UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:

CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

TESE DE DOUTORADO

CUSTO EFETIVIDADE DE TECNOLOGIAS CONTEMPORÂNEAS NO MANEJO DA DOENÇA ARTERIAL CORONARIANA: *STENTS* FARMACOLÓGICOS E CATETER DE MEDIDA DE FLUXO (FFR)

STEFFAN FROSI STELLA

Orientadora: Prof[a] Dr[a]. CARÍSI ANNE POLANCZYK

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Construímos muros demais e pontes de menos.

Isaac Newton

Não existe um caminho para a felicidade. A felicidade é o caminho.

Mahatma Gandhi

Nunca se afaste de Deus.

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SUMÁRIO

LISTA DE ABREVIATURAS EM PORTUGUÊS

ACTP - Angioplastia Coronariana Percutânea

AI - Angina Instável

CE - Custo Efetividade

CRM - Cirurgia de Revascularização Miocárdica

DAC - Doença Arterial Coronariana

DCV - Doenças Cardiovasculares

ECR - Ensaios Clínicos Randomizados

FFR - Reserva Fracional de Fluxo

IAM - Infarto Agudo do Miocárdio

QALY - Ano de Vida Ajustado para Qualidade

RCEI - Relação de Custo Efetividade Incremental

RVA - Revascularização de Vaso Alvo

SC - *Stent* Convencional

SCA - Síndrome Isquêmica Aguda

SF - *Stent* Farmacológico

SUS - Sistema Único de Saúde

TT - Trombose Tardia

WTP - Disposição a Pagar

LISTA DE ABREVIATURAS EM INGLÊS

AHA - American Heart Association

AMI - Acute Myocardial Infarction

BMS - Bare Metal *Stent*

CABG - Coronary Artery Bypass Graft Surgery

CAD - Coronary Artery Disease

CHEERS - Consolidated Health Economic Evaluation Reporting Standards Statement

DATASUS - Brazilian Epidemiological Database

DES - Drug Eluting *Stent*

EES - Everolimus Eluting *Stent*

EQ-5D - European Quality of Life–5 Dimensions

FAME - Fractional Flow Reserve versus Angiography for Multivessel Evaluation Study

FFR - Fractional Flow Reserve

GDP - Gross Domestic Product

I$ - International Dollars

ICER - Incremental Cost Effectiveness Ratio

MACE - Major Adverse Cardiac Events

MTC - Mixed Treatment Comparison

PCI - Percutaneous Coronary Intervention

PES - Paclitaxel Eluting *Stent*

PPP - Purchasing Power Parity Conversion

PTCA - Percutaneous Transluminal Coronary Angioplasty

QALY - Quality-Adjusted Life-Year

SES - Sirolimus Eluting *Stent*

ST - Stent Thrombosis

SUS - Brazilian Public Health System

TTO - Time Trade Off

TVR - Target vessel revascularization

WHO - World Health Organization

WTP - Willingness to Pay

ZES - Zotarolimus Eluting *Stent*

ZESr - Zotarolimus Eluting *Stent resolute*

LISTA DE TABELAS E FIGURAS

ARTIGO 1

ARTIGO 2

INTRODUÇÃO

A expectativa de vida no Brasil tem aumentado significativamente nos últimos anos. Melhorias nos serviços de saúde e incorporação de tecnologias que melhoram desfechos clínicos têm sido os principais fatores para uma maior sobrevida da população brasileira.[1] No entanto, a descoberta de novas tecnologias tem seguido um fluxo intenso, o que impossibilita que os sistemas de saúde consigam incorporar todas estas estratégias num contexto de recursos finitos e orçamentos limitados.[2]

As doenças cardiovasculares (DCV), por serem a principal causa de mortalidade no Brasil e no mundo, desempenham um papel fundamental na utilização de novas tecnologias e nos gastos em saúde. A doença arterial coronariana (DAC) lidera como maior causa de mortalidade dentre as DCV. Neste cenário, a DAC exige atenção especial nos planejamentos e ações em saúde, sendo além de um importante fator de morbi-mortalidade da população, um enorme gerador de gasto para o orçamento dos sistemas de saúde.[2,3]

DOENÇA ARTERIAL CORONARIANA

A DAC se caracteriza pelo estreitamento da luz das artérias coronárias, principalmente devido à fisiopatologia da aterosclerose. A doença aterosclerótica se desenvolve progressivamente através de um processo complexo que envolve principalmente a oxidação lipídica, gerando acúmulo de colesterol e de debris celulares, juntamente com a ativação do processo inflamatório com liberação de citocinas pró-inflamatórias, recrutamento leucocitário e proliferação de células musculares lisas e de macrófagos na parede arterial.[4,5] Este processo de remodelamento vascular progride ao longo dos anos, provocando uma redução do fluxo sanguíneo para o coração. Quando ocorre um desbalanço entre a oferta de sangue e a demanda de oxigênio miocárdico, como em situações de estresse emocional e exercício físico, têm-se a isquemia miocárdica.

A DAC estável é geralmente caracterizada por episódios reversíveis de isquemia ou hipóxia associada com desconforto torácico transitório (angina de peito). A angina é finalmente causada pela liberação de metabólitos isquêmicos, tais como a adenosina, que estimulam as terminações nervosas sensíveis. Entretanto, a presença de placas coronárias estáveis também pode ser completamente assintomática.[6] A gravidade funcional das lesões coronárias pode ser avaliada através de dispositivos que avaliam a medida da reserva de fluxo coronariano e as pressões arteriais intracoronárias como será descrito mais adiante.

Apesar da doença aterosclerótica ser tradicionalmente uma doença crônica, agudizações podem ocorrer em alguns indivíduos manifestando-se como síndrome isquêmica aguda (SCA) nas formas de infarto agudo do miocárdio (IAM) ou angina instável (AI). Nestes casos, geralmente ocorre obstrução coronariana total ou subtotal, usualmente

decorrente da ruptura ou erosão da capa fibrosa da placa aterosclerótica com formação de trombo subsequente, com ou sem vasoconstrição concomitante, causando obstrução crítica do fluxo sanguíneo.[7]

Do ponto de vista diagnóstico, a história, o exame físico e uma multiplicidade de exames complementares invasivos e não invasivos são utilizados para a avaliação individualizada do paciente e sua respectiva estratificação de risco, tanto no contexto da cardiopatia isquêmica estável, como na instável, dependendo da apresentação clínica do paciente. [8]

TRATAMENTO DA CARDIOPATIA ISQUÊMICA

Atualmente, o tratamento da cardiopatia isquêmica está embasado em três pilares: tratamento clínico, tratamento percutâneo e cirurgia cardíaca. De uma forma geral, todos os pacientes se beneficiam do tratamento clínico. Entretanto, em muitos casos, apesar de otimização plena dos medicamentos antianginosos, os pacientes permanecem apresentando angina ou sintomas de isquemia grave.[6,8,9] Nestes casos, o tratamento invasivo, seja por angioplastia coronariana percutânea (ACTP) com balão, angioplastia com *stent* ou cirurgia de revascularização miocárdica (CRM), podem agregar benefício ao paciente, dependendo da condição clínica e da anatomia coronariana do indivíduo.[10,11] Todas estas modalidades terapêuticas têm suas limitações e riscos específicos.[12]

Contemporaneamente, diversas tecnologias têm surgido para aperfeiçoar as estratégias já utilizadas no manejo da doença arterial coronariana e também para reduzir os riscos inerentes a estas terapias. Dentre estas tecnologias contemporâneas pode-se ressaltar: os *stents* farmacológicos (SF) e o cateter de medida da reserva fracional de fluxo (FFR). O primeiro tem comprovadamente reduzido as taxas de revascularização percutânea

devido a reestenose intra-*stent* em comparação ao *stent* convencional (SC). Já o segundo tem tido potencial benefício atribuído a intervenção seletiva apenas do(s) vaso(s) responsável(is) pela isquemia miocárdica.[13]

No entanto, os avanços na área da saúde em geral estão associados a um custo elevado. Sendo assim, para incorporação de tecnologias deve-se, não somente considerar a efetividade isoladamente, mas também ponderar a sua magnitude em relação aos custos relativos a sua aplicação. Como já comentado anteriormente, a manutenção de um equilíbrio sustentável nos sistemas de saúde deve ser pautada na escolha de estratégias consideradas prioritárias para serem disponibilizadas para a população. Dessa forma, existe a necessidade da construção de modelos de análises econômicas bem conduzidas que possibilitem a tomada de decisão estruturada por parte dos gestores em saúde dentro do contexto local no qual a determinada tecnologia será implementada.

ANGIOPLASTIA PERCUTÂNEA COM *STENT*

A angioplastia coronariana percutânea consiste na abertura ou desobstrução da luz da artéria coronária por meio de um cateter balão, que é insuflado, rechaçando a placa ateromatosa contra a parede do vaso. Esta modalidade terapêutica é eficaz no alívio dos sintomas do paciente, podendo ter, no entanto, uma durabilidade limitada, principalmente devido ao retorno da placa tratada, estreitando novamente a luz da artéria, processo este definido como reestenose.[8,13]

No intuito de reduzir a taxa de reestenose dos tratamentos percutâneos com balão surgiram dispositivos metálicos, chamados *stents*, que ao serem insuflados junto ao cateter balão se expandem produzindo uma abertura mais su*stent*ada do lúmen arterial. As plataformas metálicas dos *stents* podem ser feitas de aço inoxidável, cromo-cobalto ou cromo-platina. As ligas de cromo cobalto e cromo-platina buscam maior força radial e maior conformabilidade em comparação as de aço inoxidável.[14] No seguimento destes tratamentos, porém identificou-se que existe, por vezes, uma reepitelização do *stent*, o qual se comporta como um corpo estranho provocando reação inflamatória e consequente reestenose no *stent*.[15]

Apesar dos *stents* metálicos reduzirem significativamente as taxas de reestenose em comparação com angioplastia por balão, estas continuaram elevadas, sendo este seu principal limitante. Com isso, na busca de taxas cada vez menores de reestenose, surgiram *stents* recobertos com medicações que inibem o crescimento epitelial na luz do *stent*, assim reduzindo significativamente as reestenoses e por consequência a necessidade de nova intervenção.[16]

No entanto, os estudos com *stents* farmacológicos não conseguiram demonstrar benefícios em termos de desfechos duros como redução de IAM e mortalidade. Além disso, na literatura recente, surgiram indícios de que a não reepitelização intra-*stent* o deixaria em maior risco para desenvolver trombose tardia (TT), um evento grave e potencialmente fatal observado neste tipo de tratamento.[17-21]

STENTS FARMACOLÓGICOS

Os *stents* farmacológicos são compostos por três componentes: uma plataforma de *stent* metálico e um revestimento de polímero (comum aos *stents* convencionais), e um agente antiproliferativo. Dentre os diversos agentes antiproliferativos já testados, alguns tiveram melhor performance ou segurança e foram comercialmente mais difundidos. No escopo desta revisão forma considerados os seguintes fármacos: sirolimus, paclitaxel, everolimus e zotarolimus.[14]

Stents recobertos com sirolimus ou paclitaxel

Uma meta-analise de comparação direta e indireta, demonstrou que existe uma redução acentuada na taxa de repetição da revascularização com ambos os *stents* recobertos com sirolimus e *stents* recobertos com paclitaxel, em comparação com *stent* convencional. No entanto, os *stents* que liberam sirolimus ou paclitaxel têm sido associados com um aumento risco de trombose muito tardia, em comparação com *stents* convencionais.[18,22] Em contraste, os riscos de morte e infarto do miocárdio com o uso de *stent* recoberto com sirolimus e *stents* recobertos com paclitaxel foram semelhantes quando comparados com *stents* convencionais.[23]

Dados de uma metanálise que incluiu 47 ensaios clínicos randomizados (ECR) demonstram que não houve diferença entre estas duas modalidades terapêuticas para os desfechos de morte, IAM ou trombose. Apesar destes achados, houve redução de revascularização de vaso alvo (RVA) em 6 meses (OR 0,18; IC 95% 0,14 - 0,25) e em 5 anos de seguimento (OR 0,21; IC 95% 0,15 - 0,29) com o *stent* recoberto com sirolimus quando comparado com o *stent* convencional. Da mesma forma, em pacientes que utilizaram *stents* recobertos com paclitaxel, os achados foram semelhantes: redução de revascularização de lesão alvo em 6 meses (OR 0,35; IC 95% 0,28 - 0,45) e em 4 anos (OR 0,33; IC 95% 0,24 - 0,45). Estes achados corroboram a manutenção do benefício em longo prazo.[11]

