UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

TESE DE DOUTORADO

Estudo da Efetividade e da Custo-Efetividade de Unidades Dedicadas no Atendimento às Síndromes Coronarianas Agudas

ANDRÉ LUIS FERREIRA DA SILVA

Orientador: Profª. Drª. Carisi Anne Polanczyk

Porto Alegre, Dezembro de 2013

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BANCA EXAMINADORA

Prof. Dr. Otávio Berwanger, Hospital do Coração, São Paulo

Prof. Dr. Ricardo Kuchenbecker, Programa de Pós-Graduação em Epidemiologia, Universidade Federal do Rio Grande do Sul

Prof. Dr. Miguel Gus, Programa de Pós-Graduação em Cardiologia, Universidade Federal do Rio Grande do Sul

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**In memoriam*

SUMÁRIO

LISTA DE SIGLAS E ABREVIATURAS

ACTP: angioplastia coronariana transluminal percutânea

AI: angina instável

AVAQ: anos de vida ajustados para qualidade

AVAI: anos de vida ajustados para incapacidade

AVC: acidente vascular cerebral

AVCi: acidente vascular cerebral isquêmico

AVCh: acidente vascular cerebral hemorrágico

BAVT: bloqueio atrioventricular total

CRM: cirurgia de revascularização do miocárdio

CTI: Centro de Terapia Intensiva

DALY: *disability adjusted life years*

DAC: doença aterosclerótica coronariana

DE: departamento de emergência

ECR: ensaios clínicos randomizados

EPA: embolia pulmonar aguda

IAM: infarto agudo do miocárdio

IAMST: infarto agudo do miocárdio com elevação do segmento ST

PA: pressão arterial

PDA: protocolo de diagnóstico acelerado

QALY: *quality adjusted life years*

RCEI: razão de custo-efetividade incremental

RCUI: razão de custo-utilidade incremental

RMC: ressonância magnética cardíaca

SCA: síndromes coronarianas agudas

SCASSST: síndrome coronariana aguda sem supradesnivelamento do segmento ST

SE: serviço de emergência

SED: simulação de eventos discretos

SUS: Sistema Único de Saúde

UCC: Unidade de Cuidados Coronarianos

UDT: Unidades de Dor Torácica

UV: Unidade Vascular

RESUMO

Introdução: Os serviços de emergência (SE) enfrentam o desafio de prestar cuidados de qualidade em face à superlotação. A ocorrência de tempos de espera prolongados e de excessiva permanência nos SE pode comprometer a qualidade do atendimento às doenças vasculares agudas através de erros diagnósticos ou do retardo na instituição de tratamentos para reperfusão tecidual, como nos casos de infarto agudo do miocárdio (IAM) e de acidente vascular cerebral (AVC). Em janeiro de 2006, foi implementada a Unidade Vascular (UV) no SE do Hospital de Clínicas de Porto Alegre. Trata-se de uma unidade de cuidados de complexidade intermediária voltada ao atendimento das doenças vasculares agudas. Um estudo clínico com controle histórico demonstrou o impacto positivo dessa unidade nos casos de síndromes coronariana aguda (SCA) no período após a implementação da UV (anos de 2006 e 2007) em comparação com o período anterior (anos de 2000 e 2001). No entanto, restam questionamentos referentes ao efeito da UV e de outras modalidades de unidades dedicadas em desfechos clínicos relacionados às SCAs e a outras doenças vasculares agudas, bem como em relação ao impacto econômico da implementação de unidades assemelhadas.

Objetivos: O primeiro objetivo desta tese foi estimar o impacto da implementação da UV na mortalidade por doenças vasculares agudas. O segundo objetivo foi estimar a efetividade de unidades de dor torácica em geral no atendimento à SCA em comparação ao atendimento em hospitalização convencional ou em um serviço de emergência. O terceiro objetivo foi identificar e sumarizar os

estudos de análise de decisão e custo-efetividade de unidades dedicadas no atendimento às SCAs.

Métodos: A estimativa do impacto da implementação da UV na mortalidade por doenças vasculares agudas foi realizada através de um estudo comparativo transversal da prevalência-período de casos de óbito entre os períodos anterior (2002-2005) e posterior à implementação da UV (2007-2010). Nesse estudo, foram identificados através dos códigos CID-10 na alta, indivíduos que receberam atendimento inicial na emergência em razão de seis doenças-alvo da UV: (1) síndromes coronarianas agudas; (2) acidente vascular cerebral isquêmico (AVCi); (3) acidente vascular cerebral hemorrágico (AVCh); (4) dissecção e ruptura aórtica aguda; (5) embolia pulmonar aguda (EPA) e (6) insuficiência cardíaca agudamente descompensada.

Para estimação da efetividade das Unidades de Dor Torácica (UDTs) no atendimento da SCA sem supradesnivelamento do segmento ST (SCASSST) em comparação ao à hospitalização convencional ou ao atendimento no SE, foi conduzida uma busca sistemática da literatura por ensaios clínicos randomizados (ECRs) abrangendo as bases de dados MEDLINE, EMBASE e Cochrane CENTRAL. Desfechos clínicos e desfechos relacionados à eficiência do processo de atendimento, como taxas de utilização de angiografia coronariana e de procedimentos de revascularização, foram extraídos em duplicidade. Estimativas do efeito sumário das alternativas comparadas foram obtidas por metanálise de comparações diretas através do método do efeito randômico.

Por fim, a identificação de estudos de avaliação econômica de unidades dedicadas em comparação ao atendimento no SE ou hospitalização convencional foi

realizada através de uma segunda revisão sistemática da literatura compreendendo as bases de dados MEDLINE, EMBASE e NHS-Economic Evaluation Database (NHS-EED). Para a busca nas duas primeiras bases de dados, foi aplicado o filtro para avaliações econômicas do NHS-EED. Os resultados das avaliações econômicas encontradas foram sumarizados. Os valores para as razões de custo-efetividade e utilidade incrementais (RCEI e RCUI) foram ajustados para inflação e convertidos para dólares do ano 2012.

Resultados: No estudo de estimativa do impacto da implementação da unidade vascular, foram identificados, através dos códigos CID-10 na base de dados administrativa do hospital, 4164 pacientes atendidos no período anterior à implementação da UV (2002-2005) e 6280 pacientes atendidos no período posterior à implementação da UV (2007-2010). No geral, a prevalência-período de casos de óbitos decorrentes das doenças cardiovasculares agudas delimitadas sofreu uma redução de 9% para 7,3% com a implementação da UV em 2006 (p=0,002). A mortalidade intra-hospitalar para SCA sofreu redução significativa de 6% para 3,8% (p=0,003), e a mortalidade por EPA sofreu redução de 32,1% para 10,8% (p<0,001). Não foram observadas reduções na mortalidade para as demais doenças avaliadas.

A revisão sistemática de ensaios clínicos randomizados de UDT versus atendimento convencional identificou 7 artigos para a síntese qualitativa da evidência, dos quais 6 puderam ser combinados em uma metanálise. A avaliação da qualidade metodológica foi limitada devido à frequente omissão do relato dos itens de qualidade. Não houve tentativa de cegamento em nenhum dos estudos, e, em dois deles, foi utilizada randomização em *cluster*, o que exigiu ajuste na metanálise. Na comparação com a hospitalização convencional, as UDTs estiveram associadas a

menores taxas de admissão hospitalar (RR 0,47; 0,29 a 0,77), duração da hospitalização (-8,74h; -16,92 a -0,55), angiografias realizadas no seguimento (RR 0,22; 0,05 a 0,86) e procedimentos de revascularização em geral (RR 0,30; 0,09 a 0,96). Dois desfechos apresentaram um elevado grau de heterogeneidade no teste da inconsistência: admissão hospitalar (I^2=98%) e readmissão hospitalar (I^2=77%). A análise de subgrupos identificou o tipo de desenho do estudo como possível fonte para parte da heterogeneidade observada. Não houve diferença no efeito sumário de mortalidade ou de eventos cardiovasculares incidentes.

Por fim, na segunda revisão sistemática, foram identificados 16 estudos de avaliação econômica de unidades dedicadas: 5 avaliações econômicas baseadas em estudos observacionais, 6 avaliações econômicas baseadas em ensaios clínicos randomizados e 5 estudos de modelagem para análise de decisão e custo-efetividade. As unidades incluídas nesses estudos foram: unidade de cuidados coronarianos (UCC), UCC-móvel, unidade de cuidados intermediários e UDT. Além dessas unidades, as seguintes alternativas foram elencadas entre os comparadores: hospitalização de rotina, atendimento ambulatorial e programa de rastreamento da hipercolesterolemia. Os modelos foram representados graficamente e foram, no geral, considerados válidos, excetuando-se um estudo que centralizou a efetividade da UCC simulada no efeito da lidocaína na prevenção e tratamento de arritmias no pós IAM. Para o atendimento às SCAs de risco baixo a intermediário, a RCUI para a implementação de uma UDT em comparação à hospitalização de rotina foi estimada entre U$ 6.416,23 / ano de vida ajustado para qualidade (AVAQ) e U$ 40.944,39 /AVAQ. Na comparação de UCC com unidade intermediária, a RCEI foi estimada entre U$ 73.165,71 /ano de vida ganho (AVG) e U$ 307.156,55 /AVG. A comparação

de UCC com hospitalização de rotina obteve uma RCEI de U$ 89.556,47 /AVG em um único estudo. A eficiência econômica da internação em UCC foi sensível à idade e à probabilidade de IAM na população-alvo.

Conclusões: No contexto brasileiro, a implementação da UV para o atendimento aos casos suspeitos de SCA esteve relacionada a uma redução no risco de morte. Esse achado contrasta com a ausência de efeito das UDTs norte-americanas e europeias no risco de morte, provavelmente em razão de riscos basais distintos entre as populações atendidas na UV brasileira e nas UDTs de outros países. A implementação de UDTs está relacionada a uma redução nos custos decorrentes de internações hospitalares (indicação e duração), angiografias coronarianas e procedimentos de revascularização miocárdica e as estimativas da RCUI dessas unidades em comparação à hospitalização de rotina podem ser consideradas custo-efetivas para pacientes com dor torácica de risco baixo a intermediário. A implementação de UCCs obteve estimativas de RCEI consideradas elevadas para o atendimento dessa população. No contexto brasileiro, a implementação de unidades dedicadas para o atendimento à SCA pode ter uma relação de custo-efetividade mais favorável do que os valores relatados para países desenvolvidos.

ABSTRACT

Introduction: Quality of emergency department (ED) care for acute vascular diseases faces the challenge of overcrowding. Prolonged ED waiting time and length of stay (LOS) compromise the quality of care, including delayed reperfusion for MI and stroke. In January 2006, the vascular unit (VU) of Hospital de Clinicas de Porto Alegre was implemented. The VU is an intermediate complexity care unit dedicated to the care of acute vascular conditions. A clinical study with historical control has demonstrated the impact of VUs on ACS patients and reported improved cardiovascular outcomes following VU implementation (years 2006 and 2007 vs. 2000 and 2001). However, the subjects of the clinical effects and the economic outcomes of VU's and other dedicated unit's implementation on clinical outcomes related to ACS and to other vascular conditions remain unresolved.

Objectives: This thesis' first objective was to estimate the impact of VU implementation on mortality rates due to acute vascular conditions. The second objective was to estimate the effectiveness of chest pain units in general on the initial evaluation of ACS in comparison to the routine hospitalization or ED assessment. The third objective was to identify and to summarize cost-effectiveness studies of dedicated units in the care of ACS.

Methods: The impact of VU implementation on mortality rates due to acute vascular conditions was estimated through a historical comparative cross-sectional study of case-fatality rates of acute vascular conditions in the periods before (2002-2005) and after VU's implementation (2007-2010). In this study, individuals that

have been initially evaluated in the ED due to selected acute vascular conditions were identified through discharge ICD-10 code: (1) ACSs, (2) ischemic stroke, (3) hemorrhagic stroke, (4) acute aortic dissection or rupture, (5) acute PE and (6) acute decompensated heart failure.

CPU's effectiveness on the initial evaluation of no-ST elevation ACS (NSTEACS) in comparison to routine hospitalization or ED care was estimated through a systematic review of literature to identify clinical trials. Literature search was conducted in MEDLINE, EMBASE and the Cochrane CENTRAL. A sensitive search strategy was elaborated with MeSH terms, Emtree terms and text words. Study selection and data extraction were performed by two independent reviewers. Quality of evidence was assessed according to the framework suggested by the Cochrane Handbook for Systematic Reviews of Interventions. Direct evidence was computed with random effects model meta-analysis of head-to-head comparisons.

Finally, economic evaluation studies of dedicated units for ACS care were identified through a second systematic review of literature. The following databases were searched: MEDLINE, EMBASE and NHS-EED. A sensitive search strategy was built using MeSH terms, Emtree terms and text words. To identify economic evaluation studies, the NHS Economic Evaluation Database (NHS EED) search filter was used. The results of the identified economic evaluations were qualitatively summarized. Values for incremental cost-effectiveness and utility ratios (ICER and ICUR) were inflated and converted to Dollars from the year 2012.

Results: In the study of VU's impact on mortality rates, the period prior to VU implementation (2002-2005) comprised 4164 patients, and the VU period (2007-2010), 6280 patients. Overall, the case fatality rate for acute vascular conditions was

reduced from 9% to 7.3% with VU implementation (p=0.002). The in-hospital mortality rates for acute coronary syndrome dropped from 6% to 3.8% (p<0.001), and acute PE rates dropped from 32.1% to 10.8% (p<0.001). The stroke case-fatality rate did not decrease despite improvements in the quality of stroke healthcare indicators.

The systematic review of clinical trials yielded seven full papers for the qualitative synthesis of evidence, of which six were included in the meta-analysis. Evaluation of the risk of bias was limited due to lack of reporting of quality assessment parameters. Compared to routine hospitalization, CPU care was associated to reductions in hospitalization rates (RR 0.47; 0.29 to 0.77), length of hospital stay (-8.74h; -16.92 to -0.55), need for follow-up coronary angiography (RR 0.22; 0.05 to 0.86) and overall rate of revascularization procedures (RR 0.30; 0.09 to 0.96). A high heterogeneity was found for two outcomes: hospital admission (I^2 = 98%) and hospital readmission (I^2 = 77%). Subgroup analysis identified study design as a possible source for part of the observed heterogeneity. There was no difference in mortality or cardiovascular event rates.

Finally, in the second systematic review, 16 economic evaluation studies of dedicated units were identified: five based on observational studies, 6 based on randomized clinical trials and 5 decision analytic models for cost-effectiveness analysis. Types of dedicated care units included: coronary care unit (CCU), mobile-CCU, intermediate care unit and CPU. Comparators included routine hospitalization, outpatient care and a hypercholesterolemia-screening program. Models were graphically represented. Overall, they were considered valid, with the exception of one study that centered its simulated CCU effectiveness in lidocaine effect on

prevention and treatment of post-MI arrhythmias. Reported ICUR for CPU care in comparison to routine hospitalization in the management of low-to-intermediate risk ACS, varied from U$ 6,416/QALY to U$ 40,944/QALY. The comparison of CCU with intermediate unit care results in reported ICER from U$ 73,166/life year gained (LYG) to U$ 307,157/LYG. The comparison of CCU with routine hospitalization resulted in a reported ICER of U$ 89,556 /LYG. CCU's economic efficiency was sensitive to age and to MI probability in target-population.

Conclusions: VU's implementation was associated to a reduction in the case-fatality rate of ACS in Brazil. This contrasts with published literature on American and European CPUs, where there was not observed reductions in mortality rates. This discrepancy is probably attributable to distinct baseline risks among these units' target population. CPU's implementation was associated to costs reduction related to shorter length of hospital stay and lower rates of hospitalization, coronary angiography and revascularization procedures in comparison to routine hospitalization. ICER estimates for the comparison of CPU care to routine hospitalization may be considered cost-effective for patients with low-to-intermediate risk chest pain. ICER estimates associated to CCU care are considered high for this population. In Brazil, the implementation of dedicated units for the care of ACS might yield more favorable cost-effectiveness ratios than values reported for developed countries.

1. APRESENTAÇÃO

Este trabalho consiste na tese de doutorado intitulada “Efetividade e Custo-Efetividade de Unidades Dedicadas no Atendimento às Síndromes Coronarianas Agudas”, apresentada ao Programa de Pós-Graduação em Epidemiologia da Universidade Federal do Rio Grande do Sul.

Para a avaliação da eficácia e da efetividade das unidades dedicadas, foram utilizadas duas abordagens. A primeira delas constituiu em um estudo original que visou complementar a avaliação de efetividade da UV do Hospital de Clínicas, publicado por Furtado e colaboradores em 2011.[1] Tratou-se da análise da taxa de letalidade das SCAs e de cinco outras síndromes cardiovasculares agudas observada naquela instituição abrangendo um período total de 8 anos. A segunda abordagem consistiu em uma revisão sistemática da literatura visando identificar os ensaios clínicos randomizados que compararam as unidades dedicadas a outras modalidades de atendimento às SCAs.

Para a avaliação de custo-efetividade (eficiência) das unidades dedicadas, realizou-se uma revisão sistemática da literatura visando identificar estudos de avaliação econômica que compararam as unidades dedicadas a outras modalidades de atendimento às SCAs. Não houve restrição a delineamentos de pesquisa, sendo incluídos todos os estudos que relataram desfechos econômicos dessas unidades.

O trabalho é apresentado em três partes, na ordem que segue:

- Introdução, Revisão da Literatura e Objetivos

- Artigos originais
- Conclusões e Considerações Finais.

Documentos de apoio são apresentados nos anexos.

2. INTRODUÇÃO

Os serviços de emergência dos hospitais foram criados para o atendimento a problemas de saúde graves e que requeiram atenção imediata. A superlotação desses serviços tem sido causa de preocupações para a comunidade sanitária, para os gestores dos sistemas de saúde público e suplementar, e para a sociedade em geral[2-4].

No Brasil, foram observadas mudanças demográficas e econômicas importantes na última década, cujas principais consequências foram o aumento na proporção de indivíduos idosos na população e um incremento no poder de compra da população em geral. Como consequência, tem sido verificado um aumento nas condições de risco ligadas ao aparecimento das doenças crônico-degenerativas e dos eventos cardiovasculares agudos.[5]

As doenças vasculares agudas, como o infarto do miocárdio e o acidente vascular cerebral, são responsáveis por uma grande parte da carga de doença em todo mundo. Em nosso país, aproximadamente 200.000 pacientes são submetidos a avaliação para SCA nos serviços de emergência anualmente, ocorrendo mais de 90.000 mortes relacionadas a esses eventos. Os acidentes vasculares encefálicos (AVE) são atualmente a principal causa de morte, tendo sido responsáveis por 97.000 mortes em 2011. Por essas razões, as doenças cardiovasculares são responsáveis por um custo elevado para o Sistema Único de Saúde (SUS).[5-7]

A ocorrência de tempos de espera prolongados e de excessiva permanência nos SE pode comprometer a qualidade do atendimento, como, por exemplo, através

de atrasos na instituição de tratamentos com impacto no risco de morte, como nos casos de infarto do miocárdio e AVE.[8,9]

A unidade vascular é uma unidade de cuidados de complexidade intermediária voltada ao atendimento das doenças vasculares agudas. Foi implementada em Janeiro de 2006 no Hospital de Clínicas de Porto Alegre; trata-se de uma área física limitada (9 leitos), onde é possível a aplicação de atendimento médico de maior qualidade, sendo as condutas orientadas por protocolos baseados em evidências. Os diagnósticos que prioritariamente são atendidos na UV incluem: (1) síndromes coronarianas agudas, (2) acidente vascular encefálico isquêmico (3), acidente vascular encefálico hemorrágico (4), dissecção aguda ou ruptura da aorta e (5) embolia pulmonar aguda. Além disso, os pacientes com (6) insuficiência cardíaca descompensada com frequência são manejados nesta unidade.[1]

A UV compartilha muitas das características das unidades de cuidados intensivos especializados, tais como: área física dedicada, equipes médica e de enfermagem próprias, atendimento orientado por protocolos, sistemas de monitoramento de pacientes, equipamentos para ventilação mecânica, além de acesso rápido a especialistas, a diagnóstico por imagem, ao laboratório de hemodinâmica e à área cirúrgica.[10-13]

Como o sucesso no tratamento das síndromes vasculares agudas é notoriamente tempo-dependente, sendo mais efetivo quando iniciado precocemente no curso da doença, atrasos associados à disfunção estrutural e a ineficiências do sistema de saúde são inaceitáveis.[14-16]

3. REVISÃO DA LITERATURA

3.1. As unidades dedicadas como tecnologias em saúde

A presente tese avalia um grupo de tecnologias em saúde que denominaremos unidades dedicadas (ou especializadas) à avaliação e ao tratamento da SCA confirmada ou suspeita. Essa denominação visa agrupar os conceitos de unidades de cuidados coronarianos, unidades de dor torácica, unidades de observação de cuidados intermediários (unidades intermediárias), bem como o conceito de unidade vascular. A estrutura física, os recursos humanos e o conjunto de práticas associadas a essas unidades dedicadas são os elementos componentes dessas tecnologias em saúde.

3.2. Tipos de avaliações econômicas aplicadas à área da saúde

A etapa inicial da avaliação de uma nova tecnologia em saúde, tanto do ponto de vista clínico quanto de políticas de saúde, consiste na demonstração de sua eficácia e efetividade. A primeira consiste na aferição do tamanho do efeito obtido quando de sua aplicação em ensaios clínicos, enquanto a segunda, quando da implementação da intervenção nas condições da prática clínica real.[17-19]

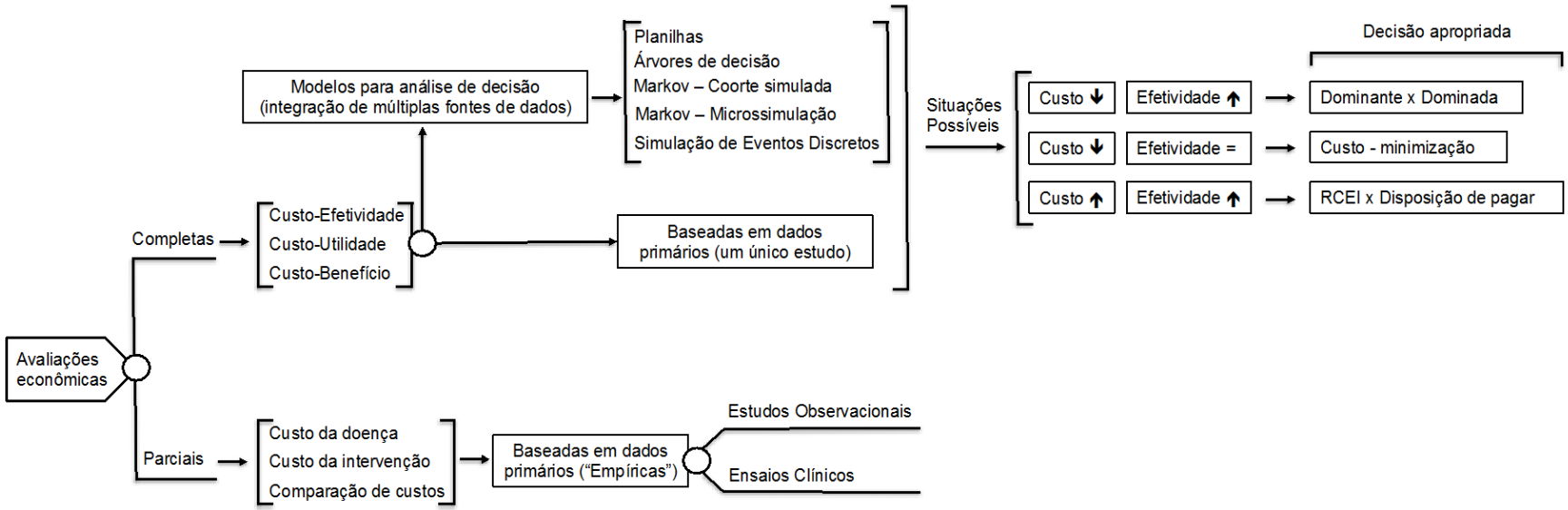
A etapa seguinte, consiste na mensuração da eficiência das intervenções, que se trata da estimativa da proporção de benefício em saúde obtido em relação aos custos incorridos em seu financiamento. De forma imprecisa, o termo "estudos de

custo-efetividade" é frequentemente usado como sinônimo para estudos de avaliação econômica ou estudos de eficiência. Embora os estudos de custo-efetividade sejam o principal método dentre os estudos de eficiência, existem outros tipos de avaliações econômicas, com interpretação prática distinta.[19]

Os estudos de avaliação econômica podem ser classificados em análises parciais, também chamados de estudos de custos, e análises completas, nas quais são comparados custos e consequências de duas ou mais tecnologias em saúde.[18,19] Em razão da ausência da comparação dos custos com as consequências para a saúde em termos populacionais, as avaliações parciais apresentam aplicabilidade limitada na tomada de decisões quanto a políticas de saúde.[20,21]

Por outro lado, os estudos de avaliação econômica completa vêm sendo cada vez mais utilizados por governos, planos de saúde privados, hospitais e indústria para apoio à tomada de decisão quanto à incorporação de uma tecnologia em saúde e quanto às condições dessa incorporação (valores, sistemas de reembolso, e compartilhamento de riscos).[17,22,23] Um esquema abrangente dos tipos de estudos de avaliação econômica e suas interpretações é apresentado na figura 1.

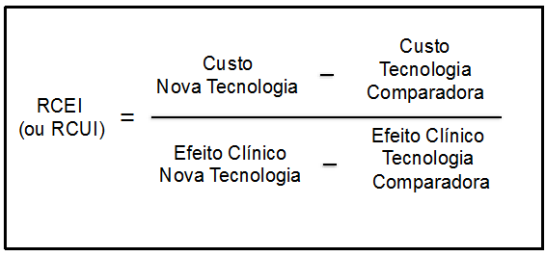
Figura 1 – Estudos de avaliação econômica classificados por metodologia e fontes de dados utilizadas



Existem três tipos principais de estudos de avaliação econômica completa. Todos contrapõem unidades monetárias (custos) com alguma medida de efeito para a saúde, diferenciando-se pelo método usado na contabilização das consequências sanitárias das intervenções. Nos estudos de custo-efetividade (1), o efeito da intervenção é medido em unidades clínico-epidemiológicas naturais, como por exemplo, R$ por mg/dL de glicose reduzido, ou R$ por mmHg de pressão arterial reduzido, ou ainda R$ por morte e evento clínico evitado. Estudos de custo-utilidade (2), por sua vez, contrapõe aos custos a utilidade, que se trata de uma medida de efeito que combina a expectativa de tempo de vida com uma estimativa da qualidade de vida. Os resultados desses estudos são apresentados na forma de R$ por ano de vida ajustado para a qualidade (R$ por AVAQ ou R$ por QALY) ou ajustados para incapacidade (R$ por AVAI ou R$ por DALY). Por fim, os estudos de custo-benefício (3) contrapõem os custos ao benefício em saúde convertido para unidades monetárias, obtendo um benefício financeiro líquido (por exemplo, R$ gastos no tratamento divididos pela estimativa em Reais do valor de um ano de vida adicional; resultados inferiores a 1 representariam economias monetárias líquidas com a adoção da nova tecnologia).[19,21,24]

Ao final dos estudos de custo-efetividade e de custo-utilidade, uma razão de custo (efetividade ou utilidade) incremental (RCEI ou RCUI) é calculada e reflete o custo adicional incorrido para aquisição de uma unidade de efeito clínico advindo do emprego da nova tecnologia em substituição à alternativa comparada (figura 2).

