante a vida do paciente.

A hipótese da "linearidade sem limiar" é atualmente a mais aceita em termos de estimativa das consequências de exposição a radiação em baixas doses (41), e considera que mesmo exposições mínimas possam causar aumento no risco de câncer, com aumento progressivo desse risco de acordo com a magnitude da exposição. Esse conceito gerou a recomendação de exposição a radiação "tão baixa quanto razoavelmente atingível" (ALARA, na sigla em inglês) por parte das grandes sociedades de cardiologia (42).

Ainda assim, os riscos associados à realização de testes como SPECT e angio-TC, com doses de radiação próximas de 10 mSv, parecem ser baixos: o risco atribuível de câncer fatal é de cerca de 0,5 casos por 1000 indivíduos expostos (42, 43). Esses riscos são mais altos quanto mais jovens forem os indivíduos expostos (43), e há uma latência de 10 a 15 anos antes que qualquer mudança do risco seja detectável (41).

Figura 2. Padrões de idade-tempo para risco de qualquer câncer sólido após exposição a 1 Sv de radiação. Notar o tempo de latência (mais curto na figura devido à magnitude da exposição modelada) e o aumento progressivo do risco de acordo com o tempo após a exposição. Adaptado de (41).



2.5. Papel da análise econômica no processo de incorporação de tecnologias

O crescimento progressivo dos gastos com saúde, associado à finitude dos recursos públicos potencialmente destinados a este fim, trouxeram a tendência mundial de uso de análises de custo-efetividade com o objetivo de possibilitar a alocação racional dos recursos disponíveis (44, 45).

Nos estudos de custo-efetividade, a medida mais importante é a razão de custo-efetividade incremental (RCEI), que quantifica o custo a ser pago pelo benefício adicional – frequentemente medido em anos de vida ajustados para a qualidade (QALY) – trazido pela tecnologia avaliada.

Uma peculiaridade das avaliações econômicas é o seu caráter mais regional, quando comparadas com as análises de eficácia. Isso se deve a múltiplos fatores, sendo os mais

importantes as diferenças de custo das tecnologias, a organização dos serviços de saúde, e as características culturais e demográficas da população-alvo (44).

Sendo assim, é importante que haja capacitação e organização nacionais suficientes para produzir estudos econômicos para a realizada brasileira. Nos últimos anos houve considerável avanço neste campo, com o surgimento de entidades especializadas em avaliação de tecnologia como o IATS (Instituto de Avaliação de Tecnologia em Saúde) e a REBRATS (Rede Brasileira de Avaliação de Tecnologias em Saúde), e o uso de estudos de custo-efetividade no processo decisório para a incorporação de novas tecnologias pelo Ministério da Saúde (46).

2.6. Análises econômicas previamente realizadas

Na década de 90, Patterson *et al* compararam ergometria, SPECT, tomografia com emissão de prótons (PET), e CAT para o diagnóstico de DAC estável na perspectiva do sistema de saúde dos Estados Unidos (13). A análise foi feita com horizonte temporal de 10 anos, sem possibilidade de re-estratificação após o diagnóstico inicial, e com o objetivo de escolher a tecnologia com o menor custo por variação de QALY (sem usar um limiar de WTP). Para probabilidades pré-teste até 70%, a tecnologia com o menor custo/QALY foi a PET; probabilidades pré-teste maiores do que 70% tornam o CAT a tecnologia com o menor custo/QALY.

Outro estudo de custo-efetividade para o contexto norte-americano, desenvolvido por Kuntz *et al*, e utilizando o conceito mais amplamente aceito de escolha de tecnologia

baseada em limiar de WTP, avaliou ergometria, eco-estresse, e SPECT, em um modelo de Markov com horizonte temporal ao longo da vida (17). As RCEIs encontradas no contexto de média probabilidade pré-teste (homens de 55 anos com angina atípica) foram de US$ 57.700 / QALY para ergometria contra nenhum teste, US$ 41.900 / QALY para eco-estresse versus ergometria, US$ 54.800 para SPECT contra ergometria, e US$ 36.400 / QALY para CAT em comparação com eco-estresse. Os autores concluíram que ergometria e eco-estresse são alternativas recomendáveis com risco baixo ou moderado, e CAT sem teste provocativo é razoável para avaliação de casos com probabilidade pré-teste alta.

No contexto da Alemanha, Dewey *et al* (15) avaliaram angio-CT e RNM-estresse em um modelo de decisão de curto prazo com perspectiva da sociedade, relatando apenas os resultados de custo-efetividade média, sem descrever RCEI. Com probabilidade pré-teste de DAC menor que 50%, angio-TC custou € 1.500 a 4.400 por diagnóstico correto, e dominou as outras tecnologias. Com probabilidade pré-teste alta, CAT foi a opção mais custo-efetiva. A RNM-estresse foi dominada em todos os cenários.

O estudo Cost-effectiveness of functional Cardiac Testing (CECaT) incluiu uma análise econômica aninhada a um ensaio clínico, visando avaliar os testes funcionais eco-estresse, SPECT e RNM-estresse como "porta de entrada" antes da realização de CAT, para o contexto do Reino Unido (47). O grupo submetido a SPECT teve o melhor desempenho, gerando menores custos a médio-prazo. Como houve mínima diferença entre os grupos quanto a QALY acumulados, SPECT foi a estratégia preferida, sendo eco-estresse e RNM-estresse dominados. Os resultados negativos de eco-estresse e RNM-estresse neste

estudo podem ser atribuídos, pelo menos em parte, ao grande número de falhas de realização desses dois testes: 12% e 21% respectivamente, contra 4% da SPECT.

Para o contexto canadense, a entidade de ATS de Ontario avaliou eco-estresse, SPECT, RNM-estresse e angio-TC em um modelo de decisão de curto prazo com análise de impacto orçamentário (48). Nos resultados principais, eco-estresse foi o teste mais custo-efetivo, desde que realizado com contraste; angio-TC foi uma alternativa mais efetiva e mais cara, com RCEI de Can$ 1.500 por diagnóstico correto. RNM-estresse e SPECT foram dominadas. O estudo conclui, ainda, que substituir 25% das SPECT realizadas por eco-estresse com contraste ou angio-CT poderia gerar redução de custos de 42 milhões e 29 milhões de dólares canadenses, respectivamente.

Para o contexto da Inglaterra, o National Institute for Health and Care Excellence (NICE) já realizou múltiplas análises bastante aprofundadas a respeito do desempenho do uso de testes diagnósticos em cardiopatia isquêmica. O trabalho de Mowatt *et al*, em 2004, avaliou ergometria, SPECT, e CAT (11). Um modelo de decisão de curto-prazo avaliou custo por diagnóstico, e um modelo de Markov foi criado para avaliar resultados de longo prazo por QALY, em um horizonte temporal de 25 anos. Com probabilidades pré-testes baixas (10%), a estratégia de ergometria seguida de SPECT e CAT foi a mais barata; a estratégia de realizar SPECT seguida de CAT teve desempenho melhor, com RCEI de £ 14.000; SPECT seguida de CAT se mantém custo-efetiva com prevalência de 30%, mas a partir deste ponto realizar CAT como primeiro teste foi mais efetivo, com RCEI aceitável. A estratégia prevendo ergometria seguida de CAT foi dominada em probabilidades pré-testes baixas, mas teve melhor desempenho com probabilidades pré-

teste mais altas; no contexto de risco acima de 50% SPECT foi dominada de forma extendida pelas estratégias de ergometria-CAT e CAT como primeiro teste.

Em 2010, o NICE publicou novo estudo de custo-efetividade, desta vez incluindo angio-TC e escore de cálcio coronariano na análise, além dos testes citados no parágrafo anterior (49). Neste trabalho, os autores focaram na análise de curto-prazo, por considerar que os resultados de longo-prazo obtidos em suas análises de 2004 (11) e 2008 (16) são semelhantes aos de curto-prazo, com pontos de incerteza em relação a re-estratificação. Os resultados mostraram um bom desempenho da angio-TC, e a "estratégia anatômica" de escore de cálcio coronariano seguido de angio-TC foi recomendada pelos autores para probabilidade pré-teste abaixo de 30%.

2.7. Conclusões

- Os testes provocativos disponíveis para o diagnóstico de DAC estável possuem desempenho variável. A ergometria, teste mais amplamente disponível e de custo mais baixo, tem sensibilidade e especificidade mais baixa do que os testes de imagem mais modernos, o que pode aumentar o risco de falso-positivos ou falso-negativos, particularmente nos extremos de probabilidade pré-teste.

- Os resultados das comparações entre SPECT e eco-estresse sugerem acurácia semelhante entre os dois testes, com ligeira vantagem de sensibilidade para SPECT, e de especificidade para eco-estresse. A RNM-estresse, disponível há menos tempo, parece ter uma acurácia no mínimo comparável à dos demais testes de imagem. A angio-TC

demonstrou acurácia ligeiramente superior à dos demais testes provocativos, com sensibilidade particularmente boa.

- Todos os métodos diagnósticos estudados possuem a capacidade de fornecer informações prognósticas independentes da acurácia propriamente dita. Sendo assim, mesmo em pacientes com DAC, testes negativos identificam pacientes com risco mais baixo.

- Análises econômicas previamente realizadas tiveram resultados bastante diversos, o que é compreensível levando-se em conta a variação dos valores de reembolso praticados nos diferentes contextos. Esses resultados não são diretamente generalizáveispara o contexto brasileiro, demonstrando a carência de uma análise econômica dos testes diagnósticos para cardiopatia isquêmica estável, especificamente para a perspectiva do sistema de saúde do Brasil.

3. OBJETIVOS

1. Avaliar o desempenho diagnóstico e a custo-efetividade de estratégias baseadas nos testes diagnósticos disponíveis no SUS, e compará-los a testes ainda não disponíveis, especificamente angio-TC e RNM-estresse, quantificando custos por diagnóstico correto, e percentual de testes falso-positivos e falso-negativos.