Stents recobertos com Everolimus

Ensaios clínicos randomizados demonstraram que os *stents* recobertos com everolimus apresentaram melhores resultados clínicos em comparação com os *stents* convencionais, reduzindo os riscos de revascularização, infarto do miocárdio e trombose de *stent*.[24,25] Estudos randomizados comparando *stents* que liberam everolimus e aqueles com liberação de sirolimus apontaram resultados semelhantes em relação às taxas de morte, infarto do miocárdio e revascularização.[26,27] Já os ECR comparando *stents* recobertos com everolimus e aqueles recobertos com paclitaxel demonstraram menores taxas de RVA, IAM e trombose do *stent*, não diferindo em termos de mortalidade.[28,29] Quando comparado com os *stents* recobertos com zotarolimus, principalmente o resolute, teve efetividade e segurança semelhante.[30,31]

Stents recobertos com Zotarolimus

Stents recobertos com zotarolimus parecem reduzir o risco de infarto do miocárdio, sem comprometer a eficácia, quando comparados com *stents* recobertos com paclitaxel.[32,33] Já os estudos que compararam pacientes tratados com *stents* recobertos com zotarolimus

em comparação com pacientes tratados com *stents* recobertos com sirolimus, demonstraram um maior risco de revascularização entre os pacientes tratados zotarolimus (5,6% vs 3,5% , P <0,001), enquanto os pacientes tratados com *stents* com sirolimus tinham um risco maior de trombose do *stent* (0.3% vs. 1.1%, P<0.001).[33,34] O *stent* recoberto com zotarolimus Resolute© foi comparado com o *stent* recoberto com everolimus em dois ensaios randomizados, onde foi demonstrado riscos semelhantes de morte, infarto do miocárdio, nova revascularização e trombose de *stent* ao longo de um período de 2 anos.[30,31]

Uma metanálise com comparação direita e indireta, com método de MTC (mixed treatment comparison) avaliando *stents* convencionais e *stents* farmacológicos referidos nesta revisão (sirolimus, paclitaxel, everolimus, zotarolimus e zotarolimus resolute©) concluiu que os *stents* farmacológicos são altamente eficazes na redução do risco de revascularização do vaso alvo, sem um aumento significativo nos dados de segurança, inclusive trombose de *stent* quando considerados os *stents* recobertos com everolimus e zotarolimus resolute. No entanto, entre os tipos de *stents* farmacológicos havia diferenças consideráveis, tais que os *stents* recobertos por everolimus, sirolimus e zotarolimus resolute foram os mais eficazes e o recoberto por everolimus o *stent* mais seguro.[35]

Segundo as diretrizes da *American Heart Association* (AHA) a utilização de *stents* convencionais deve ser indicada em pacientes com alto risco de hemorragia, a incapacidade de cumprir pelo menos 12 meses de dupla antiagregação plaquetária, ou quando previsto procedimentos invasivos ou cirúrgicos dentro dos próximos 12 meses, durante o qual tempo dupla antiagregação plaquetária podem ser interrompidos (Recomendação nível I e grau de evidência B).[13]

A utilização de *stents* farmacológicos está indicada como alternativa aos stents convencionais para reduzir o risco de restenose, em casos em que o risco de restenose é aumentada e o paciente possa ser incapaz de tolerar e respeitar o uso prolongado de dupla antiagregação plaquetária: [13]

- Recomendação nível I e grau de evidência A para angioplastias eletivas e IAM com supra desnivelamento do segmento ST).

- Recomendação nível I e grau de evidência C para Angina instável e IAM sem supra desnivelamento do segmento ST).

De uma forma geral, mesmo sem demonstrar benefícios em termos de redução de mortalidade, o beneficio de alívio de sintomas e diminuição da necessidade de reintervenções, principalmente na população de alto risco de reestenose, seriam suficientes para uma boa aceitação dos *stents* farmacológicos, não fossem seus elevados custos, principalmente o custo inicial na implantação do dispositivo e a manutenção a longo prazo de dupla antiagregação plaquetária. [11,35,36]. Para países onde as questões econômicas são secundárias no processo de decisão, os stents farmacológicos são empregados em mais de 90% de procedimentos percutâneos coronarianos, ao passo em que para outros, eles têm sido restritos para grupos de mais alto risco ou através de renegociação de preços. Sendo assim, o custo agregado desta tecnologia tem sido determinante da sua incorporação parcial ou plena, e requer uma análise mais aprofundada no que se refere à sua relação de custo-efetividade, na tentativa de se acessar o seu real papel no contexto da saúde pública com orçamentos extremamente limitados.

CUSTO EFETIVIDADE DO STENT FARMACOLÓGICO

Na última década, muitas avaliações econômicas sobre *stents* farmacológicos foram realizados, principalmente nos países desenvolvidos, com a análise de diferentes cenários.[37-40] Os resultados variam de acordo com preços de mercado e seletividade do uso de *stents* farmacológicos.

Um estudo canadense mostrou uma relação de custo efetividade incremental (RCEI) de Can$ 58.721 no resultado do caso-base, com RCEI variando de Can$ 40.129 a Can$ 72.464 entre os subgrupos com base na idade e estado de diabetes.[41] Um recente estudo, também do Canadá, demonstrou um RCEI de Can$ 52,585 por RVA evitada, e Can$ 1.569.875 por ano de vida ajustado para qualidade (QALY) ganho, variando, respectivamente, de Can$ 13.888 para Can$ 278.499, e de Can$ 419.202 para Can$ 9.142.603, refletindo os pacientes com maior e menor risco de reestenose.[42] Em 2013, Wijeisundera et al compararam três estratégias para o tratamento inicial de CAD: terapia médica, ACTP com SC e ACTP com SF, e eles demonstraram que SC produziu um RCEI de 13.271 dólares / QALY sobre a terapia médica e os *stents* farmacológicos foram dominados pela estratégia com *stents* convencionais.[43]

Hill et al. reavaliaram a custo efetividade (CE) dos *stents* farmacológicos e concluíram que estes não são custo efetivos nas atuais disposições a pagar (WTP) para o sistema de saúde do Reino Unido. Estes podem ser CE em subgrupos definidos com altos riscos de reintervenção. Os *stents* farmacológicos também poderiam ser CE para grupos maiores de pacientes, se o diferencial de preço fosse consideravelmente reduzido.[39] Estudos de custo-efetividade produzidos na Suécia e Suíça têm mostrado resultados semelhantes, que os *stents* farmacológicos são custo efetivos apenas em pacientes de alto risco de reestenose.

Os autores sugerem que para uma utilização mais liberal, o preço dos *stents* farmacológicos deveria ser substancialmente reduzido.[44,45]

Dois estudos de custo-efetividade avaliando os *stents* farmacológicos com especial atenção para trombose de *stent*, ambos na perspectiva do sistema de saúde dos Estados Unidos. Garg et al concluíram que mesmo um pequeno aumento absoluto na trombose dos SF (> 0,14% / ano) resultaria em escolha da estratégia com *stents* convencionais para a população em geral.[20] Filion et al descobriram que os eventos adversos tardios relacionados trombose do *stent* e a necessidade de terapia antiplaquetária dupla prolongada aumenta substancialmente os custos associados com a implementação de *stent* farmacológico. A inclusão destes custos torna o uso generalizado de *stents* farmacológicos não custo efetivas nos Estados Unidos em termos de custo por QALY e custo por revascularização evitada.[19]

No cenário brasileiro, foram conduzidos, em 2007 e 2010, estudos de custo efetividade comparando estratégias com implante do *stents* convencionas versus *stents* farmacológicos, nas perspectivas do Sistema Único de Saúde (SUS) e do sistema suplementar. As relações de custo efetividade do *stent* farmacológico foram elevadas no modelo brasileiro. O uso de *stent* farmacológico foi mais favorável em pacientes de alto risco de reestenose, com elevado custo do manejo de reestenose e sob a perspectiva não pública.[46,47]

ANGIOPLASTIA PERCUTÂNEA GUIADA POR MENSURAÇÃO DA RESERVA FRACIONAL DE FLUXO (FFR)

Dados fisiológicos da artéria coronária podem ser usados para facilitar a decisão clínica nos laboratórios de cateterismo. Somente a angiografia, não consegue determinar a importância clínica e fisiológica de estenoses coronárias entre 40% e 80% do diâmetro normal. No sentido de diminuir estas limitações alguns dispositivos, como o cateter de medida da reserva fracional de fluxo (FFR), podem ser usados antes de realizar intervenções coronarianas.[48-50]

O FFR é um cateter de diâmetro 0,014" e permite a medida do fluxo e pressão distal a estenose do vaso. Este cateter usa a medida de pressão translesional em hiperemia. A hiperemia é induzida por adenosina intravenosa ou intracoronária. A razão da pressão distal da coronária pela pressão aórtica durante a máxima hiperemia é chamada de reserva fracional de fluxo e é uma estimativa da porcentagem de fluxo sanguíneo que estaria disponível para o miocárdio. O valor normal é 0,95-1, enquanto valores menores 0,75 estão associados com provável isquemia.[51] A correlação de isquemia no teste de estresse com os valores de FFR <0,80 foi estabelecida em estudos comparativos com alta sensibilidade (88%), especificidade (100%), valor preditivo positiva (100%) e acurácia geral (93%).[50]

As medidas de pressão coronária identificam a severidade clínica das lesões individuais em pacientes com DAC. O papel potencial da medida da FFR para todas as lesões angiograficamente significativas antes da intervenção percutânea tem sido avaliado.

O estudo DEFER, um ensaio clínico randomizado, que seguiu por 5 anos 325 pacientes com DAC e lesões coronarianas com estenose intermediária referenciados para

angioplastia percutânea. Foi realizada a medida de FFR imediatamente antes da intervenção planejada. Se a medida de FFR fosse maior do que 0,75, os pacientes eram aleatoriamente designados para diferimento da angioplastia (grupo Defer, n 91) ou a execução da angioplastia (grupo Perform, n 90). Se FFR fosse menor do 0,75, a angioplastia era realizada conforme o planejado (grupo de referência, n 144). A sobrevida livre de eventos não foi diferente entre os grupos Defer e Perform (80% e 73%, respectivamente; p=0,52), mas foi significativamente pior no grupo de referência (63%, p=0,03). O desfecho composto de morte cardíaca e infarto agudo do miocárdio nos grupos Defer, Perform e referência foi de 3,3%, 7,9% e 15,7%, respectivamente (p=0,21 para Defer vs Perform; p=0,003 para o grupo Referência vs ambos os outros grupos). A percentagem de pacientes livres de dor no peito durante o acompanhamento não foi diferente entre os grupos Defer e Perform.[52,53]

O estudo FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) avaliou 1005 pacientes com doença multiarterial que foram designados para estratégia com implantação de *stent* farmacológico em todas as lesões indicadas pela angiografia (estenoses maiores do que 50%) ou estratégia com avaliação da FFR para decisão da intervenção somente nas lesões em que a medida de FFR fosse menor do que 0,80. Após 1 ano de seguimento o desfecho primário de morte, IAM não fatal e procedimento de revascularização ocorreu significativamente menos no grupo ACTP guiada por FFR (13,2 vs 18,3%), principalmente devido a menores taxas de IAM (5,7 vs 8,7%) e revascularização (6,5 vs 9,5%).[23] Além disso, o número médio de *stents* foi significativamente menor no grupo FFR (1,9 vs 2,7). Aproximadamente 80% dos pacientes em ambos os grupos ficaram livres de angina em 1 ano. No seguimento de dois anos observou-se manutenção da redução da taxa de IAM, além do desfecho combinado de morte e IAM não fatal (p=0,003).[54,55]

Miller et al realizaram um estudo coorte prospectivo de pacientes consecutivos encaminhados para angiografia coronária em que forma encontradas lesões de gravidade intermediária. Foram realizadas medidas de FFR e a revascularização foi adiada naquelas lesões com uma medição maior do que 0,8. Um total de 151 pacientes foram estudados, sendo que 57 pacientes (37,7%) foram submetidos à revascularização com base em sua medida do FFR. O tempo médio de acompanhamento foi de 6,1 anos (variação, 5-10 anos). No final do período de seguimento, 107 doentes (70,9%) estavam vivos. Comparando-se o grupo de revascularização inicial com o grupo em que a revascularização foi adiada, 64,9% e 74,5% estavam vivos, respectivamente (p = 0,29). Do grupo inicial de revascularização, 12,3% haviam sido submetidos a revascularização tardia da lesão em que FFR foi apresentado originalmente, em comparação com 11,7% no grupo de diferido (p = 0,99). Os autores concluíram que o FFR é um complemento útil para a angiografia coronária na seleção de pacientes com lesões de gravidade angiográfica intermediário em quem revascularização coronária pode ser adiada com segurança.[56]