Figura 2 – Metodologia para o cálculo da razão incremental de custo-efetividade ou de custo-utilidade nas avaliações econômicas completas



Em relação aos métodos usados para se obter e para integrar as estimativas de custo com as estimativas de efeitos para a saúde, os estudos de avaliação econômica completa podem ainda serem classificados em dois tipos: (1) estudos baseados em uma única fonte de dados primários (avaliações econômicas empíricas) e (2) modelos para análise de decisão, que integram informações de diversas fontes de dados, como a literatura publicada, valores de mercado, relatórios governamentais e dados clínicos primários, na obtenção de estimativas econômicas mais sólidas e com maior validade externa.[20] Os modelos para análise de decisão podem se utilizar de diversos métodos matemáticos e computacionais na integração das informações, tais como: árvores de decisão, coorte simulada em modelo de Markov, microssimulação por método de Markov e simulação de eventos discretos.[23,25-28]

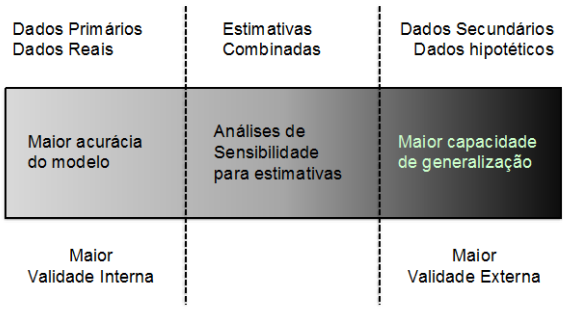
Independentemente do método utilizado, os estudos de avaliação econômica completa podem identificar basicamente a ocorrência de três relações possíveis entre custos e consequências para a saúde. Na primeira delas, uma nova terapia tem um melhor efeito clínico e um menor custo do que a terapia convencional, sendo identificada a situação de dominância da nova terapia em relação ao comparador. Neste caso, não faz sentido o cálculo de uma razão de custo-efetividade incremental, e a decisão a ser tomada é pela incorporação da nova tecnologia. A segunda situação caracteriza-se pela equivalência da efetividade do novo tratamento comparativamente ao tratamento convencional. O tipo de estudo de avaliação econômica indicado nesse caso é a análise de custo-minimização (i.e. para terapias equivalentes, qual tem menor custo). Por fim, a terceira situação (e a mais frequentemente identificada) ocorre quando uma nova terapia está associada a melhores desfechos clínicos, porém maiores custos do que o comparador. É sobretudo para essa situação que se destinam os estudo de custo-efetividade formais, nos quais uma razão de custo-efetividade incremental deve ser contraposta a um valor limiar para a disposição de pagar na decisão por incorporação ao não da nova tecnologia.[19]

3.3. *Trade-off* entre a maior validade interna dos estudos baseados em dados primários e a maior capacidade de generalização dos modelos para análise de decisão

Quando da realização de um estudo de avaliação econômica, é preciso determinar como será estimada a efetividade da tecnologia estudada e das alternativas em comparação. Tal estimativa pode ser procedente de dados primários (estudo econômico aninhado em estudo clínico), de um único estudo clínico (observacional ou experimental) ou de uma revisão sistemática com metanálise de estudos clínicos.[17,20,23,26,29]

Em geral, os estudos baseados em dados primários clínicos e econômicos coletados prospectivamente apresentam maior validade interna, no entanto suas conclusões não são necessariamente aplicáveis a outros contextos.[30] Por outro lado, os estudos econômicos baseados em modelos para análise de decisão alimentados com informações de múltiplas fontes, frequentemente provenientes de revisões sistemáticas com metanálise, apresentam maior validade externa.[31,32] Entretanto, possuem as limitações advindas da incerteza nas estimativas e dos componentes adicionais de variabilidade introduzidos pelo uso múltiplas fontes de dados.[26,29] A figura 3 representa o contrabalanço entre o emprego de dados primários ou de múltiplas fontes de dados na realização de avaliações econômicas.

Figura 3 - *Trade-off* da capacidade de generalização de resultados entre estudos primários e modelos para análise de decisão



3.4. Efetividade da Unidade Vascular

O estudo publicado por Furtado e colaboradores em 2011 demonstrou o impacto da implementação da UV nos casos de síndromes coronarianas agudas.[1] Através da coleta prospectiva de dados, foi realizada a comparação de dois períodos de 19 meses: antes (anos de 2000 e 2001) e após o funcionamento da UV (anos de 2006 e 2007). Não foi demonstrada diferença estatisticamente significativa na frequência de mortes na análise principal. Entretanto, a análise de regressão logística ajustada para características basais e fatores de risco cardiovasculares indicou o período pós-UV como um fator protetor para morte (OR 0,35; IC 95% 0,14-0,88). Com relação ao consumo de recursos, foi observado um incremento na realização de angiografia coronariana de 60,2% para 77% e uma redução na indicação de ACTP de 39% para 31% de com a implementação da unidade. Além disso, houve melhora nos indicadores de qualidade assistencial e na adesão a protocolos clínicos no período após a implementação da UV.

O estudo de Furtado e colaboradores é a principal evidência do impacto da UV em desfechos clínicos e no consumo de recursos até momento. No entanto, esse estudo apresenta informações limitadas para informar os gestores de hospitais e dos sistemas de saúde quanto às consequências clínicas e econômicas da replicação dessa estratégia de atendimento à SCA.

3.5. Unidade Vascular versus Unidades de Dor Torácica e Unidades de Cuidados Coronarianos

A existência de semelhanças entre a UV, as UDTs e as UCCs presentes em outros países, principalmente nos Estados Unidos, permitem supor que o conhecimento das características de efetividade e segurança daquelas unidades propiciariam uma melhor compreensão do impacto de outras unidades dedicadas, como a UV, no atendimento a casos suspeitos de SCA. Entre as características compartilhadas por essas modalidades de atendimento, encontram-se: a delimitação de uma área física dedicada dentro ou próximas do SE, a presença de equipes médica e de enfermagem próprias, uma proporção de pacientes por enfermeiro (ou técnico de enfermagem, no Brasil) de 2 ou 3:1, o emprego de protocolos assistenciais, o uso de leitos monitorizados, a disponibilidade de ventilação mecânica e o acesso facilitado a consultorias de especialistas clínicos e cirúrgicos, ao laboratório de hemodinâmica e aos testes diagnósticos.[33-35]

Entretanto, no que se refere ao atendimento às SCAs, a UV, as UDTs e as UCCs foram criadas por razões essencialmente distintas. Como consequência,

existem diferenças no contexto geral em que essas unidades funcionam e no perfil de risco dos pacientes por elas atendidos.

A estratégia UV tem por objetivos principais otimizar o emprego de recursos compartilhados por um grupo de doenças com características semelhantes e remover pacientes com SCA da área superlotada do SE, realocando-os em uma área "à prova de lotação excessiva". Nesse contexto, a UV atende a pacientes coronarianos de variados graus de complexidade, inclusive a pacientes portadores de IAM com elevação de ST (IAMST).

Por outro lado, as UDTs foram criadas em um cenário onde não havia escassez de leitos hospitalares e onde os pacientes coronarianos de risco elevado eram tradicionalmente direcionados a unidades de cuidados coronarianos (UCCs), que geralmente não se situam no SE e que são dirigidas por cardiologistas. Nesse contexto, as UDTs cumprem o papel de unidade de avaliação rápida para pacientes com suspeita de SCA de risco baixo a intermediário, objetivando evitar internações e consumo desnecessário de recursos diagnósticos e terapêuticos.[35-37]

Em relação às UCCs, essas unidades foram criadas com o propósito de identificar rapidamente e de intervir nas complicações de SCAs estabelecidas. Embora a UV e as UCCs compartilhem de características semelhantes, essas unidades apresentam as seguintes características que as distinguem da UV: localização geralmente fora do SE, cobertura médica por cardiologistas, atendimento exclusivo a casos coronarianos e admissão preferencial de casos de SCA de risco moderado a alto.[14,38]

3.6. Revisões sistemáticas prévias de unidades dedicadas no tratamento das síndromes coronarianas agudas

Quin G, 2000[39]

No ano de 2000, Quin conduziu uma revisão sistemática da literatura pertinente às UDT visando identificar: (1) protocolos de tratamento das UDTs; (2) evidência de efetividade clínica; (3) estimativas da custo-efetividade e (4) avaliação da percepção de qualidade do atendimento pelos pacientes. A busca foi realizada nas bases de dados MEDLINE, EMBASE e Cochrane CENTRAL e não foi limitada a ensaios clínicos randomizados. Não houve dupla seleção de artigos ou extração de dados.

Foram identificados 5 estudos para a avaliação da efetividade das UDTs. No entanto, esse autor optou por avaliar a efetividade das UDTs com base na acurácia diagnóstica da unidade na identificação de SCA, e não através de seu impacto em desfechos clinicamente relevantes, aferido em ensaios clínicos. Como resultado, foram incluídos na avaliação de efetividade: 1 estudo com delineamento para avaliação de teste diagnóstico, 3 estudos de coorte e somente 1 ensaio clínico randomizado. A sensibilidade e a especificidade de um protocolo para avaliação de dor torácica em um dos estudos identificados foram estimadas em 90 e 50%, respectivamente, assumindo uma sensibilidade de 100% para o protocolo de investigação em hospitalização convencional.[40] Foram relatados 2 IAM e 4 mortes não cardíacas ocorridos entre 1461 pacientes que receberam alta a partir de UDTs em 4 estudos.[41-44] Adicionalmente, o diagnóstico de SCA foi confirmado em 2 a 9% dos pacientes admitidos nas UDTs dos estudos selecionados.[41-45]

Na avaliação de custo-efetividade, não foram identificadas estimativas da RCEI, sendo que os desfechos avaliados foram limitados a comparação de custos em 2 ensaios clínicos[43,46] e em dois estudos observacionais.[42,47] Todos estudos identificados relataram custos significativamente menores entre os pacientes avaliados em UDTs em comparação a pacientes hospitalizados.

Goodacre SW, 2000[48]

No mesmo ano, Goodacre publicou uma revisão sistemática da literatura acerca da efetividade clínica e eficiência econômica das UDTs. Não houve restrição para ensaios clínicos, e a única base de dados pesquisada foi a MEDLINE. Não houve dupla seleção de artigos ou extração de dados. Foram identificados 5 estudos comparando UDTs a um grupo controle no atendimento à SCA, sendo que 3 deles eram ensaios clínicos randomizados.[43,46,49-51] Além desses, foram encontrados 6 estudos de coorte sem grupo controle.[42,44,52-55] Essa revisão sistemática limitou-se à descrição da variação observada nas taxas de eventos entre os grupos em comparação e não foi realizada estimativa de um efeito sumário para os desfechos avaliados, sendo relatados 28 IAM e 22 mortes entre 9665 pacientes incluídos em 11 estudos. Houve relato de desfechos econômicos em 9 estudos, todos apresentando resultado favorável às UDTs, com economia monetária estimada entre U$ 567 e U$ 2030 em relação à avaliação de dor torácica através de hospitalização convencional.

D'Ascenzo et al, 2012[56]

Essa revisão sistemática com metanálise comparou estratégias para avaliação inicial da SCASSST baseadas em angiotomografia computadorizada coronariana (ATCC) com estratégias convencionais. A busca foi conduzida nas bases de dados MEDLINE, EMBASE e Cochrane CENTRAL, sendo a seleção de artigos e a extração de dados realizada de forma independente por três autores. Quatro ensaios clínicos foram identificados.[57-60] No entanto, em nenhum deles o desenho do estudo permitia identificar o efeito da UDT nos desfechos, dado que se trata de estudos desenhados para avaliar o efeito da ATCC. A leitura dos estudos individuais permite depreender que os pacientes randomizados para ambos os braços dos estudos eram manejados no mesmo ambiente, possivelmente um uma UDT, e que não houve comparação quanto ao tipo de unidade. O uso de estratégias baseadas em ATCC esteva associado a maior taxa de procedimentos de revascularização em geral (OR 1,88, IC 95% 1,21 a 2,92) a um menor tempo para o diagnóstico (-7,68h, IC 95% -12,7 a -2,66) e a menores custos gerais do atendimento, embora não tenha sido conduzida uma avaliação econômica formal (- U$ 680; IC 95% -1,060 a -270). A heterogeneidade (I^2) entre os estudos foi elevada para os seguintes desfechos: taxa de alta diretamente do SE (97%), tempo até o diagnóstico (98%) e custos (99%).

3.7. Estudos de avaliação econômica prévios

Foram identificados 16 estudos de avaliação econômica, classificados em três categorias: (1) 5 avaliações econômicas parciais baseadas em estudos observacionais; (2) 6 ensaios clínicos randomizados com análise de custo aninhada; e (3) 5 modelos de análise de decisão e custo-efetividade. A intervenção avaliada nesses estudos foi a UDT ou a UCC, e os comparadores incluíram: hospitalização convencional, UCC móvel, unidade intermediária e atendimento ambulatorial.

3.7.1. Avaliações econômicas parciais, baseadas em estudos observacionais

Avaliações econômicas parciais, também chamadas de avaliações econômicas empíricas, são estudos de comparação de custos a partir de dados primários. Nesses estudos, não são usados métodos de modelagem (como árvores de decisão ou modelos de Markov) e as estimativas de custos obtidas não são baseadas em revisão sistemática da literatura, o que limita a validade externa desse método.[20,61]

Entre os estudos identificados, 2 não apresentaram grupo controle.[62,63] Quanto às unidades avaliadas, 2 incluíram UCC (como comparador ou intervenção principal)[50,62] e 4 incluíram UDT.[50,55,63,64] Nos três estudos comparativos, uma estratégia baseada em uma UDT produziu economia de recursos estimada em 52 a 80% em comparação a uma estratégia mais invasiva.

Bloom et al, 1973[62]

Considerando o razoável grau de incerteza a respeito da efetividade e dos custos das UCCs ao final dos anos 60 nos Estados Unidos, Bloom e colaboradores descreveram as características clínicas e os custos associados a essas unidades em uma amostra aleatória derivada de 32 hospitais. As UCCs avaliadas não estavam necessariamente situadas próximas ao departamento de emergência dos hospitais, e algumas delas estavam integradas à unidade de terapia intensiva geral. Foram revisados os prontuários dos pacientes e informações administrativas hospitalares, e os resultados foram relatados de acordo com o tipo de hospital: hospitais universitários (7), outras modalidades de hospitais de ensino (5) e hospitais sem ensino (20). O diagnóstico de infarto do miocárdio (IAM) foi o mais prevalente nas UCCs avaliadas (50,4%). A taxa média geral de mortalidade foi de 9,6%; entre os pacientes com IAM, a letalidade foi de 18,1%. Quanto à duração da hospitalização, a estimativa geral foi de uma estada média de 4,7 dias (variação inter-hospital de 2,9 a 8,8 dias). A avaliação econômica nesse estudo foi limitada a uma análise de custos. O gasto total para o atendimento em UCCs no conjunto dos 32 hospitais avaliados foi estimado em U$ 4.491.552 (dólares de 1973). Na avaliação da composição da estrutura de custos, verificou-se que 52,4% desse montante decorria de despesas com pessoal de enfermagem; 17,5%, de custos fixos; 12,5%, de custos com pagamentos de médicos; 13,7%, de custos com outras modalidades de recursos humanos (inclusive internos e residentes); e 3,9%, a custos com materiais. O custo médio da estada no hospital foi estimado em U$ 560,39 por paciente. Foram observadas discrepâncias nas taxas de ocupação de leitos, que tenderam a ser mais elevadas em hospitais de grande porte ou de ensino. Os autores concluíram que

decisões quanto à distribuição das UCCs devem tomar em consideração as necessidades regionais, e não somente depender da iniciativa individual dos hospitais em estabelecer tais unidades.

De Leon Jr et al, 1989[55]

Nesse estudo, foram comparados custos entre duas estratégias para a avaliação inicial de pacientes considerados de baixo risco cardiovascular que procuraram o atendimento por dor torácica. A primeira delas consistia em admissão hospitalar e avaliação em uma UCC; a segunda, em observação em uma unidade de dor torácica (UDT), onde os pacientes seriam avaliados e realizariam ECGs e aferições seriadas de marcadores de lesão miocárdica por um período inferior a 20h. Dor torácica de baixo risco foi definida como ECG normal e ausência de complicações clínicas. Os custos por paciente foram estimados a partir dos registros financeiros do hospital (macrocusteio). O custo médio incorrido para pacientes em que foi possível a liberação hospitalar com o diagnóstico provisório de "IAM excluído" após o período de observação na UDT foi de U$ 598 (dólares de 1989) após uma estada média de 11,1 horas. Pacientes comparáveis, admitidos na UCC e liberados após a exclusão de IAM permaneceram em média 3 dias no hospital, ao custo total médio de U$ 3101. Os autores concluíram que a utilização da UDT na avaliação inicial de pacientes com dor torácica de risco baixo a intermediário era capaz de economizar recursos.

Gaspoz et al, 1994[50]

Com o objetivo de comparar diferentes estratégias para o manejo inicial de pacientes com dor torácica de baixo risco, esse estudo obteve informações de custos e de desfechos clínicos entre pacientes avaliados em uma UDT ou através de quatro outras estratégias: (1) alta para casa após avaliação no serviço de emergência (SE-AC); (2) internação em enfermaria clínica; (3) internação em unidade intermediária (*stepdown unit*); (4) internação em uma UCC. Nesse estudo, a UDT consistia em dois dentre dez leitos de uma unidade de observação adjacente ao SE, e contava com monitorização por telemetria e uma proporção entre pacientes e enfermeiros de 5:1. Cobertura médica era fornecida por médicos residentes do SE, quando necessário. A UDT destinava-se a pacientes com uma probabilidade de IAM ≤ 10% e com uma expectativa de estada no hospital inferior a 48h. Pacientes admitidos na UDT não poderiam apresentar sintomas isquêmicos ativos, achados eletrocardiográficos de isquemia miocárdica em evolução ou arritmias graves. Os dados de custo incluídos foram procedentes da revisão das despesas hospitalares dos pacientes em até 6 meses após o atendimento inicial e incluíram: (1) despesas hospitalares e honorários profissionais na internação inicial; (2) custos do SE; e (3) custos incorridos no seguimento de seis meses, decorrentes do uso de serviços médicos relacionados a cardiopatia isquêmica ou dor torácica. Verificou-se que a UDT resultaria no menor custo mediano total por paciente (U$ 1927, dólares de 1994), seguida pela admissão em unidade intermediária (U$4031), enfermaria clínica (U$ 4712) e UCC (U$ 9201). Essas diferenças de custos foram estatisticamente significativas após ajuste por regressão linear para características clínicas e gravidade dos pacientes na triagem. Não foram encontradas diferenças nas taxas de

mortalidade e de eventos clínicos entre a UDT (0,68%) e o conjunto de comparadores (0,91%). Os autores concluíram que a UDT pode ser uma estratégia segura e capaz de economizar recursos na avaliação de SCA de risco baixo a intermediário.

Goodacre et al, 2001[63]

Este estudo tratou-se de uma análise preliminar de custos com base em uma amostra aleatória de 300 pacientes avaliados por dor torácica no SE de um hospital na cidade de Sheffield (Reino Unido). Através de um estudo de custeio simples, os autores estimaram os custos que poderiam ser evitados através da avaliação desses pacientes em uma UDT hipotética, que operasse em molde similar ao das UDTs norte-americanas. No total, 106 pacientes (37%) foram considerados estar em baixo risco para IAM e poderiam, em tese, ser avaliados em uma UDT. O custo por admissão na UDT foi estimado em U$ 733 (dólares de 2001) com a inclusão das despesas com cardiologia invasiva e em U$ 570 descontando-as. Não foi realizada avaliação econômica comparativa com a hospitalização convencional ou com outras estratégias na avaliação de pacientes com dor torácica de baixo risco.

Shah et al, 2012[64]

De forma semelhante à publicação de 2001 de Goodacre e colaboradores, esse estudo realizou a uma estimativa de custos potencialmente evitáveis pela avaliação de pacientes com dor torácica de baixo risco em uma UDT hipotética a partir de custos incorridos por pacientes avaliados em um hospital sem UDT. Os autores assumiram o pressuposto de que, na UDT hipotética, a duração da

observação no hospital e a probabilidade de internação em pacientes com SCASSST poderiam ser determinadas pelo escore de risco TIMI na admissão, com estada de 12h para pacientes com escores de 0 a 2, de 20h para pacientes com escore de 3 ou 4 e com internação hospitalar para os pacientes com escore acima de 4. Assumiu-se também que a história de doença aterosclerótica coronariana (DAC) conhecida implicaria a realização de teste não invasivo. A estimativa de custos incluía a duração da estada no hospital e o custo com teste não invasivo. O custo total para os 202 pacientes foi estimado em U$ 300.528 (dólares de 2012) com a adoção da UDT, enquanto o custo de fato incorrido pelos 202 pacientes foi de U$ 658.400 em um hospital sem UDT. Este estudo foi publicado somente na forma de resumo nos anais do *61st American College of Cardiology Annual Scientific Session and Expo* (2012).

3.7.2. Estudos de avaliação econômica aninhados a ensaios clínicos

Todos os seis ensaios clínicos randomizados que incluíram desfechos econômicos encontraram redução estatisticamente significativa no custo mediano por paciente com o emprego da UDT em substituição a outras modalidades de unidades.[12,43,46,49,66,67] Somente o ECR realizado por Goodacre e colaboradores em 2004 obteve estimativa da qualidade de vida, resultando em uma RCUI de £ 2750 por QALY.[6]

Gomez et al, 1996[43]

Um protocolo de diagnóstico acelerado para descartar IAM realizado em uma unidade de observação no SE foi a intervenção testada nesse estudo, que foi o

primeiro ensaio clínico randomizado a testar o conceito das UDTs em comparação à estratégia convencional de avaliação no SE e hospitalização para investigação complementar. No total, 100 pacientes foram randomizados, sendo incluídos pacientes com idade ≥ 30 anos, com suspeita de SCA, porém com uma probabilidade basal de IAM ≤ 7% (de acordo com o algoritmo de Goldman) e sem alterações isquêmicas no ECG inicial. Os critérios de exclusão foram os seguintes: alterações isquêmicas no ECG inicial, presença de arritmias que necessitassem de manejo com medicamentos intravenosos, bloqueis atrioventriculares de 2º ou 3º graus, angina requerendo nitroglicerina, PA > 220/120 mmHg, presença de insuficiência cardíaca agudamente descompensada ou outras doenças que necessitassem de monitorização ou de medicações intravenosas. A intervenção consistia em um período mínimo de 9h de observação em uma UDT, com administração de aspirina e oxigênio suplementar por protocolo. Os marcadores de lesão miocárdica (CK e CK-MB) eram aferidos na admissão e a cada 3h. Ao final do período inicial de observação, todos os casos indefinidos eram submetidos a uma modalidade de teste de estresse (teste ergométrico ou ecocardiograma com estresse farmacológico). O grupo controle era manejado de forma não-sistemática, a critério do médico assistente, que poderia solicitar internação na enfermaria clínica, na UCC ou em outra unidade monitorizada.

Nos resultados, não foram observadas diferenças estatisticamente significativas na mortalidade e na incidência de eventos cardiovasculares, tanto no período hospitalar quanto nos 30 dias de seguimento. Entretanto, a duração da estada no hospital foi significativamente menor no grupo intervenção em relação à hospitalização convencional (15,4h versus 56,6h, em média, p<0,001). Além disso, as

despesas hospitalares foram significativamente menores no grupo intervenção. Os autores concluíram que a estratégia do protocolo de diagnóstico acelerado em uma UDT apresentava eficácia semelhante à hospitalização convencional, no entanto possibilitando um menor tempo de estada no hospital e redução nos custos.

Roberts et al, 1997[46]

Na avaliação de pacientes com suspeita de SCA, esse ensaio clínico comparou um protocolo de diagnóstico acelerado (PDA) conduzido em uma unidade de observação no SE com a hospitalização convencional em uma unidade com telemetria. A população-alvo do estudo consistia em pacientes com idade ≥ 20 anos, com suspeita de SCA, porém com probabilidade de IAM ≤ 7% pelo algoritmo de Goldman e sem contraindicações ao teste ergométrico. Foram excluídos pacientes com DAC conhecida, complicações pré-hospitalares da SCA, alterações isquêmicas no ECG inicial, fibrilação atrial, extrassístoles supraventriculares frequentes, angina recorrente, diagnóstico alternativo que necessitasse de hospitalização e ECG basal que não permitisse interpretação de teste ergométrico. Os desfechos principais foram taxas de admissão hospitalar, duração da estada no hospital e custos totais. As taxas de mortalidade dos pacientes avaliados através do PDA foram apresentadas no formato de estudo transversal em outra publicação, de forma que não foi realizada a comparação randomizada da mortalidade nesse ensaio clínico.[40] O grupo controle era submetido a um período de 24h de observação em uma unidade monitorizada por telemetria, com série de 3 aferições de CK-MB e realização de 2 ECGs, enquanto o grupo PDA era submetido a um período de 12h de observação, com 4 dosagens da CK-MB (tempos 0, 4, 8 e 12h) e 3 ECGs (tempos 0, 6 e 12h), além

de receber administração de aspirina e oxigênio por protocolo. Pacientes de qualquer um dos grupos cuja avaliação inicial fosse indicativa de isquemia miocárdica eram hospitalizados. Do contrário, eram submetidos a teste ergométrico, sendo admitidos em caso de teste positivo e liberados em caso de teste negativo. Na comparação com o grupo controle, a estratégia PDA foi associada a menores taxas de hospitalização (45% versus 100%; $p < 0,001$), menor duração da estada no hospital (média de 33,1h versus 44,8h; $p <0,01$) e menor proporção de pacientes com diagnóstico indeterminado na alta (13% versus 45%; $p<0,01$). Além disso, foi observada redução estatisticamente significativa no custo médio por paciente (U$ 1528 para estratégia PDA e U$ 2095 no grupo controle; $p<0,01$). Não ocorreram mortes ou diferenças na incidência de eventos coronarianos entre os grupos no período hospitalar ou no seguimento de 56 dias. Os autores concluíram que a estratégia PDA tem o potencial de economizar recursos para o hospital na avaliação de pacientes com dor torácica de baixo risco.

Farkouh et al, 1998[49]

Farkouh e colaboradores conduziram um ensaio clínico que randomizou 424 pacientes que procuraram o SE por dor torácica para receberem avaliação inicial e tratamento em uma UDT ou em uma hospitalização convencional. O principal critério de inclusão foi a presença de angina instável de risco intermediário para eventos cardiovasculares no curto-prazo (de acordo com diretrizes da *Agency for HealthCare Policy Research*). Pacientes com depressão ou elevação definidas do segmento ST foram considerados como portadores de angina de alto risco e não foram arrolados.

A intervenção consistia em um período de observação mínimo de 6h, com determinação da CK-MB a cada 2h. Todos pacientes recebiam aspirina por protocolo. Casos que permanecessem indefinidos após essa avaliação inicial eram submetidos a um teste de estresse (ergometria, cintilografia miocárdica ou ecocardiografia). Pacientes cujos testes provocativos resultassem negativos recebiam alta hospitalar e eram reavaliados ambulatorialmente por um cardiologista em 72h. O grupo controle consistia na internação em leitos monitorizados sob os cuidados do serviço de cardiologia, porém não havia padronização de cuidados e investigação.

Não foram observadas diferenças na mortalidade ou na incidência de eventos cardiovasculares durante a internação ou após o seguimento de 180 dias. Entretanto, foi observada uma redução de 45,8% na taxa de internação hospitalar no grupo UDT em relação ao grupo da hospitalização convencional. Além disso, o grupo da hospitalização convencional apresentou um maior uso de exames e procedimentos diagnósticos e de re-hospitalizações para cuidados cardíacos durante o seguimento.

Goodacre et al, 2004[67]

Após três anos da publicação de ume estudo de custos preliminar sobre o impacto potencial das UDTs no Reino Unido, Goodacre e colaboradores publicaram esse ensaio clínico em cluster que comparou a hospitalização convencional com uma UDT para avaliação de pacientes com dor torácica de baixo risco. A unidade em questão estava situada no SE e consistia em dois leitos monitorizados e em uma área adjacente não-monitorizada, sem um número limite de pacientes. A equipe da UDT consistia em três enfermeiros com treinamento em dor torácica e habilitados a supervisionar testes ergométricos. A cobertura médica era proporcionada pelos

médicos da emergência, quando necessário. Os critérios para inclusão foram os seguintes: idade ≥ 25 anos, dor torácica aguda indiferenciada, com ECG inicial não-diagnóstico. Pacientes apresentando as seguintes características foram excluídos no processo de arrolamento: história de angina instável, presença de comorbidades graves, diagnóstico alternativo grave para a dor torácica e recusa em consentir na participação do estudo.

Ao todo, 972 pacientes com dor torácica foram alocados para atendimento na UDT ou para hospitalização convencional de acordo com uma tabela de randomização previamente definida que não era do conhecimento da equipe de triagem, na recepção. Nesse estudo, foram os dias da semana, e não os pacientes individuais, que foram randomizados para manejo das SCAs na UDT ou na hospitalização convencional, assim definido "clusters" de 1 a 3 pacientes por dia de semana. Os desfechos foram aferidos durante a hospitalização e em 6 meses. Foram obtidas estimativas da qualidade de vida através do instrumento EQ-5D, que foi aplicado após 2 dias, 1 mês e 2 meses do atendimento inicial. A estimativa de custos foi realizada sob a perspectiva do hospital através de um método de microcusteio que incluía despesas decorrentes de recursos humanos do hospital, tempo de hospitalização, exames diagnósticos em geral, exames radiológicos, ecocardiograma, reavaliações ambulatoriais, visitas ao SE e procedimentos cardiológicos.

Foram observadas duas mortes em cada grupo durante o seguimento, duas decorrentes de causas cardíacas e duas decorrentes de causas não cardíacas, não havendo, portanto, diferença na mortalidade entre os grupos. O custo médio por paciente para o atendimento recebido na UDT foi de £ 478 (correspondentes a U$ 875,13 dólares de 2004) e de £ 556 (U$ 1017,94) para a hospitalização convencional.

Com base em um incremento estatisticamente significativo observado de 0,0143 anos de vida ajustados para qualidade (AVAQ) para os pacientes tratados na UDT em relação aos hospitalizados, foi calculada uma RCUI de £ 2750 / AVAQ (U$ 5034,78 / AVAQ). Não foram utilizados métodos de modelagem para análise de decisão, no entanto, foi realizada uma análise de sensibilidade quanto à estimação dos custos que determinou 95% de probabilidade do valor da RCUI situar-se abaixo da estimativa pontual calculada.