2. Avaliar as repercussões de saúde a longo prazo das estratégias de investigação de DAC estável, comparando testes disponíveis e não-disponíveis, e quantificar custo por QALY, fornecendo dados úteis para os gestores em relação a políticas públicas de saúde a serem implementadas.

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5. ARTIGO ORIGINAL 1

Cost-effectiveness of Diagnostic Tests for Stable Chest Pain: Should Cardiac Magnetic Resonance and Coronary Computed Tomography Be Reimbursed As First Strategy?

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Abstract

Background. Proper evaluation and diagnosis of coronary artery disease (CAD) is an essential part of public health strategies. For decades, health plans reimburse exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), and single-photon emission computed tomography (SPECT), but not coronary computed tomography angiography (CTA) or stress cardiac magnetic resonance (MRI) for this indication.

Methods and Results. Decision-analytic model, comparing eleven strategies of sequential tests for evaluating patients with possible stable angina in low, intermediate and high pretest probability of CAD, built from the perspective of a public healthcare system. Data from published meta-analyses for test performance and risks were applied, and Brazilian reimbursement rates as the source for costs of diagnostic tests. Costs of CTA and MRI were estimated based on costs in the private sector. Strategies using Ex-ECG as initial test were the least costly alternatives, but generated a larger number of false-positive initial tests and false-negative final diagnosis. Strategies based on CTA or ECHO as initial test were the most attractive and resulted in similar cost-effectiveness ratios (I$ 286 and I$ 305 per correct diagnosis, respectively). A strategy based on C-MRI was highly effective for diagnosing stable CAD, but its high cost resulted in unfavorable ICERs in moderate- and high-risk scenarios. Noninvasive strategies based on SPECT generated unfavorable results, due to high cost of SPECT compared to other tests, and have been dominated in all scenarios.

Conclusions. Incorporation of CTA into healthcare systems would add a cost-effective option for CAD diagnosis. C-MRI yielded acceptable ICER only at low pretest

probability. Stress echocardiography is an attractive option among currently available tests.

Key Words: cost-benefit analysis, coronary disease, diagnosis, electrocardiography, echocardiography, nuclear medicine, tomography, magnetic resonance imaging,

Introduction

Proper evaluation and diagnosis of coronary artery disease (CAD) is an essential part of public health strategies, given the importance of CAD in worldwide morbidity and mortality (1). When a patient presents with chest pain symptoms, his or her probability of having CAD can vary from less than 10% to more than 90%, depending on clinical and epidemiological characteristics (2). In the frequent cases with intermediate pre-test probability, additional diagnostic tests can aid in clinical decision-making and risk stratification.

Nowadays, several noninvasive tests for diagnosing coronary artery disease are widely available, and have varying accuracy and costs. In Brazil, the Unified National Health System (SUS) currently reimburses exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), and single-photon emission computed tomography (SPECT), but not coronary computed tomography coronary angiogram (CTA) or stress cardiac magnetic resonance (MRI) (3).

Although Bayes' Theorem principles ought be applied in clinical practice to indicate one test over another, it is well known that in most occasions, individual physician preference and/or local availability are the main determinants in choosing among these tests. This may overlook several other important factors, from the efficacy of each test for a given pretest probability, to economic issues such as added cost per diagnosis when an inexpensive test such as Ex-ECG is systematically replaced by a more expensive, albeit more accurate test such as SPECT.

We aimed to compare the cost-effectiveness of different testing strategies, measured as cost per correct diagnosis for patients with suspected CAD. This information can supplement efficacy data in decision-makers' choice of approved exams for health plans, and provide grounds for the development of nationwide protocols for the management of stable angina.

Methods

Model

Decision-analytic model, comparing strategies for evaluating patients with possible stable angina, from the public health system's perspective was built; **Figure 1** schematically depicts the model structure. The model, developed in Treeage Pro 2013 (Williamstown, MA; TreeAge Software, Inc.), considered a hypothetical cohort of patients with pretest probability of CAD between 20% and 70%.

We defined eleven strategies combining exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), single-photon emission computed tomography (SPECT), coronary computed tomography coronary angiogram (CTA), stress cardiac magnetic resonance (MRI), and coronary angiography (CA) in clinically realistic sequences of tests (**Table 1**); in each strategy, the patient undergoes an initial test, moving on to further testing in case of positive or indeterminate results. Negative results do not generate additional tests. Strategy 1, for example, begins with Ex-ECG as a first test. Patients with positive or indeterminate results perform the second test, ECHO; if the second test is positive or indeterminate, patients move on to invasive coronary angiography (CA) as a final test. In scenarios with high pretest probability, we also considered strategies that use CA as first test, and reserve noninvasive test for equivocal CA results, such as coronary lesions of unknown hemodynamic significance.

Outcomes

The model ends with a test result (positive or negative), potentially true or false depending on the accuracy of the tests, resulting in a final cost per correct diagnosis. There is also a small risk of death due to test-related adverse events (Table 2).

Data sources

After systematic review of previous studies of accuracy, we used available data from published meta-analyses of test performance and risks to populate the model (**table 2**).

Brazilian National Health System (Sistema Único de Saúde – SUS) 2013 reimbursement rates were the source of costs for diagnostic tests for currently reimbursed tests (3); costs of CTA and MRI were estimated based on rates for currently reimbursed tests (chest computed tomography and rest cardiac magnetic resonance), inflated proportionally to cost differences among these tests in the private sector (4) (**Table 2**).

All costs were converted from Brazilian Real to International Dollars (I$), using the World Bank's latest available purchasing power parity conversion factor of 1.89 (5).

Assumptions

We assumed 100% sensitivity and specificity for coronary angiography, since it is the gold standard for diagnosing coronary artery disease. Another assumption was that for the last test in any strategy, the probability of indeterminate results is zero, be it a CA (as in strategies 1-9) or a noninvasive test (as in strategies 10-11).

We assumed myocardial infarction (MI) as an example of serious investigation-related complication, and applied SUS data regarding average national costs for MI admissions in 2012, I$ 1,670 (3), as reference for cost of complications (including death).

Separate analyses were performed, with low (20%), medium (50%) and high (70%) pretest probabilities of CAD, corresponding to the range of pretest probability in which noninvasive tests are most useful, according to the American Heart Association's guidelines on stable angina (2).

Sensitivity Analysis

Aiming to test the robustness of the model and the weight of individual parameters on results, during sensitivity analysis, we varied test accuracies and rates of complications and indeterminacy around their 95% confidence intervals. Alternative costs of tests ranged from half the original values to double those values.

In addition to one- and two-way sensitivity analyses, we performed probabilistic sensitivity analysis (PSA) with 10,000 samples, with simultaneous variation of model parameters around their confidence intervals. We used beta distributions for test accuracies and gamma distributions for costs.

Additionally, taking into account that in some situations CA may be considered an unacceptable first test due to patient or physician preferences, we considered an alternative scenario excluding strategies that begin with CA (strategies 10-11).

Willingness-to-pay

There is no broadly accepted willingness-to-pay (WTP) threshold for additional costs per correct diagnosis. For results per quality-adjusted life years, the World Health Organization (WHO) recommends a WTP threshold between 1 and 3 times a nation's gross domestic product (GDP) per capita (6) for middle income countries. For Brazil, these figures are I$ 11,700 to 35,200 per QALY.

Since per-diagnosis results could be considered to be of a lower magnitude than per-QALY results, we assumed the lower limit of the range proposed by the WHO in our analysis, currently I$ 11,700 for Brazil.

Results

Table 3 shows average costs, accuracy, and comparative cost-effectiveness results from testing a population with low (20%) to high (70%) pretest probability of CAD with each diagnostic strategy. In **Figure 2,** cost-effectiveness results for each pretest probability are illustrated, excluding dominated strategies.

Low pretest probability (20%)

With low probability of CAD, strategy 2 (Ex-ECG -> CTA -> CA) was the least costly strategy, with a mean cost per diagnosis of I$ 135, while retaining good overall performance (92.6% correct diagnosis, 5% invasive CA in patients without CAD). Upgrading to strategy 9 (CTA -> CA) increases effectiveness to 97.6% of correct diagnosis, with mean cost per diagnosis of I$ 200 and incremental cost-effectiveness ratio (ICER) of I$ 1,420. Substituting strategy 9 with strategy 8 (C-MRI -> CA) modestly increases diagnostic accuracy to 97.9%, but raises mean cost per diagnosis to I$ 320, resulting in a much higher ICER of I$ 47,800.

The other strategies were either absolutely or relatively dominated. However, strategy 1 (Ex-ECG -> ECHO -> CA) had accuracy results that were practically identical to strategy 2 (92.4% correct diagnosis), with mean cost per diagnosis only marginally higher, I$ 150.

Moderate pretest probability (50%)

In moderate CAD probability scenario, strategy 2 (Ex-ECG -> CTA -> CA) remained the least costly strategy, at I$ 230 per correct diagnosis; however, in this scenario, this strategy resulted in a relatively low overall accuracy of 81%, with over 18% false negative final diagnoses. Strategy 4 (Ex-ECG -> CA) improves overall accuracy to 86%, with 14% false negative results, and costs I$ 240 per correct diagnosis. Resulting in an ICER over strategy 2 of I$ 415.

In this range of pretest probability, the strategy based on CTA coronary angiography as initial test (strategy 9) yields significantly better outcomes, with 94% overall accuracy. Mean cost per diagnosis is I$ 285, resulting in an ICER over strategy 4 of I$ 750 per correct diagnosis. Strategy 8, based on C-MRI, raises accuracy to 95%, while increasing mean cost per diagnosis to I$ 410. ICER for strategy 8 over strategy 9 is I$ 17,800 per correct diagnosis.