Foi recentemente publicado resultados de acompanhamento de pacientes submetidos a angioplastia guiada por FFR do Registre Francais de la FFR (R3F). [57] Foram investigados 1.075 pacientes consecutivos submetidos à angiografia diagnóstica, incluindo uma investigação FFR em 20 centros franceses. Os investigadores foram convidados a definir a sua estratégia de revascularização prospectivamente a priori com base na angiografia antes de realizar o FFR. A estratégia final de revascularização, reclassificação da estratégia por FFR, e 1 ano de seguimento clínico foram registrados prospectivamente. A estratégia a priori com base na angiografia foi terapia médica em 55% e de revascularização em 45% (intervenção coronária percutânea, 38%, cirurgia de revascularização do miocárdio, 7%). Os pacientes foram tratados de acordo com o FFR em 1028 dos 1075 pacientes

(95,7%). A estratégia aplicada após FFR foi terapia médica em 58% e de revascularização em 42% (intervenção coronária percutânea, 32%, cirurgia de revascularização do miocárdio, 10%). A estratégia final aplicada diferia da estratégia a priori em 43% dos casos: em 33% dos pacientes em tratamento clínico a priori, em 56% dos pacientes submetidos a intervenção coronária percutânea a priori, e em 51% dos pacientes submetidos a cirurgia de revascularização miocárdica a priori. Em pacientes tratados e reclassificados com base no FFR e em desacordo com a estratégia baseada em angiografia (n = 464), o resultado na taxa de eventos cardíacos maiores (11,2%) foi semelhante a dos pacientes nos quais a estratégia aplicada concordou com angiografia com base em uma decisão a priori (11,2 vs 11,9%; p = 0,78). Em 1 ano de seguimento, mais de 93% dos pacientes estavam assintomáticos, sem diferença entre os pacientes reclassificados e não reclassificados (p = 0,75). Este estudo sugere que a realização FFR durante a angiografia diagnóstica está associada a reclassificação da decisão de revascularização em cerca de metade dos pacientes. Demonstra, ainda, que ele é seguro para prosseguir uma estratégia de revascularização divergente do que sugerido pela angiografia.[57]

A utilização do FFR está indicada como ferramenta adjuvante para avaliar pacientes com lesões angiográficas de severidade intermediária (entre 50% a 70% de estenose) e pode ser útil para orientar a revascularização decisões em pacientes com DAC estável (Recomendação nível IIa e grau de evidência A).[13]

CUSTO EFETIVIDADE DO FFR

Usando dados do estudo DEFER foi conduzido estudo de custo efetividade, na perspectiva do sistema de saúde dos Estados Unidos comparando angiografia, imagem nuclear em estresse e medidas de FFR. Este estudo concluiu que a estratégia baseada no FFR poderia ser "cost-saving" em relação às demais. As análises de sensibilidade não mostraram conclusões diferentes em relação ao caso base, sendo a estratégia com a utilização de imagem nuclear em estresse mais atrativa, somente se sua especificidade fosse 25% maior que a especificidade proposta para a estratégia baseada no FFR.[58]

Foi conduzido estudo de avaliação econômica com os dados do estudo FAME e foi encontrada uma diminuição significativa na média dos custos gerais no grupo de intervenção guiada por FFR ($14.315 vs $16.700), atribuída principalmente a redução do uso de *stents* farmacológicos. A conclusão do estudo foi que a estratégia de intervenção guiada por FFR era "cost-saving" em relação à intervenção guiada por angiografia somente. Os resultados foram robustos para uma grande variação nos parâmetros de incerteza, sendo que a análise de *bootstrap* a estratégia com uso de FFR foi dominante (cost-saving) em 90% das simulações.[59]

RACIONAL DO ESTUDO

Sabe-se, atualmente, que os custos iniciais do procedimento são maiores com o uso de *stents* farmacológicos. No entanto, o uso destes está atrelado a uma menor taxa de revascularização. Em longo prazo, os custos com o seguimento parecem ser maiores com o *stent* convencional, porém possivelmente não suplantem os custos iniciais. Além disso, não há até momento benefício comprovado com relação à redução de desfechos duros como mortalidade e infarto agudo do miocárdio quando comparadas as duas modalidades terapêuticas. No entanto, devido preocupação com a possibilidade aumentada de trombose tardia nos *stents* farmacológicos, uso prolongado de antiagregação plaquetária e com surgimento de *stents* farmacológicos de 2ª geração, além do melhor registro do uso em longo prazo destes dispositivos, fazem-se necessários novos estudos de custo efetividade no contexto de saúde pública brasileira.

A utilização de cateteres de medida de pressão para a estimativa da FFR tem-se mostrado efetiva na complementação e na tomada de decisão de procedimentos percutâneos coronarianos. Existe uma tendência de que os custos adicionais relacionados ao uso desta ferramenta se equalizem com a diminuição do número de *stents* e eventos relacionados a reestenose. Além disso, um estudo de custo efetividade mostrou esta estratégia ser menos custosa e mais efetiva no cenário do sistema de saúde americano.[58,59] Até o presente momento ainda não existem estudos realizados acessando a custo efetividade deste dispositivo no cenário do sistema de saúde brasileiro.

OBJETIVOS

1. Avaliar a relação de custo efetividade dos *stents* farmacológicos no manejo terapêutico da doença arterial coronariana estável como alternativa ao *stent* convencional.

2. Avaliar a relação de custo efetividade da utilização da medida de fluxo fracional (FFR) como ferramenta adjuvante nos procedimentos percutâneos para o tratamento da doença arterial coronariana multiarterial.

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Drug Eluting Stents in Brazil: the price should be lower

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ABSTRACT

BACKGROUND: Although Drug Eluting Stents (DES) have been widely incorporated into clinical practice in developed countries, several countries restrict their use mainly because of their high cost and unfavorable incremental cost effectiveness ratios (ICER).

OBJECTIVE: This study aims to evaluate the ICER of DES as an alternative to bare metal stents (BMS), in the Brazilian public health system (SUS) scenario, for treatment of coronary artery disease (CAD), considering updated effectiveness and costs of commercially available stents.

DESIGN: Markov decision analytic model.

DATA SOURCES: Published literature, government database and CAD patients' cohort.

TARGET POPULATION: CAD patients aged 60 years or older.

TIME HORIZON: 1 year and lifetime.

PERSPECTIVE: Brazilian Public Health System (SUS).

INTERVENTION: The model was structured to analyze six different therapeutic strategies composed of: percutaneous intervention with a BMS or one of five DES (paclitaxel, sirolimus, everolimus, zotarolimus and zotarolimus resolute). It was based on a cohort of patients with symptomatic, single-vessel CAD that could undergo any of the six strategies.

OUTCOME MEASURES: ICER for 1-year target vessel revascularization (TVR) avoided and quality-adjusted life-year (QALY) gained, expressed in International dollars (I$).

RESULTS OF BASE-CASE ANALYSIS: In short term analysis the ICER for the DES were estimated at I$20,642 to I$32,001 per TVR avoided comparing to BMS. Among the DES, SES was the more efficacious and less costly stent, followed by EES, ZESr, PES and ZES. In the lifetime analysis the ICERs vary from I$ 62,761 to 441,462 per QALY. The ZESr had the most favorable ICER among the DES, followed closely by EES, SES, PES and ZES, even though all the results were above the willingness to pay (WTP) of 3 times the gross domestic product (GDP) per capita (I$ 35,307).

RESULTS OF SENSITIVITY ANALYSIS: Both the EES and the ZESr performed similarly, and had the best results among the DES. However, at current commercial prices they are not cost effective at any setting. Price difference between BMS and DES lower than I$ 1,125 produces ICER below the WTP for both ZESr and EES.

CONCLUSION: As valued in the Brazilian market, DES is not a good value for money for QALY and for TVR avoided. Since the cost-effectiveness of DES is mainly driven by the price difference in comparison with BMS, they should cost less than twice the BMS price, in order to be a cost-effective alternative.

KEYWORDS: cost effectiveness, drug eluting stent, bare metal stent, coronary artery disease.

INTRODUCTION

Through the last decade of clinical use, drug-eluting stents (DES) have proven efficacy in reducing the incidence of in-stent restenosis and target vessel revascularization (TVR), with no significant effect on rates of death or myocardial infarction (AMI), compared with bare-metal stents (BMS). First-generation DES have been associated with an increased risk of late stent thrombosis (ST); newer DES have claimed to be safer. [1-4]

Although DES have been widely incorporated into clinical practice in developed countries, several countries restrict their broad use, mainly because of their high cost and unfavorable incremental cost-effectiveness ratios (ICER). [2,5-13]

In the Brazilian Public Health system (SUS), only BMS are approved for use in percutaneous procedures, and the number of stents is growing. In 2012 approximately 87,500 stents were implanted, amounting about $405 million Reais spent [14]. In 2007 and 2010, cost effectiveness studies comparing DES and BMS were conducted from the SUS perspective., and DES use only have a favorable ICER in patients at high risk of restenosis, such as diabetic patients. [11,12,15,16] Nonetheless, because of thrombosis risks and overall financial impact on the healthcare system, DES were not approved for routine use in public assistant patients.

This study aims to revaluate the ICER of DES as an alternative to bare metal stents (BMS), in the Brazilian public health system (SUS) scenario, for treatment of coronary artery disease (CAD), considering updated effectiveness and costs of commercially available stents.

METHODS AND MATERIALS

An analytic Markov model was built to simulate short-term (within 1 year) and long-term (lifetime) outcomes and costs after a percutaneous coronary intervention procedure (PCI) with BMS or one of the following DES: sirolimus (SES), paclitaxel (PES), everolimus (EES), zotarolimus (ZES) or zotarolimus resolute (ZESr).

POPULATION

The model simulated a hypothetical cohort of 60 year-old patients with symptomatic single-vessel CAD, who were eligible for PCI using a BMS or a DES, in the SUS perspective.

DECISION MODEL STRUCTURE

Along the first year after the index procedure, the model considered the possibility of occurrence of stent-related outcomes (TVR and ST), as well as outcomes related to CAD natural course (AMI and percutaneous or surgical revascularization for worsening angina). After the first year, the cohort is free of stent-related outcomes, except for the possibility of very late stent thrombosis. If the patient undergoes another percutaneous procedure, risk of stent-related outcomes is again applied during one year. A schematic representation of the decision tree is demonstrated in figure 1.

MODEL ASSUMPTIONS

The model assumes implantation of one stent per patient in index and subsequent procedures. Cases of symptomatic restenosis were treated with angioplasty and implantation of the same stent used in the first procedure. Patients could be referred to coronary artery bypass graft (CABG) in case of a third episode of restenosis. One year after the index procedure, the patient was considered free of risk of restenosis and target lesion revascularization.

Stent thrombosis could present as fatal or nonfatal AMI; those who survive it were subjected to a percutaneous transluminal coronary angioplasty (PTCA) with stent implantation. Lifetime risk of ST was considered in the base-case, and in sensitivity analysis shorter periods at risk were tested. We assumed exposure to dual antiplatelet therapy for 12 months after DES implantation, and 1 month after BMS implantation.

A one-year year cycle length was modeled to adequately represent the period at risk for stent-related events, and lifetime horizon to assess the results in terms of QALYs. Costs and utilities were discounted by 5% per year, according to national guidelines.[17]

DATA SOURCES

Parameters for the main clinical outcomes and transition probabilities were extracted from the medical literature and from a cohort of CAD patients assisted at a tertiary public hospital in southern Brazil (CAD cohort HCPA). Table 1 and table 2 summarize the key transition probabilities in the model and the outcomes effects, respectively. Survival data were obtained from 2011 Brazilian life tables, produced by Brazilian Institute of Geography and Statistics (IBGE). [18]

Cost parameters were based on the Brazilian epidemiological database (DATASUS) and on SUS reimbursement tables. [14] A search on DATASUS was performed, surveying mean monthly cost of reimbursed procedures and hospitalizations for SUS in 2012 and 2013. DES cost was estimated based on information provided from private hospital and private health insurance provider, reflecting average market price. All costs were converted from Brazilian Real to International Dollars (I$), using the World Bank's latest available purchasing power parity conversion (PPP) factor of 1.89, relative to 2012. [19] Table 3 summarizes unitary cost parameters in the model.

A CAD patients cohort in a tertiary hospital was subjected to preference-based measure of health data (SF-6D), to estimate utility for health states in the model (table 4).