Conti et al, 2005[12]

Nesse ensaio clínico conduzido na Itália, 210 pacientes com SCASSST de risco intermediário (escore de risco TIMI não-ST ≥ 3) foram randomizados para receber atendimento inicial em uma UDT ou em uma UCC. Não foram incluídos nesse estudo pacientes com elevação de ST, angina secundária, história de distúrbios das plaqueta, pacientes considerados sob risco para sangramento ativo, pacientes classificados como classes de Killip III ou IV na admissão e pacientes que tivessem sofrido AVC nos 6 meses anteriores. A UDT desse estudo consistia em 4 leitos dedicados e situava-se adjacente ao SE. Era equipada com monitorização para eventos e monitorização contínua do segmento ST. A equipe dessa unidade consistia em dois enfermeiros disponíveis 24h por dia e em um médico clínico durante o horário comercial e em regime de sobreaviso à noite. A equipe da UCC incluía cardiologistas do laboratório de hemodinâmica disponíveis 24h por dia. Uma abordagem de macrocusteio foi adotada e não houve modelagem para análise de decisão, tampouco houve estimativa da RCEI, sendo os resultados econômicos apresentados somente como comparação de custos. Os autores relataram as

seguintes reduções estatisticamente significativas nos custos dos pacientes manejados na UDT em comparação à UCC: -51% no custo médio de diagnósticos e procedimentos, -6% no custo médio com medicamentos e -22% no custo total da internação por paciente (€ 9913 para UDT e €12056 para UCC, euros de 2005, p=0,01). Pacientes no grupo UDT foram submetidos a menos procedimentos de revascularização do que os pacientes do grupo UCC (53 versus 76%, respectivamente; p=0,002). Não houve diferença em termos de internações evitadas. Em relação à duração da hospitalização, embora os pacientes do grupo UDT tenham permanecido menos tempo na unidade do que aqueles do grupo UCC, a duração do tempo adicional de internação na enfermaria foi menor no último grupo, o que determinou uma maior duração total da hospitalização no grupo UDT (7,5 dias na UDT versus 5,7 dias na UCC, p = 0,003). Na análise de subgrupos, verificou-se que a redução nos custos ocorreu às custas do subgrupo de pacientes com escore de risco TIMI ≤ 4, em que foi observada queda de 29% no custo total da internação por paciente (€10599 para UDT e €13699 para UCC; p=0,004).

O estudo de Conti e colaboradores apresentou duas importantes diferenças em relação aos outros ensaios clínicos de UDTs. E primeiro lugar, foram incluídos pacientes de maior risco para desfechos adversos (60% dos pacientes pontuaram acima de 4 no escore de risco TIMI, e 30% possuíam diagnóstico estabelecido de DAC). Em segundo lugar, esse foi o único estudo a comparar a UDT com uma intervenção "melhor" (ou mais intensiva), a UCC. Em outras palavras, tratou-se de um ensaio clínico que mediu as consequências de se atender a pacientes de maior risco, que normalmente seriam admitidos em uma UCC, em uma unidade menos complexa e de menor custo, a UDT. Os resultados desse estudo estão em sintonia

com os demais ensaios clínicos de UDTs, favorecendo o uso dessas unidades para pacientes de risco baixo a intermediário, e ilustrando que não houve vantagem da substituição da UCC pela UDT para os pacientes considerados de risco elevado.

Goodacre et al, 2007[68]

Os resultados encorajadores relatados nos estudo de 2004, que demonstrou efeito da UDT na redução na taxa de hospitalizações e melhora na qualidade de vida, levaram esses autores a realizar esse grande ensaio clínico multicêntrico, denominado de estudo ESCAPE. Nesse ensaio clínico com desenho em cluster, 14 hospitais do Reino Unido que não contavam com UDTs foram randomizados para implementar ou não esse tipo de unidade para a avaliação inicial e tratamento dos pacientes com dor torácica de risco baixo a intermediário. Os critérios de inclusão e de exclusão para participação no ensaio clínico foram os mesmo do estudo de 2004, e se pretendia que as UDTs criadas fossem similares àquela do estudo original.

Essa publicação foi pobre em informações clínicas, centralizando suas análises nas taxas de visitas ao SE, de internações e de reinternações. Os clusters foram delimitados pelos hospitais incluídos no estudo, com um tamanho médio de 3411 pacientes por hospital. O efeito cluster foi levado em consideração no cálculo do tamanho da amostra, tendo sido estimado em 4. Isso significa que, considerando o tamanho e número de clusters, a amostra teria de ser 4 vezes àquela necessária para um ensaio clínico de pacientes individuais.

No total, 27454 pacientes foram incluídos na fase após a implementação das UDTs nos hospitais sorteados para essa intervenção. Não foram observadas diferenças nas taxas de internações entre os hospitais com e sem UDTs. Por outro

lado, verificou-se um aumento nas taxas de retorno ao SE (OR 1,1; p = 0,036) e uma tendência de aumento nas taxes de readmissão hospitalar (OR 1,3; p = 0,083) entre os pacientes atendidos em hospitais com UDTs em comparação àqueles atendidos em hospitais sem UDTs. Também foi observada tendência a maior taxa diária de internações hospitalares nos hospitais com UDTs.

Os autores reconhecem que ocorreram limitações e na implantação das UDTs do estudo ESCAPE, que pode não ter sido capaz de reproduzir em larga escala o efeito observado nos estudos de UDT de um único centro. Além disso, em uma publicação posterior desse mesmo grupo, foram identificadas possíveis falhas na identificação e arrolamento de pacientes para o estudo ESCAPE.

Não houve avaliação econômica realizada em conjunto com o estudo ESCAPE. No entanto, informações procedentes da etapa de arrolamento foram utilizadas na elaboração de um modelo para análise de decisão e custo-efetividade publicado em 2008.

Miller et al, 2010 e 2011[66,69]

Outro estudo comparando estratégias para avaliação e manejo iniciais de pacientes com suspeita de SCA foi realizado por esses autores. Nesse estudo, 109 pacientes com SCA de risco baixo a intermediário foram randomizados para hospitalização convencional ou para uma UDT associada a estratificação de risco por ressonância magnética cardíaca (RMC) para casos sem elevação de troponina após 8h de observação.

Foram incluídos pacientes com idade igual ou maior a 18 anos que procuraram o SE por dor torácica e com escore de risco TIMI não-ST intermediário a

alto (≥2). Os critérios de exclusão foram: elevação na troponina T inicial, ECG inicial com depressão ou supradesnivelamento de ST, ortopneia, PA sistólica inferior a 90 mmHg, presença de contraindicações à RMC, recusa em ser submetido aos procedimentos indicados, gravidez, expectativa de vida inferior a 3 meses, doença hepática ou renal crônica e receptores de transplante de órgãos. Os resultados do seguimento de 1 ano foram apresentados em uma publicação subsequente. O desfecho principal do estudo consistia nos custos médicos diretos do atendimento hospitalar inicial (perspectiva do hospital), que sofreu uma redução significativa com o emprego da estratégia UDT+RMC em comparação à hospitalização convencional (U$ 2062 versus U$ 2680, respectivamente, dólares de 2010). Essa diferença foi atribuída principalmente à menor taxa de hospitalização no atendimento inicial que foi verificada no grupo UDT+RMC (21% versus 95%, respectivamente). Nos 30 dias iniciais do seguimento, não foram detectados eventos cardiovasculares que não houvessem sido diagnosticados na primeira avaliação em qualquer uma das estratégias. Achados similares foram relatados em relação ao seguimento de 1 ano, durante o qual não foram observadas diferenças na ocorrência de eventos cardiovasculares maiores entre os grupos avaliados (6% versus 9%, respectivamente).

Em muitos aspectos, o estudo de Miller e colaboradores é comparável a outros ensaios clínicos de UDTs, apresentando similaridade quanto a: critérios de inclusão e de exclusão, intervenção estudada (avaliação inicial dos casos de dor torácica em uma unidade de observação fechada, com protocolos definidos, seguida pela realização de um teste não invasivo para os casos indeterminados) e comparador (hospitalização convencional, com investigação e manejo a critério do

médico assistente). Por outro lado, trata-se do único ensaio clínico a usar a RMC como método não-invasivo na estratificação de risco dos casos indefinidos. A despeito dessa diferença, nós consideramos que esse estudo deve ser listado entre os ensaios clínicos de UDTs, pois o uso de uma unidade de observação nos moldes das UDTs claramente fazia parte da intervenção.

3.7.3. Avaliações econômicas baseadas em modelos de análise de decisão

Os modelos de análise de decisão são atualmente considerados o método de excelência na realização de estudos de avaliação econômica. Nesse tipo de estudo, informações de diversas fontes, como resultados de ensaios clínicos ou de revisões sistemáticas, bem como estimativas de custos, são combinados em modelos matemáticos que buscam reproduzir a o comportamento de uma coorte simulada de pacientes expostos às alternativas em comparação.

Foram identificados 5 estudos de análise de decisão baseados em modelos. Entre os métodos identificados, apenas um modelo de Markov[70] foi encontrado, os demais tendo sido elaborados em árvores de decisão. Juntamente da revisão narrativa abaixo, são apresentadas representações gráficas dos modelos.

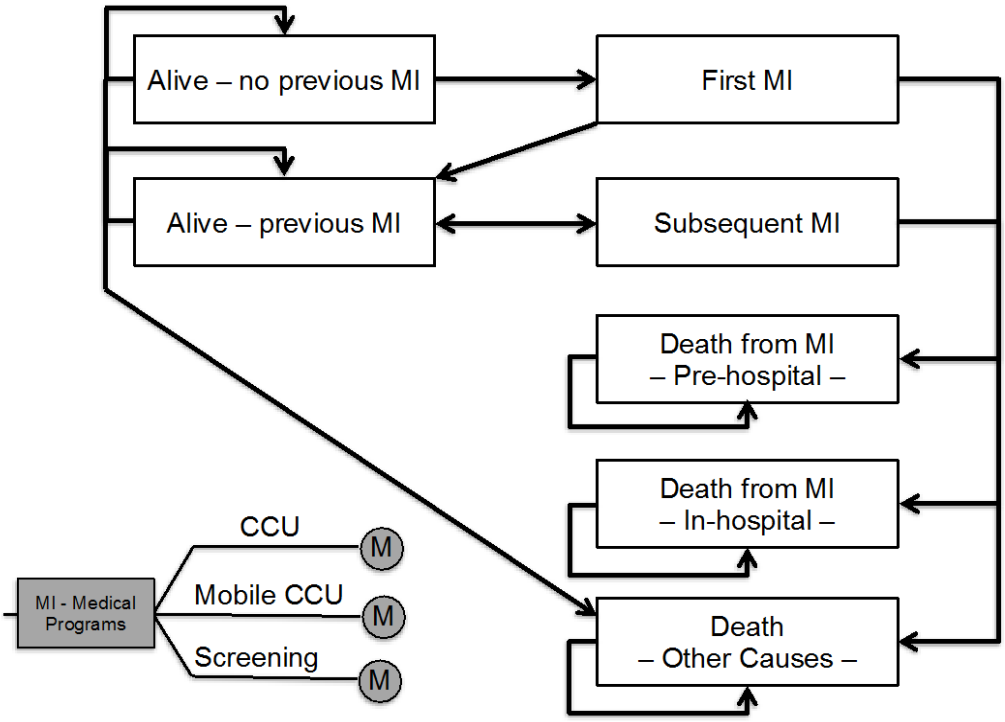
Cretin et al, 1977[70]

O objetivo desses autores foi comparar custos e consequências de estratégias que atuassem em diferentes momentos da história natural da cardiopatia isquêmica. Para isso, três estratégias foram consideradas em um modelo de Markov: (1) as UCCs, que atuariam o risco de morte intra-hospitalar no IAM; (2) as UCCs móveis, que atuariam no risco de morte pré-hospitalar por IAM; e (3) um programa de

rastreamento para hipercolesterolemia com intervenção dietética em crianças, que seria capaz de reduzir a incidência de IAM. O modelo de Markov elaborado consistia em sete possíveis estados de saúde: (1) vivo, sem IAM prévio; (2) primeiro IAM; (3) vivo, com IAM prévio; (4) segundo ou subsequente IAM; (5) morte por IAM antes de chegar ao hospital; (6) morte por IAM antes da alta hospitalar; (7) morte por outras causas (figura 4).

Foi realizada uma extensa análise de sensibilidade a respeito das taxas de desconto, considerando os resultados com descontos de 0, 5 e 10% ao ano. Em todas as análises, a estratégia das UCCs obteve a melhor custo-efetividade média, com uma estimativa na análise principal de U$ 3068 /ano de vida adicional em relação a um sistema de saúde sem UCCs. A estratégia baseada em UCCs móveis foi a segunda melhor classificada, e a estratégia do rastreamento de hipercolesterolemia foi considerara a menos custo-efetiva. Considerando as incertezas a respeito das estimativas de custos dessas estratégias e do efeito das diferentes taxas de desconto em custos e consequências clínicas, os autores foram conservadores em suas conclusões, estabelecendo que seu modelo não permitia a obtenção de respostas definitivas na comparação de estratégias para prevenção de mortes por IAM.

Figura 4 – Representação gráfica do modelo de Markov desenvolvido por Cretin e colaboradores



Fineberg et al, 1984[71]

Um modelo de análise de decisão foi construído por Fineberg e colaboradores para estimar a custo-efetividade comparativa de quatro possíveis estratégias no manejo da SCA. O agrupamento dos custos relacionados às estratégias comparadas e a contabilização das probabilidades de ocorrência de eventos seguiram a lógica da modelagem em árvore de decisão simples, porém o modelo não foi representado graficamente como árvore nessa publicação. Posteriormente, a representação em árvore de decisão foi feita por outros autores, que declaradamente buscaram reproduzir o modelo original de Fineberg e colaboradores (figura 5).[72]

O modelo consistia em uma coorte simulada fechada de 100.000 indivíduos que procuraram o hospital por dor torácica aguda. Quatro estratégias foram comparadas (1) UCC (capacidade operacional totalmente comparável a de uma unidade de terapia intensiva, proporção de pacientes: enfermeiro de 2:1, disponibilidade de lidocaína profilática e terapêutica para arritmias ventriculares e disponibilidade de marca-passo de urgência para bloqueio atrioventricular total – BAVT); (2) unidade intermediária (leitos monitorizados, proporção pacientes : enfermeiro de 4:1 e disponibilidade de lidocaína profilática e terapêutica para arritmias ventriculares); (3) hospitalização convencional em enfermaria (sem lidocaína prontamente disponível); e (4) atendimento ambulatorial (consultas em dias alternados após o atendimento inicial na emergência). A prevalência de IAM confirmado nesse modelo foi de 4,8%, no entanto as estimativas de custo-efetividade calculadas referem-se exclusivamente aos pacientes com IAM confirmado.

O principal desfecho de efetividade era a letalidade do IAM. As mortes poderiam ocorrer por fibrilação ventricular ou por BAVT. O principal pressuposto assumido para explicar diferenças na letalidade do IAM entre as opções comparadas foi a capacidade da lidocaína, profilática ou terapêutica, de evitar mortes decorrentes de arritmias ventriculares. Esse fármaco estaria disponível na UCC e na unidade intermediária (mais prontamente da UCC), mas não na enfermaria ou no ambulatório. Sabe-se hoje, entretanto, que esse pressuposto era falho em razão da não comprovação da efetividade da lidocaína na prevenção de mortes no pós-IAM, além do surgimento de dúvidas em acerca da segurança desse antiarrítmico.[75,76] A despeito dessa premissa equivocada, o modelo era simples e bem construído, permitindo ponderações interessantes sobre o grau de terapia intensiva que seria necessário e economicamente eficiente no manejo inicial de pacientes com IAM.

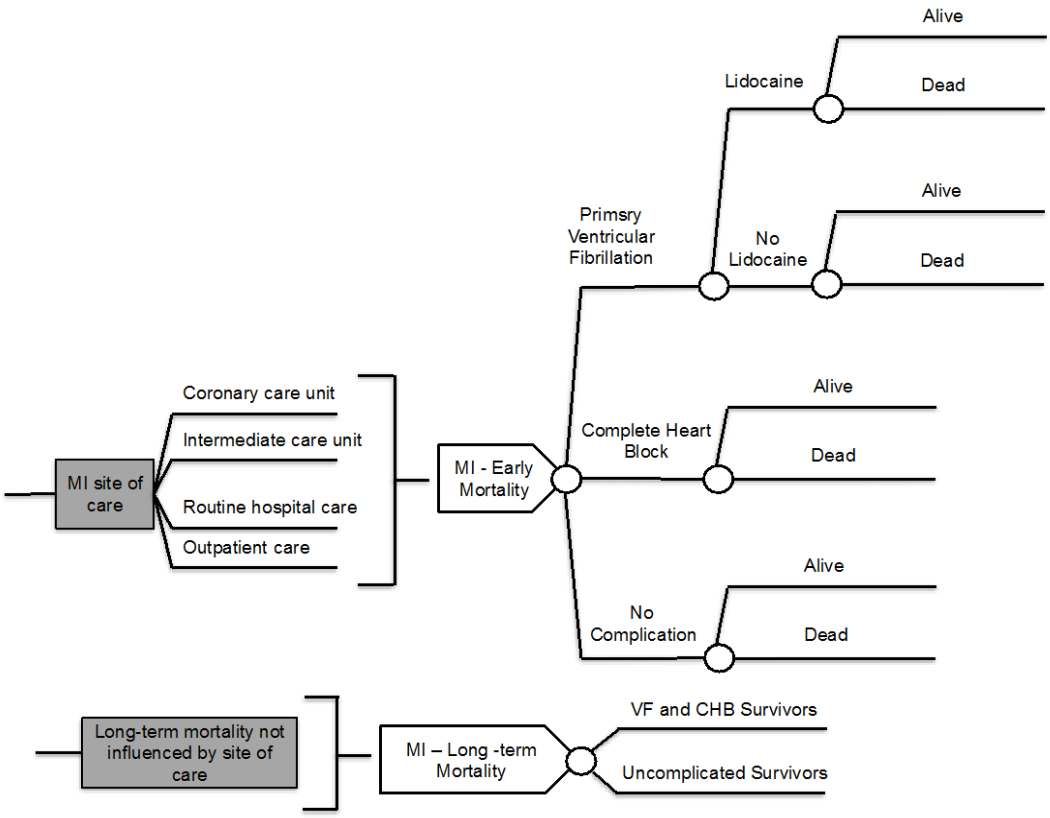
A expectativa de vida para os primeiros 5 anos após um IAM foi derivada de dados clínicos primários. A partir desse ponto, assumiu-se que a mortalidade tardia para os sobreviventes do IAM seria o dobro daquela observada na população em geral.

Os custos foram estimados a partir de um estudo prévio de macrocusteio baseado nas despesas hospitalares de 15 pacientes selecionados aleatoriamente. Os principais fatores afetando os custos foram a duração da estada no hospital e o tipo de unidade escolhida para a internação.

Ao final, verificou-se que a unidade intermediária foi a intervenção mais eficiente economicamente, obtendo uma RCEI de U$ 43000/ ano de vida ganho em relação à hospitalização convencional (dólares de 1984). Para obter um incremento

acima disso, foi estimada uma RCEI de U$ 139000 / ano de vida ganho com a adoção da UCC em lugar da unidade intermediária.

Figura 5 – Representação gráfica da árvore de decisão desenvolvida por Fineberg e colaboradores



Wears et al, 1987[72]

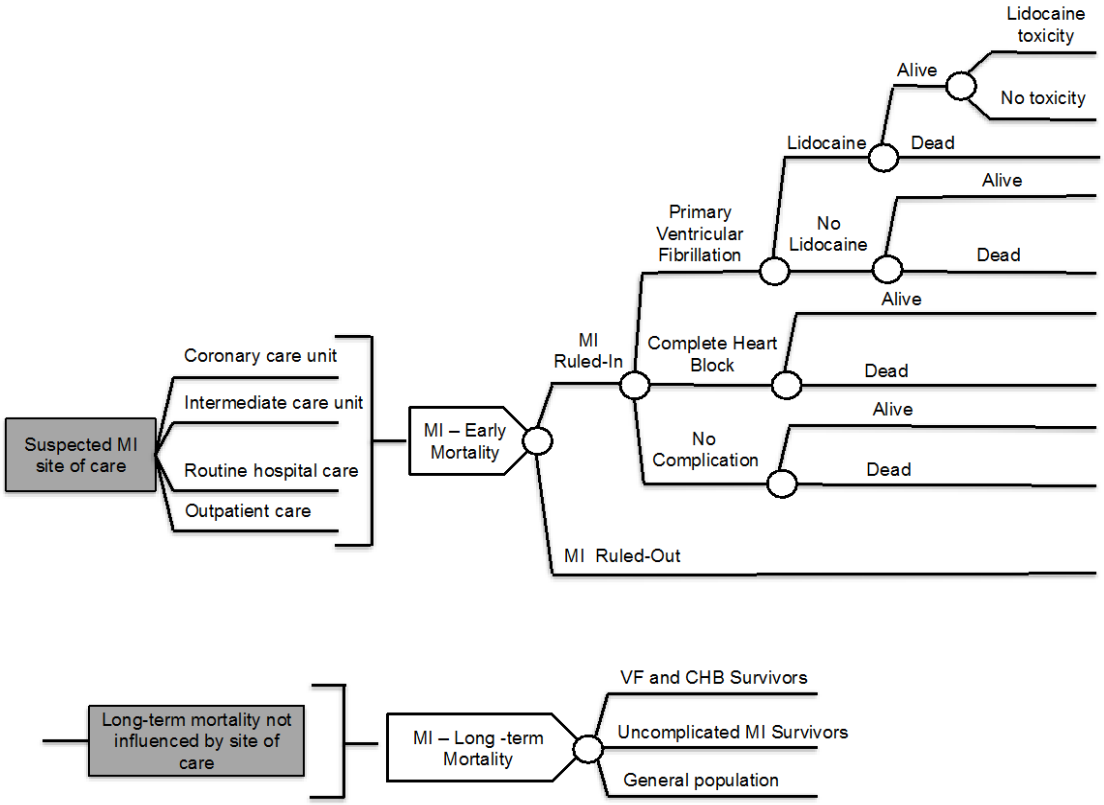
O objetivo principal desse estudo foi o de estabelecer, entre pacientes com dor no peito, a probabilidade esperada de IAM a partir da qual a admissão em unidades com diferentes graus de complexidade seria considerada custo-efetiva.

Esse modelo foi basicamente uma extensa análise de sensibilidade do modelo proposto por Fineberg e colaboradores, inclusive mantendo as premissas a respeito da efetividade da lidocaína e usando as mesmas estimativas de custos, de sobrevida esperada e de probabilidades de ocorrência de eventos (figura 6). Entretanto, o modelo foi adaptado no sentido de incluir a toxicidade potencial por lidocaína e custos associados a eventos adversos da hospitalização em geral. Foi realizada uma análise de sensibilidade probabilística (método de Monte-Carlo) na obtenção dos valores-limiares de custo-efetividade para diferentes probabilidades prévias de IAM.

Os autores concluíram que, para pacientes com probabilidade prévia de IAM cima de 2%, o tratamento em unidades mais intensivas obtém sempre maior efetividade do que unidades menos intensivas, sempre incorrendo em custo incremental. Para manter a custo-efetividade observada, a proporção de internação de casos falso-positivos foi estimada em 70 a 80%, e a de liberação inapropriada de casos falso-negativos, entre 2 e 5%.

O valor da RCEI foi estimado em menos de U$ 50.000/morte evitada como resultado da adoção de uma estratégia mais intensiva em diferentes comparações (UCC versus intermediária ou enfermaria; intermediária versus enfermaria), conquanto que a probabilidade prévia de IAM na coorte hipotética fosse ≥ 24%.

Figura 6 – Representação gráfica da árvore de decisão desenvolvida por Wears e colaboradores



Tosteson et al, 1996[73]

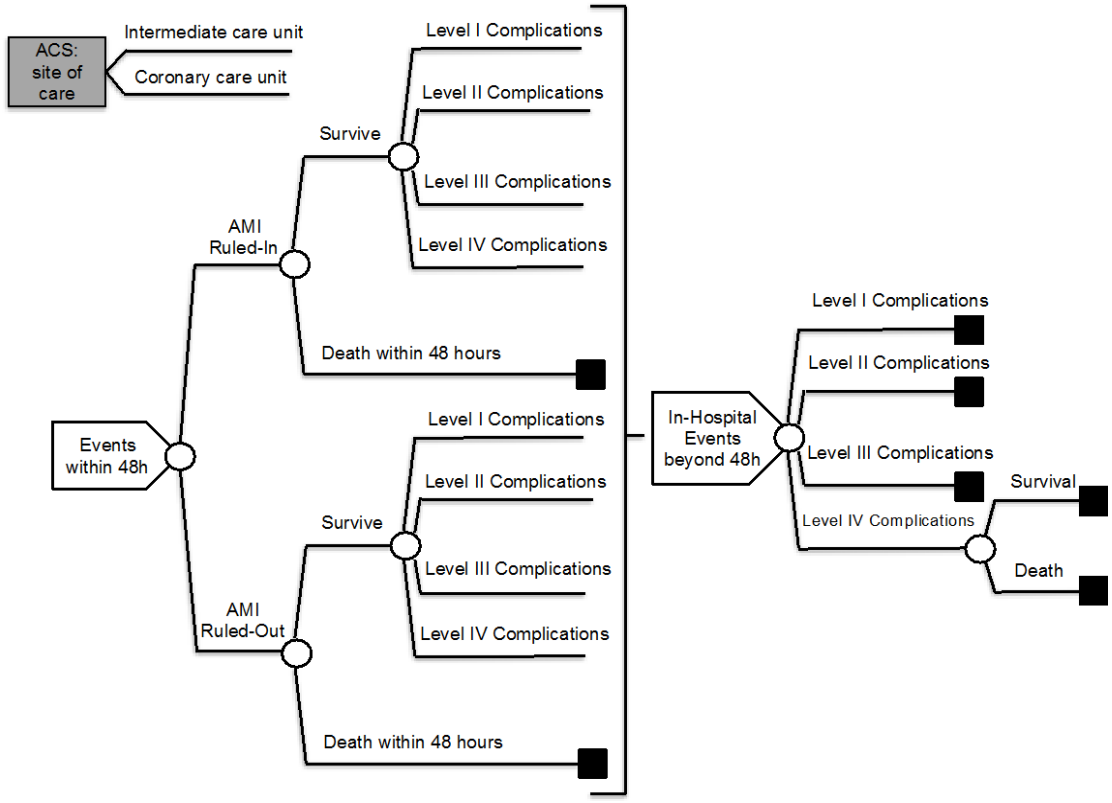
Um modelo de árvore de decisão foi desenvolvido por esses autores para estimar a custo-efetividade incremental do manejo de pacientes com suspeita de IAM em uma UCC ou em uma unidade intermediária (figura 7). Como nos modelos publicados anteriormente, não foi feita distinção entre IAM com e sem elevação de ST. As probabilidades de eventos clínicos e a taxa de utilização de recursos derivaram de uma coorte de 12139 pacientes a partir de uma análise de regressão logística. Os custos medianos foram estimados a partir das despesas hospitalares desses pacientes.

Para a estimativa da sobrevida de longo prazo, a expectativa de vida foi calculada a partir das tábuas de sobrevida para a população dos Estados Unidos em 1987, que foi adaptada para refletir a mortalidade adicional por IAM. Com o objetivo de considerar a variação observada na probabilidade de IAM entre pacientes que se apresentam com dor torácica, as estimativas de custo-efetividade foram calculadas para cinco faixas etárias (30–44; 45–54; 55–64; 65–74 e ≥75 anos).

O modelo foi dividido em duas partes, as primeiras 48 horas de atendimento e após as 48h desde o atendimento inicial. Essa abordagem permitiu levar em consideração diferenças nas probabilidades de morte e de complicações observadas entre esses períodos, entretanto resultou na desvantagem de tornar o modelo incapaz de testar pressupostos a respeito da duração da estada no hospital. Outra limitação desse estudo foi o uso de uma classificação arbitrária da gravidade das complicações em quatro graus e o pressuposto de que haveria um incremento de 15% na mortalidade dos pacientes atendidos na unidade intermediária em comparação aos pacientes atendidos na UCC, um pressuposto que não estava

embasado nos dados clínicos. Os autores concluíram que, em comparação com a unidade intermediária, o atendimento inicial aos pacientes com dor torácica de risco baixo a intermediário na UCC somente obteria uma RCEI inferior a U$ 50000 / ano de vida salvo para pacientes de 65 anos ou mais com probabilidade prévia de IAM acima de 23%.

Figura 7 – Representação gráfica da árvore de decisão desenvolvida por Tosteson e colaboradores



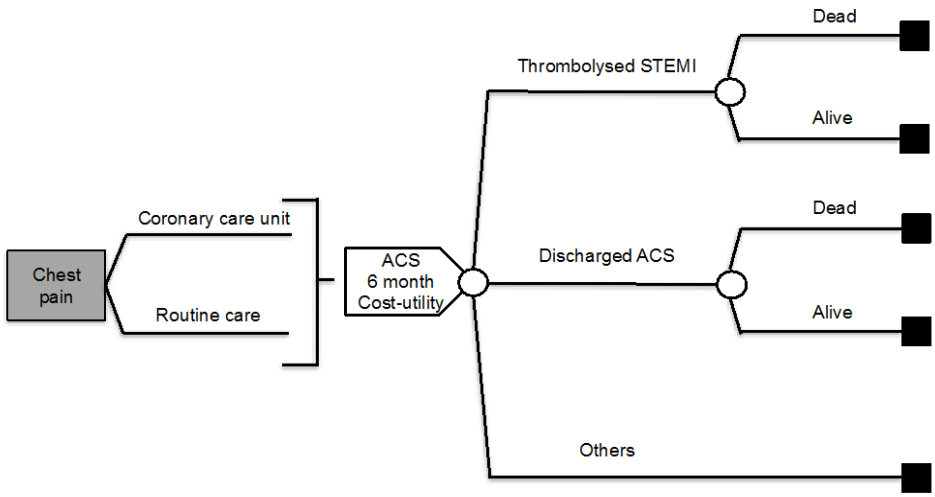
Oluboyede et al, 2008[74]

Essa análise de custo-utilidade baseou-se principalmente em informações procedentes do estudo ESCAPE, que foi um ensaio clínico randomizado em cluster que comparou o atendimento a pacientes com dor torácica realizado em UDTs com o atendimento convencional no SE com hospitalização subsequente em 14 hospitais do Reino Unido. Os dados foram modelados e analisados sob a perspectiva do sistema de saúde público (NHS). Foi elaborada uma árvore de decisão (figura 8) que considerava três possíveis fontes para melhores desfechos em pacientes atendidos em hospitais com UDTs: (1) facilitação no acesso à trombólise para os pacientes com IAMST; (2) redução na ocorrência de liberação inapropriada de pacientes com SCA e (3) melhora na qualidade de vida decorrente do fato do paciente ter recebido uma avaliação mais rigorosa nas UDTs. Estimativas de custos e de utilidades foram obtidas para dois períodos: os primeiros 6 meses, com dados derivados do estudo ESCAPE, e a partir de 6 meses (por toda a vida), com dados derivados de outras fontes, como a outros estudos publicados e curvas de sobrevida populacionais. Na análise principal, a estratégia UDT dominou a hospitalização convencional, e uma análise de sensibilidade probabilística (simulação de Monte-Carlo) estimou em 70% a probabilidade das UDTs obterem uma RCUI igual o menor a £ 20000/AVAQ.