Remaining strategies have been dominated by strategies 2, 4, 9 and 10. Once again, it should be noted that strategy 6 (Echo -> CA) yields accuracy results very close to the ones obtained with strategy 9 (93.6%), at a marginally higher mean cost per diagnosis of I$ 305.

High pretest probability (70%)

With a higher prevalence of CAD, strategies that involve two noninvasive tests before CA are dominated by strategy 4 (Ex-ECG -> CA), which results in 80% correct

identification at I$ 280 per diagnosis. However, in this range of CAD risk, strategy 4 results in 20% false negative results, seriously hindering its usefulness in practice.

If strategies with false negative rates above 20% (1-4) are excluded from analysis, strategy 9 (CTA -> CA) emerges as an attractive option, with overall accuracy 92%, and mean cost per diagnosis of I$ 345. Strategy 6 (Echo -> CA) results in practically identical effectiveness (91%) at a somewhat higher cost per diagnosis of I$ 400.

A strategy based on invasive CA as first test (strategy 10) results in 98% accuracy, mean cost per diagnosis I$ 346, and ICER I$ 273 over strategy 9.

Sensitivity Analysis

In one-way sensitivity analysis, the choice between CTA and ECHO-based strategies was sensitive to procedure costs and test sensitivity. For instance, in low-probability scenarios, CTA dominates ECHO if it costs less than I$ 129, has higher cost and higher effectiveness with costs between I$ 129 and 182, and is dominated by ECHO at higher costs. With high pretest probability, ECHO is the preferred noninvasive method if it costs up to I$ 56; and at its maximum price, ECHO is dominated by CTA.

Variation in cost and accuracy of other tests modified cost per diagnosis for each strategy, but did not alter base-case results to the extent of changing preferred strategies.

In probabilistic sensitivity analysis, there was significant overlap between CTA and ECHO in terms of cost-effectiveness, demonstrating a high level of uncertainty as to which of the two strategies would be preferred (**Figure 3**).

In the alternative scenario that excludes CA as an initial test, even in the high pretest probability group, strategy 8, based on C-MRI as first test, becomes the strategy with highest accuracy, with an ICER over strategy 9 (CTA -> CA) slightly above our estimated WTP threshold: $ 12,200 with 70% pretest probability.

Focusing on currently available imaging modalities, we performed two-way sensitivity analysis on the choice between ECHO-based and SPECT-based strategies, which showed ECHO-based strategies to be dominant across the defined spectrum of sensitivity analysis. SPECT-based strategies are preferred only if the cost of SPECT is no more than 10% higher than the cost of ECHO.

Discussion

Coronary artery disease is still the leading cause of morbidity and mortality worldwide. Although in high-income countries there is clearly a trend towards reducing related mortality, its global burden continues expressive, more so for developing countries. New technologies for the diagnosis of the disease have grown significantly in the last decades, challenging physicians and decisions makers on how to make better use of the several options available. In this study, we performed a cost-effectiveness analysis to assess currently available strategies for investigating chest pain in Brazil, and to compare them with new strategies, that could become available if the SUS includes CTA and C-MRI to its list of reimbursed tests.

Our study shows that the least costly diagnostic strategies are conservative ones, using Ex-ECG as a "gatekeeper", and proceeding to additional noninvasive tests only when results are positive. These low-cost strategies have the disadvantage of generating a larger number of false-positive initial tests, thus subjecting patients without CAD to additional tests. Furthermore, their performance deteriorates as pretest probability rises, so that at 70% pretest probability their false-negative rate is above 20%. Therefore, such strategies may be an option for very constrained budgets, but only when pretest probability is low or moderate (≤ 50%).

As pretest probability increased, costs per correct (positive or negative) diagnosis becomes higher for strategies based on sequential tests, since positive initial tests are more frequent, leading to further testing in more patients. This is particularly true for conservative strategies that require two noninvasive tests before proceeding to invasive CA.

Strategies based on CTA and ECHO as initial test, result in almost superimposable cost-effectiveness results. These strategies would increase accuracy, at an ICER over Ex-ECG-based strategies well below I$ 11,909 per correct diagnosis. This makes them attractive options across the entire spectrum of pretest probabilities.

Diagnostic strategies based on C-MRI showed to be highly effective, but their relatively high (estimated) cost resulted in unfavorable ICERs in moderate- and high-risk scenarios. If C-MRI costs could be reduced to figures lower than I$ 200 estimated, it could become cost-effective enough to recommend for widespread implementation in SUS. Nonetheless, it is important to emphasize that, for this cost, availability and acquisition values were not taken into account.

Noninvasive strategies based on SPECT generated consistently unfavorable results, due to the high cost of SPECT when compared to other noninvasive tests, and have been dominated in all scenarios. In addition, radiation-related risks were not included in our short-term model because potential effects of radiation exposure take more than a decade to manifest. Still, this could be an additional cause for concern regarding widespread use of tests such as SPECT and CTA.

Our study's main limitation is that, since SUS does not currently reimburse CTA and C-MRI, we had to estimate procedure costs from private practice. It is expected that in case of incorporation of these tests into the public system, actual reimbursement values may be different. Still, our results were robust even when we halved or doubled the value of our initial cost estimate.

Current practice in Brazil usually prioritizes SPECT-based over ECHO-based strategies for diagnosing CAD. Based on the national database, in the year 2012, the Brazilian PHS reimbursed over 100,000 SPECT tests and less than 18,000 ECHO tests for outpatients (3). Our results suggest that ECHO-based strategies should be more widely employed in the SUS, especially considering their absence of radiation and low costs for implementation and maintenance.

Updating reimbursement values for ECHO may stimulate the availability of this test in the PHS, and seems justified, since our sensitivity analysis showed that ECHO would remain more cost-effective than SPECT even with costs up to 4 times higher than current rates.

Conclusions

For the diagnosis of stable CAD, strategies based on exercise ECG are the least expensive, but their lower effectiveness means they should be considered only for very constrained budgets, and when pretest probability is low or moderate.

Regarding technologies that are currently available in SUS, stress echocardiography is more cost-effective than SPECT, and should generally be preferred if available.

Incorporation of coronary computed tomography into SUS would add a cost-effective option for CAD diagnosis. Stress cardiac magnetic resonance yielded acceptable ICER only at low pretest probability. Our results suggest that the immediate incorporation of coronary computed tomography into SUS is advisable if actual test costs can match our estimated cost of I$ 100 per test. Incorporation of stress cardiac MRI should be considered only if its costs can be reduced to values significantly lower than our estimate of I$ 200.

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Conflicts of interest:

None.

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Figures and legends

Figure 1. Schematic representation of model structure.

Figure 2. Base-case cost-effectiveness results for predefined risk categories. Strategies 1-4 excluded from high-probability analysis (see text for details).

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Figure 3. Scatterplot of incremental cost-effectiveness of strategy 9 (CTA-CA) over strategy 6 (ECHO-CA).

ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; CA = invasive coronary angiography

Figure 1.

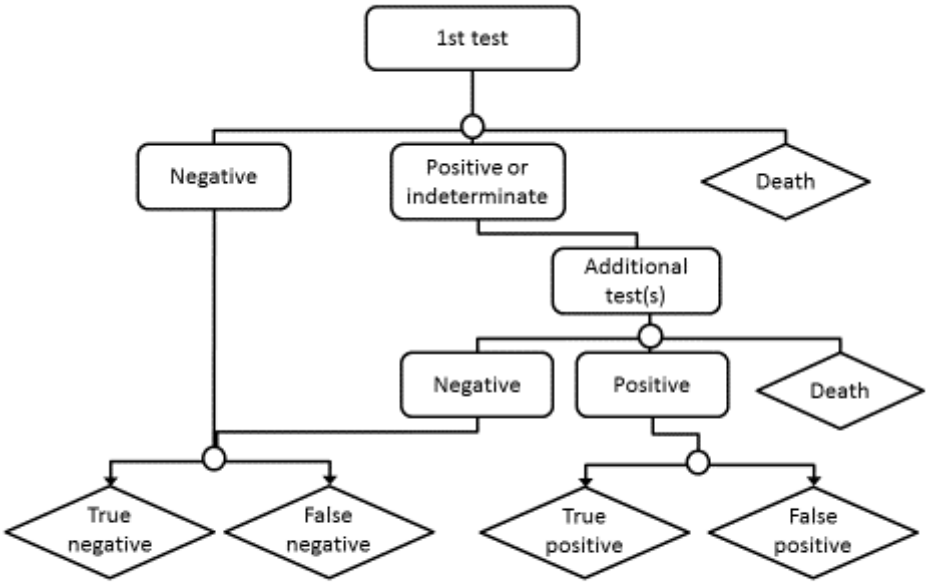

1st test
Negative
Positive or indeterminate
Death
Additional test(s)
Negative
Positive
Death
True negative
False negative
True positive
False positive

Figure 2.