Disutility associated with revascularization procedures was assumed to be the difference between utility values from patients immediately before the procedure and 3 months after. Disutility values were applied only in the current cycle.[20]

ENDPOINTS AND THRESHOLDS

Primary endpoints were ICER for 1-year target vessel revascularization (TVR) avoided and for lifetime QALY gained. Since in Brazil there is no an official willingness-to-pay (WTP) threshold, we use the World Health Organization (WHO) recommendation of economic values between 1 to 3 times the Gross Domestic Product (GDP) per capita. [21] We assume 1 GDP/capita (I$ 11,769) for TVR avoided and 3 GDP/capita (I$ 35,307) for QALY gained as willingness-to-pay thresholds. [22]

ANALYSIS

The base-case analysis was performed estimating the ICER with BMS as a reference strategy, relative to each of the five DES. All the parameters were tested in 1-way and 2-way deterministic sensitivity analysis, to assess how the variation impacts the outcomes of the model. We evaluated different assumptions for critical model parameters, including TVR rate, ST rate, cost of BES and cost of DES. In addition, to estimate the uncertainty surrounding the ICERs, we conducted probabilistic sensitivity analysis with 10,000 random trials, with variation of the different parameters according to a distribution estimated from published data or clinically plausible ranges. The model was constructed and all analyses were performed usign TreeAge Pro 2013 (TreeAge software Inc.).

RESULTS

BASE-CASE ANALYSIS

Cumulative 1-year incidence of TVR was 15.1% for BMS, ranging from 4.0% to 7.3% for DES. One-year costs were I$4,400 for BMS, and I$6,707 to I$6,907 for DES (Table 5). ICERs for DES were estimated at I$20,642 to I$32,001 per TVR avoided, comparing to BMS. Among the DES, SES was the most effective and least costly stent, followed by EES, ZESr, PES and ZES. All ICERs were above the WTP threshold of 1 GDP per capita (I$ 11,769), and much higher than the cost of a procedure with a BMS (I$ 3,687).

Table 6 shows the cumulative life years (LY), QALYs, costs and ICERs of each strategy in lifetime horizon. ZESr had the most favorable ICER among the DES, followed closely by EES, SES, PES and ZES, even though all the results were above the WTP of 3 GDP per capita (I$ 35,307). The modeled population survival was 11.2 years for 60-year old symptomatic CAD patient after a PCI, about 2 years lower than expected for the Brazilian population in general (73.1 years).[18]

DETERMINISTIC SENSITIVITY ANALYSIS

In the short term analysis, our results were sensitive to the rate of TVR, the costs of DES and the number of stents used per patient. Considering a WTP of 1 GDP per capita for TVR avoided, the strategy using SES would be cost-effective only for a TVR rate above 25.5% for BMS associate a stent cost below I$ 2,525. When cost of a PCI procedure with BMS implantation was used as WTP threshold, DES were not cost-effective with any variation of the parameters. The model was robust to all other parameters, showing no significant changes in our base-case conclusions.

In the long term analysis, our results were sensitive to cost of DES, number of stents used per patient, baseline probability and duration of risk of ST, and marginally to baseline rate of BMS TVR (Table 7 and Figure 2). The price difference between BMS and DES had an important impact in the cost-utility results. This means that aiming at a cost difference of less than I$ 1,125, the ZESr could be a cost effectiveness alternative. When annual ST probability is greater than 0.014 for longer than 5 years, the ICER for EES (I$ 34,925) would stay below the WTP threshold. Even for subgroups with high risk of TVR, such as diabetic patients, long lesions and small vessels diameters, the use of DES would only be cost effective with baseline TVR rate of 30%, which seems unrealistic in the modern era of PCI.

PROBABILISTIC SENSITIVITY ANALYSIS

Probabilistic sensitivity analysis with 10,000 random trials demonstrated in the cost-effectiveness acceptability curve that BMS has 81% probability of being the strategy of choice, while EES and ZESr both have 9% probability, when a WTP threshold of I$ 35,307 was considered (figure 3). When we simulated in head to head analysis, EES vs BMS and ZESr vs BMS, the scatter plot shows similar results: in 15% of trials DES were cost effective, in 72% the ICER were above the WTP and in 13% DES were dominated by BMS (figures 4 and 5).

DISCUSSION

Our results point out that DES are effective in reducing TVR, thereafter improving quality of life, and highlight better performance of new DES in terms of stent thrombosis safety. Nevertheless, the initial costs are higher than BMS and in almost all scenarios DES have an unfavorable ICER both for TVR avoided and for QALY gained. In addition to considering the use of DES only in patients with high risk of restenosis, price reduction for all DES should be pursuit in order to turn them an interesting alternative for the public health system.

Sensitivity analysis has shown that both EES and ZESr had similar performance, and the best performance among DES. At current prices, DES are not cost effective in any setting; even assuming WTP for TVR avoided (1 GDP per capita), and assuming probabilities of ST and TVR that result in marginally acceptable ICER, DES would still be restricted to a small proportion of CAD patients. It is also important to emphasize that even with no difference between BMS and DES costs, the results are not cost-saving, given the need of more drug resources with DES. Price difference between BMS and DES below I$ 1,125 could result in ICERs below the WTP threshold for ZESr and for EES.

In the last decade, many economic evaluations on DES have been performed, mostly in developed countries, with analysis in different scenarios[5,8,9]. The results vary depending on market prices and selectiveness of use of DES. A Canadian study has shown an ICER of Can$ 58,721 in the base-case results, with ICER varying from $40,129 to $72,464 among subgroups based on age and diabetes status.[31] A recently study, also from Canada, has demonstrated an ICER of Can$ 52,585 per TVR avoided, and Can$ 1,569,875 per QALY gained, varying respectively from Can$ 13,888 to Can$ 278,499, and from Can$ 419,202 to Can$

9,142,603, reflecting patients with higher and lower risks of restenosis.[6] In 2013, Wijeisundera et al have compared three strategies for initial treatment of CAD: medical therapy, PCI with BMS and PCI with DES, and they have demonstrated that BMS has produced an ICER of $13,271/QALY over medical therapy and DES were dominated by the BMS strategy.[32]

Hill *et al* have reevaluated the cost effectiveness of DES and concluded that they are not cost-effective at standard thresholds in the UK setting. They may be cost effective in defined subgroups with high risks of reintervention. DES could be cost effective for wider groups of patients if the price premium were greatly reduced. [13] Cost-effectiveness studies produced in Sweden and Switzerland have shown similar results, that DES are cost-effective only in high-risk patients. The authors suggest that for more liberal use, the price of DES should be substantially reduced.[7,33]

Two cost-effectiveness studies evaluated DES with special attention to ST and late ST, both in the US healthcare settings. Garg *et al* concluded that even a small absolute increase in DES thrombosis (>0.14%/year) would result in BMS being the preferred strategy for the overall PCI population.[10] Filion *et al* have found that late ST-related adverse events and the need for extended dual antiplatelet therapy substantially increase the costs associated with the implementation of DES. The inclusion of these costs renders the widespread use of DES not cost-effective in the United States in terms of cost per QALY gained and cost per revascularization avoided.[34] The newer DES, EES and ZESr, have a better performance in terms of ST [3], and had the most favorable ICER in our analysis, fact that could change the conclusions in countries with different economic realities than Brazil.

This study updates the previous economic analysis in the Brazilian heath system [12]. Beyond the short-term analysis computing costs per revascularization procedure avoided, a

lifetime analysis was done with results in terms of QALY, which was possible by using an estimation of quality of life among Brazilian CAD patients.[20] Moreover, 3 new generation DES were included, as well as data regarding ST occurrence and increased duration of antiplatelet drugs prescription.

Our results were robust among the different scenarios and parameters variations. The main parameter that could change the conclusions of the analysis was the difference between the stents' prices. The probability of ST and TVR could produce favorable ICER only in strict assumptions and for a small proportion of CAD patients.

Over time, the stents' prices may change, as suggested by a French study that demonstrated that DES become cost-effective after a reduction on stents price difference from €1,200 in 2008, to €400 in 2012.[35] It is worth noting that previous economic evaluations have brought awareness about the greater importance of price difference than absolute reduction in the DES cost, as BMS cost could also fall over the time.[7,13]

Our study has some limitations, mainly in the clinical model assumptions and the CAD mortality specific rates. A Brazilian large registry of CAD natural course, following patients in clinical treatment, after PTCA procedures and after CABG, could be of great value for further economic evaluation in this context. Another issue is that the source of cost data is a government reimbursement database, that can sometimes have imprecise values, but in our point of view this does not affect results substantially. There is no established WTP threshold for TVR avoided, and the arbitrary value of 1 GDP per capita can be a nonconservative assumption, although it was important to have a threshold in order to interpret the results.

CONCLUSION

As priced in the Brazilian market, DES do not bring good value for money, considering QALY gained and TVR avoided. Since the cost-effectiveness of DES are mainly driven by the price difference in comparison with BMS, they should cost less than twice the price of BMS, in order to be a cost-effective alternative.

The economic evaluation of DES should be systematically revisited, given the fact that BMS have a good safety and effectiveness profile, and the decision to generalize the use the DES could have a tremendous impact in fixed healthcare budget of middle- and even high-income countries.

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TABLES

Table 1. Baseline estimates of the parameters probability.

Variables	Value	Low	High	Distribution	Standard Deviation	Reference
Non-cardiac mortality	life tables					[18]
PCI Procedure mortality	0.002	0.001	0.003	Beta	0.0008	[23]
Stent associate cardiac mortality (first year)	0.002	0.001	0.016	Beta	0.0040	[3]
Annual cardiac mortality post CABG	0.01	0.005	0.020	Beta	0.0046	CAD cohort HCPA [3,24]
Annual cardiac mortality post PCI	0.01	0.005	0.020	Beta	0.0046	CAD cohort HCPA [3,24]
TVR probability	0.158	0.075	0.300	Beta	0.0093	[3]
AMI presentation, if restenosis	0.107	0.075	0.140	Beta	0.0165	[3 25 26]
PCI probability, if restenosis	1					Model assumption
CABG probability, if restenosis	Third restenosis					Model assumption
ST probability (short term)	0.002	0.000	0.014	Beta	0.0034	[3]
Fatal AMI, if ST	0.2	0.100	0.300	Beta	0.0649	[23]
CAD natural course						
Annual PCI probability	0.038	0.030	0.045	Beta	0.0062	[27]
Annual CABG probability	0.014	0.010	0.030	Beta	0.0038	[27]
Annual AMI probability	0.014	0.010	0.020	Beta	0.0010	[27]

CAD - Coronary Artery Disease; TVR - Target Vessel Revascularization; ST - Stent Thrombosis; PCI - Percutaneous Coronary Intervention; CABG - Coronary Artery Bypass Graft; AMI – Acute Myocardial Infarction.

Table 2. Relative Risks estimatives.[3]

Variables	RR	LI (CI 95%)	LS (CI 95%)	Distribution	Standard Deviation
RR Thrombosis					
BMS	1				
SES	0.75	0.57	1.04	LogNormal	0.15
PES	0.96	0.7	1.33	LogNormal	0.16
EES	0.44	0.29	0.69	LogNormal	0.22
ZES	1.05	0.6	1.78	LogNormal	0.28
ZES-r	0.58	0.27	1.25	LogNormal	0.39
RR Restenosis					
BMS	1				
SES	0.26	0.22	0.31	LogNormal	0.09
PES	0.47	0.39	0.56	LogNormal	0.09
EES	0.28	0.21	0.37	LogNormal	0.14
ZES	0.48	0.36	0.66	LogNormal	0.15
ZES-r	0.31	0.17	0.57	LogNormal	0.31
RR AMI					
BMS	1				
SES	0.67	0.53	0.84	LogNormal	0.12
PES	0.87	0.71	1.04	LogNormal	0.10
EES	0.55	0.41	0.73	LogNormal	0.15
ZES	0.66	0.49	0.84	LogNormal	0.14
ZES-r	0.55	0.38	0.82	LogNormal	0.20
RR Cardiac Mortality					
BMS	1				
SES	0.97	0.74	1.21	LogNormal	0.13
PES	0.97	0.74	1.25	LogNormal	0.13
EES	0.87	0.64	1.16	LogNormal	0.15
ZES	1.28	0.85	1.8	LogNormal	0.19
ZES-r	0.66	0.36	1.18	LogNormal	0.30

BMS – Bare Metal Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute;

Table 3. Baseline estimates of the parameters costs (I$).

Variables	Value	Low	High	Distribution	Standard deviation	Reference
BMS	1,076	529	1,587	-	-	[14]
DES	3,439	2,116	4,762	-	-	Market price
Cardiac Catheterization	325	212	423	-	-	[14]
PTCA	1,755	1,729	1,780	Gamma	14	[14]
Ballon PTCA	1,920	1,805	2,088	Gamma	90	[14]
Urgent PTCA	2,156	2,050	2,257	Gamma	76	[14]
CABG	6,594	6,492	6,723	Gamma	70	[14]
AMI management	1,723	1,629	1,894	Gamma	64	[14]
Restenosis management	531	509	558	Gamma	13	[14]
Medical Therapy	1,272	1,164	1,376	-	-	CAD cohort HCPA
Antiplatelet monthly cost	26	25	86	-	-	[14]

CAD – Coronary Artery Disease; BMS – Bare Metal Stent; DES – Drug Eluting Stent; PTCA - Percutaneous transluminal coronary angioplasty; CABG - Coronary Artery Bypass Graft; AMI – Acute Myocardial Infarction.