A despeito de ter sido baseada em dados de um ensaio clínico, esse estudo resultou em uma avaliação econômica de baixa validade interna e externa. Em primeiro lugar, a maior parte das informações derivadas do estudo ESCAPE consistia em dados não publicados. Por exemplo, o estudo excluiu pacientes com IAMST. Contudo, a proporção de pacientes com IAMST entre os pacientes com dor torácica e a mortalidade por IAMST foram obtidas a partir de dados da fase de arrolamento

do ensaio clínico. Em segundo lugar, o estudo ESCAPE foi negativo a respeito de efeitos benéficos das UDTs. De fato, o único achado que obteve significância estatística foi um aumento de 10% no risco de pacientes atendidos na UDTs retornarem à emergência por queixas relacionadas a dor torácica. Outras limitações desse modelo incluem o uso de trombólise como a única estratégia de reperfusão considerada e a não consideração de fatores determinantes dos custos, como a duração da estada no hospital, a probabilidade de internação e a probabilidade de retorno à emergência ou de readmissão. De forma apropriada, os autores reconhecem algumas dessas limitações e concluem que as UDTs não podem ser consideradas mais eficientes do que a hospitalização de rotina.

Figura 8 – Representação gráfica da árvore de decisão desenvolvida por Oluboyede e colaboradores



3.8. Conclusões da Revisão da Literatura

A leitura do conjunto dos estudos identificados acerca das unidades especializadas para o atendimento às síndromes coronarianas permite depreender as seguintes observações:

- A estratégia da UV é comparável às outras modalidades de unidades especializadas somente em alguns aspectos, como estrutura física, organização da alocação de recursos e desfechos relacionados aos pacientes portadores de SCASSST, sobretudo de risco baixo a intermediário.
- As modalidades de unidades dedicadas encontradas na literatura que apresentam características em comum com a UV são as UDTs e as unidades de cuidados intermediários associadas aos SEs. No entanto, essas unidades diferem da UV por não se destinarem ao atendimento das SCASSST de alto risco ou do IAMST.
- A UCC foi o tipo de unidade predominantemente avaliado por estudos de avaliação econômica com métodos de modelagem para análise de decisão (4 dentre 5 estudos).
- O único estudo de modelagem que avaliou as UDTs foi o de Oluboyede e colaboradores, que também foi o único estudo a incluir pacientes com IAMST. Esse estudo apresenta importantes limitações metodológicas e a inclusão de IAMST para manejo em uma UDT não nos parece suficientemente embasada na literatura para um modelo desse tipo de unidade.
- Tomados individualmente, as avaliações econômicas indicam que as UDTs sejam poupadoras de recursos em comparação a estratégias que envolvam

atendimento no SE e hospitalização convencional no atendimento às SCAs suspeitas ou confirmadas, de risco baixo a intermediário.

- Quanto às UCCs, os resultados dos estudos de avaliação econômica indicam que sua adoção para o atendimento de uma população de pacientes de risco intermediário resultaria em um consumo incremental de recursos, com estimativas de RCEI (ou RCUI) superiores a U$ 50.000 / AVG (ou AVAQ) na comparação com estratégias menos intensivas.
- A eficiência econômica da adoção de uma estratégia mais intensiva em relação a uma estratégia menos intensiva para o atendimento a casos suspeitos de SCA é dependente da probabilidade pré-teste de IAM na população-alvo da unidade. Em geral, o uso de unidades mais intensivas acaba tornando-se excessivamente dispendioso para pacientes cuja probabilidade inicial de IAM seja inferior a 20%.
- Com relação à avaliação da efetividade das unidades, as revisões sistemáticas identificadas estão desatualizadas e apresentam importantes limitações metodológicas, como o fato de terem sido conduzidas sem dupla extração de dados e a falta de definições claras quanto ao tipo de estudo a ser incluído. Além disso, não foi identificada revisão sistemática com metanálise.
- Não foram identificadas revisões sistemáticas de estudos de avaliação econômica das unidades dedicadas para o manejo da SCA.
- Não foram identificadas avaliações econômicas de unidades dedicadas para o manejo das SCAs no Brasil.

4. OBJETIVOS

O objetivo geral da presente tese de doutorado é estimar a efetividade e a custo-efetividade das unidades dedicadas ao atendimento às síndromes coronarianas agudas em comparação com o atendimento prestado na ausência destas. Para que esse objetivo seja atingido, foram delimitados os seguintes objetivos específicos:

- Estimar o efeito da UV do Hospital de Clínicas de Porto Alegre na mortalidade por doenças vasculares agudas em comparação ao atendimento no departamento de emergência convencional;
- Estimar a efetividade das UDTs no atendimento às SCAs em comparação ao atendimento em serviços de emergência ou em internação hospitalar convencional;
- Revisar sistematicamente a literatura para identificar e sumarizar os resultados dos estudos de avaliação econômica de unidades dedicadas no atendimento às SCAs.

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6. ARTIGOS

Artigo 1

Implementation of a dedicated cardiovascular and stroke unit (vascular unit) in a crowded emergency department of a tertiary public hospital in Brazil: Impact on mortality rates

Implementação de uma unidade dedicada para doenças cardiovasculares e acidente vascular cerebral (unidade vascular) em um departamento de emergência superlotado de um hospital público terciário no Brasil: Impacto nas taxas de mortalidade

André Luís Ferreira da Silva, Doutorando em Epidemiologia pela UFRGS;

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

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Implementation of a dedicated cardiovascular and stroke unit (vascular unit) in a crowded emergency department of a tertiary public hospital in Brazil: Impact on mortality rates

Luiz Antônio Nasi[1], MD, MSc; André Luis Ferreira-Da-Silva[2,3], MD, MSc; Sheila Cristina Ouriques Martins[4] MD, ScD; Mariana Vargas Furtado[5] MD, MSc; Andrea Garcia de Almeida[4] MD, MSc; Rosane Brondani[4] MD, MSc; Letícia Wirth[5] MD; Marisa Kluck[6] MD; Carisi Anne Polanczyk[3,5,6], MD, ScD.

1. Emergency Department, Hospital de Clínicas de Porto Alegre

2. Internal Medicine Department, Hospital de Clínicas de Porto Alegre

3. Graduate Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre

4. Neurology Division, Hospital de Clínicas de Porto Alegre

5. Cardiovascular Division of Hospital de Clínicas de Porto Alegre

6, Medical Informatics Division, Hospital de Clínicas de Porto Alegre

6. Graduate Program in Cardiology and Cardiovascular Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

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Abstract

Background: Emergency department (ED) care for acute vascular diseases faces the challenge of overcrowding. A vascular unit (VU) is a specialized, protocol-oriented unit in the ED with a team trained to manage acute vascular disorders, including stroke, coronary syndromes, pulmonary embolism (PE) and aortic diseases. **Study Objectives**: To compare case fatality rates for selected cardiovascular conditions before and after the implementation of a VU. **Methods**: Patients with the selected diagnoses admitted to the ED in two different time periods, 2002 to 2005 (before VU period) and 2007 to 2010 (VU period), were identified by ICD-10 codes, and their electronic records were reviewed. Case fatality rates were calculated and compared for both periods. **Results**: The period prior to VU implementation (2002-2005) included 4164 patients, and the VU period (2007-2010) included 6280 patients. Overall, the case fatality rate for acute vascular conditions was significantly reduced from 9% to 7.3% with VU implementation (p=0.002). The in-hospital mortality rates for acute coronary syndrome dropped from 6% to 3.8% (p=0.003), and acute PE rates dropped from 32.1% to 10.8% (p<0.001). Regarding ACS care, there was a reduction in the length of hospital stay (196 to 163h) and an increase in median hospital charges (BRL$ 3062 to 5402) and re-hospitalization rates (11% to 20%) (p<0.001). **Conclusions:** The VU strategy has the potential to reduce overall mortality for acute vascular conditions, however it may be associated to increased consumption of resources.

Keywords: vascular unit; myocardial infarction; stroke; chest pain unit; stroke unit

Introduction

Acute vascular diseases, including myocardial infarction (MI) and stroke, have a large disease burden worldwide.[1] In Brazil, approximately 200,000 patients are evaluated for acute coronary syndrome (ACS)-related events in emergency departments (EDs) annually, resulting in more than 90,000 deaths. Stroke is currently the leading cause of death, causing 97,000 fatalities in 2011.[2,3] Other serious acute conditions affect the final diagnosis of patients initially presenting with acute chest pain or respiratory distress, including acute aortic dissection, pulmonary embolism (PE) and decompensated heart failure.

In Brazil, EDs are challenged to provide quality care despite overcrowding, a problem with roots in structural issues in primary and secondary care and an insufficient number of hospital beds.[4,5] This situation leads to prolonged ED stays, and some patients spend their entire "hospitalization" in the ED without admission to a hospital bed.

Prolonged ED waiting times and lengths of stay (LOSs) compromise the quality of care, including delayed reperfusion for MI and stroke.[6,7] A vascular unit (VU) is a protocol-oriented specialized unit in the ED staffed by a team trained to manage acute vascular disorders.[8] VUs deliver first-line, timely, protocol-oriented care for patients presenting six selected acute neurovascular or thoracic syndromes: (1) ACSs, (2) ischemic stroke, (3) hemorrhagic stroke, (4) acute aortic dissection or rupture and (5) acute PE. Patients presenting (6) acute decompensated heart failure can also be admitted to this unit.

Our VU shares many features with chest pain units (CPUs) and stroke units, including a dedicated physical area, a 24-h dedicated medical and nursing staff, a 2:1 nurse-patient ratio, protocol-oriented care, patient monitoring systems, mechanical ventilation, rapid access to specialists and diagnostic imaging, a hemodynamic laboratory and a surgical area.[9] It is adjacent to the ED and functions as a "crowding-proof" area to allow better quality care. As the management of acute vascular syndromes is time dependent, delays associated with ED structure and healthcare system inefficiencies are unacceptable.

Lott et al have demonstrated that specialized critical care units perform similarly to general critical care units.[10] We believe that this finding can be extrapolated to the VU model. However, few data are available regarding the impact of a dedicated unit for acute vascular conditions.

We previously demonstrated the impact of VUs on ACS patients and reported improved cardiovascular outcomes, quality of healthcare indicators and adherence to clinical protocols following VU implementation (years 2006 and 2007 vs. 2000 and 2001).[11] We now present the extended experience of the VU's impact on ACSs and five other conditions: ischemic stroke, hemorrhagic stroke, aortic dissection or rupture, acute PE and acute decompensated heart failure.

Materials and Methods

Hospital and VU

Hospital de Clinicas de Porto Alegre, is a major university hospital in Brazil and a tertiary referral center for the treatment of acute vascular diseases[11]. The hospital has 125,000 m² of floor space, distributed over 13 floors, and 741 beds. Its ED has capacity for 50 patients; however, it is constantly overcrowded, caring for 100 to 150 patients. This excess of ED patients is thought to derive from a mismatch between hospital bed availability and actual demand. The VU was created to remove acute vascular patients from this overcrowded environment, where diagnostic and therapeutic processes are thought to occur at a slower pace. The VU was implemented to reduce wait time and consolidate the personnel and resources needed for similar emergencies.

The VU is a high acuity area with nine beds that is capable of providing intermediate complexity care. It is located within our hospital's ED. Admission to five of the VU beds is restricted to the six acute vascular conditions previously outlined. Four beds were also used for acute vascular conditions; however, they could be used in the management of general ED patients requiring mechanical ventilation or hemodynamic stabilization in special circumstances.

The goals of the VU are to provide initial stabilization and assessment for patients with suspected acute vascular conditions. However, it does not provide the full range of care required for more complex vascular conditions. For example, surgical patients (e.g., ruptures aortic aneurysm or dissection) are transferred to surgical units after initial diagnostic evaluation and stabilization.

Likewise, non-surgical vascular patients are transferred to appropriate units with specialized teams (e.g., Coronary Care Unit, Clinical or Surgical Intensive Care Unit) after the acute phase.

Patients suspected of having an acute vascular condition are immediately transferred from the triage or ED first medical evaluation to the VU for comprehensive assessment and stabilization. All patients undergo a standardized systematic observation and examination of vital signs, neurological deficits, cardiac monitoring, glucose level and fluid and electrolyte balance. Oxygen therapy and respiratory support were employed as required by the patient's respiratory condition.

All patients admitted to the VU are treated based on evidence-based protocols and evaluated by trained emergency physicians (available 24 h per day) and consulting specialists (on demand). The specialist staff consists of cardiologists, neurologists, neurosurgeons, vascular surgeons, cardiac surgeons, pulmonologists and nephrologists. Other specialties are available in special instances. In addition, prompt access to radiological tests and hemodynamic evaluations is granted.

Patients

Patients with the following selected acute vascular conditions were identified by ICD-10 codes and had their electronic records reviewed: acute MI, unstable angina, ischemic stroke, hemorrhagic stroke of any kind, aortic dissection, aortic rupture and PE.

The study was approved by the institution's ethics committee, and researchers signed a confidentiality term regarding the handling of patient data.

Data collection

The administrative electronic records of patients admitted to the ED during two different periods, 2002 to 2005 (before VU period) and 2007 to 2010 (VU period), were reviewed. The choice of a four years period before and after 2006 was based on the availability of reliable and consolidated information from our institutions' administrative information system. Data from the year 2006 were not included in the current analysis because that year represented a transition from the older ED model to the VU concept. Moreover, data regarding the unit's initial impact on ACSs (year 2006) have been published elsewhere.[11] From 2007 onward, the VU achieved its current format, which consists of nine beds and a larger dedicated physical area.

Data regarding socio-demographic characteristics, length of ED stay and final diagnosis were gathered through a query into our institution's electronic patient records for both periods. All diagnoses were defined as the final medical diagnosis recorded by the attending physician. The available dataset consisted primarily of administrative information, which also contained in-hospital outcomes. In-hospital outcomes included death due to cardiovascular causes and death by any cause. For stroke patients, data regarding time from arrival to medical evaluation and treatment initiation were prospectively collected.

A second query was performed in the clinical electronic patient record system in order to obtain resource utilization estimates among patients with ACS-related discharge ICD-10 codes.

Sensitivity analysis on stroke classification

The potential for misclassification of a stroke was assessed in a sensitivity analysis, as the available dataset was limited in the discrimination between ischemic and hemorrhagic stroke. Patients with either ischemic or hemorrhagic strokes could have been recorded as ICD-10 code I-64 (stroke, not specified as hemorrhagic or infarction). In the main analysis, patients with ICD-10 code I-64 were assumed to be diagnosed as ischemic strokes. Alternatively, in the sensitivity analysis, patients under this ICD code were assumed to be diagnosed as hemorrhagic strokes. A further analysis was done after excluding ICD code I-64 patients.

Statistical analysis

Categorical variables are reported in percentages and 95% confidence intervals, and continuous variables are reported as the mean ± standard deviation. Mortality rates due to cardiovascular disease were compared between the two four-year time periods of interest, which were as follows: (1) the before VU period (2002-2005) and (2) the VU period (2007-2010). Comparisons were performed using the chi-square test with continuity correction. Average length of ED stay of the studied periods were compared with a t-test.

Data were analyzed using the statistical package PASW 18 for Windows. Differences were considered statistically significant for p values < 0.05. A Bonferroni correction was applied in order to adjust for multiple comparisons, which rendered an adjusted p value of < 0.005 for statistical significance.

Results

According to the query performed in the administrative information system, 11687 patients were admitted to our institution's ED due to the six acute conditions previously defined from January 2002 to December 2010. After excluding patients from the year 2006, 10,445 patients were included in the analysis. As for gender, 53.9% and 54.4% were males in the periods before and after VU implementation, respectively. The patient characteristics in the studied periods are presented in table 1.

Comparing the period prior to VU implementation with the VU period, there was an increase in the number of admissions for all conditions, specifically ischemic stroke, which increased from 753 admissions (2002-2005) to 1849 admissions (2007-2010), a 2.4-fold increase. The VU's implementation made our institution the reference center for stroke cases in which thrombolysis was being considered, and this explains the magnitude of this increase. Nonetheless, the case fatality rate for ischemic stroke remained unchanged.

For suspected acute ischemic stroke patients, the average evaluation time from ED arrival to intervention dropped significantly following the implementation of a stroke thrombolysis critical pathway in the VU period. The

waiting time for the first evaluation dropped from 7 hours to 10 minutes. The time to the initial CT scan dropped from 9 hours to 28 minutes. Finally, the time from arrival to diagnostic confirmation and the beginning of specific therapy (aspirin or fibrinolysis) dropped from 14 hours to 50 minutes.

Overall, the case fatality rate for acute vascular conditions was significantly reduced from 9% to 7.3% with the implementation of the VU, corresponding to a 20% reduction, which was statistically significant (p=0.002). The in-hospital mortality rate due to ACSs dropped from 6% to 3.8% after VU implementation (p=0.003). A similar phenomenon was observed for the in-hospital mortality rate from acute PE, which dropped from 32.1% to 10.8% (p<0.001). There were no other statistically significant reductions in the in-hospital mortality rates among the other studied conditions. Regarding ischemic and hemorrhagic case fatality rates, the use of different discriminatory criteria in a sensitivity analysis did not change the main analysis' results. The comparative mortality rates between the studied periods are summarized in table 2.

With regard to the length of stay in the ED or in the VU for patients with the selected cardiovascular conditions, there was a reduction from 2.12 days in the ED to 1.69 days in the VU (p=0.015). There were no changes in the availability of hospital beds in either of the studied periods.

Data for resource utilization estimates in ACS management was available for 572 patients in the period before VU and for 601 patients in the VU period (table 3). There was no change in the proportion of patients discharged in 24h or less; however, the VU period was associated with a reduction in the length of hospital stay from 8.2 to 6.8 days (p<0.0001). Conversely, the VU period was

associated to an increase from 10.8% to 19.8% in the frequency of hospital readmissions, as well as to an increase in the median hospital charge per patient (hospital perspective) from BRL$ 3063 to BRL$ 5402 ($p< 0.0001$).

Discussion

Dedicated units improve the overall quality of care for specific conditions, while simultaneously optimizing the allocation of ED and hospital resources.[10] In addition to pooling patients with similar conditions and treatment needs, specialized units may benefit from economies of scale to improve efficiency.

To our knowledge, this is the first study to report the outcomes of VU care, specifically of the concept of clustering patients with vascular disease whose conditions share characteristics and demands for hospital resources in the ED. Overall, there was a statistically significant reduction in mortality for patients admitted to the VU compared with those treated in the general ED prior to the VU implementation. This reduction in mortality was driven by the marked improvement in survival observed in patients with ACS and PE.

Farkouth et al conducted a community-based, prospective randomized trial to compare the safety, efficacy and resource use of a CPU and hospital admission for patients with unstable angina at short-term intermediate risk for cardiovascular events.[12] In this study, the CPU comprised four beds in a separate ED area and was equipped with event monitors and staffed by a full-time nurse. Mortality and event rates did not differ between CPU and hospital ward; however, the hospitalization rates and hospital LOS were reduced. Other studies

on CPUs have reported similar findings.[13,14] Beckett et al demonstrated a similar benefit when the initial management of ACSs occurred in an admission unit that was not exclusive for cardiac patients.[15]

Conversely, our study shows a defined impact in mortality from ACSs. Apparently, this contrasts with published studies on CPUs, which have failed to show a survival benefit to ACS patients managed in such units. We believe the reasons for this discrepancy are the following: first and foremost, VU and CPUs are essentially distinct in concept, as the benefits from the VU are partially derived from the early identification and intake of ACS patients from all risk categories, while CPUs function as a post-evaluation alternative to inpatient management for intermediate- and low-risk patients; thus, we think a direct comparison between VU and CPU is of limited value. Second, suboptimal management may have been provided in the crowded ED prior to the implementation of the VU; finally, the availability of specialized consultants and the existence of critical pathways for the evaluation of ACS patients may have positively affected the indication and timing for invasive procedures such as percutaneous or surgical myocardial revascularization.

As for the observed survival benefit among PE patients, we also attribute part of the VU's effect to the sub-diagnostic and suboptimal treatment provided in the crowded general ED, a finding which has already been reported.[7] Once a patient is admitted to an adequately staffed unit, there is likely better adherence to protocol-oriented care. Thus, the possibility for the rapid assessment of suspected PE cases and the prompt availability of diagnostic imaging techniques, such as multi-detector CT and pulmonary perfusion scintigraphy, in the VU may

have contributed to the early initiation of treatment and subsequent diagnostic confirmation.

Regarding acute stroke care, several randomized controlled trials have been performed in different countries and environments to assess the effectiveness of stroke units for hospitalized stroke patients[16,17], and a Cochrane systematic review reported a definitive benefit of stroke unit care.[18] Additionally, in an observational study with two years of follow-up and more than 10,000 stroke unit patients in Italy, Candelise et al demonstrated improvements in stroke in-hospital case fatality and the long-term risk of death or disability, indicating that the benefits observed in stroke unit care trials can be attained in practice.[19]

However, our analysis failed to demonstrate a significant reduction in stroke mortality in the VU period. The in-hospital mortality rate from ischemic stroke remained unchanged (7.8% versus 7.2%) after VU implementation despite the massive increase (2.4-fold) in the number of patients admitted for that condition between the studied periods. The expected mechanisms for VU benefit in stroke mortality would be similar to those described in stroke units, which include the following: increased rate of ischemic stroke thrombolysis, reduced incidence of infections and early rehabilitative care.[17,20] The lack of effect of the VU on stroke mortality could be because our unit's stroke care is centered in the management of the acute phase of the disease, whereas there is evidence that a significant part of a stroke unit's benefits derive from post-stroke and rehabilitative care. Although our data did not show a mortality benefit for ischemic stroke patients, we believe that the adoption of the VU strategy will likely increase the proper

indication of thrombolytic therapy, an intervention whose efficacy and cost-effectiveness have been demonstrated in many settings, including Brazil.[3,16,21]

Regarding resource utilization among the subset of ACS patients, despite a statistically significant reduction in the length of hospital stay, there was observed an increase in median hospital charges and in readmission rates. This contrasts with reported cost savings from adoption of CPU care in developed countries and further highlights context and concept differences between CPU and VU strategies. It seems that the implementation of the VU strategy in a resource constrained setting, with ED crowding and inadequate processes of care, resulted in more diagnostic procedures (as reported by Furtado et al[11]) and in increased costs, but also in reduced ACS case-fatality rate. The reasons for the increased readmission rate are unclear to us, but we especulate that VU creation converted our institution in the reference for more patients, with increased proportion of more severe coronary disease. Another reason might be insufficient access to secondary prevention interventions and to outpatien support for discharged patients.

The VU's staff is composed by ED physicians (2 physicians during daytime and 1 physician at night), four operational nurses (2:1 nurse-to-patient ratio) and one supervising nurse. At its beginning, VU was mainly staffed through relocation and training of existing ED personnel. Other resources necessary to the creation of the VU included the conversion of an available physical area in the ED to the nine beds format with cardiac monitors and mechanical ventilators. Additional staff was hired in the period after the establishment the VU; however, we are unable to estimate specific VU driven hires due to

concomitant expansion of other parts of our ED. The favorable experience with the VU has lead our institution to consider the implementation of other units dedicated to a group of conditions (resource clustering units) as an alternative to specific specialty care units.

The VU concept is unique and has been implemented in only a few university hospitals in Brazil. Our unit was the first to be implemented in 2006, and it is unclear whether the VU strategy may be reproduced successfully elsewhere. However, the data we currently present regarding the prototype VU are reassuring with respect to its safety and efficacy. The limited data regarding resource utilization and costs prevent us from estimating the cost-effectiveness ratio compared to the management of acute vascular conditions in the general ED. An economic evaluation of the VU is currently underway.

Limitations

Complex interventions such as VUs are notoriously difficult to evaluate given the lack of standards to which they can be compared in the published literature[22,23]. During the development of the VU, we assumed that the literature on units dedicated to specific vascular conditions, such as CPUs and stroke units, would allow for comparisons and the development of insights. However, the VU is exceptional in the sense that it promotes the early identification and gathering of patients with acute vascular conditions to optimize resource utilization in a setting of scarcity. Thus, we do not consider this report to be a step backward in

terms of methodological rigor in comparison to published clinical trials of chest pain units, coronary care units and stroke units, but rather a preliminary study on this new proposal of an intermediate care unit for the setting of overcrowded EDs.

Our analysis is based on data estimates from retrospective data comprising two different time periods, 2002 to 2005 (before VU period) and 2007 to 2010 (VU period), and patients were identified by ICD-10 codes. We acknowledge that there is a potential for bias due to nonsystematic registry of information. Furthermore, we were unable to exclude repeated visitors to the ED. However, such biases would likely affect both periods in the same way, and our findings thus remain valid.

Given the expanse of the time period studied (a decade), it is possible that we could actually be measuring "progress in medical science" as opposed to an effect from the VU. However, the observed reduction in the PE case-fatality rate (from 32.1% in the 2002-2005 period to 10.8% in the 2007-2010 period) was of greater magnitude than the reductions observed in other long-term studies of PE in the absence of specific intervention programs. For example, the in-hospital all-cause case fatality rate for all patients with PE decreased from 11.8% in 1999 to 7.4% in 2008, in a study representative of hospitals from across the United States (US), and this change was driven by a reduction in case-fatality rates among stable patients.[24] This figure suggests that the implementation of the VU allowed us to achieve a case-fatality rate from PE in the 2007-2010 period comparable to the one observed in the US in 1999, likely by the identification and treatment of stable patients that could otherwise have been missed. In contrast, the

implementation of a national program for the detection and treatment of PE in China may have contributed to a decrease in the PE case fatality-rate, the magnitude of which was comparable to ours (from 25.1% in 1997 to 8.7% in 2008)[25]. With regard to the reduction in the case-fatality rate from ACS, the magnitude of the observed value (-36%) was twice the reduction observed in Brazil during the same period (-2.1% annually), which favors the hypothesis of an additional mortality benefit arising from VU implementation.[26]

In addition, our data were limited with respect to the discrimination of ischemic and hemorrhagic stroke patients, as the diagnosis of stroke was frequently non-specific, a problem that has already been noted in observational studies.[27] The lack of mortality reduction in this population makes our results conservative given the extensive literature demonstrating a survival benefit in stroke unit care. A prospective cohort study specifically designed to evaluate stroke treatment and outcomes in the VU unit is currently underway.

Finally, the observed 10.5 hours reduction in the length of ED stay must be interpreted with caution, as this figure could have been partially accounted for by reduction in the wait time. The statistical significance of this finding disappeared with the corrected p value for multiple comparisons. Nonetheless, the clinical plausibility of reduction in the length of ED stay in the studied setting makes us cogitate this adjustment may be causing type II error.[28]

Despite the limitations presented above, we believe that we have compelling historical data that demonstrate a significant effect size for the implementation of VUs in the Brazilian setting. Of particular importance, the VU approach was able to achieve a significant decrease in mortality due to

cardiovascular conditions, specifically among ACS and PE patients, even under the highly adverse circumstances of overcrowding and scarce resources. The VU approach is relatively easy to implement. It can be initially staffed through relocation existing ED personnel, however additional staff will likely have to be hired with unit's expansion. At the beginning of implementation, our unit was comprised of as few as four dedicated beds (years 2006 and 2007), after which it increased in size to the current nine beds and was relocated to a new physical area.

Conclusion

A specialized VU in the ED has reduced overall mortality for acute vascular conditions with feasible additional demand for human and material resources. Our findings highlight the relevance of the VU strategy in crisis-like settings, such as crowded EDs in developing countries. Our experience in the creation of a prototype VU may be particularly relevant for healthcare systems that are seeking to expand their critical care capability to meet present and future demands while struggling to organize emergency medical care in a setting of limited resources.