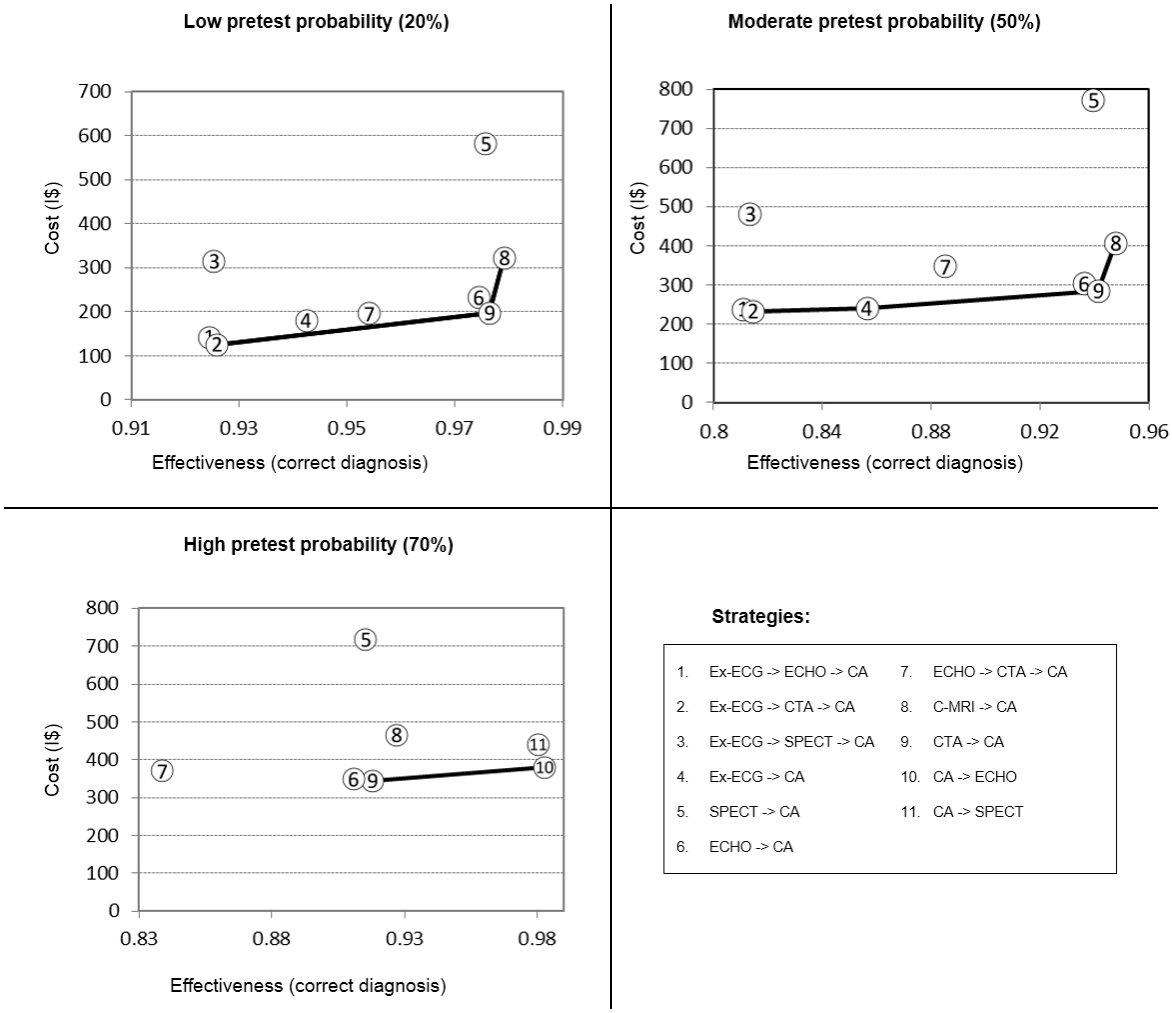
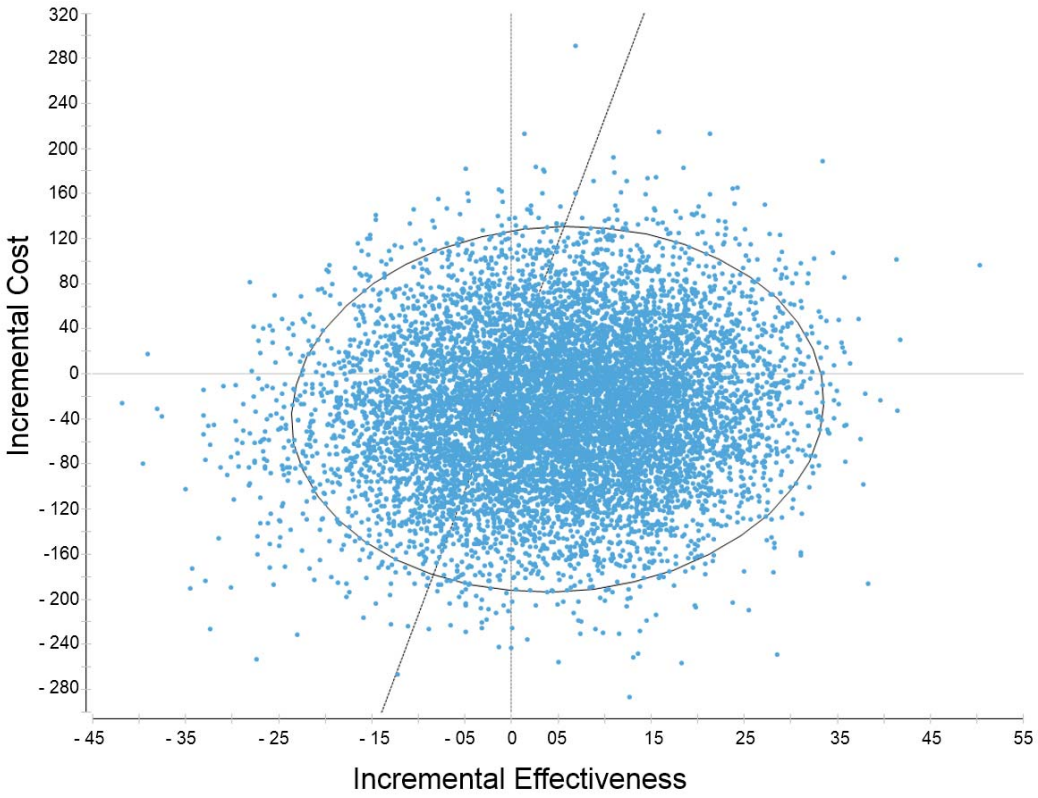

Low pretest probability (20%)
Cost (I$)
Effectiveness (correct diagnosis)
Moderate pretest probability (50%)
Cost (I$)
Effectiveness (correct diagnosis)
High pretest probability (70%)
Cost (I$)
Effectiveness (correct diagnosis)
Strategies:
1. Ex-ECG -> ECHO -> CA
2. Ex-ECG -> CTA -> CA
3. Ex-ECG -> SPECT -> CA
4. Ex-ECG -> CA
5. SPECT -> CA
6. ECHO -> CA
7. ECHO -> CTA -> CA
8. C-MRI -> CA
9. CTA -> CA
10. CA -> ECHO
11. CA -> SPECT

Figure 3.


Incremental Cost
320
280
240
200
160
120
80
40
0
- 40
- 80
- 120
-160
- 200
- 240
- 280
- 45
- 35
- 25
- 15
- 05
0
05
15
25
35
45
55
Incremental Effectiveness

Tables

Table 1. Test sequence in each modeled strategy.

* Strategies 10 and 11, in which invasive coronary angiography is the first test, are only considered in scenarios with high pretest probability.

SPECT = single-photon emission computed tomography; MRI = cardiac magnetic resonance.

Table 2. Characteristics of tests; range of values used in sensitivity analysis; and costs.

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 3. Base-case results for different pretest probabilities. Dominated strategies not shown, except when significant uncertainty regarding dominance on sensitivity analysis.

Prob = pretest probability; C-E = cost-effectiveness; ICER = incremental cost-effectiveness ratio; FN = false-negative; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 1. Test sequence in each modeled strategy.

	1st test	2nd test	3rd test
Strat. 1	exercise ECG	stress echocardiography	coronary angiography
Strat. 2	exercise ECG	coronary CT angiography	coronary angiography
Strat. 3	exercise ECG	SPECT	coronary angiography
Strat. 4	exercise ECG	coronary angiography	
Strat. 5	SPECT	coronary angiography	
Strat. 6	stress echocardiography	coronary angiography	
Strat. 7	stress echocardiography	coronary CT angiography	coronary angiography
Strat. 8	stress cardiac MRI	coronary angiography	
Strat. 9	coronary CT angiography	coronary angiography	
Strat. 10*	coronary angiography	stress echocardiography	
Strat. 11*	coronary angiography	SPECT	

Table 2. Characteristics of tests; range of values used in sensitivity analysis; and costs.

Test	Sensitivity (%) [range]	Specificity (%) [range]	Indeterm. (%)	Mortality (‰)	Cost (I$)	Sources
Ex-ECG	65 [42 – 92]	67 [43 – 83]	18	0.05	16	(3, 7, 8)
ECHO	85 [83 – 87]	77 [74 – 80]	15	0.05	87	(3, 9, 10)
SPECT	87 [84 – 88]	64 [60 – 76]	6.9	0.05	419	(3, 9, 10)
CTA	88 [83 – 92]	87 [80 – 92]	2	0.01	101	(3, 11-13)
MRI	89 [88 – 94]	80 [75 – 87]	5	0.01	200	(3, 10, 14)
CA	100	100	10	0.2	325	Assumption, (3, 15, 16)

Table 3. Base-case results for different pretest probabilities.

Pretest Proba-bility	Strategy	C-E (I$/diag)	ICER (I$/diag)	Accuracy (%)	FN (%)	Deaths (%)	Invasive CA (%)	Negative invasive CA (%)
LOW	2 (Ex-ECG -> CTA -> CA)	135	-	93	7.4	0.009	18	5
	1 (Ex-ECG -> ECHO -> CA)	153	-	92	7.6	0.012	25	12
	9 (CTA -> CA)	202	1,420	98	2.4	0.007	29	12
	8 (C-MRI -> CA)	322	47,800	98	2.1	0.008	37	19
MODERATE	2 (Ex-ECG -> CTA -> CA)	231	-	81	18.5	0.013	35	3
	4 (Ex-ECG -> CA)	240	415	86	14.3	0.017	58	23
	9 (CTA -> CA)	286	750	94	5.9	0.011	51	7
	6 (ECHO -> CA)	305	-	94	6.4	0.017	61	17
	8 (C-MRI -> CA)	407	17,800	95	5.2	0.012	57	12
HIGH	4 (Ex-ECG -> CA)	278	-	80	20.1	0.018	63	14
	9 (CTA -> CA)	345	790	92	8.2	0.014	66	4
	6 (ECHO -> CA)	351	-	91	8.9	0.019	71	10
	10 (CA -> ECHO)	381	273	98	1.7	0.02	100	30

6. ARTIGO ORIGINAL 2

Cost-effectiveness of Diagnostic Tests for Assessing Stable Chest Pain

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Abstract

Background: Several tests are available for diagnosing coronary artery disease (CAD), with varying accuracy and cost. Choosing one test over another can influence healthcare costs and patient prognosis.