Table 4. Quality of life estimatives for health states.

Variables	Value	Low	High	Distribution	Standard Deviation	Reference
Utility Stable Angina	0.70	0.68	0.72	Beta	0.10	[20]
Utility PCI stable	0.74	0.72	0.77	Beta	0.07	[20]
Utility CABG stable	0.74	0.72	0.75	Beta	0.05	[20]
Disutility for PCI procedure	-0.04	-0.03	-0.05	Beta	0.05	[20,28,29]
Disutility for CABG procedure	-0.08	-0.07	-0.09	Beta	0.06	[20,28,29]
Disutility for Acute AMI	-0.04	-0.03	-0.05	Beta	0.04	[20,29,30]

PTCA - Percutaneous transluminal coronary angioplasty; CABG - Coronary Artery Bypass Graft; AMI – Acute Myocardial Infarction.

Table 5. Short term base case results for TVR avoided at 1 year.

Strategy	Total Costs (I$)	Incremental cost (I$)	TVR rate	Incremental effectiveness	ICER per TVR avoided (I$)
BMS	4,400		15.1%		
SES	6,707	2,307	4.0%	-11.2%	20,642
EES	6,723	2,323	4.3%	-10.9%	21,385
ZESr	6,751	2,351	4.7%	-10.4%	22,603
PES	6,900	2,501	7.1%	-8.0%	31,234
ZES	6,907	2,507	7.3%	-7.8%	32,001

BMS – Bare Metal Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute; TVR – Target Vessel Revasculatization; ICER – Incremental Cost Effectiveness Ratio; I$ - International Dollars.

Table 6. Long term base case results for QALYs gained.

Strategy	Total Costs (I$)	Incremental cost (I$)	LYs	QALYs	Incremental effectiveness	ICER per QALY gained (I$)
BMS	18,765		11.239	8.213		
ZESr	21,349	2,584	11.274	8.254	0.041	62,761
EES	21,321	2,556	11.272	8.253	0.040	63,945
SES	21,337	2,572	11.257	8.242	0.029	88,215
PES	21,399	2,634	11.247	8.231	0.018	148,098
ZES	21,387	2,622	11.232	8.220	0.006	411,462

BMS – Bare Metal Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute;
LY – Life years; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

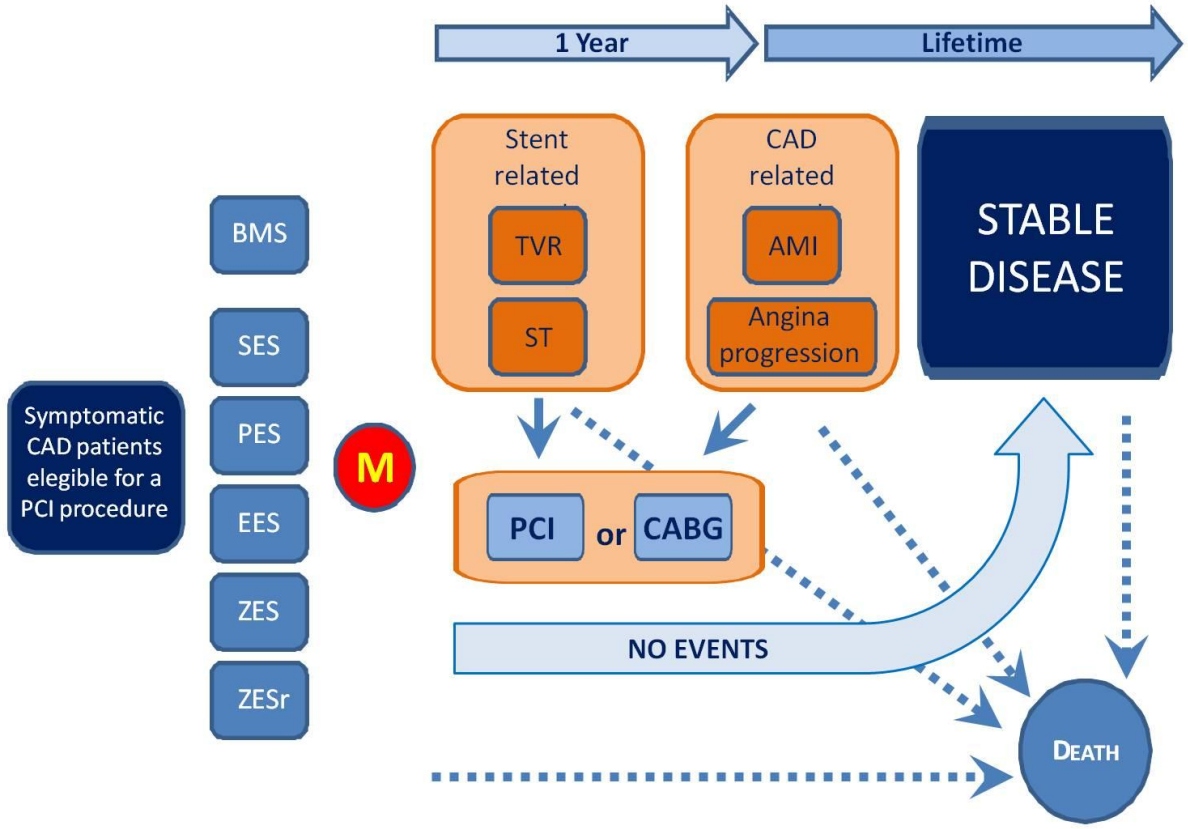
Table 7. ICER by price difference between BMS and DES.

	ICER (I$/QALY)				
Absolute price difference between BMS and DES (I$)	ZESr	EES	SES	PES	ZES
0	5,007	4,660	6,344	13,251	34,197
125	8,250	7,993	10,937	20,807	55,316
250	11,493	11,326	15,530	28,363	76,436
375	14,736	14,659	20,123	35,918	97,555
500	17,980	17,992	24,716	43,474	118,674
625	21,223	21,325	29,309	51,030	139,794
750	24,466	24,658	33,902	58,585	160,913
875	27,710	27,991	38,495	66,141	182,032
1,000	30,953	31,325	43,088	73,697	203,152
1,125	34,196	34,658	47,682	81,252	224,271
1,250	37,439	37,991	52,275	88,808	245,390

BMS – Bare Metal Stent; DES – Drug Eluting Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

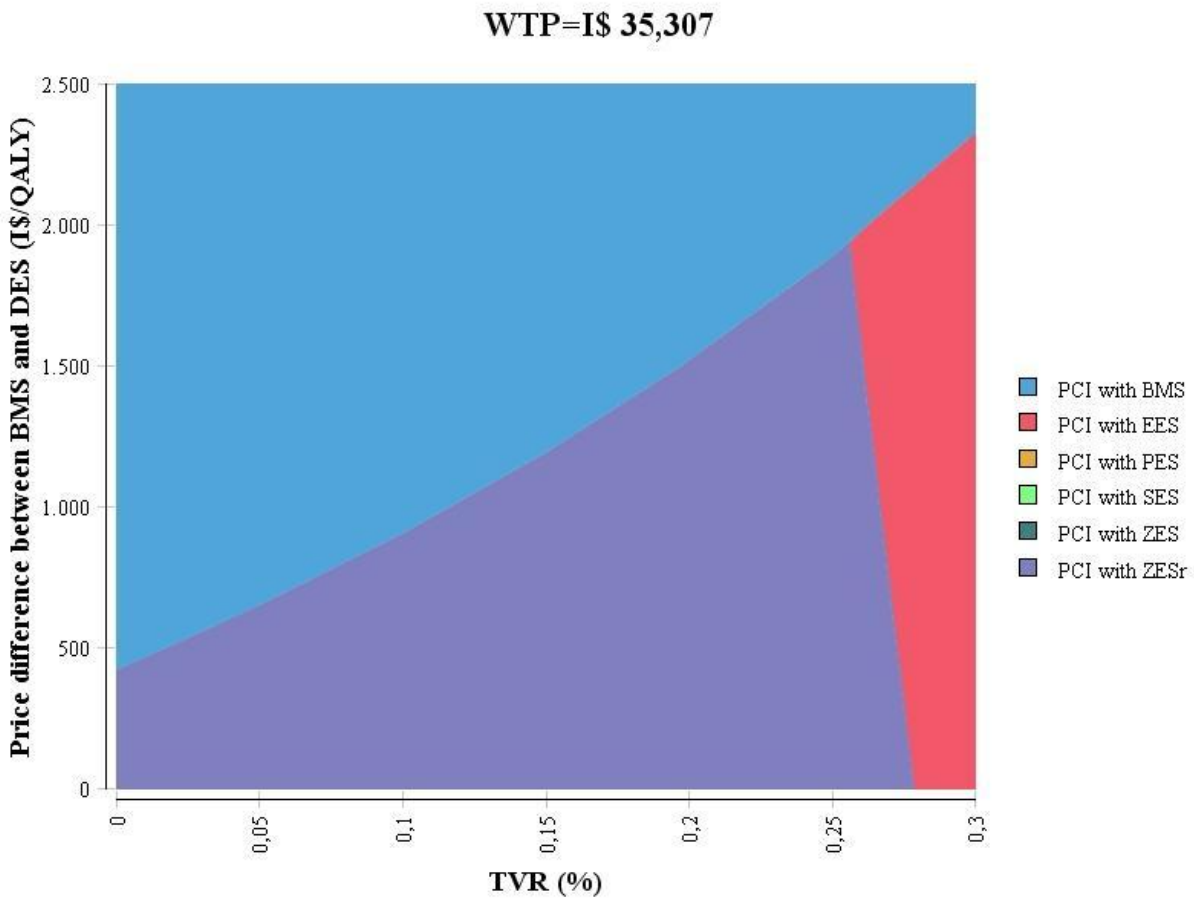
FIGURES

Figure 1. Schematic models structure.



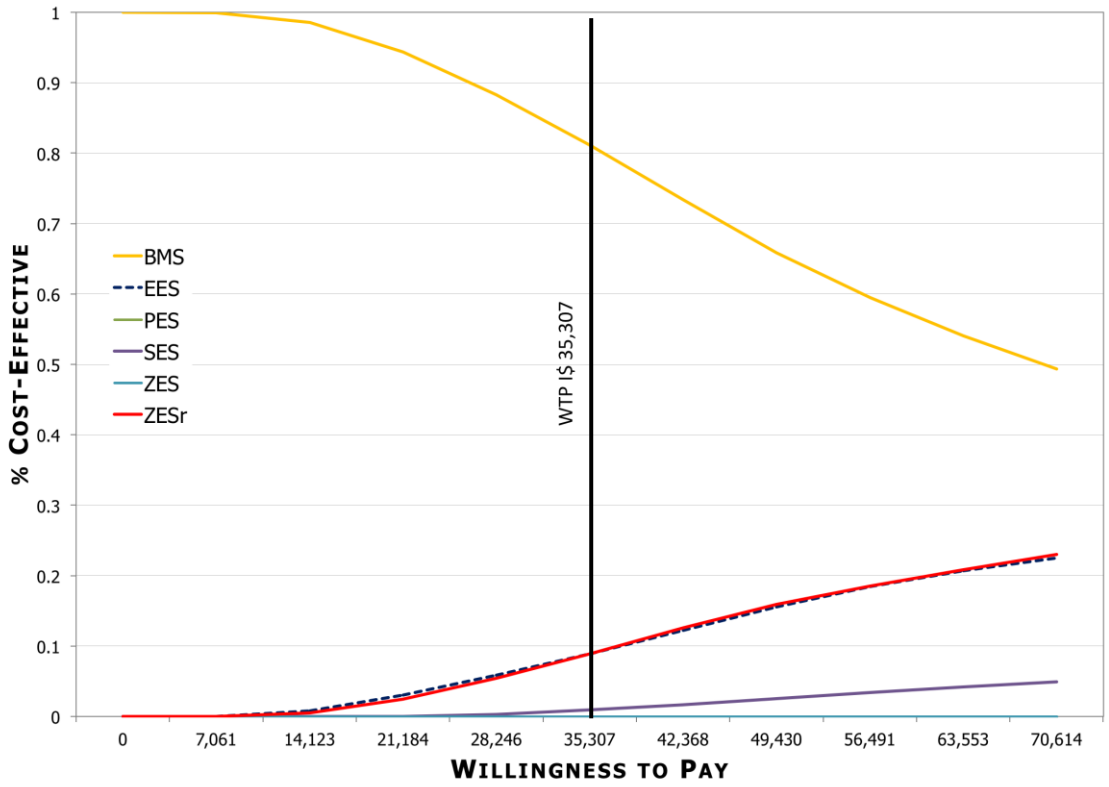
The Markov model included 4 health state: the first year after a stent PCI, stable disease after a stent PCI, stable disease after CABG and death. CAD – Coronary Artery Disease; BMS – Bare Metal Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute; TVR – Target Vessel Revascularization; ST – Stent Thrombosis; PCI - Percutaneous Coronary Intervention; CABG - Coronary Artery Bypass Graft; AMI – Acute Myocardial Infarction.