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Tables

Table 1. Characteristics of patients diagnosed with acute vascular diseases according to period

Characteristic	Period without VU n = 4165 (%)	Period with VU n = 6280 (%)
Age, years*	63.58 (±23)	63.80 (±23)
Male gender	2247 (53.9)	3416 (54.4)
Public Healthcare System	3515 (84.4)	5338 (85)
Non-public healthcare system	650 (15.6)	942 (15)
Final diagnosis		
Acute coronary syndromes	1674 (40.2)	1999 (31.8)
Ischemic stroke	879 (21.1)	2064 (32.9)
Hemorrhagic stroke	151 (3.6)	194 (3.1)
Complicated aortic aneurysm**	24 (0.6)	31 (0.5)
Pulmonary embolism	84 (2)	139 (2.2)
Decompensated heart failure	1062 (25.5)	1524 (24.3)
Arrhythmias and cardiopulmonary arrest	291 (7)	329 (5.2)

* Mean (±SD).

** Includes all acute aortic conditions requiring emergency surgery

Table 2 - Comparative frequency of fatalities between study periods according to the vascular conditions of interest.

	Before VU period (2002-2005)			VU period (2007-2010)			
Vascular Condition	**Patients**	**Deaths**	**Case fatality rate**	**Patients**	**Deaths**	**Case fatality rate**	**p value***
Acute Coronary Syndrome	1674	100	6%	1999	76	3.8%	<0.001
Ischemic Stroke	879	61	6.9%	2064	137	6.6%	0.827
Hemorrhagic Stroke	151	41	27.2%	194	59	30.4%	0.587
Aortic rupture	24	16	66.7%	31	19	61.3%	0.898
Pulmonary embolism	84	27	32.1%	139	15	10.8%	<0.001
Acute decompensated heart failure	1062	88	8.3%	1524	103	6.8%	0.166
Atrial fibrillation	247	16	6.5%	279	17	6.1%	0.999
Cardiac arrest	44	26	59.1%	50	31	62.0%	0.939
All vascular conditions	4165	375	9.0%	6280	457	7.3%	0.002

* Chi-square test with continuity correction

Table 3 – Resource use in the periods before and after VU implementation

Characteristic	General ED (2002 – 2005)	VU (2007 – 2010)	p*
Patients	572	601	-
STEMI	106 (18.53)	148 (24.62)	NS
NSTEACS	466 (81.47)	453 (75.38)	NS
Percent discharged in 24h or less	25 (4.37)	35 (5.82)	NS
Submitted to diagnostic coronary angiography at index evaluation (%)	Unavailable	161 (26.79)	-
Submitted to PCI at index evaluation (%)	Unavailable	321 (53.4)	-
Submitted to CABG at index evaluation (%)	52 (9.1)	44 (7.3)	NS
Average length of hospital stay in hours (SD)	196.69 (180.32)	163.40 (168.31)	<0.0001
Median hospital charges (BRL, IQR)**	3062.73 (1024.26 - 8411.05)	5402.40 (1159.33 - 10311.22)	<0.0001
ED re-attendances or hospital readmissions (%)	62 (10.83)	120 (19.81)	<0.0001

BRL, Brazilian Real (R$); CABG, coronary artery bypass grafting; ED, emergency department; IQR, interquartile range; NSTEACS, no ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST elevation myocardial infarction; VU, vascular unit;

* Chi-square test with continuity correction for categorical data, T test for continuous data and non-parametric testing for costs, two-sided corrected p value for significance < 0.005 (Bonferroni correction for 10 comparisons)

** All financial values were inflated to December 2010 BRL according to official Brazilian inflation index (IPCA)

Resumo em Português - Artigo 1

Contexto: O atendimento às doenças vasculares agudas nos serviços de emergência (SE) deparam-se com o desafio da superlotação. Uma unidade vascular (UV) é uma unidade especializada, orientada por protocolos, localizada no SE e com uma equipe treinada no atendimento das urgências vasculares agudas como o acidente vascular cerebral (AVC), as síndromes coronarianas, a embolia pulmonar (EP) e as doenças aórticas. **Objetivos:** Comparar a letalidade por síndrome vasculares selecionadas antes e após a implementação de uma UV. **Métodos:** Através dos códigos CID-10, foram identificados e revisados os registros eletrônicos dos pacientes atendidos no SE por doenças cardiovasculares selecionadas em dois períodos temporais, anos 2002 à 2005 (período pré-UV) e anos 2007 à 2010 (período UV). As letalidades foram calculadas e comparadas entre os períodos de tempo. **Resultados:** Foram incluídos 4164 pacientes referentes ao período pré-UV (2002-2005) e 6280 pacientes referentes ao período UV (2007-2010). No geral, a letalidade combinada pelas doenças vasculares agudas sofreu uma redução significativa de 9% para 7,3% com a implementação da UV (p=0,002). A letalidade intra-hospitalar por síndromes coronarianas agudas caiu de 6% para 3,8% (p=0,003), e a letalidade por EP caiu de 32,1% para 10,8% (p<0,001). A respeito do atendimento às síndromes coronarianas, foi observada uma redução na duração média da hospitalização de 8,2 para 6,8 dias, além de um aumento no custo mediano de internação por paciente (R$ 3062 to R$ 5402) e na frequência de re-hospitalizações (11% para 20%) (p<0,001). **Conclusões:** A estratégia UV tem o potencial de reduzir a mortalidade geral por doenças vasculares agudas, porém pode estar associada a aumento no consumo de recursos.

Palavras-chave: unidade vascular; infarto do miocárdio; acidente vascular cerebral; unidade de dor torácica; unidade de AVC

Artigo 2

Chest pain units for patients with no ST elevation acute coronary syndrome: a systematic review of literature and meta-analysis

Unidades de dor torácica na avaliação de pacientes com síndrome coronariana aguda sem elevação de ST: revisão sistemática e metanálise

André Luís Ferreira da Silva, Doutorando em Epidemiologia pela UFRGS;

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

A ser enviado para publicação.

Chest pain units for patients with no ST elevation acute coronary syndrome: a systematic review of literature and meta-analysis

André Luís Ferreira-Da-Silva[1,2], MD, MSc; Silvana Perini[3], MSc; Pedro Henrique Rigotti Soares[2], MD; Carisi Anne Polaczyk[1,2,4,5], MD, ScD.

1. Graduate Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

2. Hospital de Clinicas de Porto Alegre

3. Graduate Program in Medical Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

4. Graduate Program in Cardiology and Cardiovascular Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

5. Cardiovascular Division of Hospital de Clínicas de Porto Alegre.

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Abstract

Background: Despite its widespread use, the effectiveness of chest pain units (CPUs) in the evaluation and management of low- and intermediate-risk NSTEACS patients remains unclear. **Objective:** To evaluate the clinical effectiveness and resources utilization of CPU care in comparison to routine hospitalization in the management of NSTEACS. **Methods:** A systematic review of literature to identify clinical trials comparing CPU care to routine hospitalization was conducted in MEDLINE, EMBASE and Cochrane CENTRAL. Study selection and data extraction were conducted by two independent reviewers. Quality of evidence was assessed according the Cochrane Handbook for Systematic Reviews of Interventions. Direct evidence was computed with random effects model meta-analysis of head-to-head comparisons. Summary effect for binary outcomes was calculated from the risk ratios, while weighted mean difference was used for the length of hospital stay, in hours. **Results**: Seven full papers were included in the descriptive synthesis of evidence and six were included in the meta-analysis. Compared to routine hospitalization, CPU care was associated to reductions in hospitalization rates (RR 0.47; 0.29 to 0.77), length of hospital stay (-8.74h; -16.92 to -0.55), need for follow-up coronary angiography (RR 0.22; 0.05 to 0.86) and overall rate of revascularization procedures (RR 0.30; 0.09 to 0.96). There was no difference in mortality or cardiovascular event rates. **Conclusion**: The available evidence indicates that CPU care might reduce resources utilization in comparison to routine hospitalization, with no impact in mortality or event rates. Studies designed to evaluate CPUs in the current era of modern strategies for risk stratification are needed.

Keywords: chest pain unit; acute coronary syndrome; systematic review; metanalysis

Introduction

Chest pain units (CPUs) have evolved since the 80's as an alternative to conventional hospital admission for patients with low- and intermediate-risk non-ST elevation acute coronary syndrome (NSTEACS).[1] Such units have incorporated progresses in chest pain evaluation and management, such as protocol oriented drug administration, cardiac monitoring, serial ECG, serial measurements of cardiac biomarkers and systematic use of non-invasive tests for indeterminate cases.[2-5]

Both observational studies and clinical trials have assessed CPUs' safety and efficacy in comparison to routine hospitalization, the first randomized clinical trials dating from the decade of 1990.[6] Based on the results of individual studies, it is generally accepted that CPU care is capable of reducing resource utilization without adversely affecting the outcomes of such patients.[7]

In 2000, two systematic review of literature were performed evaluating the benefit of CPUs' management on clinical effectiveness, cost-effectiveness and patient satisfaction. The first one, performed by Quin G, focused on CPUs diagnostic accuracy and, due to limited information, the authors did not reach conclusions regarding CPUs' efficacy.[8]

In the other one, Goodacre SW published a systematic review of literature on CPUs' effectiveness and economic efficiency. Search was limited to Medline database and there was no restriction to clinical trials. Five studies comparing CPU care to a control group were identified, three of them were randomized clinical trials. [6,9,10] Additionally, there were found six cohort studies with no control group. This review was limited to describing the range of event rates

between compared groups with no attempt to estimate a summary effect for the outcomes. The author reported no significant difference in any objective outcome measurement among the comparative studies.[11]

D'Ascenzo et al have recently published a systematic review of clinical trials comparing strategies based on coronary computer tomographic angiography (CCTA) to non-CCTA strategies for the evaluation of low to intermediate risk NSTEACS in the emergency department (ED). However, none of the included trials' design allowed effect size evaluation of CPU care.[12-16]

Despite its widespread use, CPUs' effectiveness in the evaluation and management of low to intermediate risk NSTEACS patients remains inappropriately quantified. We have conducted a systematic review of randomized clinical trials comparing CPU care with routine hospitalization regarding clinical and resource utilization outcomes in this population.

Methods

Search strategy

We conducted a systematic review of literature to identify clinical trials comparing CPU care to routine hospitalization. CPU care was defined as systematic observation of low-to-intermediate risk chest pain patients in a dedicated unit adjacent or inside the ED. Such strategy of care encompasses cardiac monitoring, serial ECG and serial measurements of cardiac injury markers for a finite amount of time. After the initial observation period, indeterminate cases should be evaluated with at least one non-invasive test, such as stress testing (e.g., treadmill, stress echocardiography, or stress nuclear testing) or noninvasive cardiac imaging study (i.e. CCTA

or cardiac magnetic resonance - CMR). Routine hospitalization comprised a heterogeneous group of practices for the in-hospital chest pain evaluation of the same target population. Important elements in defining this group were the absence of a time limit for chest pain evaluation, the lack of clearly defined evaluation protocols and the choice of non-invasive or invasive tests (if any) at the physician assistant discretion.

The literature search was conducted in MEDLINE, EMBASE and the Cochrane CENTRAL databases. As there was no MeSH or Emtree term for chest pain unit (or equivalent) and considering the potential for literature overlap between studies on chest pain units and coronary care units (CCUs), we have decided to include the MeSH terms, Emtree terms and text words for CCUs along with text words for CPUs. The following search terms were used in the MEDLINE search on the studied intervention (text words and MeSH): coronary care unit, chest pain unit, chest pain observation unit, short-stay ED coronary care unit, short-stay coronary care units, short-stay observation units, CPU and CPOU.

Regarding definition of patient population, the following search terms were used in the MEDLINE search (text words and MeSH): acute coronary syndrome, myocardial infarction, myocardial infarct, unstable angina, preinfarction angina unstable angina pectoris, angina at rest and myocardial preinfarction syndrome.

Additionally, a highly sensitive string of words proposed by Haynes RB et al (ref) was used in the search for randomized controlled trials.

An equivalent search strategy was developed for EMBASE. The Cochrane CENTRAL search was similar, with the omission of the string for clinical trials. All search strategies are available

from authors on request. There was no idiom restriction. The reference list of selected articles was manually searched in order to identify other relevant publications.

Outcomes of interest

The outcomes of interest were the following: in-hospital mortality, hospital admission rate in the index evaluation, length of hospital stay, confirmed myocardial infarction in the index evaluation, diagnosed unstable angina in the index evaluation, angiography rate in the index evaluation, percutaneous intervention rate in the index evaluation, coronary artery bypass grafting in the index evaluation, rate of indeterminate diagnoses in the index evaluation, overall mortality, incident myocardial infarction (MI) or unstable angina (UA) in the follow-up, ED re-attendance rate, hospital readmission rate and overall rate of revascularization procedures. All outcomes were recorded as defined by the authors in the original publications.

Eligibility criteria

We included randomized clinical trials comparing CPU care against routine hospitalization for the evaluation of low-to-intermediate risk NSTEACS patients.

There was no restriction as to study duration or number of patients. Studies evaluating strategies centered in specific diagnostic tests with no indication of observation unit were not included.

Study selection

The references identified by the literature searches were scrutinized in two phases. All studies were initially scanned for relevance by title and abstract. Studies that could not be

excluded according to our eligibility criteria in the abstract review had their full text retrieved for further evaluation. Study selection was independently performed by two investigators (A.L.F.S. and S.P.). Disagreements were solved by consensus.

Data extraction and assessment of quality

Two reviewers independently abstracted data from included articles (A.L.F.S. and P.H.S.). Disagreements were resolved by consensus and, if necessary, with the opinion of a third reviewer (C.A.P.). Extracted information comprised patient population's characteristic, characteristics of the studied CPUs, comparator characteristics, outcomes assessed, and study quality. The latter used the framework suggested by the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0)[17], i.e. separately appraising methodological aspects instead of using study quality scales. The following criteria were evaluated in the assessment of risk of bias: random sequence generator method, allocation of treatment concealment, blinding of participants and personnel, blinding of outcome assessment, potential for incomplete outcome data and for selective reporting.

Statistical analysis

The direct evidence was computed with random effects model meta-analysis of head-to-head comparisons. Summary effect for binary outcomes was calculated from the risk ratios, and weighted mean difference was used for the length of hospital stay, in hours. Heterogeneity was evaluated by the means of the inconsistency test proposed by Higgins, where values below 25% were considered as low heterogeneity, and above 75%, high heterogeneity. Meta-analysis was

carried out in Review Manager 5.1.4 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

Missing data

Meta-analysis level imputation of the missing standard deviations (SD) was done through the weighted mean of available standard deviations from remaining studies. This method is conservative in comparison to other methods suggested in the literature, whose use would yield more narrow dispersion estimates.[18,19]

The study by Farkouh et al have reported the in-hospital fatality rate and the average length of stay for the CPU group, however, data on the routine care arm was missing.[9] Likewise, the study by Roberts et al failed to report of MI cases in the routine care group.[10] We made no attempt for data imputation and these studies were excluded from the analysis of the affected outcomes.

Data derived from cluster-randomized trials

Improper handling of data derived from cluster trials is a known source of bias in meta-analysis[20]. Cluster design was used in two of the identified clinical trials, both developed by the same research group[21,22].

The ESCAPE clinical trial (2007)[22,23] was designed to evaluate the performance of large-scale implementation of CPUs in the United Kingdom. Study clusters were fourteen hospitals, which were randomly assigned to implement or not a CPU. Cluster size averaged 3,412 patients (ranging 1,386 to 6,423). The cluster effect was taken into account on sample size calculations,

and the authors have reported an estimated design effect of four. We have included data from the reported outcomes in this trial after adjusting for cluster design effect through the ratio estimator approach[24], which consists in dividing the study counts by the estimated design effect.

In their 2004 publication[21], Goodacre et al have randomized 442 days to either CPU or routine care of incoming patients with chest pain. Cluster size averaged 2.2 patients per day. The small cluster size was the reason given by the authors to not adjust sample size calculation for cluster effect. Therefore, no estimate of design effect was provided in this publication, nor was the intraclass correlation coefficient (ICC), which is required in the design effect estimation. To overcome this difficulty, we used data from the 2007 publication to estimate a surrogate ICC, which was calculated to be 0.00087.[22,24,25] Then we have adjusted for cluster design effect through the ratio estimator approach, which resulted in a negligible effect on study data, determining no discounts in the study counts in the main analysis.

Results

The search strategy yielded 3,393 references after removal of duplicate records. Seven full papers were selected for the descriptive synthesis of evidence and six were included in the meta-analysis.[6,9,10,21,22,26-28]

The study flowchart is shown in Figure 1. There were six studies comparing CPU care to routine hospitalization and one study comparing CPU care to CCU care for higher risk patients. The characteristics of the included trials are presented in Table 1.

Descriptive synthesis of evidence

Patient inclusion and exclusion criteria were similar among the included studies. In general, studies aimed at including adult patients presenting to the ED with acute onset chest pain, excluding patients with ST elevation or depression, arrhythmias, alternative diagnosis or patients with clinical instability.

Despite the use of similar criteria, the objective of the work by Conti et al was to evaluate the performance of a CPU in the management of patients that were initially candidates to CCU admission. This resulted in the recruitment of patients at a higher risk (TIMI risk score >4 in 60% of patients).[26] The risk profile of patients from the included studies is presented in Table 2.

Characteristics of the CPUs among the seven identified studies were comparable (Table 3). The number of dedicated beds was reported in four studies and varied from 2 to 6. CPUs were located inside the ED in all studies, except in the cluster multicenter trial by Goodacre et al (2007), which included CPUs located in other hospital departments.[22] Six studies reported continuous cardiac monitoring and dedicated nurses. Medical coverage was provided by ED physicians in the five studies that reported this information. Serial ECG protocols varied from one ECG every 15 minutes to one ECG every 6 hours. All trials reported serial measurement of a cardiac lesion marker at 2 to 6 hours intervals. Troponin was the lesion marker in all studies from 2004 on. In four studies, aspirin was routinely administered according to protocol. Routine anticoagulation was performed in only one trial, which also reported routine administration of tirofiban. CPU protocols from 5 trials performed systematic non-invasive testing for patients whose ischemic nature of chest pain could not be safely discarded after the observation period in the unit. Such tests comprised graded exercise ECG and myocardial scintigraphy or echo-stress as

alternatives in 2 of these trials. The protocol used in the work by Conti et al included coronary angiography to all indeterminate cases (unless contraindicated), and the work by Miller et al employed CMR to all patients with no troponin elevation during initial evaluation in the observation unit.[26,28] Duration of the observation period varied from 2 to 12h among the studied CPUs.

Quality of evidence assessment

The evaluation of the risk of bias was limited due to lack of reporting of quality assessment parameters. The least reported items were random sequence generation method and blinding of outcome assessment. All of the identified trials have reported no blinding of participants and study personnel. The study by Roberts et al reported all quality assessment items except blinding of outcome assessment.[10] This study was considered to be at the lowest risk of bias among the identified articles. On the other hand, the study by Goodacre et al (2004) reported a potentially biased cluster randomization method, using an open schedule according to the day of the week.[21] The study by Conti et al was the one with the most incomplete report of quality assessment items.[26] Quality assessment is summarized in Table 4.

Meta-analysis

Outcomes related to the index evaluation

The forest plot of the summary effects of the seven binary outcomes related to the index evaluation is presented in Figure 2. The only continuous outcome was length of hospital stay, whose forest plot is available at Appendix 1.

In-hospital mortality

Four studies have reported in-hospital mortality rates[6,9,10,28], however, there were no events in either study arm in three of them[6,10,28]. Farkouh et al have reported one fatality in the CPU arm, but data on the routine care arm was missing. This corresponded to one in-hospital death among the 798 patients from four trials.

Hospital admissions

All of the six included studies have measured hospital admission rates. The comparator in the studies by Roberts et al, Farkouh et al and Miller et al was hospital admission by definition, which artificially generated a high "event rate" for this outcome.[9,10,28] Although this 100% admission rate might in fact reflect the "routine care" for low-risk chest pain patients in the studied settings, it seems to us that evaluation in the general ED without a CPU would have provided a comparator more capable of discriminating CPU's ability to avoid hospital admissions. The study by Gomez et al also defines its comparator group as hospital admission as well; however, it is reported that 17 out of the 50 patients in the routine care group were "discharged

without further diagnostic testing other then ECGs and serum enzyme determinations".[6] Therefore, we accounted 33 hospital admissions in the comparator group.

Assuming that there is external validity in the choice of comparators that represent 100% hospitalization rates, a comparison of data from all studies reveals statistical differences favoring the CPU care in 5 out of 6 trials. Although the summary effect of all six trials yields a statistically significant benefit of the CPU care over routine care (RR 0.47; 95% CI 0.29 to 0.77), the resulting heterogeneity was too high (I^2=98%) to consider this to be a valid estimate of the average effect of this intervention. Sources of heterogeneity were assessed in a sensitivity subgroup analysis.

Length of hospital stay

Four studies have reported the average length of hospital stay[6,10,21,28]. The study by Farkouh et al has reported only the average length of stay in the CPU, without informing the total length of hospitalization for either the intervention or the control group. The studies by Goodacre et al (2004) and Miller et al (2010) did not report the standard deviation (SD) for the length of hospital stay, which had to be imputed from the two remainder trials.

It was found a statistically significant difference in the length of hospital stay at the study level in 2 out of 4 trials[6,10], which favored the CPU care. At the meta-analysis level, there was a statistically significant reduction in the summary effect of length of hospital stay, which favored the CPU group (point estimate -8.74 h; 95% CI -16.92 to -0.55). Heterogeneity was estimated to be at an intermediate level (I^2=38%). The forest plot of the mean difference of length of hospital stay is available in Appendix 1.

Confirmed Myocardial Infarction at index evaluation

This analysis was conducted and interpreted as a measurement of the unit's ability to establish the diagnosis of MI among incoming chest pain patients. In other words, MI diagnosis was treated as "good" outcome. Five studies have reported MI rates. However, the study by Roberts et al was excluded due to missing report of MI cases in the routine care group, thus four studies have been included in the meta-analysis[6,9,21,28]. There was no statistically significant difference in confirmed MI rates between CPU and routine care either at the study or at the meta-analysis level. Heterogeneity was considered low for this outcome (I^2 = 12%).

Diagnosed unstable angina at index evaluation

This analysis was also conducted and interpreted as a measurement of the unities' diagnostic capability (UA diagnosis as a "good" outcome). Three studies have reported UA rates at the index evaluation. However, the study by Roberts et al was excluded due to missing report of UA cases in the routine care group, thus two studies have been included in the meta-analysis.[6,28] There was no statistically significant difference in confirmed UA rates between CPU and routine care at either the study or at the meta-analysis level. Heterogeneity was estimated to be low for this outcome (I^2 = 0%).

Combined diagnoses of MI or UA at the index evaluation

This analysis was conducted to evaluate the unities' ability to establish the diagnoses of either MI or UA among incoming chest pain patients (diagnoses regarded as "good" outcomes). Five studies have reported either MI or UA rates at the index evaluation. The study by Roberts et

al was excluded due to missing report of events in the routine care group, thus four studies have been included in the meta-analysis[6,9,21,28]. There was no statistically significant difference in confirmed event rates between CPU and routine care either at the study or at the meta-analysis level. Heterogeneity was considered intermediate for this outcome (I^2 = 33%).

Coronary Angiography at index evaluation

Only two studies have reported the number of coronary angiographies performed at the index evaluation[6,28]. There were no statistically significant differences between the compared interventions either at the study level or at the meta-analysis level. Heterogeneity was considered intermediate for this outcome (I^2 = 48%).

Indeterminate diagnosis at index evaluation

Two studies have reported rates of indeterminate diagnosis at index evaluation.[6,10] At study level, the publication by Roberts et al have reported fewer cases of indeterminate diagnosis among patients managed in the CPU, a statistically significant difference. This result has driven the summary effect estimate in the same direction. Heterogeneity was estimated to be low (I^2 = 0%).

Outcomes related to the follow-up period

There were five outcomes measured in the follow-up period. The forest plot of the summary effects of binary outcomes related to the follow-up period is presented in Figure 3.

Follow-up mortality

Five studies have reported mortality rates in the follow-up period[6,9,10,21,27]; however, events have occurred in only three of them[9,21]. All of the included trials have reported additional mortality rate (i.e. excluding in-hospital mortality rate) over a 6-month period. There were no statistical differences between CPU and routine care either at the study level or at the meta-analysis level. Heterogeneity was considered low for this outcome (I^2=15%).

Follow-up myocardial infarction or unstable angina

Three studies have reported incident MI or UA in the follow-up period.[9,21,27] There were no statistical differences between CPU and routine care either at the study level or at the meta-analysis level. Heterogeneity was considered low for this outcome (I^2=0%).

Emergency Department Re-attendances

Re-attendances to the ED during the follow-up period were evaluated in 5 studies[6,9,21,22,27]. Only in 2 trials there was a statistically significant reduction in re-attendance rates favoring the CPU care[21,27]. At the meta-analysis level, there was no statistical difference in re-attendance rates between CPU and routine care for the estimated summary effect. Heterogeneity was considered intermediate for this outcome (I^2=66%). Subgroup analysis by trial design (cluster versus individual randomization) did not alter the results or the heterogeneity estimate.

Hospital Readmissions

Five studies have reported hospital readmission rates[6,10,21,22,27]. There was a statistically significant reduction in hospital readmissions only in the study by Miller et al.[27] There was no statistical difference between CPU and routine care at the meta-analysis level. Heterogeneity was considered high for this outcome (I^2 = 77%), and neither the summary effect, nor the inconsistency estimator have substantially changed with the exclusion of the study by Miller et al.

Follow-up Cardiac Angiography

Three studies have reported angiography rates in the follow-up period[6,10,27]. A comparison of data from all studies reveals statistical differences favoring the CPU care only in the study by Miller et al[27]. However, at the meta-analysis level, there was a statistical significant difference in favor of the CPU strategy with a combined relative risk o 0.22 (95% CI 0.05 – 0.86). The resulting heterogeneity for this analysis was low (I^2=0%).

Outcomes considering the overall length of studies

This includes overall mortality rate and revascularization outcomes that were reported by some studies without specifying the moment of occurrence. Figure 4 presents the forest plot of summary effects for outcomes related to the overall period.

Overall Mortality

This outcome refers to death from any cause that has occurred either during the in-hospital period or during the follow-up period. Two studies have been included[9,21]. There were no statistical differences between CPU and routine care either at the study level or at the meta-analysis level. Heterogeneity was considered intermediate for this outcome (I^2=37%).

Overall use of percutaneous coronary intervention

Two studies have reported the rates of PCI usage comprising both the index evaluation and the follow-up period[10,27]. Although the point estimate for the relative risk of performing PCI has been in the same direction in all of the included trials, with fewer events in the CPU group, there was no statistically significant difference. Heterogeneity was low (I^2 = 0%).

Overall surgical revascularization

Two studies have reported the rates of CABG comprising both the index evaluation and the follow-up periiod[6,27]. There were no statistically significant differences either at the study level or at the meta-analysis level. Heterogeneity was intermediate (I^2 = 59%).

Overall revascularization

Three studies have reported the rates of both PCI and CABG comprising the index evaluation and the follow-up period[6,10,27]. The point estimate for the relative risk of performing any revascularization procedure has been in the same direction in all of the included trials, with fewer procedures in the CPU group, however, there were no statistically significant differences at the study level. However, at the meta-analysis level, it was observed a statistically significant reduction in the summary effect of undergoing a revascularization procedure among patients treated in the CPU as compared to routine care (summary RR = 0.30; 95% CI 0.09 - 0.96). Heterogeneity was low (I^2 = 0%).

Sensitivity Analysis

Assessing differences in trial design as sources of heterogeneity in hospital admissions

Subgroup analysis was made in order to identify possible sources for the observed heterogeneity in estimating the summary effect of hospital admissions. First, we have separated trials with a fixed 100% admission rate in the comparator from those with a variable admission rate (Appendix 2). Second, we have grouped trials by similarity in trial design and in choices of interventions and comparators (Appendix 3). Studies with patient level randomization and similar protocols for intervention and comparator were grouped in one subgroup[6,9,10]; another subgroup was more heterogeneous, including the two trials by Goodacre et al (both with cluster randomization) and the study by Miller et al (the only to use CMR in the risk stratification strategy).[21,22,28] Nevertheless, heterogeneity was still too high in both subgroup analyses (I^2 ≥

84%). For this reason, we have chosen not to consider valid the estimate of a summary effect of CPU on hospital admission rates.

Assessing differences in trial design as sources of heterogeneity in hospital readmissions

Subgroup analysis was made in order to identify possible sources for the observed heterogeneity in estimating the summary effect of readmissions. We have grouped trials by similarity in trial design and in choices of interventions and comparators (Appendix 4). Studies with patient level randomization and similar protocols for intervention and comparator were grouped in one subgroup[6,10]; another subgroup included the two cluster randomization trials by Goodacre et al and the study by Miller et al.[21,22,27] Heterogeneity has disappeared in the first subgroup (I^2 = 0%), though there was still no difference in readmission rates in the summary effect estimate.

Assessing the effects of including data from Conti et al restricted to patients with TIMI risk score ≤ 4

The study by Conti et al was not included in the main analysis due to differences in patient population (overall higher risk) and in the choice of a comparator (CCU instead of routine hospitalization), which might be major sources of bias and heterogeneity.[26] This study reported the following outcomes for patients with NSTEACS TIMI risk score ≤ 4: in-hospital mortality, follow-up mortality, overall mortality, confirmed MI at index evaluation, diagnosed UA at index evaluation, follow-up MI and follow-up UA. Reanalysis of these outcomes with data from the subgroup at lower risk resulted in no modification in the meta-analysis' results.