Methods: We built a state-transitions (Markov) model including several diagnostic strategies, based on either exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), single-photon emission computed tomography (SPECT), tomography angiography (CTA) or stress cardiac magnetic resonance (C-MRI) as initial test. A systematic review of published literature provided input data for test accuracy and long-term prognosis. Cost data were derived from Brazilian public health system (SUS) reimbursement values, and estimated from the private sector for tests not currently reimbursed (CTA and C-MRI). We used the SUS perspective and a lifetime horizon.

Results: Diagnostic test strategy had a small but measurable impact in quality-adjusted life-years (QALY) gained. Switching from Ex-ECG to CTA-based strategies improved outcomes at an incremental cost-effectiveness ratio (ICER) of 3,100 international dollars (I$) per QALY. ECHO-based strategies resulted in cost and effectiveness almost identical to CTA, and SPECT-based strategies were dominated because of much higher cost. Strategies based on C-MRI were the most effective, but ICER over CTA was higher than proposed WTP threshold of 3 times GDP per capita. Invasive strategies were dominant in high pretest probability setting. Sensitivity analysis showed that the results

were sensitive to costs of CTA, ECHO and MRI; variation of other parameters did not change results. Threshold analysis showed that MRI would be cost effective if its reimbursement value is below I$ 160.

Conclusions: Coronary computed tomography is a cost-effective alternative for the diagnosis of CAD and should be included in the Brazilian public health system. Stress echocardiography has a similar performance and is an acceptable alternative for most patients, while invasive strategies should be reserved for patients at high risk.

Introduction

In the last decades, several noninvasive tests for diagnosing coronary artery disease have become widely available for physicians in clinical practice. Although international guidelines based their recommendations on best strategic options (1-3), it is perceived that final decisions to order these tests also take into account other factors, such as availability, experience and insurance covering. In Brazil, the Unified National Health System (SUS) currently reimburses exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), and single-photon emission computed tomography (SPECT), but not coronary computed tomography coronary angiogram (CTA) or stress cardiac magnetic resonance (MRI) (4)

Cost-effectiveness studies of diagnostic tests for coronary artery disease (CAD) frequently focus on immediate test results, and provide information on the cost per correct diagnosis. However, long-term results analyzing impact of diagnosis on morbidity and mortality are also important, and provide results that might be compared to o other interventions in medicine (5).

Our aim is to compare the long-term effects, of choosing among available diagnostic tests in the Brazilian Unified National Health System (SUS), such as exercise electrocardiogram (Ex-ECG), stress echocardiogram (ECHO), and single-photon emission computed tomography (SPECT), and also to estimate the potential performance of currently unavailable tests (4) such as computed tomography coronary angiogram (CTA) or stress cardiac magnetic resonance (MRI).

Methods

Model

Our model, developed in Treeage Pro 2013 (Williamstown, MA; TreeAge Software, Inc.) has a short-term component and a long-term transitional states model, built in a hypothetical cohort of patients with pretest probability of CAD between 20% and 70%; in the base-case analysis, patients enters the model at age 60.

The short-term portion is based on a decision tree with varying strategies for evaluating patients with possible stable angina. Eleven possible sequences of tests were defined **(Table 1**); each starts with a specific test, progressing to further testing if initial results are positive or indeterminate, with coronary angiography (CA) as a final test. For example, in strategy 9, a patient presenting with chest pain could undergo CTA, have a positive test result and thus be subjected to CA; if CA results are negative, the patient is classified as low-risk; conversely, positive CA results would result in classification as moderate or high risk.

After a diagnostic is established in this initial stage, patients progress to a long-term Markov model, in which members of the hypothetical cohort may remain stable, suffer cardiovascular (CV) events, undergo percutaneous or surgical revascularization procedures, or die from CV disease, cancer, or other causes.

Patients will enter the long-term model in one of several disease states: low risk (represented by patients without significant CAD), medium risk (such as patients with single- or two-vessel CAD), high risk (patients with extensive CAD or associated left ventricular dysfunction), medium risk with false negative (incorrectly diagnosed as low

risk), high risk with false negative (incorrectly diagnosed as low risk), and low risk with false positive (incorrectly diagnosed as medium risk).

Results of initially performed tests influence the probability of each outcome in the long-term model: true negative tests identify patients at low risk of CV events, and determine low risk of revascularization; true positive tests identify patients at higher risk of CV events, and generate more revascularization procedures. In the case of false-negative results, patients have a high risk of CV events, but are misdiagnosed as low-risk; this further increases CV risk, but results in fewer revascularization procedures. False-positive results signal low risk of CV events, but misdiagnosis leads to more revascularization procedures, with consequent risks and costs.

Figure 1 represents a simplified version of the model structure**.** We performed our analysis from the perspective of the public health system (SUS), and measured outcomes in quality-adjusted life-years. The model ran yearly cycles over a lifetime horizon.

Input data

We conducted a systematic review of available data on accuracy and risks of noninvasive tests and CA, as well as long-term prognosis of patients with stable CAD. Studies identified in this review served as sources for input data, as described in **Table 2** (test performance) and **Table 3** (long term model).

Because of its large sample size and long-term follow-up, we considered the REACH registry (6) to be a valid study to retrieve long-term probability of CV events, stratified by initial risk group.

We based long-term costs and utilities for CAD patients on local cohorts (7, 8), since these data are prone to wide variation in different countries and settings. Health-related quality of life was measured using SF-6D, and disutility resulting from complications and procedures was assumed as the difference between utility immediately before and 3 months after events (9).

Impact of radiation exposure on the lifetime risk of cancer was based on available studies (10, 11) and assumes an average dose of 10mSv for CTA, SPECT and CA (11). After a 10-year latency period, risk of fatal cancer due to radiation increases exponentially, reaching 0.5 per 1000 in the second decade after exposure, 1.5 per 1000 in the fourth decade after exposure, and 3.5 per 1000 in the sixth decade after exposure.

Brazil's SUS 2013 reimbursement rates were the source of costs for diagnostic tests for currently reimbursed tests (4); costs of CTA and MRI were estimated based on rates for currently reimbursed tests (chest computed tomography and rest cardiac magnetic resonance), inflated proportionally to cost differences among these tests in the private sector (12) **(Table 2**). Costs have been converted from Brazilian Real to International Dollars (I$), at a rate of 1.89, corresponding to the World Bank's latest purchasing power parity conversion factor (13).

Assumptions

Since CA is the gold standard for diagnosing CAD, it was assumed to have 100% sensitivity and specificity in the model. An alternative scenario, with CA sensitivity and

specificity lower than 100% (arbitrarily defined as 95%), has been explored in sensitivity analysis. Additionally, the last test in any strategy never generates indeterminate results.

Cost of serious short-term test complications (including death) were assumed to be equivalent to SUS average national costs for MI admissions in 2012, I$1,500 (4).

As in previously published models (14), the base-case assumption is that 10% of initially misdiagnosed cases are correctly rediagnosed in the first year, with increasing numbers until the tenth year, by which all have been properly rediagnosed. This accounts for the possibility of correcting diagnostic errors in subsequent office visits or with further testing.

As per current recommendation by the Brazilian Ministry of Health, we used a 5% discount rate for costs and utilities in the base-case analysis, as well as 0 and 10% rates in sensitivity analysis.

There is no official willingness-to-pay threshold for healthcare interventions in Brazil; the World Health Organization (WHO) recommends a WTP threshold between 1 and 3 times a nation's gross domestic product (GDP) per capita (15) for middle income countries, which would represent figures between I$ 11,909 and 35,727 per QALY in Brazil.

Sensitivity Analysis

Aiming to test the robustness of the model and the weight of individual parameters on results, during sensitivity analysis, we varied test accuracies and rates of complications and

indeterminacy around their 95% confidence intervals. Alternative costs of tests ranged from half the original values, to double those values.

In addition to one- and two-way sensitivity analyses, we performed probabilistic sensitivity analysis (PSA) with 10,000 samples, with simultaneous variation of model parameters around their confidence intervals. We used beta distributions for test accuracies and gamma distributions for costs.

Regarding rediagnosis, we considered alternative scenarios in which time until all patients are correctly diagnosed varies between 5 years and 20 years.

Results

Considering the base case scenario of patients at 60 years of age and 50% pretest probability of CAD, life expectancy shows little variation with different diagnostic strategies: between 11.19 and 11.26 years with moderate pretest probability. Changing assumption to low pretest probability results in life expectancy 0.5 years higher, and high pretest probability results in loss of 0.5 years in life expectancy.

Main results are represented in **Figure 2** and **Table 4**. Strategies 1 and 2, based on Ex-ECG as a "gatekeeper" test, followed if positive by either ECHO or CTA, and then by CA if the second test is positive, were the least costly, least effective strategies, with mean lifetime cost I$ 9,500, and expected 8.06 QALY gained. Strategy 4, also including Ex-ECG as initial test, but proceeding directly to CA if positive, was marginally more costly and more effective, with an ICER over strategy 2 of I$ 2,200 per QALY gained.

Strategy 9, with CTA as initial test, fared better and yielded additional 0.3 QALY, in average, at an ICER of I$ 3,100. Strategy 6, based on ECHO and CA, had almost identical results to strategy 9 (QALY difference 0.0022, cost difference I$ 14).

Strategy 8, based on C-MRI as initial test, emerged as the most effective strategy with an average of 8.11 QALY, but came at a higher cost, so that ICER over strategy 9 is I$ 50,500.