Figure 2. Two-way sensitivity analysis on price difference between BMS and DES and TVR rates.



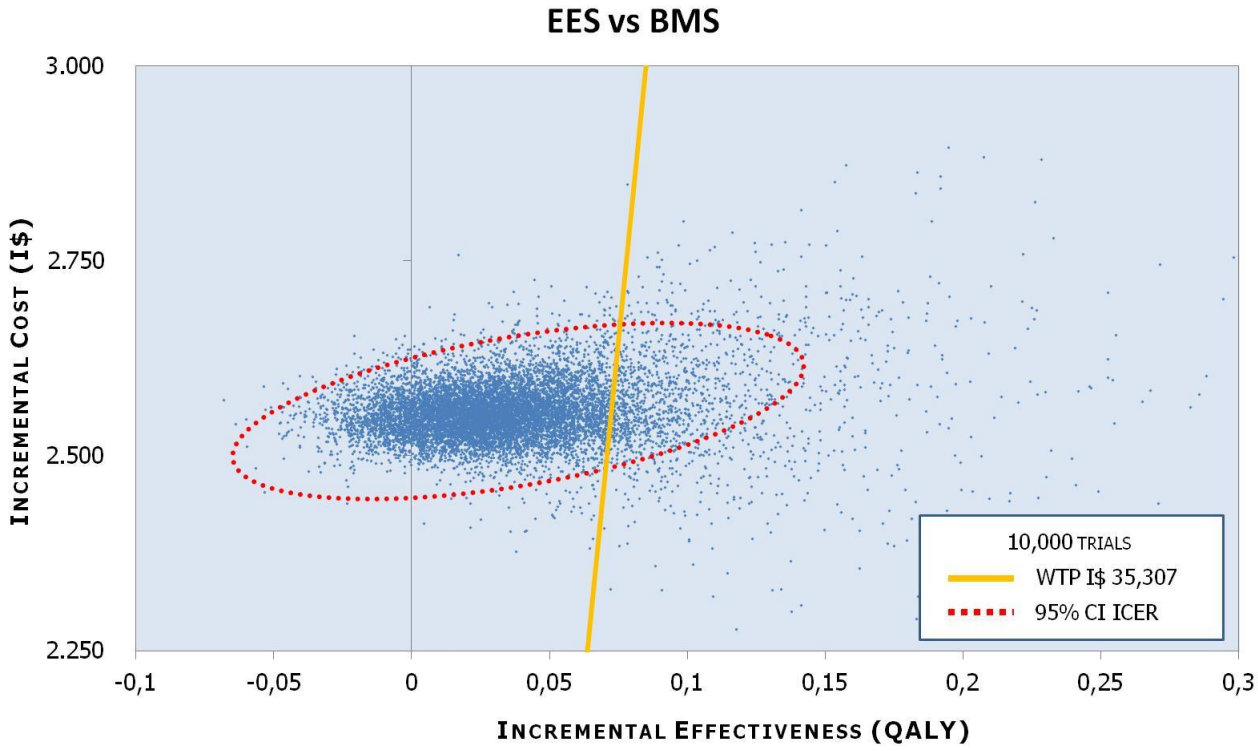
BMS – Bare Metal Stent; DES – Drug Eluting Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute; TVR – Target Vessel Revascularization; PCI -Percutaneous Coronary Intervention; WTP – Willingness to Pay; QALY – Quality adjusted life years; I$ - International Dollars.

Figure 3. Cost-effectiveness acceptability curve.



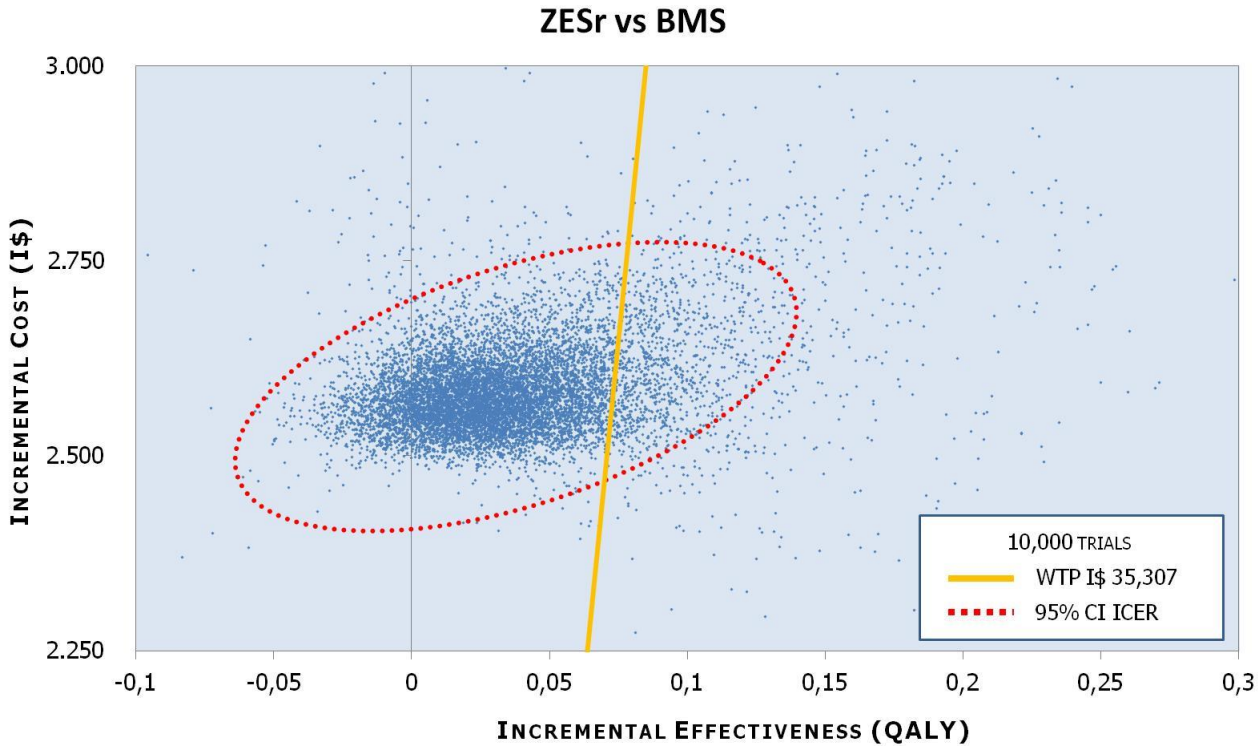
BMS – Bare Metal Stent; DES – Drug Eluting Stent; SES – sirolimus; PES – paclitaxel; EES – everolimus; ZES – zotarolimus; ZESr - zotarolimus resolute; WTP – Willingness to Pay; I$ - International Dollars.

Figure 4. Scatter plot EES vs BMS.



BMS – Bare Metal Stent; EES – everolimus; WTP – Willingness to Pay; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

Figure 5. Scatter plot ZESr vs BMS.



BMS – Bare Metal Stent; ZESr - zotarolimus resolute; WTP – Willingness to Pay; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

Cost utility of fractional flow reserve guided percutaneous coronary intervention in multivessel coronary artery disease in Brazil

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ABSTRACT

PURPOSE: The Fractional Flow Reserve (FFR) versus Angiography for Multivessel Evaluation (FAME) study has demonstrated that FFR substantially reduces the resources utilization and event rates in multivessel coronary artery disease (CAD) patients. Many developed countries have already performed economic evaluations showing that FFR could be cost saving in their health systems. We aim to accesses the cost utility of FFR in multivessel CAD patients undergoing percutaneous coronary interventions (PCI) from the perspective of the Brazilian Public Health System (SUS).

METHODS: A patient-level cost-utility analysis along the trial was performed using data from the previous published FAME study. We considered patients with multivessel CAD who could have a FFR guided PCI or PCI guided by angiography alone, with use of bare metal stent (only available stent in SUS). The index procedure costs were based on mean amount of unitary resource utilization multiplied by the prices from SUS reimbursement list or the 2013 government drug price list. The utilities were derived using Brazilian weights for time trade-off EQ-5D. We determined the incremental cost effectiveness ratio (ICER) in International Dollars (I$) per QALY gained during the 1-year trial horizon. We performed sensitivity analyses varying the price of the FFR catheter and utilization proportions of bare metal stent (BMS) and drug eluting stents (DES).

RESULTS: One-year costs were I$ 8,789 for the angiography guided PCI and I$ 8,826 for the FFR guided PCI, resulting in an incremental cost of I$ 37. Effectiveness during one year was 0.798 QALYs in angiography guided PCI and 0.811 in FFR guided PCI, resulting in an incremental effectiveness of 0.013 QALYs. The base case ICER of FFR versus angiography guided was I$ 2,736 I$/QALY. For a DES use of ≥25%, the FFR guided strategy was cost-saving. Assuming 100% BMS use, cost-savings are achieved with a FFR catheter price reduction of at least 2.2% (from I$ 1376 to I$ 1346).

CONCLUSION: Developing countries, with fixed and limited budgets, need to give attention to strategies that have proven to be cost effective in other health systems. In our analysis, FFR guided PCI is cost effective in the Brazilian SUS, in addition to improving patient safety. With a moderate price reduction of the device, FFR measurement can be even cost-saving.

KEYWORDS: cost utility analysis, fractional flow reserve, FFR, coronary artery disease.

INTRODUCTION

Increasingly new technologies with proved benefits have emerged in diagnostic cardiology field in the last years. Most countries have limited health budgets, which often makes the economic viability of the new technologies as important as its benefit in health outcomes and safety. There is growing evidence for measurement of the fractional flow reserve (FFR) to support decision making in percutaneous coronary interventions (PCI).[1-9] The Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) study has demonstrated that FFR substantially reduces the resources utilization and major adverse cardiac events (MACE) rate, with similar symptoms control, compared to angiography alone in multivessel coronary artery disease (CAD) patients.[1] Many developed countries have already performed economic appraisals showing that FFR could be cost saving in their health systems scenarios.[10-12]

The FFR has not been evaluated economically in developing countries like Brazil, where important part of its budget goes to cardiovascular diseases, including CAD.[13] Alternatives that have been proven cost saving in other countries should be evaluated, given its potential impact in saving money and improving outcomes where it could be even more necessary.

The objective of this study is to evaluate FFR as adjuvant tool in PCI for multivessel CAD, in terms of costs and quality adjusted life years, based on patient-level original data from FAME study, applied in the Brazilian Public Health system (SUS) setting.

METHODS AND MATERIALS

The FAME study is a randomized clinical trial that evaluated patients with multivessel CAD after a FFR guided PCI or a PCI guided by angiography alone. Patients in the angiography arm have all the indicated lesions stented, while those in the FFR arm have just the lesions with a FFR measurement of less than 0.8 stented. After 1 year follow up the event rate was 13.2% in the FFR arm and 18.3% in the angiography arm (p=0.02) and the number of stents used per patient was 1.9 (SD 1.3) and 2.7 (SD), respectively. There was no significant difference in angina control at 1 year (78% vs. 81% ;p=0.2) in the angiography and FFR arms, respectively. [1]

POPULATION AND PROCEDURE

The target population is multivessel CAD patients with mean age of 64 year-old, who were eligible for PCI either guided by FFR or by angiography alone, in the SUS perspective.[1] We considered the same amount of resource consumption and rates of clinical outcomes of the original report, but differently of the FAME study, it was assumed the use of bare metal stent (BMS) instead of drug eluting stent (DES), as in Brazilian public health system only BMS are available. This assumption was made taking into account only the different prices of BMS and DES, with no further adjustment in MACE rates (at least in the base case results). For purpose of potential future utilization in SUS and for an estimative of cost effectiveness in private health sector (in which most of PCI are with DES) we considered the DES utilization in the sensitivity analysis.