Limitations

This systematic review presents several limitations that deserve to be mentioned. First, inherently to systematic reviews, any conclusions derived from the pooling of data are dependent on the statistical power and quality of the original clinical trials. The identified studies presented recognizable methodological limitations, such as the lack of blinding of participants, personnel and analysts (except for the study by Miller et al, which reported blinding of outcome assessment) and potentially inadequate allocation concealment, as in the case of the study by Goodacre et al (2004), in which research staff and chest pain nurses had access to the randomization schedule. Still, there was insufficient information to permit a clear judgment on the risk of bias for several quality evaluation items (Table 4).

Another limitation concerns to the external validity of our findings. The analyzed data refers to a very specific patient population, which are adults, presenting to the ED with acute onset chest pain, with no clinical instability and with no defined ischemic changes on initial ECG. These patients were considered to be at low to intermediate cardiac risk (NSTEACS TIMI risk score ≤4). Therefore, caution must be taken on the extrapolation of the present findings.

The identified clinical trials were designed and powered to measure resource use as their main outcome. Therefore, even with the pooling of data, there may not have been observations enough to capture differences in event rates between CPU care and routine hospitalization.

The time expanse among the identified studies (more than 15 years) might account for some of the observed heterogeneity in some outcomes. In fact, the extremely significant progresses in the management of suspected or confirmed ACSs observed in this period limits the

value of direct comparisons of dedicated units from the 90's with their contemporary counterparts. Unfortunately, the only way to deal with this limitation would be to exclude older studies from this review, which we chose not to do in order to make possible a historical perspective that could provide insights for future research. Finally, funnel plot analysis was inconclusive for publication bias due to the small number of studies and the relatively small sample size in all trials but the one by Goodacre et al.

Discussion

The present systematic review of literature have identified seven clinical trials of ED based observation units coupled with non-invasive testing for the initial evaluation of low risk undefined acute chest pain patients. Comparator groups, under the labels of "routine care", "in-patient care" and "routine hospitalization", comprised mainly hospital admittance for investigation at the physician assistant discretion, but also included an small proportion of patients cared for in monitored units (such as CCU or internal medicine telemetry unit). The study by Conti et al was the only to define the CCU as its sole comparator for the CPU and was excluded from the meta-analysis.

The inclusion of the work by Miller et al might generate some controversy, as this was the only study to use cardiac magnetic resonance as its non-invasive evaluation for exclusion of ischemic heart disease in patients whose nature of symptoms remained unclear after serial ECG and biomarkers[27,28]. We have decided to include this trial in the meta-analysis due to its similarities with other included trials regarding patient selection, comparator and outcomes

assessment. More importantly, though, is the fact that an ED based observation unit for chest pain evaluation was clearly a part of the study intervention, which renders this study comparable to other trials of observation units for chest pain evaluation that were coupled with some kind of non-invasive testing.

We have not included any of the studies on coronary computer tomographic angiography (CCTA) largely because chest pain units were not a part of the intervention being evaluated in such trials (i.e. both study arms took place at a CPU, differing by the use of CCTA, or there wasn't mention of any CPU or equivalent unit at all)[13-15]. Another reason to not include CCTA trials was the early use of CCTA as a replacement for traditional CPU protocols, and not as a non-invasive test for indeterminate cases[15,16]. In other words, none of the identified CCTA trials fitted the research question delineated in the present systematic review.

The current systematic review presents evidence that CPU care has the potential to prevent hospital admissions in the index evaluation. In fact, 5 out of the 6 trials included in the meta-analysis presented a statistically significant reduction in the relative risk of being admitted, with study-level point estimate of effect size (RR) varying from 0.06 to 1.22 for admission. However, the heterogeneity estimate for this outcome was too high (I^2 = 98%) to allow a summary effect to be reliably computed. On investigating the sources for this heterogeneity, we hypothesized that comparator group definition might have accounted to the observed elevated inconsistency. In fact, in three studies the comparator is hospital admission by default, which yielded admission rates from 95 to 100% in this study arm. It seems to us that ED care in the absence of an organized CPU would have provided a more realistic comparator. We have also

grouped studies by similarities in trial design and comparators definitions. However, subgroup sensitivity analysis was unable to isolate the source of this inconsistency.

Regarding the length of hospital stay, it was found a statistically significant difference favoring the CPU care at the meta-analysis level. The point estimate for this reduction was -8.74 h, and the confidence interval for this estimate was wide (-0.55 to -16.92). This reduction in length of hospital stay goes in the same direction as the reduction in hospitalizations after the index evaluation, both implying reductions in resource utilization and costs with the use of the CPU strategy for low to intermediate risk suspected NSTEACS patients.

Another outcome for which the CPU strategy performed significantly better then routine hospitalization was the proportion of patients with indeterminate diagnosis on discharge, with a 70% reduction in the risk of being discharged without a determinate diagnosis. However, this finding should be considered with caution, as the label "indeterminate diagnosis" lacks a clear definition. Moreover, only two trials have reported this outcome, both published more than 15 years ago, and the summary effect estimate reflects almost exclusively the study by Roberts et al. Although this result suggest that patients might have been evaluated in a more comprehensive way in the CPU strategy, we don't think this analysis allows to derive definite conclusions on CPU's diagnostic ability.

Regarding the need for invasive investigation in the follow-up period, we have found a 78% reduction in the summary relative risk of being submitted to cardiac angiography among patients that were managed in the CPU in comparison to routine hospitalization. Three studies were included in this analysis, two of them from the decade of 1990, with graded exercise ECG as their main non-invasive testing for chest pain cases that remained indeterminate after serial ECG

and measurements of CK-MB. The remainder was the study by Miller et al, whose follow-up results were published in 2011, that has used CMR as its sole non-invasive testing for chest pain cases that remained indeterminate after serial ECG and troponin I measurements. Despite the time gap and the different non-invasive method employed in the two first studies relative to the study by Miller et al, it is interesting to observe that the point estimate of all three studies went in the same direction, favoring the CPU strategy. This finding suggests that previous evaluation in a CPU might avert subsequent unnecessary invasive investigation. However, we take this as a preliminary finding that requires additional research focusing CPU protocols coupled with CCTA, CMR and future, more accurate, non-invasive diagnostic testing.

Data from the same trials previously mentioned[6,10,27] attained a statistically significant reduction in the summary RR for being submitted to a revascularization procedure (PCI or CABG) in the overall study period (point estimate 0.3; 95% CI 0.09 to 0.96). Again, we believe this to be a preliminary valid estimate, despite the time and technological gap among the included studies. This finding is probably related to the lower summary RR for follow-up angiography, as the reduction in unnecessary invasive investigation would likely result in a reduction in "unnecessary" percutaneous interventions. More studies with newer non-invasive techniques are necessary to clarify this finding.

Among the identified trials, only the work by Miller et al reflects CPU care in the present era of more sophisticated non-invasive testing for cardiac risk assessment, and none of the identified trials of CCTA permitted a direct comparison of traditional CPU (associated to CCTA for risk stratification) with routine hospitalization. A recently published systematic review of clinical trials of CCTA versus non-CCTA approaches in the evaluation of low- and intermediate-risk chest

pain patients has shown an increased risk of being submitted to revascularization procedures in patients evaluated with CCTA.[12] On the other hand, CPU care appeared to be associated to a lower rate of revascularization procedures according to our findings. We believe there are two possible reasons for this discrepancy: (1) the distinct role of CCTA in clinical trials, which was performed earlier than traditional CPU risk stratification protocols (on arrival, to all patients, or as early as the 4th h ECG and troponin were negative); (2) CCTA might be too sensible (and comparatively might lack specificity) as compared to CMR for risk stratification of low-to-intermediate risk ACS.

Finally, in the current systematic review, CPU's effectiveness was measured mainly in comparison to routine hospitalization. The underlying concept in the choice of such a comparator is the prompt availability of hospital beds and the possibility of performing diagnostic and therapeutic procedures in a favorable setting of hospital resource abundance. However, this may not the case in many developing countries, where hospital beds, diagnostic and therapeutic resources are scarce. Likewise, recent changes in US healthcare policies may be interfering with prompt access to hospital resources. CPU's effectiveness was not properly evaluated in these settings, and these units are likely to have a more important role then they had in the past.

Conclusions

In the evaluation of low to intermediate risk NSTEASC patients, strategies composed by observation in a dedicated unit adjacent to the ED, with defined protocols for initial management, serial ECG and biomarkers measurements and dedicated staff, coupled with systematic

investigation with non-invasive tests is capable of reducing hospitalization rates, length of hospital stay, need for follow-up coronary angiography and overall rate of revascularization procedures. Additionally, no increase in adverse outcomes was identified in the comparison with routine hospitalization. The use of newer, more accurate, diagnostic tests in the evaluation of undefined cases after an initial observation period, such as cardiac magnetic resonance, appears to improve this strategy's effectiveness. However, the optimum strategy for evaluating low to intermediate risk NSTEACS patients is still a subject for research.

Finally, CPU's effectiveness was not been properly evaluated in comparison to ED care in a setting of limited hospital resources, where they are likely to have a more important role then they had in the past.

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Tables

Table 1 - Characteristics of included trials

Study	Year	Intervention	Control	Patients randomized	Patient inclusion criteria	Patient exclusion criteria	Follow-up (months)
Gomez et al	1996	Rapid rule-out protocol in coronary care evaluation unit	Routine hospitalization (physician assistant)	100	Patients ≥30 years old, with suspected ACS, but with a estimated low MI probability (≤7% using the Goldman algorithm) and no ischemic changes in baseline ECG	Ventricular arrhythmias or arrhythmias requiring IV medication; 2nd or 3rd degree AV block; need for nitroglycerin; BP > 220/120; decompensated heart failure; other conditions requiring IV medication or monitoring	1
Roberts et al	1997	Accelerated diagnostic protocol for evaluation of chest pain in an ED observation unit	Telemetry unit (internal medicine service)	165	Patients ≥ 20 years old, suspected MI/unstable angina, estimated low MI probability (≤7% using the Goldman algorithm), ability to exercise testing	Known ischemic heart disease, pre-hospital complication of ACS, defined ischemic ECG changes, atrial fibrillation, frequent supraventricular extra-systoles, recurrent chest pain, other diagnosis requiring hospitalization, stress ECG not interpretable	2
Farkouh et al	1998	Chest pain unit	Routine hospital admission	424	Patients with intermediate risk chest pain according to AHCPR* criteria	ST segment depression or elevation, high risk angina in general, other conditions requiring hospitalization	6
Goodacre et al	2004	Chest pain observation unit	Routine care in ED or medical ward	972	Patients with intermediate risk chest pain and non-diagnostic initial ECG	Age < 25 years old, ECG diagnosis of ACS, history of unstable angina; comorbidity or alternative cause of severe chest pain; denied consent	6
Conti et al	2005	Chest pain unit	Coronary care unit	210	Chest pain patients with suspected NSTEACS** after initial clinical assessment, ECG, chest radiograph and laboratory evaluation	ST segment elevation, secondary angina, platelet disorder or coagulopathy, Killip classes III and IV, stroke in the previous 6 months	6

Goodacre et al	2007	Chest pain unit	Routine care in ED or medical ward	47767	Patients with acute undifferentiated chest pain, without evidence of defined ACS or alternative diagnosis	Defined ACS; alternative diagnosis	1
Miller et al	2010 / 2011	Observation unit – CMR	Inpatient care	109	Chest pain patients ≥ 18 years old, intermediate to high risk of ACS according to physician impression or TIMI ≥ 2	Elevated initial troponin, ST segment elevation or depression, orthopnea, SBP < 90 mmHg, contraindication to MRI, refusal to undergo procedures, pregnancy, life expectancy <3 months, chronic kidney or liver diseases, solid organ transplant	12

ACS, acute coronary syndrome; BP, blood pressure; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CPU, chest pain unit; ED, emergency department; NSTEACS, no-ST elevation acute coronary syndrome; TIMI, time in myocardial infarction no-ST elevation risk score;

Table 2 - Risk profile of patients from the included studies. Data in percent of randomized patients.

	TIMI CPU	TIMI control	Hypertension CPU	Hypertension control	Diabetes CPU	Diabetes control	Smoking CPU	Smoking control	Hyperlipidemia CPU	Hyperlipidemia control	Previous CAD CPU	Previous CAD control
Gomez et al, 1996	NR	NR	30%	44%	0	10%	22%	16%	34%	40%	2%	8%
Roberts et al, 1997	NR	NR	43.9%	43.4%	8.5%	14.5%	56.1%	49.9%	NR	NR	NR	NR
Farkouh et al, 1998	NR	NR	36.3%	41.0%	7.6%	10.8%	17.0%	13.7%	NR	NR	13.7%	15.1%
Goodacre et al, 2004	NR	NR	26.5%	24.3%	3.5%	5.9%	35.3%	29.0%	12.1%	14.2%	3.3%	5.5%
Conti A et al, 2005	60% ≥4	60.5% ≥4	41.9%	41.0%	18.1%	15.2%	21.9%	29.5%	16.2%	19.0%	28.6%	29.5%
Goodacre et al, 2007	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miller et al, 2010	11% ≥4	19% ≥4	68%	75%	38%	40%	34%	32%	74%	77%	21%	28%

CAD, coronary artery disease; CPU, chest pain unit; NR, not reported; TIMI, time in myocardial infarction no-ST elevation risk score.

Table 3 - Denomination of compared interventions and characteristics of the studied interventions among the identified trials

Author	Year	Intervention's name	Comparator's name	Beds	Unit location	Cardiac monitoring	Dedicated nurses	Medical coverage	ECG protocol	Biomarker protocol	Per protocol interventions	Duration of observation	Non-invasive testing
Gomez MA et al	1996	Rapid rule-out protocol in coronary care evaluation unit	Physician assistant - routine hospitalization	6	Dedicated area in ED	Yes, 2 beds	NR	NR	Continuous ECG monitoring / printed every 15 minutes	CK and CK-MB at times 0, 3, 6 and 9h	aspirin oxygen	9h	Graded exercise ECG to all indeterminate cases; Echo-stress if exercise not possible;
Roberts RR et al	1997	Accelerated diagnostic protocol in ED observation unit	Telemetry unit - internal medicine service	NR	Dedicated area in ED	Yes	1 nurse, 24h availability	ED physician	ECG at times 0, 6 and 12h	CK-MB at times 0, 4, 8 and 12h	aspirin oxygen	12h	Graded exercise ECG to all indeterminate cases
Farkouh ME et al	1998	Chest pain unit	Routine hospital admission	4	Dedicated area in ED	Yes	1 nurse, 24h availability	ED physician	NR	CK-MB at times 0, 2 and 4h	aspirin	6h	Graded exercise ECG, myocardial scintigraphy OR echo-stress to all indeterminate cases
Goodacre S et al	2004	Chest pain observation unit	Routine care in the emergency department	2	Dedicated area in ED	Yes, 2 beds	3 nurse, 6 to 8h during the day	ED physician	ECG every one hour	CK-MB at times 0 and 2h OR Troponin T at least 6h after pain started	NR	6h	Graded exercise ECG to all indeterminate cases
Conti A et al	2005	Chest pain unit	Coronary care unit	4	Dedicated area in ED	Yes	2 nurses, 24h availability	ED physician	ECG every 6 hours	Troponin OR CK-MB every 6h for the first 24h	aspirin anticoagulation (UFH) tirofiban	NR	Cardiac angiography was considered to all patients, unless contraindicated
Goodacre S et al	2007	Chest pain unit	Routine care - ED care or medical ward	NR	Dedicated area in ED or medical ward	Yes	1 to 6 chest pain nurses	NR	Serial ECG from 2 to 6 hours	CK-MB at times 0 and 2h OR Troponin T at least 6h after pain started	NR	6h	Graded exercise ECG to all indeterminate cases
Miller CD et al	2010 2011	Observation unit – CMR	Inpatient care	NR	Dedicated area in the ED	NR	"Nurse practitioners"	ED physician	NR	Troponin I at times 0, 4 and 8h	NR	Not reported	CMR to all patients without troponin elevation

ECG, electrocardiogram; ED, emergency department; UFH, unfractionated heparin; CMR, cardiac magnetic resonance.

Table 4 - Quality assessment of identified studies

Study	Risk of bias					
	Random sequence generator (selection bias)	**Allocation concealment (selection bias)**	**Blinding of participants and personnel (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**
Gomez et al, 1996	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Roberts et al, 1997	Low risk	Low risk	Unclear risk	Unclear risk	Low risk	Low risk
Farkouh et al, 1998	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk
Goodacre et al, 2004	High risk	High risk	Unclear risk	Unclear risk	Unclear risk	Low risk
Conti A et al, 2005	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Goodacre et al, 2007	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk
Miller et al, 2010	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk

Figure Legends

Figure 1: Flow diagram of the studies' selection process. ACS, acute coronary syndrome; CCU, coronary care unit; CPU, chest pain unit; MI, myocardial infarction; UA, unstable angina.

Figure 2: The forest plot of summary effect of clinical outcomes related to the index evaluation (risk ratios, Mantel-Heanszel, random effect model). Horizontal bars indicate 95% CIs; CPU, chest pain unit; MI, myocardial infarction; UA, unstable angina.

Figure 3: The forest plot of summary effect of clinical outcomes related to the follow-up period (risk ratios, Mantel-Heanszel, random effect model). Horizontal bars indicate 95% CIs; CPU, chest pain unit; ED, emergency department; MI, myocardial infarction; UA, unstable angina.

Figure 4: The forest plot of summary effect of clinical outcomes related to the overall period (risk ratios, Mantel-Heanszel, random effect model). Horizontal bars indicate 95% CIs; CABG, coronary artery bypass grafting; CPU, chest pain unit; PCI, percutaneous coronary intervention.

Figures

Figure 1

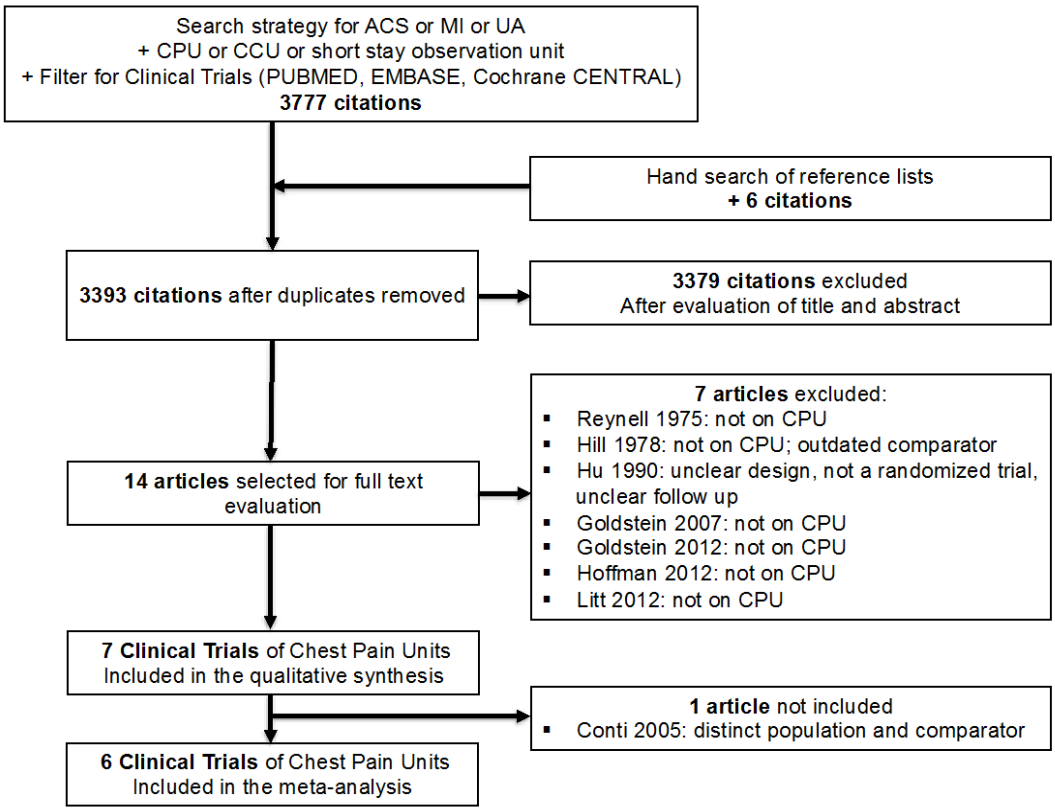


Figure 2

Outcome	Patients Randomized	Effect Estimate	I^2
Hospital admission	13712	RR 0.47 (0.29 – 0.77)	98%
Confirmed MI	1605	RR 0.81 (0.48 – 1.38)	12%
Diagnosed UA	209	RR 0.15 (0.02 – 1.24)	0%
Diagnosed MI and UA	1604	RR 0.62 (0.31 – 1.23)	33%
Coronary angiography	209	RR 0.63 (0.22 – 1.77)	48%
Indeterminate diagnosis	265	RR 0.31 (0.18 – 0.52)	0%

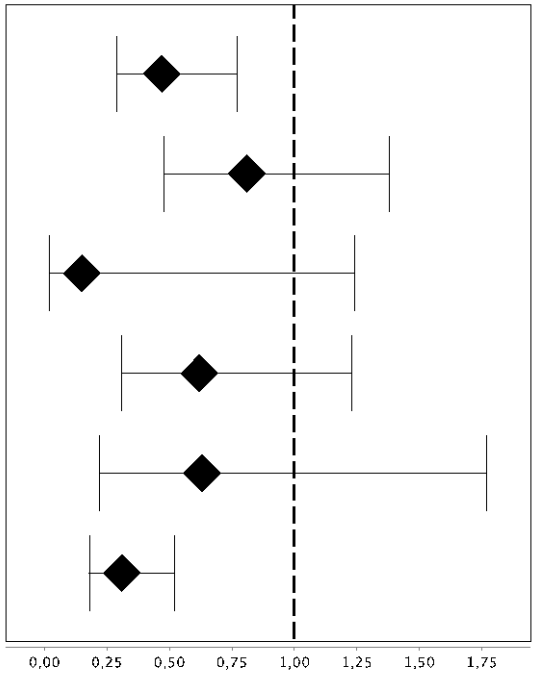


Figure 3

Outcome	Patients Randomized	Effect Estimate	I^2
All cause death	1396	RR 1.95 (0.32 – 11.97)	15%
MI and UA	1505	RR 1.18 (0.64 – 2.19)	0%
ED re-attendance	13547	RR 0.89 (0.63 – 1.26)	66%
Hospital readmissions	13288	RR 0.84 (0.48 – 1.47)	77%
Coronary angiography	374	RR 0.22 (0.05 – 0.86)	0%

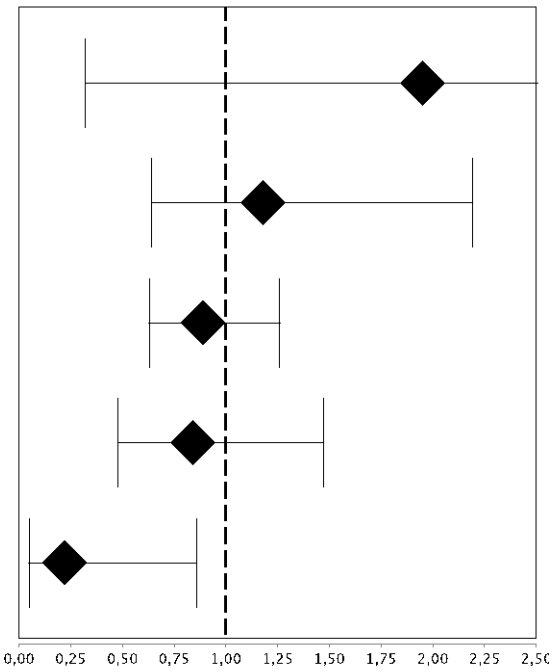
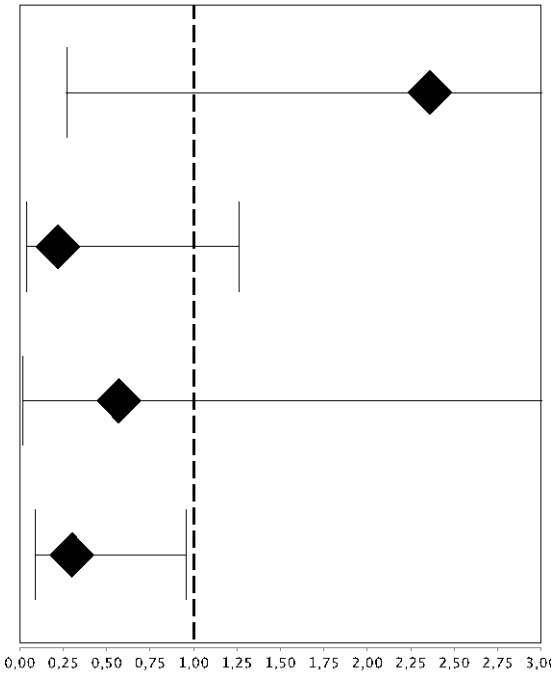


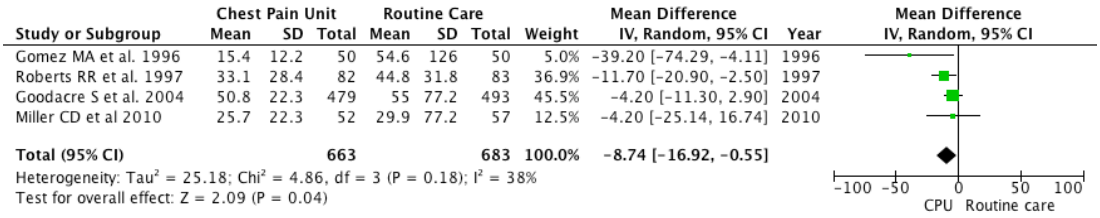
Figure 4

Outcome	Patients Randomized	Effect Estimate	I^2
All cause death	1394	RR 2.36 (0.27 – 20.36)	37%
PCI	274	RR 0.22 (0.04 – 1.26)	0%
CABG	209	RR 0.57 (0.02 – 16.02)	59%
PCI and CABG	374	RR 0.30 (0.09 – 0.96)	0%



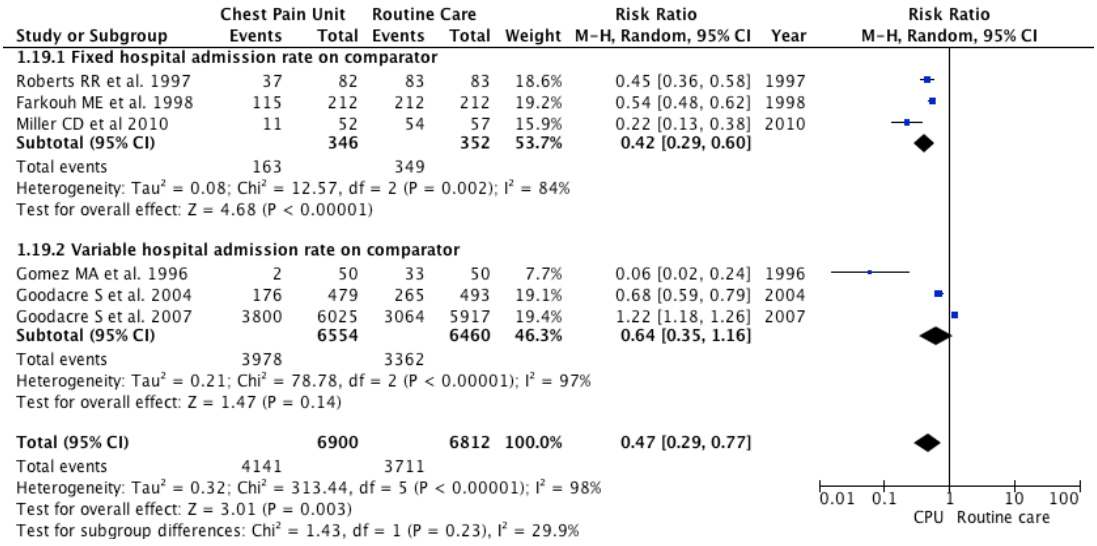
Appendix 1

The forest plot of weighted mean difference of length of hospital stay (in hours). Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.



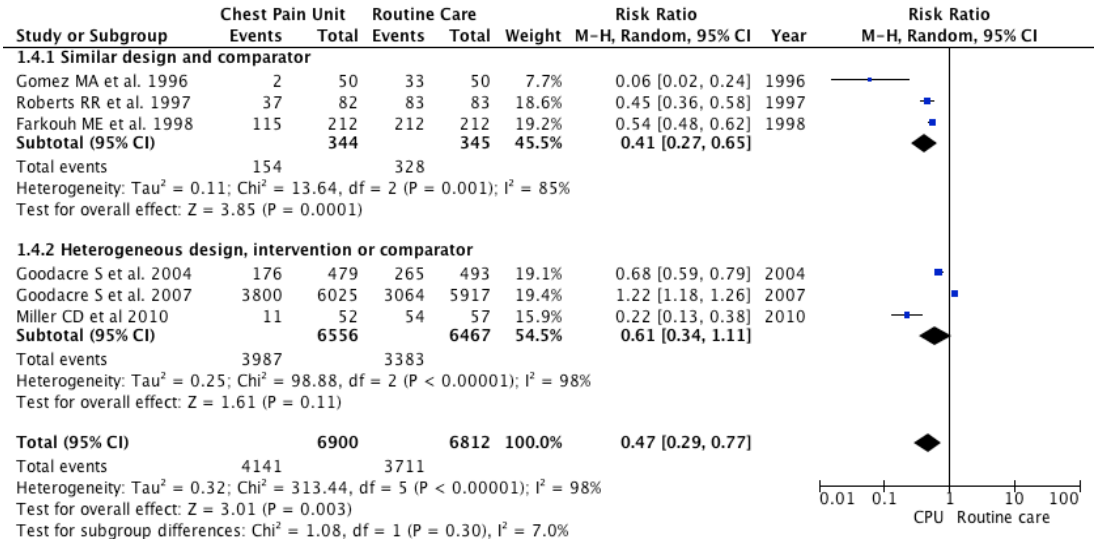
Appendix 2

The forest plot of relative risks of hospital admission. Subgroups were defined according to the use of fixed or variable admission rates in the comparator arm of the trial. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.