Strategies 3 and 5, based on SPECT, performed marginally better than equivalent strategies with ECHO or CTA, but resulted in much higher costs, and were dominated in all scenarios.

Varying pretest probability between 20 and 70% resulted in variation of overall costs, survival and QALY, but relative performance of each strategy was not changed. In all cases, Ex-ECG based strategies were least costly/least effective, ECHO- or CTA-based strategies were more effective than Ex-ECG at relatively low ICERs, C-MRI strategies were the most effective with a high ICER, and SPECT strategies were dominated.

When CA was included as an acceptable initial test, the invasive strategies became the most effective, because of the "perfect accuracy" of CA assumed by the model. When pretest probability is 65% or higher, strategy 10, based on CA as initial test, dominated all other strategies, except for Ex-ECG strategies, which remained as the least costly/least effective alternative **(Figure 3)**. However, with such high pretest probabilities, Ex-ECG-based strategies generated over 20% false-negative initial diagnosis, a performance that could be considered unacceptable in clinical practice.

One-way sensitivity analysis of relevant parameters did not affect overall results significantly, with one exception: since CTA-based and ECHO-based strategies showed almost identical base-case results, variation in cost or in accuracy of these tests changed preference between the two.

Sensitivity analysis of other parameters, including rates of test indeterminacy and complications, influenced average costs and QALY, but did not alter the relative performance of strategies.

Specifically comparing the performance of currently available imaging tests ECHO and SPECT, the results showed that ECHO-based strategies are consistently more cost-effective in our model. SPECT-based strategies were only dominant if SPECT cost was

reduced to 110% the costs of ECHO in the base-case, or to 125% the cost of ECHO when accuracy of SPECT was raised to the upper limit of the confidence interval.

We also explored threshold analysis regarding cost of C-MRI, and found that a reduction to values below I$ 160 (79% of base-case cost) resulted in an ICER over CTA-based strategies below I$ 35,700 (3 times GDP/capita). C-MRI cost under I$ 110 (54% of base-case cost) was necessary for an ICER below I$ 11,900 (1 time GDP/capita).

Probabilistic sensitivity analysis with 10,000 interations resulted in test performances consistent with base-case results. In the setting of a WTP threshold of I$ 11,909, probability of being cost-effective was 69% for strategy 9, based on CTA, and 18% for strategy 6, based on ECHO. At a higher WTP threshold of I$ 35,700, the probability of being cost-effective was 55% for strategy 9, based on CTA, 32% for strategy 8, based on C-MRI, and 10% for strategy 6, based on ECHO. Other strategies had less than 5% probability of being optimal.

Cost-effectiveness acceptability curves (**Figure 4**) show that Ex-ECG based strategies were optimal only in very constrained budgets, with WTP thresholds close to zero. CTA-based and ECHO-based strategies quickly emerged as the ones most likely to be cost-effective, and a C-MRI based strategy showed a high likelihood of being cost-effective only with WTP threshold above 5 times Brazilian GDP per capita.

Discussion

We used the large body of evidence available on the relative performance of noninvasive tests for diagnosing coronary artery disease, and performed a broad analysis on the long-term consequences of selecting one test over another.

Our results suggest that, for patients at moderate pretest probability, ECHO-based strategies are the most cost-effective among currently available tests in the public health system, and that inclusion of CTA in the role of available tests would bring an effective additional strategy at a very attractive ICER. In scenarios of high pretest probability (close to 70%), invasive strategies are dominant and seem to be the most reasonable alternative when there is diagnostic uncertainty.

In our study, investigation of stable chest pain patients with C-MRI resulted in slightly higher QALY in long-term than other noninvasive tests, but at a higher cost as compared with ECHO or CTA results, leading to an ICERs above proposed WTP threshold at the estimated base-case cost. This result is sensitive to the cost of C-MRI test, and this alternative could become cost-effective if reimbursement value upon inclusion in SUS remains below I$ 160.

In current practice, it is common for physicians to have to decide whether to choose between ECHO and SPECT when patients have contraindications to Ex-ECG. Our results suggest that, in this particular scenario, ECHO is economically more attractive, and should be preferred in the majority of cases.

Economic analyses of noninvasive tests from other countries' perspectives are not directly transferrable to our context, mainly because of the wide variation in the costs of tests and

procedures. Still, despite differences in total costs and QALY, previous works have generally shown similar results in terms of choice among tests, with either ECHO or CTA usually emerging as the recommended strategy (2, 16-18).

Significant controversy still exists regarding translation of cost-effectiveness results to clinical practice and widespread recommendation. In their latest guidance, England's National Institute for Health and Care Excellence (NICE), suggests patients with possible stable angina and a positive coronary calcium score should undergo CTA for diagnosis if pretest probability is low. Additionally, NICE specifically states that Ex-ECG should not be used to diagnose or exclude stable angina, due to its inferior performance in their analysis (3).

The American Heart Association's latests guidelines for diagnosis and management of stable angina made more traditional recommendations, maintaining Ex-ECG as preferred first-line test (class I), and giving weaker recommendations to ECHO and SPECT (class IIa) or CTA (class IIb) (1).'

In Brazil, operators and administrators in centers performing Ex-ECG or ECHO often complain that an adjustment in SUS reimbursement values is overdue. This may lead to reduced availability of tests, and could explain, at least in part, the greater emphasis on SPECT than ECHO observed in the Brazilian public health system: 793 SPECT exams were performed in 2013, and 174 ECHO tests (4).

A comparison among SUS reimbursement values of tests supports to this notion: SPECT value is nearly 5 times higher than ECHO, 25 times higher than Ex-ECG, and 1.3 times higher than CA (4). Meanwhile, in the United Kingdom's public health system, for

example, SPECT cost is only 1.5 times higher than ECHO, 5 times higher than Ex-ECG, and it is 3 times *less* costly than CA (3). Addressing these distortions could promote broader availability of cost-effective diagnostic alternatives.

One frequent concern regarding noninvasive tests is the radiation exposure associated with CTA, SPECT and CA. We have attempted to include this disadvantage in our model, by including an increase in the probability of cancer after exposure. However, the impact of radiation-related cancer was very small in our study, because of the low risk attributable to a single exposure, and the long latency before the risk arises. Still, radiation-related risks may be more pronounced for younger patients, or after repetitive testing, leading to the recommendation of keeping exposure As Low as Reasonably Achievable (ALARA) (1).

A possible limitation of our study is that input data regarding the relative performance of tests came from multiple sources obtained from the available literature. We have tried to minimize the effects of this by performing a systematic review and using large previous meta-analyses or registries as our sources of input data, but some degree of publication bias cannot be excluded.

In addition, our model did not account for costs of acquisition and implementation. These costs could have a significant additional budget impact, particularly in the case of CTA and C-MRI, currently unavailable in many – if not most – public health centers.

Our results are applicable to the choice among tests for diagnostic purposes, or, in other words, to cases in which there is uncertainty whether chest pain is due to stable angina or to an alternative diagnosis. A different use of noninvasive tests – not considered in our

analysis – is to estimate the prognosis of patients with an established diagnosis of CAD, seeking to aid in the choice of treatment modality or to assess response to therapy. In this case, some modalities that were less cost-effective for diagnosis, like Ex-ECG, may perform well enough to warrant widespread use.

Additionally, even though cost-effectiveness results are useful to determine the "standard" test for clinical use, there must be flexibility in the list of available tests, allowing physicians to select the most useful test in atypical situations.

Conclusions

For patients presenting with chest pain and low or moderate pretest probability, coronary computed tomography is cost-effective for the diagnosis of CAD, and its inclusion in the list of tests available in SUS is warranted.

Making C-MRI available in the public health system could be an attractive option, depending on what reimbursement value can be defined upon its inclusion.

Stress echocardiography is a viable alternative, and performed better than SPECT from the economic perspective.

Invasive strategies, using coronary angiography as the initial test, should be reserved for patients with high pretest probability.

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Figures and legends

Figure 1. Schematic representation of model structure.

Prob. = probability; MI = myocardial infarction; revasc. = revascularization procedures; PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft

Figure 2. Base-case cost-utility results (starting age 60 years, pretest probability 50%).

I$ = international dollars (PPP); QALY = quality adjusted life-years; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Figure 3. High pretest probability cost-utility results, including initially invasive strategies (starting age 60 years, pretest probability 70%).

I$ = international dollars (PPP); QALY = quality adjusted life-years; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Figure 4. Cost-effectiveness acceptability curve for base-case scenario

I$ = international dollars (PPP); QALY = quality adjusted life-years; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography; GDP = gross domestic product

Figure 1.