UTILITIES

Health-related quality of life was accessed by the score on the European Quality of Life–5 Dimensions [EQ-5D] during the FAME study at baseline (before PCI), at 1 month and at

1 year.[14] The utilities in which period of time (table 1) were derived using Brazilian weights for time trade off (TTO) EQ-5D.[15] Quality adjusted life years (QALY) were calculated from utilities and survival proportions from baseline until the time in follow-up (death, complete follow or loss of follow up). We use a bootstrap approach to resample with 10,000 replications and fill the missing data with the likeliest value in each arm at each period of time.

COSTS

The index procedure costs were based on mean amount of unitary resources utilization multiplied by the prices of SUS reimbursement list or government drug price list for 2013.[13] The follow up costs of new revascularization procedures, acute myocardial infarction (AMI) and Coronary Artery Bypass Graft (CABG) were accessed by a search on the Brazilian epidemiological database (DATASUS), surveying mean monthly cost of reimbursed procedures and hospitalizations in 2012 and 2013. [13] FFR and DES prices were estimated based on information provided from a private hospital and a private health insurance provider, reflecting average market price, once both are not available in the SUS. All costs were converted from Brazilian Real to International Dollars (I$), using the World Bank's latest available purchasing power parity conversion (PPP) factor of 1.89, relative to 2012.[16] Table 2 summarizes unitary and total costs parameters for each alternative.

ENDPOINTS AND THRESHOLDS

Primary endpoints were cost for QALY gained at 1 year. Since in Brazil there is not an official willingness-to-pay (WTP) threshold, we used the World Health Organization (WHO) recommendation of economic values between 1 to 3 times the Gross Domestic Product (GDP) per capita.[17] We assumed 3 GDP/capita (I$ 35,307) for QALY gained as willingness-to-pay threshold. [18]

ANALYSIS

The base-case analysis was performed accounting the incremental costs divided by the incremental health effects to generate the incremental cost effectiveness ratio (ICER). We tested all the parameters in 1-way deterministic sensitivity analysis, with the costs parameters varying in +/- 20% of its unitary value and the health effects in its range of variability observed at FAME study.[1] For an overall estimative of the uncertainty we conducted probabilistic sensitivity analysis (SA) using the bootstrap method, by generate 5,000 random trials using the FAME parameters dataset.[1] We also evaluated different assumptions to explore distinct scenarios of heath resources utilization, as the use of higher percentage of DES and for differences in the prices of both FFR and stent (BMS and DES).

This study and its results were reported in accordance to the Brazilian guideline for Economic evaluations and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement. [19,20] All the analysis was performed with SAS software, version 9.2 (SAS Institute Inc, Cary, NC).

RESULTS

The overall costs for the angiography guided strategy was I$ 8,789 and for the FFR guided strategy was I$ 8,826, resulting in an incremental cost of I$ 37. The total QALYs in the angiography guided strategy was 0.798 and in the FFR guided strategy was 0.811, resulting in an incremental effectiveness of 0.013 QALYs. The correspondent ICER was about I$ 2,736 I$/QALY. The table 3 summarizes the base case results.

The one-way SA of the price of FFR catheter demonstrated that values below I$ 1,346 would be a cost saving strategy and values until I$ 1,720 still in the cost effectiveness range. Figure 1 shows the range of variation of the FFR catheter price and its respective associate ICER. None of the variables changed the base case results above to the WTP. The price of the stent used and the hospital stay costs could change the result for the cost saving range. The Tornado diagram (figure 2) shows the results of a deterministic SA of all cost parameters varying in +/- 20% of its unitary value.

We performed a 2-way SA varying the price of the FFR catheter and the proportion of use the DES (figure 3). Starting with DES use of 25% and BMS use of 75%, the FFR guided strategy was a dominant alternative. When it was considered only BMS using (as in base case) catheter prices below I$ 1,346 produced a cost saving strategy.

Figure 4 and figure 5 show the bootstrap scatter plot, with 5,000 samples, assuming exclusively use of BMS and exclusively use of DES, respectively. When it was considered only BMS, there was 81% probability of being cost effective and 46% probability of being cost saving. On the other hand, when it was considered only DES, all samples were cost effective and 87.5% were cost saving.

DISCUSSION

As previously reported in FAME study, the FFR guided PCI strategy is effective in reducing the number of stents per procedure and the rates of MACE, besides a similar proportions of angina free patients.[1] The economic evaluations conducted in developed countries demonstrated that the FFR strategy was cost saving compared to the angiography strategy. [10-12]

Our study demonstrated that FFR guided PCI strategy is cost effective in Brazilian Public health system settings, considering a 3 GDP per capita WTP, with robust results even in a broad range of parameters variations. However, it is important to mention that we assume a BMS exclusively use. This assumption aims to characterize the public health resource availability. It is, in part, a conservative assumption, once the lower cost of BMS generated less attractive ICER than it could be assuming the DES cost. One could argue that the rates of MACE could be different with BMS, and indeed are, but our consideration is that both strategies received the same type of stent. It means that in both strategies, the patients are in the same basal stent related outcomes risk, or even more, those patients who receive fewer stents could be in a lower risk, favoring the FFR strategy.

Differently from previous economic evaluations on FFR, our results have not been cost saving in the base case analysis, although cost effective. One point is the assumption of BMS use, as described above. Another point to be highlighted is that if just a little proportion of procedures were performed with DES, the FFR strategy would be cost saving. This would be an important finding considering that in Brazilian private sector most of the PCI are with DES. The Brazilian reimbursement system for multivessel PCI is usually executed as a staged procedure payment that could eventually underestimate the cost of one complete

multivessel procedure, nonetheless this consideration would result in a even more attractive ICUR for FFR, as the procedure cost would have risen.

Our study has some limitations. As discussed above, the assumption of BMS utilization is the most important issue of this economic evaluation, once the FAME study used in almost all patients DES. Second, the FAME study evaluated only multivessel CAD patients who underwent to PCI, and the implications of some do not necessary could be assumed for single vessel CAD patient's treatment. Third, we assumed a market price for FFR, as it is not available in public health system, and maybe a government acquisition could bargain the FFR price to a lower limit. Fourth, there is a lot of uncertainty about the reimbursement or hospitalization daily costs, although no other conclusions would raise after the bootstrap analysis considering a wild range of values. Fifth, we adjusted the base line utilities in order to equate both arms. In fact this is a conservative action, once the FFR strategy have had reduced its base line utilities. Sixth, the resource allocation for the procedures in the FAME study could be different of the Brazilian angioplasty routine, but in our opinion it does not imply in a substantially difference in overall costs.

This economic evaluation also brings strengths and new considerations in this issue. It is the first cost effective study on FFR utilization in the public health system perspective of a developing country. We used Brazilian TTO weight utilities and national costs to analyze the cost effectiveness with patient level date from FAME study. Even though our results were not cost saving, like previous published economic evaluations, the ICER for the Brazilian public health perspective is considered attractive. Nevertheless, assuming the use DES could indicate a cost saving strategy, either for an extrapolation for the private sector, or a future scenario in Brazilian SUS.

CONCLUSION

Developing countries, with fixed and limited budgets, need to give attention to strategies that have proven to be cost effective in other health systems. In our analysis, FFR guided PCI for multivessel CAD management is cost effective in the Brazilian SUS, and with a moderate price reduction of the device, FFR measurement can be even cost-saving.

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TABLES

Table 1 – Brazilian weight adjusted utilities at baseline, 1 month and 1 year.

Utilities	Angiography	Standard error	FFR	Standard error
Baseline	0.749	0.0090	0.749	0.0083
1 Month	0.840	0.0088	0.838	0.0082
12 months	0.826	0.0101	0.832	0.0091

FFR – Fractional Flow Reserve catheter

Table 2 – Resources utilization and main cost parameters.

		Angiography Guided			FFR Guided		
Resource	Unit cost, I$	Resource Units, n	Mean Cost/Patient, I$	Standard Error	Resource Units, n	Mean Cost/Patient, I$	Standard Error
Guide catheter	103	2.2	228	5	2.0	210	4
Guidewire	103	2.2	224	6	1.2	116	7
Pressure wire	1,376	-	-	-	1.3	1,738	33
Balloon catheter	265	2.1	532	20	1.7	432	21
Contrast agent	2	302	508	10	272	458	10
Stent	1,076	2.8	3,057	58	1.9	2,135	62
Adenosine	10	-	-	-	1.0	10	0
GPI	762	0.4	240	23	0.3	208	23
Hospital day - floor bed	785	2.1	1,593	97	2.1	1,677	87
Hospital day - CCU	1,209	1.7	1,980	182	1.3	1,568	174
Repeat PCI	3,156	0.08	248	47	0.06	192	37
CABG	6,594	0.03	173	47	0.01	78	32
MI	1,723	0.004	7	5	0.002	3	3
Overall costs			8,789	213		8,826	223

FFR – Fractional Flow Reserve catheter; I$ - International Dollars; GPI - Glycoprotein Inhibitor; CCU - Cardiac Care Unit; CABG - Coronary Artery Bypass Graft surgery

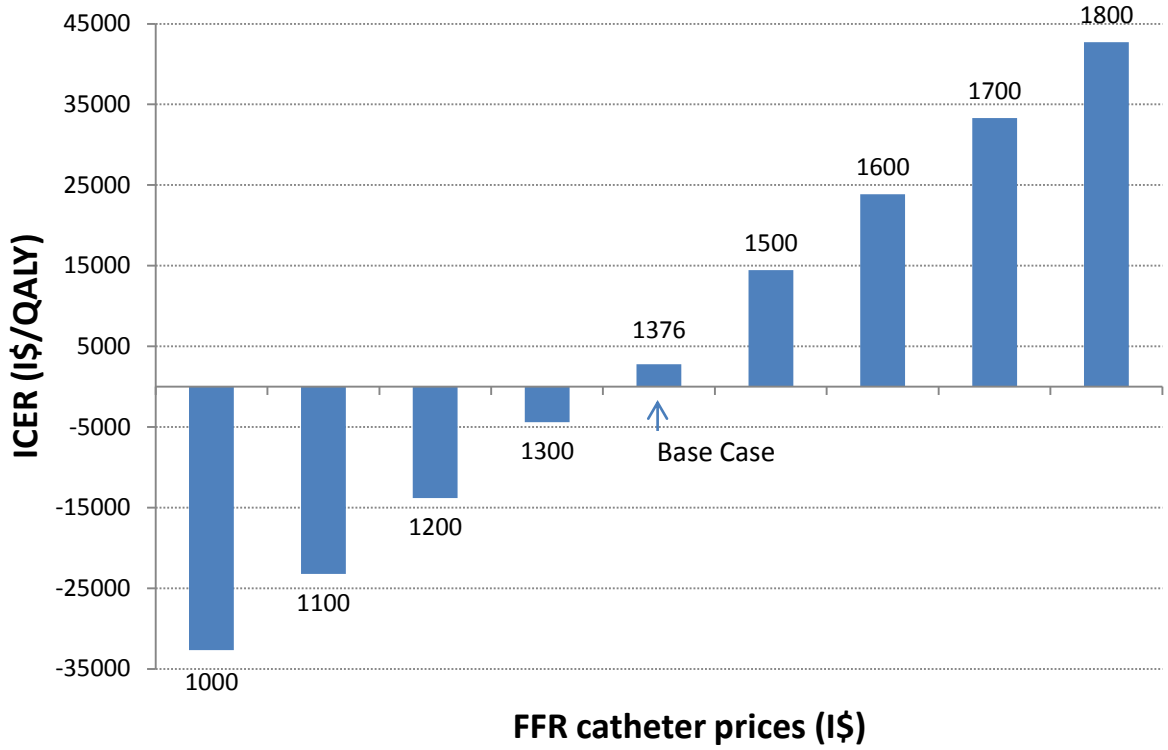
Table 3 – Base case incremental cost effectiveness ratio (ICER)

Strategy	Total Costs, I$	Incremental Cost, I$	Total Effectiveness, QALYs	Incremental Effectiveness, QALYs	ICER, I$/QALY
Angiography Guided	8,789	-	0.798	-	-
FFR Guided	8,826	37	0.811	0.,013	2,736

FFR – Fractional Flow Reserve catheter; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