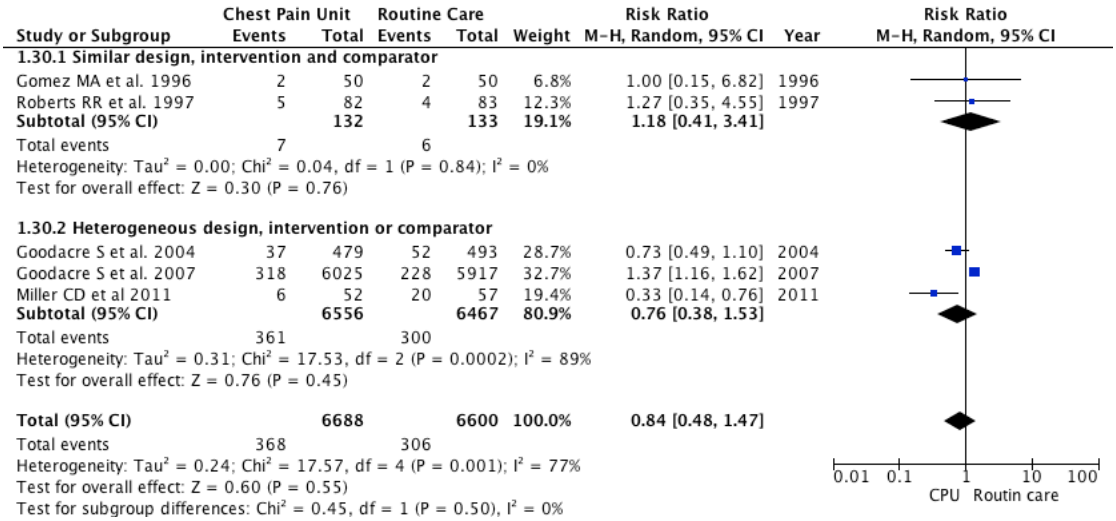
Appendix 3

The forest plot of relative risks of hospital admission. Subgroups were defined according to similarities in trial design and in choices of interventions and comparators. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.



Appendix 4

The forest plot of relative risks of hospital readmission. Subgroups were defined according to similarities in trial design and in choices of interventions and comparators. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.



Resumo em Português – Artigo 2

Antecedentes: Apesar de sua ampla utilização, a eficácia de unidades de dor torácica (UDT) na avaliação e tratamento de pacientes com síndrome coronariana aguda sem elevação de ST (SCASSST) de risco baixo a intermediário permanece obscura. **Objetivo**: Avaliar a eficácia clínica e a utilização de recursos nas UDT em relação à hospitalização de rotina no atendimento à SCASSST. **Métodos**: Uma revisão sistemática da literatura para identificar ensaios clínicos randomizados comparando UDT à hospitalização de rotina foi realizada nas bases de dados MEDLINE, EMBASE e Cochrane CENTRAL. A seleção dos estudos e a extração de dados foi realizada por dois revisores independentes. A qualidade das evidências foi avaliada de acordo com o Manual Cochrane de Revisões Sistemáticas de intervenções. As evidências diretas foram comparadas através de metanálise de efeitos aleatórios. A medida de efeito calculada para desfechos binários foi a razão de riscos, enquanto diferença média ponderada foi utilizada para o tempo de internação hospitalar, em horas. **Resultados**: Sete artigos completos foram incluídos na síntese descritiva de evidências, dos quais 6 foram incluídos na metanálise. Comparado à hospitalização de rotina, o atendimento na UDT esteve associado a uma redução nas taxas de hospitalização (RR 0,47; 0,29-0,77), tempo de internação hospitalar (-8.74h; -16,92 a -0,55), necessidade de cineangiocoronariografia no seguimento (RR 0,22; 0,05-0,86) e taxa de procedimentos de revascularização em geral (RR 0,30; 0,09-0,96). Não houve diferença na mortalidade ou nas taxas de eventos cardiovasculares. **Conclusão:** Os dados disponíveis indicam que o atendimento na UDT pode reduzir a utilização de recursos em comparação com a

hospitalização de rotina, sem impacto na mortalidade ou nas taxas de eventos. Novos estudos, desenhados para avaliar as UDT na era atual de estratégias modernas para a estratificação de risco são necessários.

Palavras-chave: unidade de dor no peito, síndrome coronariana aguda, revisão sistemática, metanálise

Artigo 3

Systematic review of economic evaluations of units dedicated to acute coronary syndromes

Revisão sistemática de avaliações econômicas de unidades dedicadas no atendimento às síndromes coronarianas agudas

André Luís Ferreira da Silva, Doutorando em Epidemiologia pela UFRGS;

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

A ser enviado para publicação.

Systematic review of economic evaluations of units dedicated to acute coronary syndromes

André Luís Ferreira-Da-Silva[1,2], MD, MSc; Silvana Perini[2], MSc; Pedro Henrique Rigotti Soares[2], MD; Carisi Anne Polanczyk[1,3,4], MD, ScD.

1. Graduate Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre

2. Hospital de Clinicas de Porto Alegre

3. Graduate Program in Cardiology and Cardiovascular Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

4. Cardiovascular Division of Hospital de Clínicas de Porto Alegre.

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Abstract

Background: Economic evaluations are increasingly required in the policy decision-making process. Several studies assessed dedicated units for the care of suspected or confirmed acute coronary syndrome (ACS), such as chest pain units (CPUs) and coronary care units (CCUs) in respects of their economic impact. However, their results have not been systematically presented and compared. **Objective:** To identify, summarize and compare the economic outcomes of studies on hospital units dedicated to the initial care of suspected or confirmed acute coronary syndrome patients. **Methods:** Systematic review of literature to identify economic evaluations of CPUs, CCUs or equivalent units. Two search strategies were used. The first one aimed to identify economic evaluations irrespective of study design and the second one to identify randomized clinical trials that reported economic outcomes. The following databases were searched: MEDLINE, EMBASE, Cochrane CENTRAL and NHS-EED. A sensitive search strategy was built using MeSH terms, Emtree terms and text words. Data extraction was performed by two independent reviewers. Cost estimates were inflated to 2012 values. **Results:** Search strategies retrieved five partial economic evaluations based on observational studies, six randomized clinical trials that reported economic outcomes and five model-based economic evaluations. Overall, cost estimates based on observational studies and randomized clinical trials reported statistically significant cost-savings of more than 50% with the adoption of CPU care instead of routine hospitalization or CCU care for suspected low-to-intermediate risk ACS patients (median per-patient cost, U$ 1,970, range U$ 1,002 - U$ 13,799). Model based economic evaluations reported incremental cost-effectiveness ratios below U$ 50,000 / QALY for all comparisons between Intermediate care unit, CPU or CCU with routine hospital admissions; however, this finding was sensible to patient probability of myocardial infarction. **Conclusion:** Published economic evaluations indicate that more intensive care is likely to be cost-effective in comparison to routine hospital admission for suspected ACS patients.

Keywords: systematic review; economic evaluations; chest pain units; coronary care units

Introduction

Chest pain units (CPUs) and coronary care units (CCUs) have evolved since the decade of 1960 as alternatives to conventional hospital admission for patients with suspected or confirmed acute coronary syndrome (ACS).[1-4] Such units have incorporated progresses in chest pain evaluation and in ACS management, such as protocol oriented drug administration, cardiac monitoring, serial ECG, serial measurements of cardiac biomarkers, systematic use of non-invasive tests for indeterminate cases, prompt access to cardiac catheterization laboratory and to reperfusion therapies when indicated.[5,6]

Both observational studies and clinical trials have compared the effects of dedicated units on clinical and economical outcomes in comparison to other dedicated units or to routine emergency department evaluation and subsequent hospitalization.[7-14] Based on the results of individual studies, it is generally accepted that dedicated units are capable of reducing resource utilization without adversely affecting the outcomes of these patients[6,10,15].

There are two types of healthcare economical evaluations in the published literature: those based on primary data, either form observational or experimental studies, and decision analytic models assembled usually from systematic gathering of information from many sources.[16,17] The latter has become increasingly accepted as the standard for full economic evaluations.[18,19]

Systematic reviews of economic evaluations have had its utility questioned in recent years. In fact, decision analytic models are usually designed to represent a healthcare system's

particular circumstances. This limits the external validity of economic models, which renders systematic reviews of economic evaluations unlikely to be useful in many instances.[17,20,21]

However, economic evaluation of systems of care and complex interventions, such as dedicated units for ACS is challenging. As such, knowledge of existing approaches for decision-analytic economic evaluations in this field is valuable to health policy decisions and to the development of future studies.[16,22]

The purposes of the present review are: (1) to identify and summarize economic evaluations of CCUs, CPUs and equivalent units; and (2) to inform the development of novel decision analytical models on the subject of the cost-effectiveness of units dedicated to the care of ACS.

Methods

Search strategy

We aimed to identify economic evaluations of closed units dedicated to the care of ACS within or adjacent to the emergency department. Two search strategies were devised; the first one to identify economic evaluations irrespective of study design, and the second one to identify randomized controlled trials that reported economic outcomes of such units.

Search for economic evaluations in general included the following electronic bibliographic databases: Medline (1966-November 2012), Embase (1988- November 2012) and NHS-Economic Evaluation Database (NHS-EED). Search for clinical trials was performed in Medline, Embase, Cochrane Central and Clinical Trials.org. There was no language restriction.

Appropriate search terms were used to identify studies on ACS in general, myocardial infarction or unstable angina. Multiple keyword sets were used to maximize results from the searches. Additional hand search from the reference lists of the selected articles was performed.

Strategies and sites of care that have been considered for the initial evaluation and management of acute coronary syndromes included: CCUs, CPUs, intermediate care units, general medical ward ("routine care" or "routine hospital admission"), and outpatient clinic. Despite some overlapping characteristics, CCU refers to more intensive and specialized care delivered preferentially to higher risk (TIMI risk score >4) ACS patients, whereas CPU refers to less intensive and specialized care designed for observation and risk stratification of lower risk suspected ACS patients. The intermediate care units usually offer care comparable to that of CPU, however they are not exclusive for suspected ACS patients. In the past, outpatient care and admission to the general medical ward were both considered acceptable options for the initial evaluation and management of suspected ACS patients, which has lead to the inclusion of these two settings in some economic evaluations.

In order to maximize search sensitivity in identifying the intervention of interest, the following terms were used in the search strategy: coronary care unit, coronary unit, coronary care observation unit, cardiac observation unit, chest pain unit, chest pain center and chest pain observation unit.

We defined the following inclusion criterion for formal review:

- Type of units evaluated: studies on units dedicated to the care of suspected or confirmed ACS; (2) cardiac monitoring capability; (3) dedicated staff;
- Type of studies: economical evaluations of any type.

To identify economic evaluation studies, we have used the NHS Economic Evaluation Database (NHS EED) search filter for Medline and Embase, which have been reported to yield a sensitivity of 99%.[21] The complete search strategy for economical evaluations used in Medline (Ovid) is presented in table 1. A similar search strategy was used in Embase.

Additionally, a highly sensitive string of words proposed by Haynes RB et al was used in the search for randomized controlled trials.[23]

Data abstraction and analysis

Data abstraction was performed by two independent reviewers (ALFS and SP). Disagreements were resolved by consensus. Data abstraction instrument included the following items: publication year, country, location of unit (within or adjacent to the ED), target population (suspected ACS in general, high versus low risk patients), number of beds, available resources, staffing characteristics, comparator interventions, modeling techniques, costing and cost-effectiveness estimates.

As model-based economic evaluations are themselves synthesis studies, we considered inadequate to employ techniques of traditional meta-analysis or the pooling of aggregate results from such studies.

Currency conversion and inflation adjustment

Original and inflation-adjusted cost estimates are presented. Dollar values were inflated to 2012 dollar value according to average US consumer price index for a given year. Values in other

currencies (sterling pounds and euros) were presented as originally reported, as well as converted to dollars. Inflation adjustment to average 2012 values was made with average annual consumer price index for the respective currency and country.

Quality assessment

We used the 10-item Drummond checklist to evaluate the methodological quality of the economic evaluation studies. However, no study was excluded from the present review on the basis of quality assessment.

Results

The search strategy for economic evaluations yielded 435 references after removal of duplicate records. Twelve papers were selected for full text assessment: five partial economic evaluations based on observational studies (cost studies), five model-based economic evaluations, and two randomized controlled trials in overlap with the second search strategy. [3,24-32] The study selection flowchart for economic evaluations is shown in Figure 1.

The search strategy for randomized clinical trials yielded 3,393 references after removal of duplicate records. Seven trials were identified and six of them reported economic outcomes.[9-13,33] The study selection flowchart for economic evaluations is shown in Figure 2.

Quality assessment

No study received "yes" in all items from the methodological quality checklist. Overall, those economic evaluations based on observational or on randomized trial data performed poorly, with no incremental or sensitivity analysis in most studies. Among the randomized trials, the study by Goodacre et al (2004) was the one with better overall quality assessment, having performed an incremental cost-utility analysis. However, discounting and sensitivity analysis were missing, as in the other clinical trials. With respect to the model-based economic evaluations, the work by Cretin et al was the one best ranked, having fulfilled 9 out of 10 of the quality assessment items. However, this study failed to report an incremental analysis. Other model-based studies presented limitations regarding their intervention's effectiveness. This was assumed to be effective either based on data from a single source or assumed to be effective based on expected benefits of CCUs or CPUs. The study by Oluboyede et al was based on data from the ESCAPE trial, which did not assessed clinical outcomes and failed to show benefit of CPUs in resource utilization. In conclusion, studies were either classified as low overall methodological quality or presented limitations related to unproved assumptions on their intervention's benefits. Quality checklist is presented in table 2.

Economic evaluations based on observational studies

Five partial economic evaluations based on primary observational data were identified.[3,29,31,32,34] With the exception of the study by Bloom et al, which described costs of CCU care among higher risk patients (confirmed MI in 50% of patients), all partial economic evaluation reported positive economic consequences of the adoption of CPU care among lower risk chest pain patients.[3] Median cost per-patient estimates were U$ 1,689 for the CPU strategy, U$ 5785 for the CCU strategy and U$ 5,560 for the hospital admission strategy (dollars, 2012). Table 3 presents characteristics and results of the economic evaluations based on observational studies. All comparative cost analyses reported savings from the adoption of a CPU in comparison to hospital admission or other dedicated units (Table 4).

Economic evaluations based on randomized clinical trials

Six randomized controlled trials have reported economic outcomes.[9-13,33] Five trials compared a CPU strategy with hospital admission and one trial compared CPU care with CCU care in initial assessment of suspected, low-to-intermediate risk suspected ACS patients.[9] In general, patient inclusion and exclusion criteria were similar among studies, with the recruitment of adult patients presenting to the ED with acute onset chest pain, excluding patients with ST elevation or depression, new onset left bundle branch block, arrhythmias, alternative diagnosis or patients with clinical instability. In the identified trials, CPU strategy consisted on a limited observation period, with serial ECGs and measurement of cardiac biomarkers, followed by a non-invasive risk-stratification test for undefined cases.

Only the study by Goodacre et al has included a full economic evaluation, which consisted of a cost-utility analysis with quality of life estimated from trial participants as measured by the EQ-5D score. The authors reported a statistically significant reduction in the proportion of hospitalization favoring the CPU (36.7% versus 53.8%) in comparison to routine care by ED staff. In addition to that, there was a 0.0137 increase in the quality adjusted life years (QALY) also in favor of the CPOU group. There were no significant differences in mortality or cardiovascular events rates between the studied groups during the in-hospital period and the 180 days follow-up. Calculated incremental cost-utility ratio was £ 2,750 / QALY (U$ 5,279 / QALY).[10]

Economic outcomes in the other clinical trials were restricted to cost estimation or resource utilization. Median cost per-patient estimates were U$ 2,178 for the CPU strategy and U$ 2,951 for the hospital admission strategy. The study by Conti et al has estimated the per-patient cost of the CCU strategy in U$ 13,939 (dollars, 2012). Table 5 presents characteristics and results of economic evaluations based on randomized clinical trials.

Model-based full economic evaluations

In 4 out of the 5 model-based economic evaluations, a CCU based strategy was the main health technology in evaluation.[24-27] A CPU based strategy was evaluated only in the study by Oluboyede et al.[28] Comparators included routine hospitalization (3 studies), outpatient care (2 studies) and a hypercholesterolemia screening program (1 study). Modeling methods included decision trees (4 studies) and a Markov model (1 study). Only one study was a cost-utility analysis, the remainder being cost-effectiveness analyses. Table 6 presents characteristics and results of the identified decision-analytic models.

Adjusting for inflation (dollars, 2012), the incremental cost-effectiveness ratio (ICER) of CCU care relative to hospital admission was estimated to be between U$ 11,624 /life year gained (LYG) and U$ 89,556 / LYG. The reported adjusted ICER for CCU care versus intermediate unit care varied from U$ 73,166 to U$ 307,157 / LYG. As for CPU care in relation to hospital admission, the work by Oluboyede et al reported an incremental cost-utility ration of U$ 40,944 / QALY. Incremental estimates were subjected to a significant level of uncertainty regarding assumptions on target-population characteristics and sources of CCU or CPU benefits. In general, target population MI risk of 21% or greater was required to attain cost-effectiveness estimates below U$ 50,000 per QALY or LYG in the original publication (corresponding to U$ 73,166 per QALY or LYG in 2012 dollars).

Discussion

In the present review, we were able to identify a number of economic evaluations designed to compare different settings for the care of acute coronary conditions.

Partial economic evaluations indicated cost reductions with the adoption of a more intensive setting for initial assessment of suspected ACSs. However, cost reductions alone are insufficient to drive healthcare policy decisions because cost comparison studies fail to compare the effectiveness and safety of the compared interventions. Yet some authors of partial economic evaluations unfortunately assumed equal effectiveness and concluded the evaluated intervention to be "cost-effective" or "less costly and as effective as" comparators interventions.

Randomized controlled trials provide an excellent opportunity for resource utilization and costing data collection, as well as for measuring quality of life in trial participants. Such information might be combined with trial's safety and effectiveness outcomes in a model-based economic evaluation. An economic evaluation based on robust trial data would allow more reliable extrapolation of long-term costs and consequences of trial interventions. In this review, only the study by Oluboyede et al have attempted such strategy, with decision-analytic model parameters primarily derived from the ESCAPE trial. The latter was a cluster-randomized trial that compared CPU care to routine hospital admission in 14 hospitals in the United Kingdom, published by Goodacre and others in 2007.[8,37-39] Unfortunately, this resulted in a questionable economic evaluation, the reasons being twofold: (1) most of the ESCAPE trial derived data were unpublished (for instance, the trial excluded STEMI patients, yet the proportion of STEMI among suspected ACS and STEMI mortality estimates derived from trial enrollment); and (2) the ESCAPE trial was negative regarding favorable effects of the CPU.

A previous clinical trial published by Goodacre et al in 2004 provided the best randomized trial-based economic evaluation of CPU care in comparison to routine hospital admission. This was a cost-utility analysis with no modeling. CPU's benefits derived from the observed reduction in the proportion of hospitalization and increased health utility among CPU-treated patients. The ESCAPE trial was an attempt to implement the CPU model from the 2004 trial in larger scale, however results were conflicting. In a later paper, authors acknowledge difficulties that might have prevented successful implementation of CPUs in other hospitals in the ESCAPE trial. Thus, we believe the cost-effectiveness estimate from the 2004 trial to be a valid one, however its external validity is yet to be proven.

Model-based economic evaluations were ingeniously designed in attempts to capture the different levels of complexity of dedicated units and other strategies for initial assessment of suspected ACS. For instance, the Markov model by Cretin et al was devised to provide higher-level cost-effectiveness estimates though strategies that acted in different moments of myocardial infarction's natural history.

Conversely, the decision tree conceived by Fineberg et al and later adapted by Wears et al, attempted to capture benefits of CCU care arising from the patient level through the assumption of reduced mortality with prophylactic and therapeutic effect of lidocaine in the risk of death in MI patients, an assumption later known to be incorrect, which rendered those models and their cost-effectiveness estimates unreliable. This illustrates the need to be careful on modeling clinical events as a result of intermediate markers of disease or processes that may not be completely understood.

Perhaps the most reliable among the identified decision-analytic models is the decision tree developed by Tosteson et al. These authors estimated the incremental cost-effectiveness of admitting suspected MI patients to either a CCU or an intermediate care unit. Clinical probabilities of events and resource utilization data were derived from a cohort of 12,139 patients through a logistic regression model. Median total costs were calculated from hospital charges. As for the main effectiveness outcome of survival, life expectancy was estimated from the 1987 United States life table, which was adapted to consider the excess mortality from MI when appropriate. In order to take into account the observed variation in MI probability among chest pain patients, the cost effectiveness estimates were calculated for five different age groups (30-44; 45-54; 55-64; 65-75 and ≥ 75years old). In addition to that, the model was separated in

two parts: the first 48h from admission and the next 48h. This approach allowed consideration of differences in the probabilities of death or complications between these time periods, though it made the model unsuited to test assumptions on length of stay. Another limitation of this model were the somewhat empirical classification of complications in four levels of severity and the assumption of an excess mortality of 15% in the intermediate-care unit as compared to the CCU, an assumption that was not supported by clinical data. The authors concluded that, in comparison with the intermediate-care unit, the CCU as the initial level of care for chest pain patients would yield an ICER ratio of U$50,000 per year-of-life-saved only from a 23% probability of MI in patients aged 65 years or more. In the sensitivity analysis, a MI probability of at least 12% was required to obtain the same ICER in other age groups.

Two limitations were common to all models. First, with the exception of the model by Oluboyede et al, no distinction was made between STEMI and NSTEACS, with the whole cohort of simulated patients consisting basically of healthy individuals, patients experiencing a MI and individuals with one or more previous MIs. This simplification leads to important consequences, such as not taken into account different risk profiles of patients with suspected or confirmed ACSs and the lack of model representation of reperfusion strategies and risk stratification strategies, with associated costs. Second, all models assumed a scenario of unconstrained resources. For instance, while this assumption facilitates the comparison of different strategies under the same "ideal" situation, on the other hand it is openly unrealistic, failing to capture the costs and clinical consequences of waits for a therapeutic or diagnostic resource.

The need for fitting available data partially explains researchers' choice for simpler models. Despite limitations inherent to the state of knowledge on occasion of model

development, the structure and the intrinsic logic of some of the identified models remain valid and could be updated to the study of current dilemmas on higher-level resource allocation regarding dedicated hospital units. Alternatively, more elaborate model approaches, such as Markov model based microsimulation and discrete event simulations (DES) would be able to more accurately take into account and compare factors influencing the outcomes, resource utilization and costs in the management of ACS, while accounting for time and resources constrains.[22,40-42]

Limitations

This systematic review presents some limitations that deserve mention. First, the definition of the interventions to be evaluated has the disadvantage of widening the scope of the research question, making it difficult to conjointly describe and compare the outcomes of the different types of dedicated units found in the literature. Second, despite our effort to adjust cost estimates for inflation, we could not adjust values for deflation or inflation specifically associated to costs of some health technologies in the past 30 years. Third, considering the expanse of time covered by the included studies (more than 30 years), the extremely significant progresses in the management of suspected or confirmed ACSs observed in this period renders inappropriate a direct comparison of a dedicated unit from the 80's or 90's with its contemporary counterpart. Unfortunately, the only way to deal with this limitation would be to exclude older studies from this review, which we chose not to do in order to make possible a historical perspective that could provide insights for future research. Finally, publication bias cannot be excluded as virtually

all economic evaluations concluded the studied unit to be cost-effective in comparison to routine hospitalization.

Conclusion

In general, more intensive and standardized assessment of chest pain patients in CPUs presented equivalent or lower costs then strategies based on universal hospitalization with unstandardized evaluation. This potential for cost reduction derived from lower hospital admission rates, shorter length-of-hospital stay and lower consumption of diagnostic tests and other hospital resources. Mortality and event rates appear not to be affected by initial evaluation setting in low-to-intermediate risk suspected ACS patients. Regarding intermediate care units and CCUs, improved health outcomes are associated with increased costs, and incremental cost-effectiveness estimates were sensible to patient probability of MI, being less favorable for younger patients and for those whose probability of MI is below 21 to 24%. There are scarce economic evaluations in the past 10 years on the subjects of dedicated units and initial strategies for evaluation of suspected ACS patients. New studies are required in order to incorporate costs and consequences of recent advances in risk stratification.

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Tables

Table 1 - Economic evaluation search strategy for Medline (Ovid). Search results as retrieved on November 13th 2012. A similar strategy was used in Embase.

#	Search terms	Results
1	economics/	26658
2	exp "costs and cost analysis"/	169788
3	economics, dental/	1862
4	exp "economics, hospital"/	18409
5	economics, medical/	8504
6	economics, nursing/	3899
7	economics, pharmaceutical/	2385
8	(economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.	378249
9	(expenditure$ not energy).ti,ab.	15649
10	(value adj1 money).ti,ab.	18
11	budget$.ti,ab.	15829
12	or/1-11	497241
13	((energy or oxygen) adj cost).ti,ab.	2483
14	(metabolic adj cost).ti,ab.	669
15	((energy or oxygen) adj expenditure).ti,ab.	14695
16	or/13-15	17196
17	12 not 16	493398
18	"acute coronary syndrom$".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	15381
19	"myocardial infarction".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	172981
20	"unstable angina".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	10076

21	or/18-20	183916
22	"coronary uni$".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	285
23	"coronary care uni$".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	6166
24	"coronary care observation uni$".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	0
25	"coronary observation unit".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	3
26	"chest pain unit".mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	132
27	or/22-26	6454
28	17 and 21 and 27	194

Table 2 - Quality assessment of economic evaluations

Study	Well-defined question	Comprehensive description of the competing alternatives	Evidence that programme's effectiveness established	All relevant outcomes and costs for each alternative identified	Outcomes and costs measured accurately in appropriate units	Outcomes and costs valued credibly	Discounting for outcomes and costs	Incremental analysis	Sensitivity analysis	Conclusions justified by the evidence
Bloom et al	Yes	No	No	No	Yes	Yes	No	No	No	Yes
De Leon Jr et al	No	Yes	No	No	Yes	Yes	No	No	No	Yes
Gaspoz et al	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes
Goodacre et al (2001)	Yes	No	No	Yes	Yes	Yes	No	No	No	Yes
Shah et al	Yes	No	No	No	No	No	No	No	No	No
Gomez et al	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No
Roberts et al	Yes	Yes	No	Yes	Yes	Yes	No	No	No	Yes
Farkouh et al	Yes	Yes	No	Yes	No	Can't tell	No	No	No	Yes
Goodacre et al (2004)	Yes	Yes	No	Yes	Yes	Yes	No	Yes	No	Yes
Conti et al	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No
Miller et al	Yes	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes
Cretin et al	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Fineberg et al	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Wears et al	Yes	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes
Tosteson et al	Yes	No	Can't tell	Can't tell	Yes	Yes	No	Yes	Yes	Yes
Oluboyede et al	Yes	No	Can't tell	Can't tell	Yes	Can't tell	Can't tell	Yes	Yes	Yes

Table 3 - Economic evaluations based on observational studies (partial economic evaluations)

Author	Year	Type of unit	Patients	Type of Economic Evaluation	Original Amount	Inflation adjusted amount (2012) *	Meaning
Bloom et al	1973	CCU	37,844 patients admitted to CCUs (50% confirmed MI)	Cost analysis	U$ 4,491,552 U$ 560.39	U$ 23,225,977 U$ 2,897.8	Overall expenditures among CCUs in 32 hospitals (CCU) in 12 months; average of U$ 140,361 per hospital (dollars from year 1973) or U$ 725,815.78 per hospital (dollars from year 2012) CCU, average cost per patient
De Leon Jr et al	1979	CPU	495 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (6% confirmed MI)	Cost analysis	U$ 598 U$ 3,103	U$ 1,891.15 U$ 9,813.09	CPU, average cost per patient Hospital admission, average cost per patient
Gaspoz et al	1994	CCU, CPU, Stepdown unit	592 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (3% confirmed MI)	Cost analysis	U$ 1,318 U$ 3,589 U$ 2,749 U$ 5,598	U$ 2,041.87 U$ 5,560.14 U$ 4,258.8 U$ 8,672.52	CPU, average cost per patient Routine hospitalization, average cost per patient Step-down unit, average cost per patient CCU, average cost per patient
Goodacre et al	2001	CPU	106 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (7.5% confirmed MI)	Cost analysis	U$ 773 U$ 570	U$ 1,002.12 U$ 738.95	CPU, average cost per patient (including cardiac catheterization laboratory expenses) CPU, average cost per patient (excluding cardiac catheterization expenditures

Shah et al	2012	CPU	202 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol	Cost analysis	U$ 1,487.76	U$ 1,487.76	CPU, average cost per patient
					U$ 3,145.54	U$ 3,145.54	Routine hospitalization, average cost per patient

CP, chest pain; AMIsch, acute myocardial ischemia; CCU, coronary care units; CPU chest pain unit;

* US Dollar adjustment, average consumer price index for a given calendar year

Table 4 - Expected cost-savings from replacing routine hospital admissions for CPU care among patients with suspected ACS, data from observational studies

Study	Intervention	Comparator	Estimated average cost-savings per patient from CPU adoption
De Leon Jr et al, 1979	CPU U$ 598	Hospital admission U$ 3,103	- 80.72 %
Gaspoz et al, 1994	CPU U$ 1,318	Hospital admission U$ 3,589 Stepdown unit U$ 2,749 CCU U$ 5,598	- 63.27 % - 52 % -76.45 %
Shah et al, 2012	CPU U$ 1,487.76	Hospital admission U$ 3,145.54	-52.7 %

CCU, coronary care units; CPU chest pain unit.