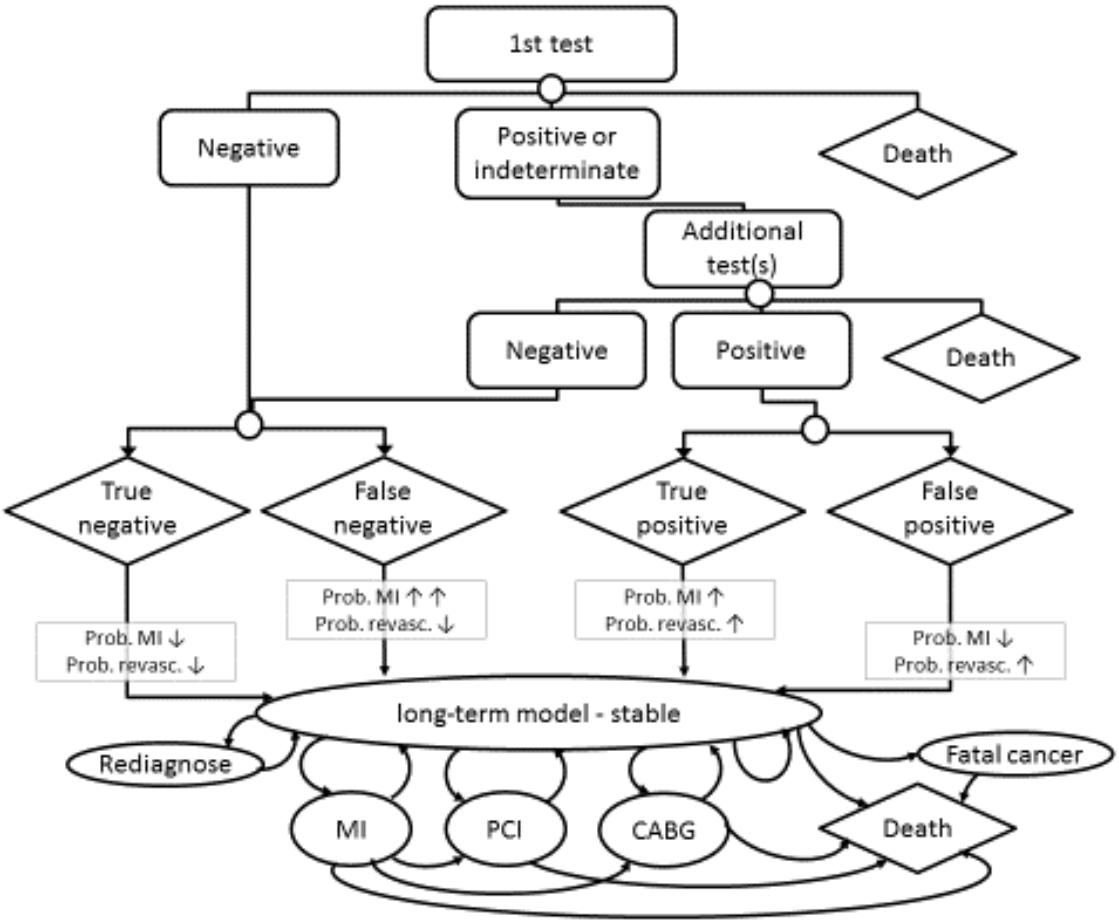

1st test
Negative
Positive or indeterminate
Death
Additional test(s)
Negative
Positive
Death
True negative
False negative
True positive
False positive
Prob. MI ↓
Prob. revasc. ↓
Prob. MI ↑ ↑
Prob. revasc. ↓
Prob. MI ↑
Prob. revasc. ↑
Prob. MI ↓
Prob. revasc. ↑
long-term model - stable
Rediagnose
Fatal cancer
MI
PCI
CABG
Death

Figure 2.

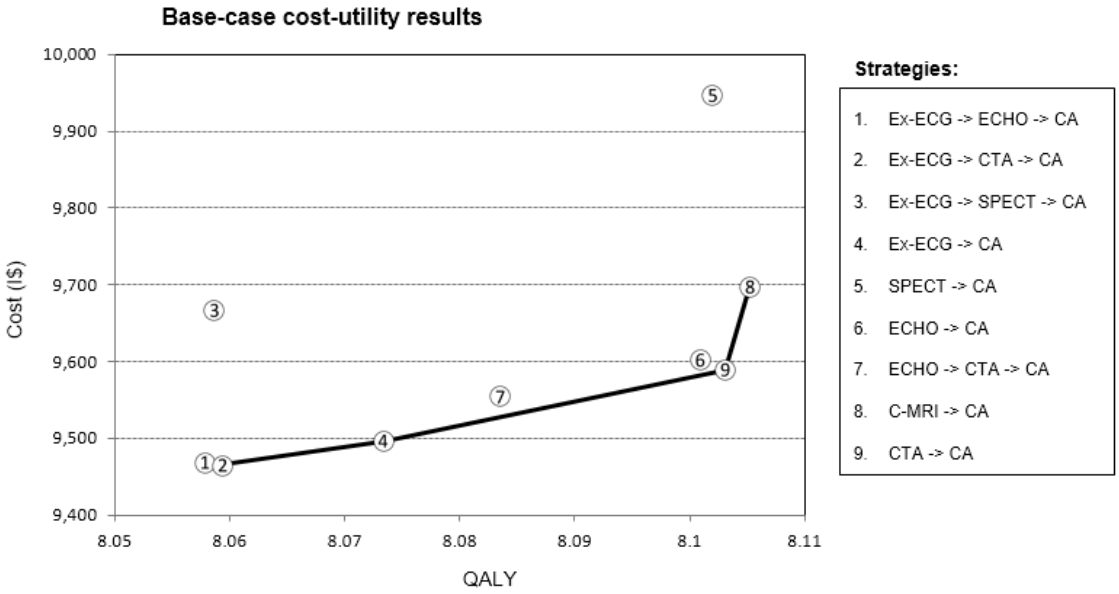

Base-case cost-utility results
10,000
9,900
9,800
9,700
9,600
9,500
9,400
Cost (I$)
8.05
8.06
8.07
8.08
8.09
8.1
8.11
QALY
Strategies:
1. Ex-ECG -> ECHO -> CA
2. Ex-ECG -> CTA -> CA
3. Ex-ECG -> SPECT -> CA
4. Ex-ECG -> CA
5. SPECT -> CA
6. ECHO -> CA
7. ECHO -> CTA -> CA
8. C-MRI -> CA
9. CTA -> CA

Figure 3.

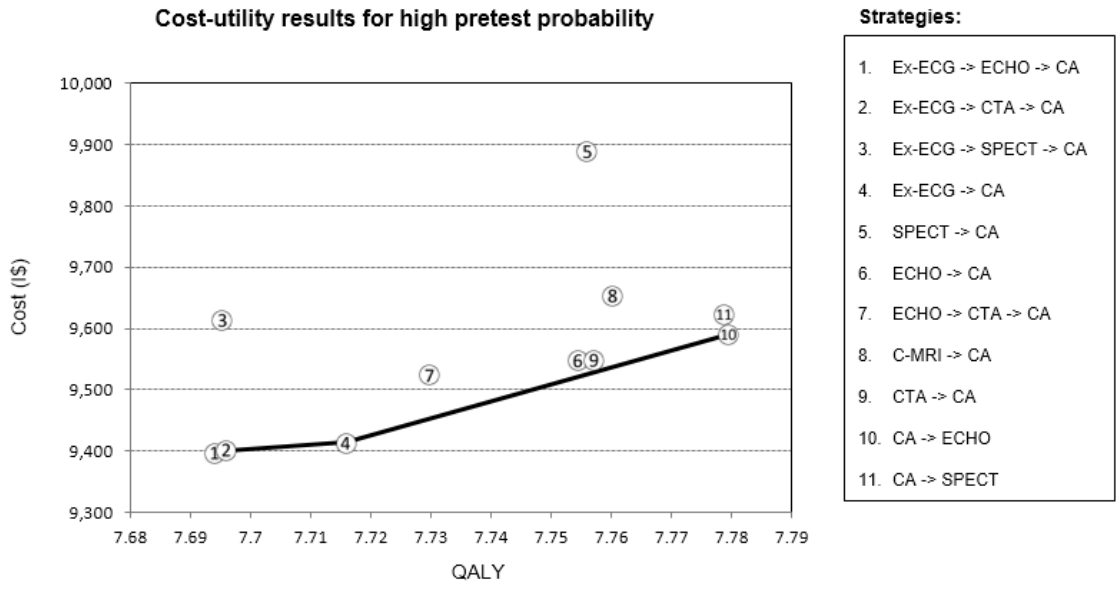
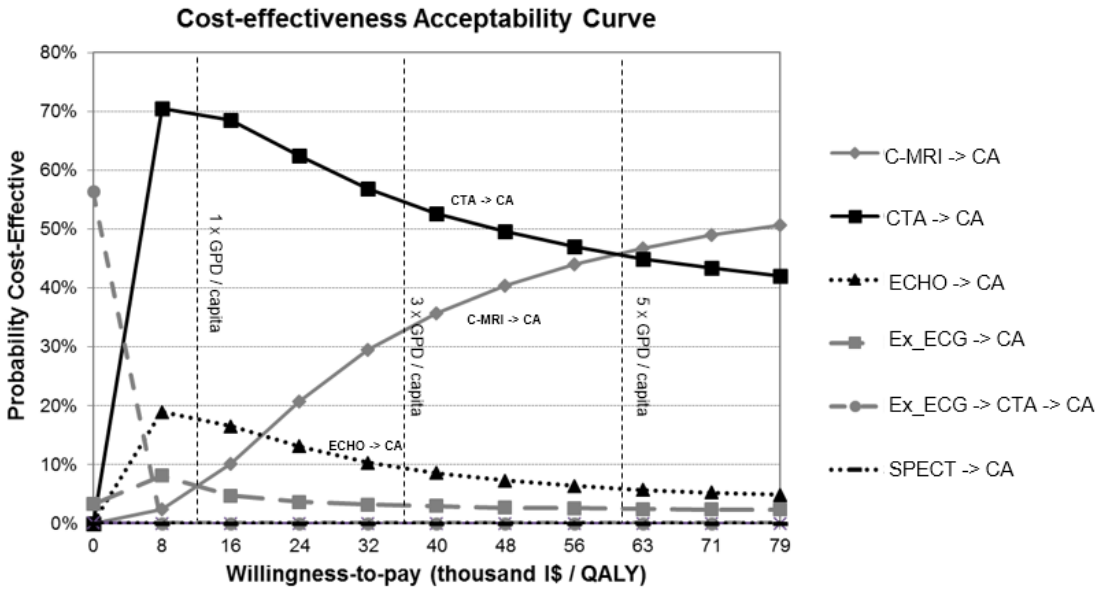

Cost-utility results for high pretest probability
Cost (I$)
10,000
9,900
9,800
9,700
9,600
9,500
9,400
9,300
7.68
7.69
7.7
7.71
7.72
7.73
7.74
7.75
7.76
7.77
7.78
7.79
QALY
Strategies:
1. Ex-ECG -> ECHO -> CA
2. Ex-ECG -> CTA -> CA
3. Ex-ECG -> SPECT -> CA
4. Ex-ECG -> CA
5. SPECT -> CA
6. ECHO -> CA
7. ECHO -> CTA -> CA
8. C-MRI -> CA
9. CTA -> CA
10. CA -> ECHO
11. CA -> SPECT

Figure 4.