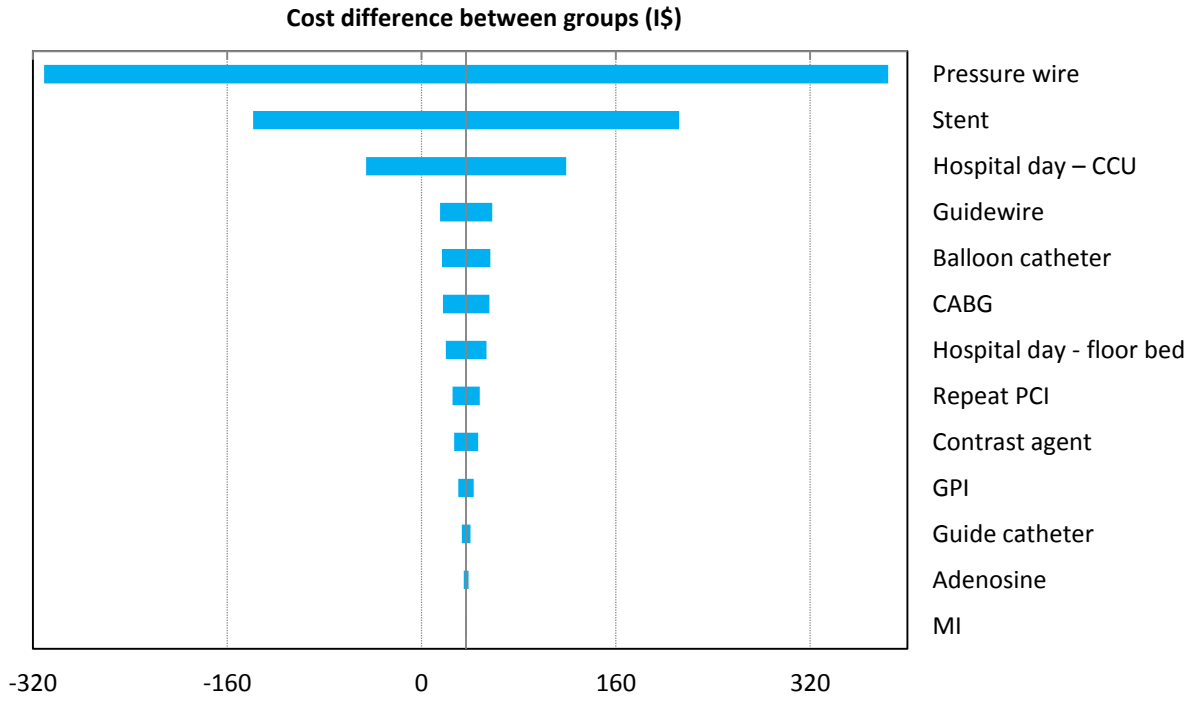
FIGURES

Figure 1 – One way sensitivity analysis of the FFR Catheter prices.



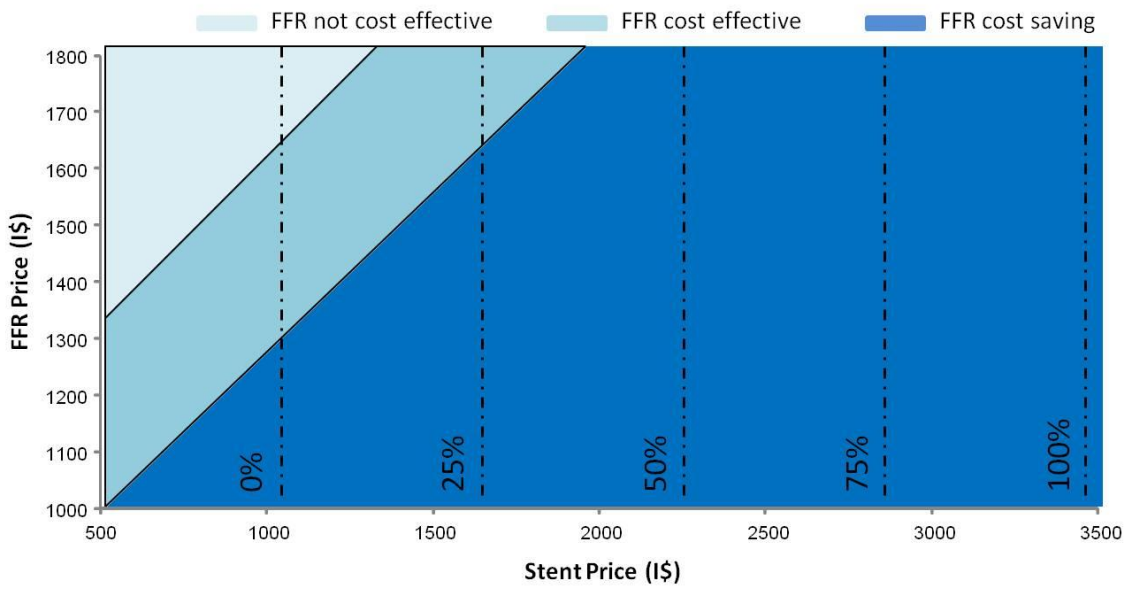
FFR – Fractional Flow Reserve catheter; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

Figure 2 – Tornado Diagram



I$ - International Dollars; CCU - Cardiac Care Unit; CABG - Coronary Artery Bypass Graft surgery; PCI – Percutaneous Cornonary Intervation; GPI - Glycoprotein Inhibitor; MI – Myocardial Infarction

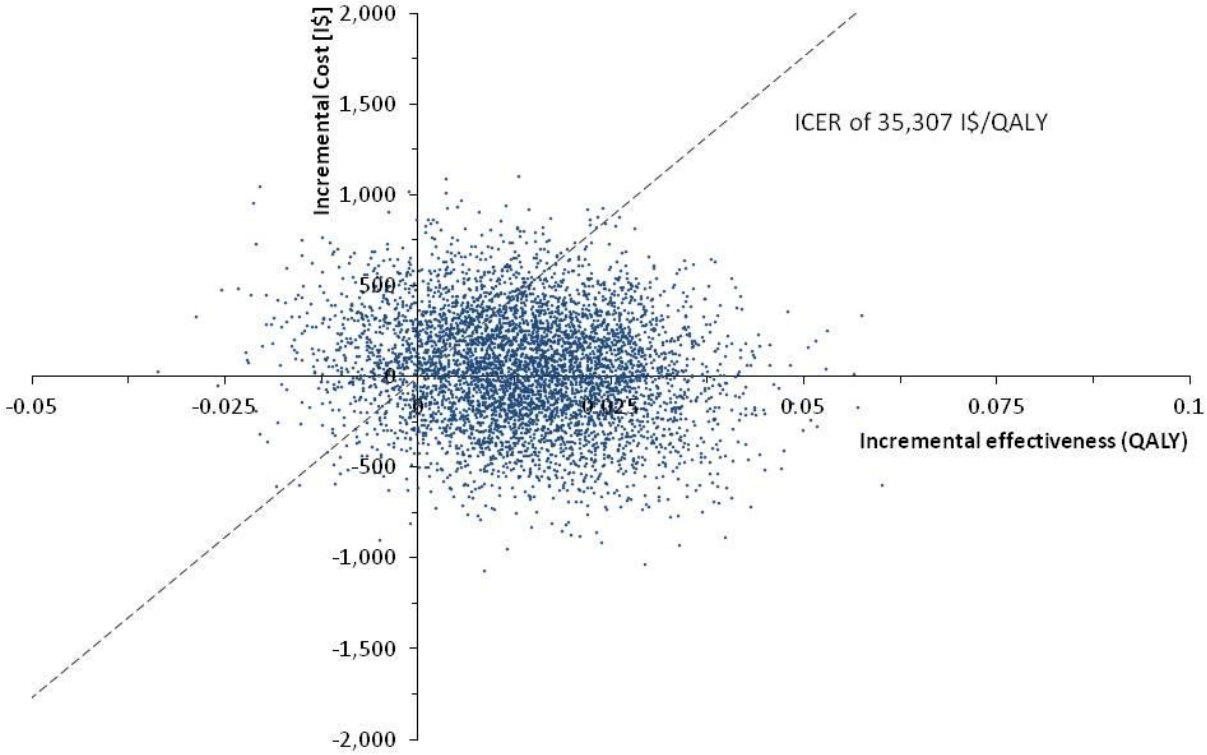
Figure 3 – Two way sensitivity analysis from FFR catheter prices and DES use



The dashed lines represents the proportion of utilization of DES.

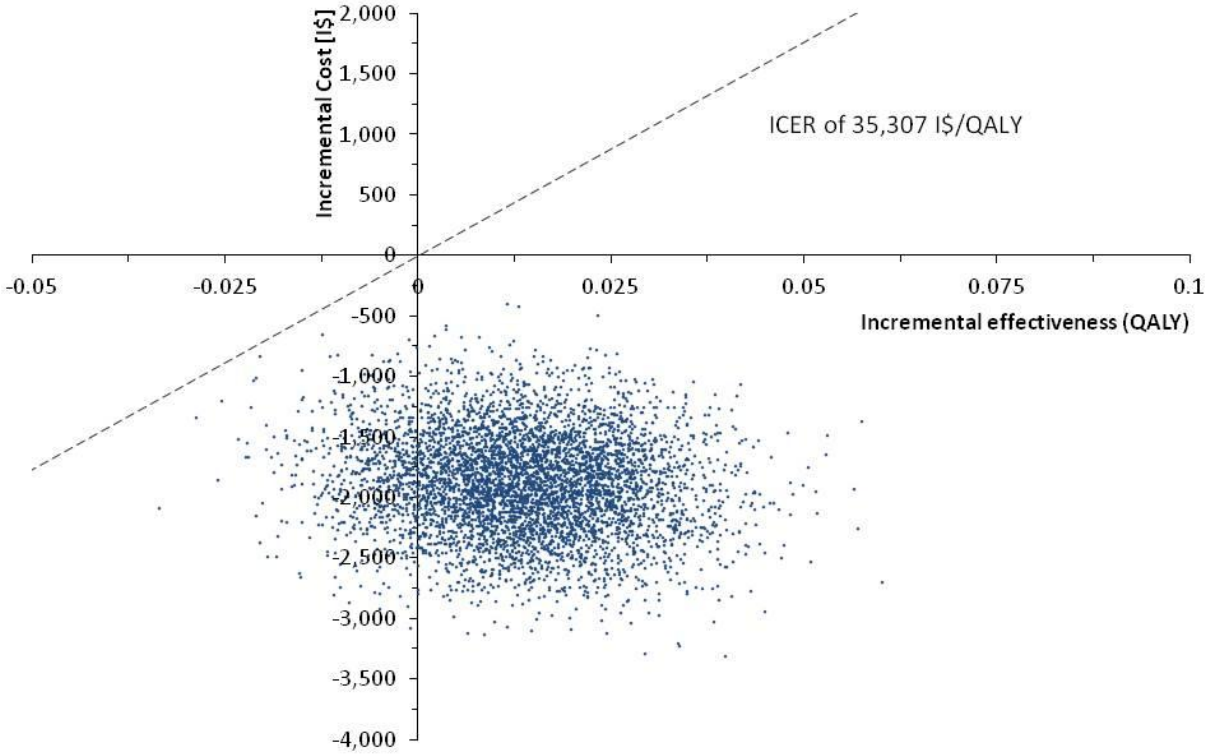
FFR – Fractional Flow Reserve catheter; DES – Drug Eluting Stent; I$ - International Dollars.

Figure 4 – Bootstrap scatter plot – All BMS



BMS – Bare Metal Stent; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

Figure 5 – Bootstrap scatter plot – All DES



DES – Drug Eluting Stent; QALY – Quality adjusted life years; ICER - Incremental Cost Effectiveness Ratio; I$ - International Dollars.

CONSIDERAÇÕES FINAIS

A conjuntura atual dos países em desenvolvimento estabelece um sutil equilíbrio entre a melhora da cobertura assistencial em saúde e uma sustentabilidade econômica capaz de absorver as novas tecnologias incorporadas ao sistema. Neste aspecto, os sistemas de saúde que souberem sistematizar e objetivar suas decisões sobre incorporação tecnologias em saúde serão capazes de aumentar a efetividade de utilização de recursos, que invariavelmente são finitos.

A utilização de *stents* farmacológicos, que comprovadamente reduz a taxa de procedimentos de revascularização, quando comparado aos *stents* convencionais permanece com uma relação de preço desfavorável. A decisão de incorporação dos *stents* farmacológicos deveria passar por uma importante renegociação de preço, que possibilitasse viabilizar a utilização deste benefício aos pacientes do sistema público de saúde Brasileiro.

O cateter de medida de fluxo coronariano apresenta-se com benefício na redução da quantidade de *stents* utilizados em procedimentos percutâneos coronarianos. A comparação entre o custo da utilização do cateter e da redução de custos com a menor utilização de *stents* mostra relação de custo efetividade atrativa no contexto de saúde pública Brasileira para pacientes com DAC multiarterial.

Os estudos apresentados nesta tese de doutorado abordaram a avaliação econômica dos *stents* farmacológicos e do cateter de medida de fluxo coronariano. Estas tecnologias são claros exemplos de inovações na área médica que trazem benefícios e melhorias aos nossos pacientes e que necessitam ser amplamente avalizados quanto a sua viabilidade econômica em países como o Brasil.