Cost-effectiveness Acceptability Curve
Probability Cost-Effective
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
8
16
24
32
40
48
56
63
71
79
Willingness-to-pay (thousand I$ / QALY)
1 x GPD / capita
3 x GPD / capita
5 x GPD / capita
CTA -> CA
C-MRI -> CA
ECHO -> CA
C-MRI -> CA
CTA -> CA
ECHO -> CA
Ex_ECG -> CA
Ex_ECG -> CTA -> CA
SPECT -> CA

Tables.

Table 1. Test sequence in each modeled strategy.

ECG = electrocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography; MRI = magnetic resonance imaging.

Table 2. Characteristics of tests, range of values used in sensitivity analysis, and costs.

Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; SPECT = single-photon emission computed tomography; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography

Table 3. Input data for long-term model.

SA = sensitivity analysis; MI = myocardial infarction; prob. = probability; revasc. = revascularization; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

Table 4. Base-case cost-utility results. Results are not meant to be highly precise; decimal places shown to make small differences apparent.

QALY = quality-adjusted life-years; LY = life years; Ex-ECG = exercise electrocardiogram; ECHO = stress echocardiogram; CTA = computed tomography coronary angiogram; MRI = cardiac magnetic resonance; CA = invasive coronary angiography; CAD = coronary artery disease

Table 1. Test sequence in each modeled strategy.

	1st test	2nd test	3rd test
Strat. 1	exercise ECG	stress echocardiography	coronary angiography
Strat. 2	exercise ECG	coronary CT angiography	coronary angiography
Strat. 3	exercise ECG	SPECT	coronary angiography
Strat. 4	exercise ECG	coronary angiography	
Strat. 5	SPECT	coronary angiography	
Strat. 6	stress echocardiography	coronary angiography	
Strat. 7	stress echocardiography	coronary CT angiography	coronary angiography
Strat. 8	stress cardiac MRI	coronary angiography	
Strat. 9	coronary CT angiography	coronary angiography	
Strat. 10	coronary angiography	stress echocardiography	
Strat. 11	coronary angiography	SPECT	

Table 2. Characteristics of tests, range of values used in sensitivity analysis, and costs.

Test	Sensitivity (%) [range]	Specificity (%) [range]	Indeterm. (%)	Mortality (‰)	Cost (I$)	Sources
Ex-ECG	65 [42 – 92]	67 [43 – 83]	18	0.05	16.13	(4, 14, 19)
ECHO	85 [83 – 87]	77 [74 – 80]	15	0.05	88.71	(2, 4, 20)
SPECT	87 [84 – 88]	64 [60 – 76]	6.9	0.05	425.59	(2, 4, 20)
CTA	88 [83 – 92]	87 [80 – 92]	2	0.01	102.67	(3, 4, 21, 22)
MRI	89 [88 – 94]	80 [75 – 87]	5	0.01	203.76	(2, 4, 23)
CA	100	100	10	0.2	330.49	Assumption, (4, 24, 25)

Table 3. Input data for long-term model.

	Base-case	Range for SA	Reference(s)
Cardiovascular mortality			
Low risk	1.1%	1.0 – 1.3 %	(6)
Medium risk	2.3%	2.1 – 2.5 %	(6)
High risk	3.9%	2.7 – 5.0 %	(6)
MI			
Low risk	0.6%	0.5 – 0.7 %	(6)
Medium risk	1.1%	1.0 – 1.3 %	(6)
High risk	1.8%	1.0 – 2.6 %	(6)
Probability of new revascularization			
Low risk	1.4%	1.1 – 1.8 %	(6)
Medium risk	3.6%	3.2 – 3.9 %	(6)
High risk	5.1%	4.6 – 5.6 %	(6)

Proportion of CABG if revascularized			
Low risk	10%	5 – 20 %	Assumption
Medium risk	25%	12.5 – 50%	Assumption
High risk	50%	25 – 90%	Assumption
Procedure-related mortality			
PCI	0.68%	0.1 – 1.0 %	(26)
CABG	1.75%	1.0 – 3.0 %	(26)
Utilities			
Stable patients	0.74	0.61 – 0.86	(7, 9)
Disutility for PCI	0.04	0.0 – 0.07	(9, 27, 28)
Disutility for CABG	0.08	0.0 – 0.07	(9, 27, 28)
Disutility for MI	0.04	0.02 – 0.07	(9, 27, 29)
Costs			
PCI	I$ 834	I$ 417 – 1,667	(4)
Stent	I$ 1,076	I$ 538 – 2,153	(4)

Annual cost - stable patients	I$ 732	I$ 366 – 1,463	(8)
CABG	I$ 3,575	I$ 1,787 – 7,150	(4)
MI	I$ 1,500	I$ 749 – 2,995	(4)

Table 4. Base-case cost-utility results.

Strategy	Adjusted Lifetime Cost (I$)	Adjusted Life Expectancy (y)	Adjusted QALY	ICER (I$ / QALY)
Low pretest probability of CAD				
2 (Ex-ECG -> CTA -> CA)	9,560	11.777	8.604	
7 (ECHO -> CTA -> CA)	9,601	11.790	8.614	8,100
9 (CTA -> CA)	9,650	11.801	8.622	11,300
8 (C-MRI -> CA)	9,765	11.802	8.623	286,000
Moderate pretest probability of CAD				
2 (Ex-ECG -> CTA -> CA)	9,465	11.194	8.059	
4 (Ex-ECG -> CA)	9,496	11.213	8.073	2,200
9 (CTA -> CA)	9,589	11.254	8.103	3,100
8 (C-MRI -> CA)	9,698	11.257	8.105	50,500

High pretest probability of CAD

2 (Ex-ECG -> CTA -> CA)	9,401	10.802	7.696	
4 (Ex-ECG -> CA)	9,414	10.832	7.716	610
10 (CA -> ECHO)	9,590	10.920	7.779	2,800

7. CONCLUSÕES E CONSIDERAÇÕES FINAIS

O objetivo principal deste trabalho é fornecer informações objetivas para auxiliar a tomada de decisão relacionada à escolha de testes diagnósticos em pacientes com suspeita de cardiopatia isquêmica estável.

Antes de tudo, deve-se salientar que, em muitos casos, a hipótese diagnóstica de cardiopatia isquêmica pode ser confirmada ou refutada com base na avaliação clínica inicial. Nesses casos, propor a realização sistemática de exames complementares com finalidade diagnóstica não seria útil. Sendo assim, nossas análises se aplicam para os casos em que a avaliação clínica não é capaz de determinar de forma definitiva se os sintomas apresentados correspondem a cardiopatia isquêmica.

No primeiro artigo, demonstramos que a escolha da sequência de testes diagnósticos influencia a frequência de falsos-positivos, falsos-negativos, e também a quantidade de cateterismos cardíacos realizados sem mostrar anormalidades coronarianas.

O segundo artigo explora o impacto da escolha dos testes diagnósticos no prognóstico de longo-prazo dos pacientes. Levando-se em conta que os pacientes incialmente diagnosticados erroneamente terão oportunidades de correção do diagnóstico ao longo do acompanhamento, o impacto da escolha do teste inicial na sobrevida é pequeno, mas ainda assim há uma diferença mensurável de sobrevida ajustada para qualidade entre as estratégias testadas.

As estratégias baseadas em ergometria como teste inicial têm custo extremamente baixo, e seriam consideradas custo-efetivas mesmo em orçamentos extremamente restritos. No

entanto, observamos que trocar estas estratégias por outras que usam testes mais acurados, como ecocardiograma de estresse ou angiotomografia de coronárias, gera resultados melhores, com razão de custo-efetividade incremental bastante atraente para o contexto brasileiro.

O desempenho das estratégias baseadas em cintilografia miocárdica, amplamente empregadas atualmente, foi semelhante ao daquelas baseadas em ecocardiograma de estresse ou angiotomografia de coronárias. No entanto, o seu valor de reembolso muito mais alto do que o dos demais testes fez com que a cintilografia fosse dominada em todos os cenários.

Com o uso de ressonância magnética cardíaca, obtivemos as estratégias não-invasivas com a efetividade mais elevada. No entanto, a razão de custo-efetividade incremental dessa tecnologia se manteve acima do limiar de disposição a pagar proposto pela Organização Mundial da Saúde, de 1 a 3 vezes o Produto Interno Bruto per capita.

Os resultados se mostraram robustos nas análises de sensibilidade, e a variação da maioria dos parâmetros não influenciou de forma significativa os resultados. Nos cenários com probabilidade pré-teste mais alta, estratégias baseadas na realização de cateterismo cardíaco e cinecoronariografia, sem realizar testes não-invasivos, se mostraram dominantes.

Há ainda algum grau de incerteza quanto ao valores de reembolso que seriam adotados caso os testes atualmente não disponíveis (angiotomografia de coronárias e ressonância magnética cardíaca) se tornem disponíveis no SUS. Nossas análises mostram que, se a

ressonância magnética puder ser incorporada com valores de reembolso mais baixos, ela se tornaria uma opção atraente e de alta efetividade.

Concluímos que a incorporação da angiotomografia de coronárias ao rol de testes diagnósticos disponíveis no SUS forneceria uma opção interessante e custo-efetiva para a investigação de cardiopatia isquêmica. Dentre os testes diagnósticos atualmente disponíveis, o ecocardiograma de estresse obteve um bom desempenho do ponto de vista de custo-efetividade, e expandir o seu uso no contexto do SUS parece razoável.