Table 5 - Economic Outcomes of randomized clinical trials comparing CPU care with routine hospitalization or CCU care

Study	Year	Comparison	Patients	Type of Economic Evaluation	Original Amount	Inflation Adjusted Amount (2012)*	Meaning
Gomez et al	1996	CPU versus Hospital admission	100 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (2% confirmed MI)	Cost analysis alongside RCT	U$ 1,297 U$ 5,719	U$ 1,897.92 U$ 8,368.69	CPU, average cost per patient Routine Hospitalization, average cost per patient
Roberts et al	1998	CPU versus Hospital admission	165 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (4.5% confirmed MI)	Cost analysis alongside RCT	U$ 1,528 U$ 2,095	U$ 2,185.79 U$ 2,950.92	CPU, average cost per patient Internal medicine telemetry unit, average cost per patient
Farkouh et al	1998	CPU versus Hospital admission	424 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (2.4% confirmed MI)	Resource utilization analysis alongside RCT	RBRVU**	RBRVU**	61% increment on cost for patients in the hospital admission group relative to the CPU group - statistically significant difference in resource utilization
Goodacre et al	2004	CPU versus Hospital admission	972 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (7.2% confirmed MI in follow-up)	Cost-utility analysis	£ 2,750 (U$ 5,279)	£ 3,468.72 (U$ 6,416.23)	£(U$)/QALY, 95% probability of cost-utility estimate equal or lower then this figure (based on 1000 bootstrap estimates)
Conti et al	2005	CPU versus CCU	210 CP patients without ECG evidence of AMIsch, admitted for ruling out protocol (1.4% confirmed MI)	Cost analysis alongside RCT	€ 9,913 (U$ 11,738) € 12,056 (U$14,275.56)	€ 11,461.23 (U$ 13,799.15) € 16,782.3 (U$ 13,938.93)	CPU, average cost per patient CCU, average cost per patient
Miller et al	2010	CPU versus	110 CP patients without ECG	Cost analysis	U$ 2,062	U$ 2,171.11	OU-CMR, average cost per patient

	Hospital admission	evidence of AMIsch, admitted for ruling out protocol (3.6% confirmed MI)	alongside RCT	U$ 2,680	U$ 2,821.81	Routine Hospitalization, average cost per patient

CP, chest pain; AMIsch, acute myocardial ischemia; CCU, coronary care units; CPU chest pain unit; OU-CMR, observation unit with cardiac magnetic resonance.

* US Dollar adjustment, average consumer price index for a given calendar year; Sterling Pound adjustment, UK composite price index (December 2004 - December 2012); Euro adjustment, European Union consumer price index (December 2004 - December 2012).** Resource-based relative value units

Table 6 - Summary of model-based economic evaluations

Study	Year	Comparison	Type of Economic Evaluation and Model	Perspective	Costs / Discounting	Original ACER / ICER / ICUR	Inflation Adjusted ACER / ICER / ICUR (2012)*	Meaning
Cretin et al	1977	- CCU ** - M-CCU ** - Hypercholesterolemia screening **	Cost-effectiveness analysis Markov	Healthcare system (not stated)	Direct and indirect costs, 5% discount rate	U$ 3,068 U$ 4,310 U$ 12,640	U$ 11,623.67 U$ 16,329.21 U$ 47,888.91	$/LYG (ACER) $/LYG (ACER) $/LYG (ACER)
Fineberg et al	1984	- Intermediate unit versus Routine hospital admission - CCU versus Intermediate unit - Routine hospital admission versus Outpatient care - Intermediate unit versus Outpatient Care	Cost-effectiveness analysis Decision Tree	Hospital	Direct costs, discount rate not reported	U$ 43,000 U$ 139,000 U$ 283,000 U$ 108,000	U$ 95,019.65 U$ 307,156.55 U$ 625,361.91 U$ 238,654.01	$/LYG (ICER) $/LYG (ICER) $/LYG (ICER) $/LYG (ICER)
Wears et al	1989	- Intermediate unit versus Routine hospital admission - CCU versus Intermediate unit - CCU versus Routine hospital admission	Cost-effectiveness analysis Decision Tree	Hospital	Direct costs, discount rate not reported	U$ 50,073 U$ 42, 099 U$ 48,368	U$ 92,713.39 U$ 77, 949.01 U$ 89,556.47	$/LYG given a MI probability ≥ 24% (ICER) $/LYG given a MI probability ≥ 24% (ICER) $/LYG given a MI probability ≥ 24% (ICER)
Tosteson et al	1996	- CCU versus Intermediate unit	Cost-effectiveness analysis Decision Tree	Hospital	Direct costs, discount rate not reported	U$ 50,000	U$ 73,165.71	$/LYG given a MI probability ≥ 21% for ages 65 to 70 and ≥ 57% for ages 30-44 (ICER)

Oluboyede et al	2008	- CPU versus Routine hospital admission	Cost-utility analysis Decision Tree	Hospital / Healthcare system	Direct costs, discounting applied, rate not reported	£ 20,000 (U$ 38,395.82)	£ 22,831.05 (U$ 40,944.39)	£(U$)/QALY - 70% probability of attaining an ICER ≤ £20000 / QALY (original value) with adoption of CPU (ICUR)

ICER, incremental cost-effectiveness ratio; ICUR, incremental cost-utility ratio; ACER, average cost effectiveness ratio; CCU, coronary care unit; M-CCU, mobile CCU; CPU, chest pain unit; LYG, life years gained; QALY, quality adjusted life years; NR, not reported; * US Dollar adjustment, average consumer price index for a given calendar year; Sterling Pound adjustment, UK composite price index (December 2004 - December 2012); Euro adjustment, European Union consumer price index (December 2004 - December 2012). ** No incremental estimate is provided; only the ACER is reported.

Artigo 3: Resumo em português

Contexto: As avaliações econômicas são cada vez mais necessárias no processo de tomada de decisão em políticas de saúde. Alguns estudos avaliaram as unidades dedicadas no atendimento à síndrome coronariana aguda (SCA) confirmada ou suspeita, tais como as unidades de dor torácica (UDTs) e as unidades de cuidados coronarianos (UCCs) a respeito de seu impacto econômico, entretanto seus resultados não foram sistematicamente apresentados e comparados. **Objetivo:** Identificar, resumir e comparar os resultados econômicos de estudos de unidades hospitalares dedicadas ao atendimento inicial de pacientes com síndrome coronariana aguda suspeita ou confirmada. **Métodos:** revisão sistemática da literatura para identificar as avaliações econômicas de UDT, UCC ou unidades equivalentes. Foram utilizadas duas estratégias de busca. A primeira teve como objetivo identificar as avaliações econômicas, independentemente do desenho do estudo; a segunda visava identificar ensaios clínicos randomizados que relataram os resultados econômicos. As seguintes bases de dados foram pesquisadas: Medline, Embase, Cochrane CENTRAL e NHS-EED. Uma estratégia de busca sensível foi construído usando termos de MeSH, Emtree e palavras do texto. A extração de dados foi realizada por dois revisores independentes. As estimativas de custos foram ajustadas para valores de 2012. **Resultados:** As estratégias de busca retomaram 5 avaliações econômicas parciais, baseadas em estudos observacionais, 6 ensaios clínicos randomizados que relataram desfechos econômicos e 5 avaliações econômicas baseadas em modelos. Em geral, as estimativas de custos baseadas em estudos observacionais e ensaios clínicos randomizados relataram redução de custos, estatisticamente significativas, de mais de 50% com a adoção de UDT em substituição à hospitalização ou cuidados de rotina ou UCC para pacientes com SCA de risco baixo a intermediário (curso médio por paciente, U$ 1.970, variação de U $ 1.002 - U $ 13.799). As avaliações econômicas baseadas em modelos relataram relações de custo-efetividade incremental abaixo de U $ 50.000 / QALY para todas as comparações entre as unidades de cuidados intermediários, CPU ou CCU com internações hospitalares de rotina. No entanto, este achado foi sensível à probabilidade de infarto do miocárdio. **Conclusão**: As avaliações econômicas publicadas indicam que o cuidado mais intensivo em unidades intermediárias

seja provavelmente custo-efetivo em comparação com a internação de rotina para pacientes com suspeita de SCA, porém essa relação é dependente da probabilidade de IAM na população avaliada.

Palavras-chave: revisão sistemática; avaliações econômicas; unidades de dor torácica; unidades coronarianas

7. **CONCLUSÕES E CONSIDERAÇÕES FINAIS**

A presente tese demonstrou que o conceito de Unidade Vascular vem apresentando um impacto positivo no tratamento das doenças vasculares agudas no Hospital de Clínicas de Porto Alegre, em especial às síndromes coronarianas agudas. Esse impacto vai além do efeito poupador de recursos que foi identificado como consequência do uso de Unidades de Dor Torácica nos Estados Unidos, no Reino Unido e na Itália. As razões para que conceitos aparentemente semelhantes de atendimento tenham repercussões clínicas tão diversas vão além da análise da composição e funcionamento desses sistemas de atendimento, ambos baseados na delimitação de uma área física, no uso de protocolos assistenciais e na presença de recursos humanos especificamente alocados.

Muito provavelmente, a queda de mortalidade determinada pela estratégia da UV provém do maior risco basal da população e do atendimento subótimo a que vinha sendo submetida na era do atendimento à SCA na emergência geral.

Considerando os estudos disponíveis sobre a efetividade da estratégia da UV e sobre a custo-efetividade de outras modalidades de unidades dedicadas ao atendimento inicial aos casos suspeitos e confirmados de síndromes coronarianas, algumas considerações podem ser feitas a respeito da adoção em larga escala de unidades dedicadas no Brasil.

As UCCs possuem a capacidade para atendimento a síndromes coronarianas agudas de maior complexidade, inclusive IAMST, porém requerem a presença de cardiologistas e estão associadas a um consumo de recursos que somente é considerado eficiente economicamente na avaliação de pacientes com risco basal de IAM superior a, pelo menos,

20%. Ou seja, os custos das UCCs somente se justificam no atendimento de pacientes triados por outros componentes do sistema de saúde, como o SE ou uma unidade de observação.

A evidência disponível sobre as UDTs indica a possibilidade de economia de recursos no atendimento a pacientes de risco baixo a intermediário, no entanto essas unidades não foram desenvolvidas para o atendimento a casos de maior complexidade, não sendo conhecidas suas características de eficácia, segurança e custo-efetividade para pacientes coronarianos de risco elevado. Portanto, a adoção do conceito estrito de UDTs no cenário brasileiro não estaria contemplando apropriadamente o conjunto dos pacientes com SCAs que atualmente procuram os SE convencionais e que acabam por ser atendidos em condições subótimas.

A estratégia da UV é de surgimento recente e não é tão bem estudada quanto as UDTs e as UCCs. Em relação a essas, possui a característica de impactar positivamente no atendimento a outras doenças vasculares agudas, além das SCAs, otimizando o aproveitamento de recursos hospitalares. Por outro lado, a UV surge como alternativa factível para a triagem inicial e o atendimento aos casos de SCA de todos os níveis de complexidade. No contexto dos SE brasileiros, o atendimento propiciado na UV parece ser capaz de reduzir o risco de morte em pacientes com SCA em geral, contudo esse benefício pode estar associado a um aumento no número de procedimentos de revascularização e a um maior risco de readmissão hospitalar.

Em relação ao atendimento da SCA, a implementação em larga-escala da estratégia UV poderá levar a uma demanda adicional por angiografias coronarianas, testes não-invasivos para isquemia miocárdica, atendimento ambulatorial especializado. Além disso, conforme demonstramos, a implementação da UV poderá aumentar a demanda de recursos

associados à avaliação do AVC e à fibrinólise para o AVC isquêmico. Ao criar uma UV, a instituição-sede converte-se em um centro de referência regional e poderá haver um incremento desproporcional na procura pelo SE por casos com suspeita de doença vascular aguda, além da demanda adicional por readmissões.

Por fim, deve-se considerar o substancial investimento inicial na criação da área física para a unidade dedicada, na aquisição de equipamentos que possibilitem atendimento de cuidados semi-intensivos, como a ventiladores mecânicos, bombas de infusão e leitos monitorizados. Adicionalmente, a contratação, a realocação e o treinamento de recursos humanos específicos para a nova unidade originarão grande parte do custo de manutenção de uma UV no longo prazo.

Idealmente, a atuação dos gestores dos sistemas de saúde público deveria ser centralizada nos determinantes socioeconômicos do estado de superlotação das emergências, bem como nos determinantes socio-econômico-biológicos das doenças cardiovasculares. Considerando que essa atuação sistêmica e etiológica certamente produzirá resultados benéficos mais provavelmente a longo prazo, parece-nos que a implantação em larga-escala de Unidades Vasculares possui maior potencial para efeito benéfico de curto prazo nas alarmantes taxas de mortalidade por doenças cardiovasculares observadas no Brasil.

ANEXOS

Anexo 1 - Lista dos 24 códigos CID-10 selecionados na execução das buscas eletrônicas nos sistemas de dados administrativos e de prontuários eletrônicos do Hospital de Clínicas de Porto Alegre

Code	Description
I20.0	Unstable angina
I20	Angina Pectoris
I20.1	Angina pectoris with documented spasm
I20.8	Other forms of angina pectoris
I20.9	Angina pectoris, unspecified
I21	Acute myocardial infarction
I21.0	Acute transmural myocardial infarction of anterior wall
I21.1	Acute transmural myocardial infarction of inferior wall
I21.2	Acute transmural myocardial infarction of other sites
I21.3	Acute transmural myocardial infarction of unspecified site
I21.4	Acute subendocardial myocardial infarction
I21.9	Acute myocardial infarction, unspecified
I22.0	Subsequent myocardial infarction
I22.1	Subsequent myocardial infarction of anterior wall
I22.8	Subsequent myocardial infarction of other sites
I22.9	Subsequent myocardial infarction of unspecified site
I24	Other acute ischaemic heart disease
I24.0	Coronary thombosisnot resulting in myocardial infarction
I24.8	Other forms of acute ischaemic heart disease
I24.9	Ischaemic heart disease, unspecified
I25.1	Atherosclerotic heart disease
I25.0	Atherosclerotic heart disease, so described
I25.6	Silent myocardial ischaemia
I25.5	Ischaemic cardiomyopathy

Anexo 2 - Figuras suplementares ao artigo 2

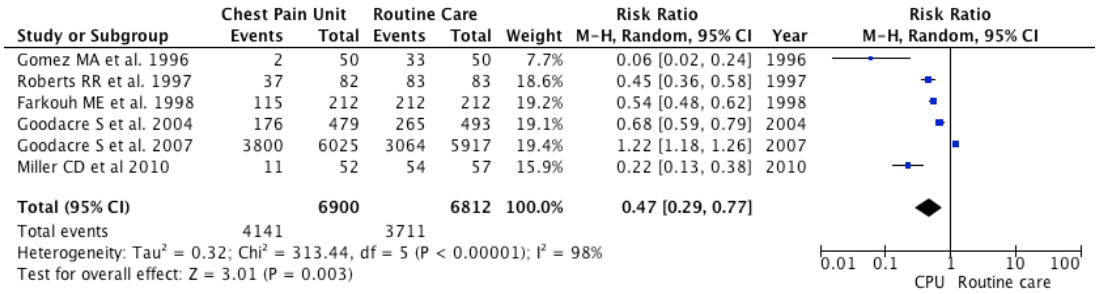

Figure 1: The forest plot of relative risks of hospital admission. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

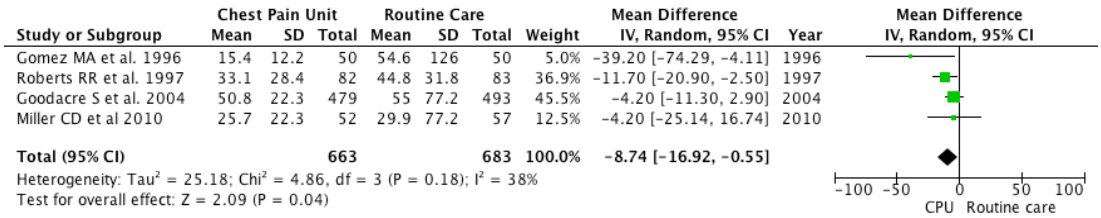

Figure 2: The forest plot of weighted mean difference of length of hospital stay (in hours). Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

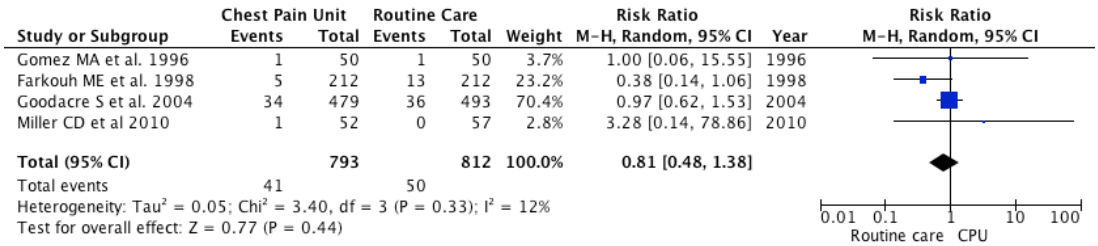

Figure 3: The forest plot of relative risks of confirmed myocardial infarction at index evaluation. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

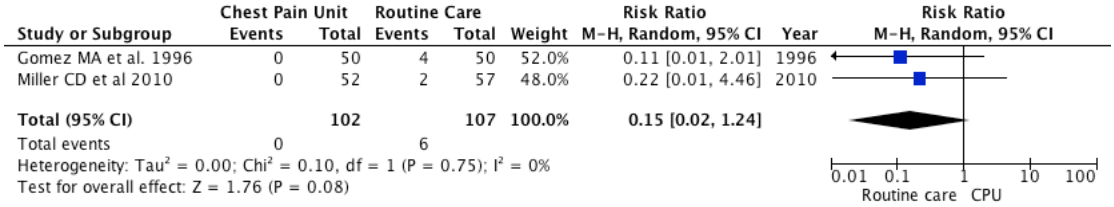

Figure 4: The forest plot of relative risks of diagnosed unstable angina at index evaluation. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

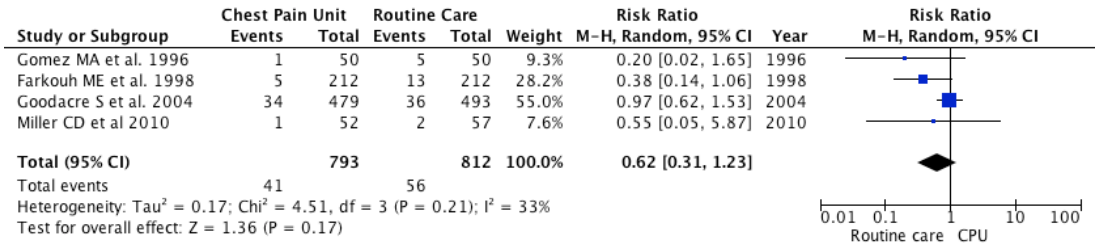

Figure 5: The forest plot of relative risks of diagnosed myocardial infarction or unstable angina at index evaluation. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

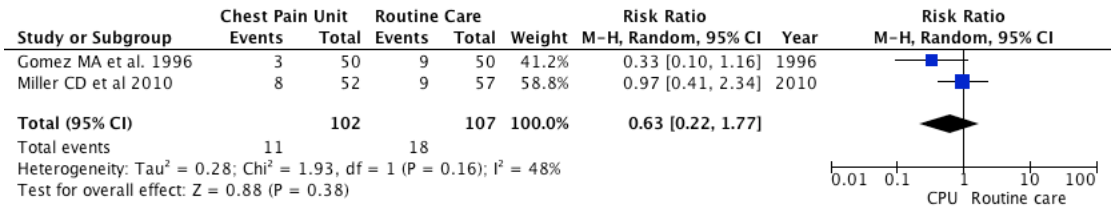

Figure 6: The forest plot of relative risks of angiographic studies performed at index evaluation. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

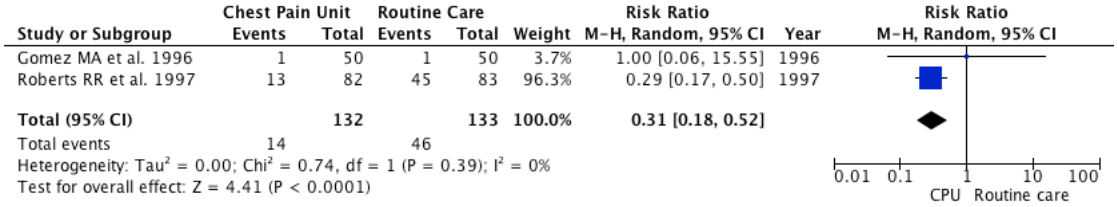

Figure 7: The forest plot of relative risks of indeterminate diagnosis at index evaluation. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

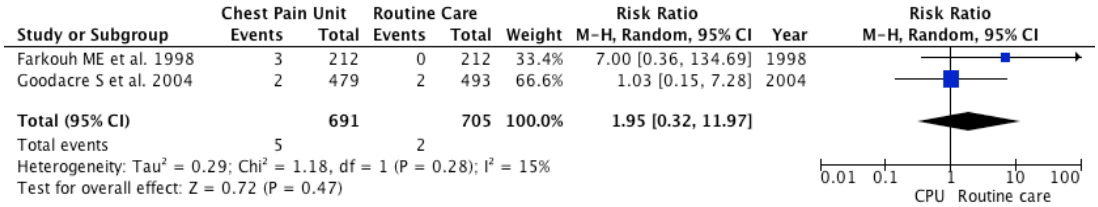

Figure 8: The forest plot of relative risks of 6 months follow-up mortality. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). The studies by Gomez et al[8], Roberts et al[10] and Miller et al[15] had no events in either arm and are, thus, not represented in the forest plot. Horizontal bars indicate 95% CIs; CPU, chest pain unit.

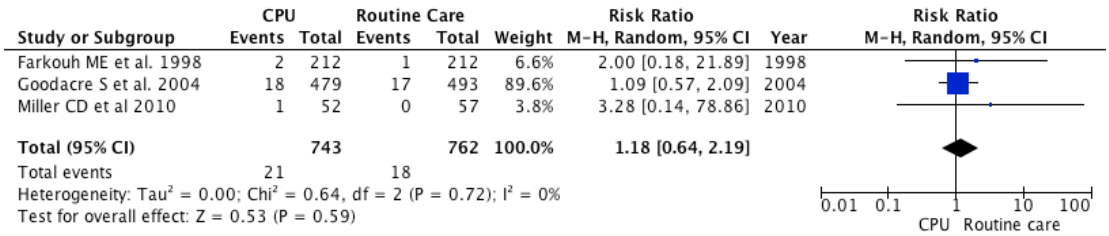

Figure 9: The forest plot of relative risks of follow-up MI or UA. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

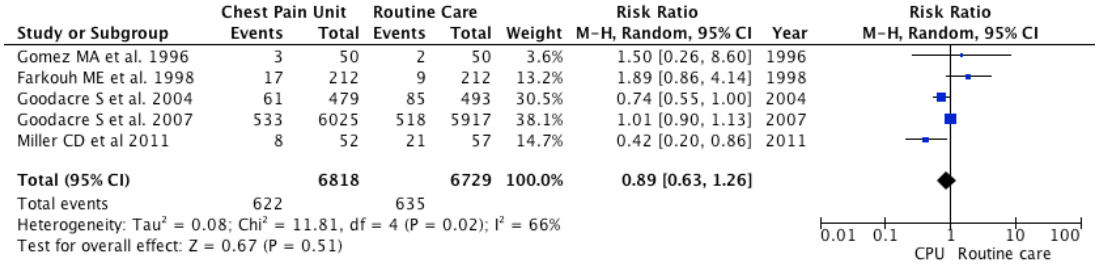

Figure 10: The forest plot of relative risks of ED re-attendance. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

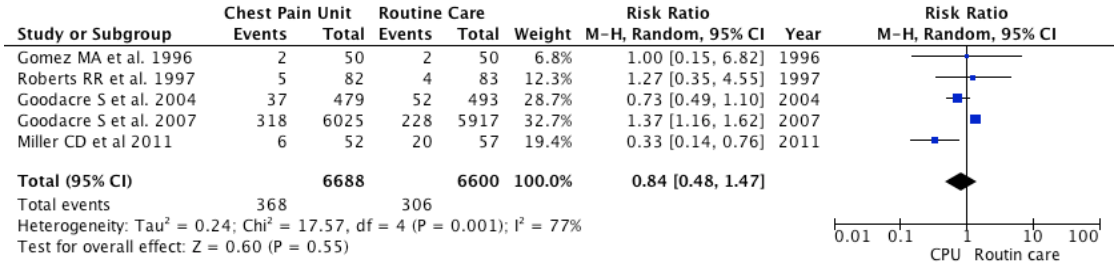

Figure 11: The forest plot of relative risks of hospital readmissions. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

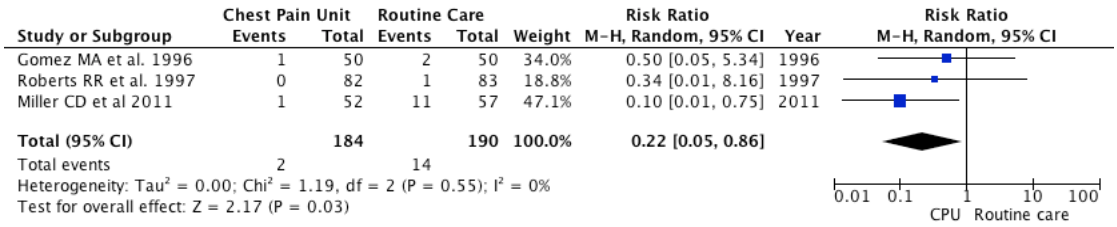

Figure 12: The forest plot of relative risks of cardiac angiography during the follow-up period. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). Horizontal bars indicate 95% CIs; CPU, chest pain unit.

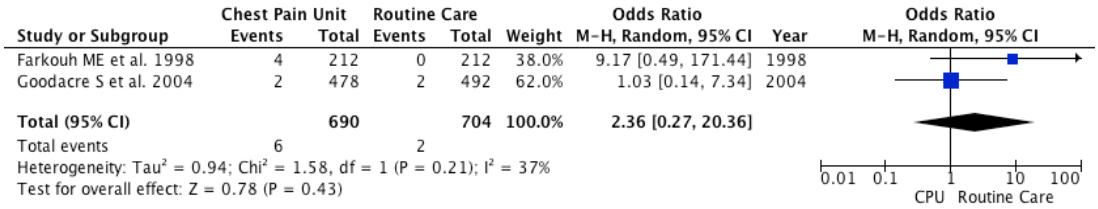

Figure 13: The forest plot of relative risks of overall mortality. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect). The studies by Gomez et al[8], Roberts et al[10] and Miller et al[15] had no events in either arm and are, thus, not represented in the forest plot. Horizontal bars indicate 95% CIs; CPU, chest pain unit.

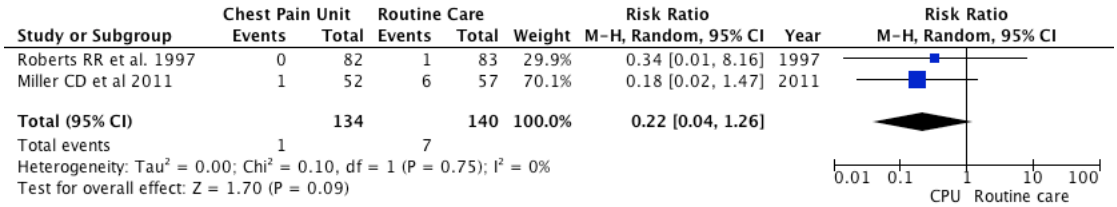

Figure 14: The forest plot of relative risks of overall use of PCI. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect. Horizontal bars indicate 95% CIs; CPU, chest pain unit; PCI, percutaneous coronary intervention.

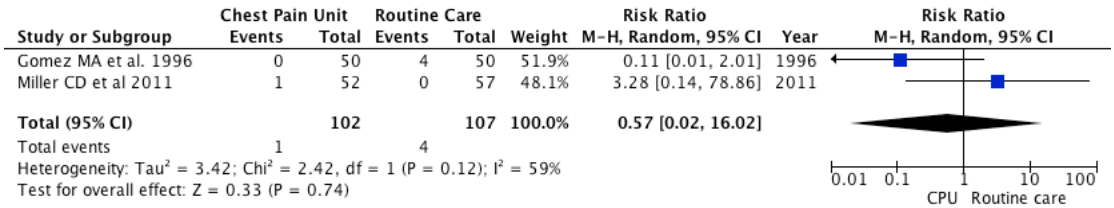

Figure 15: The forest plot of relative risks of overall rate of CAGB. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect. Horizontal bars indicate 95% CIs; CPU, chest pain unit; CABG, coronary artery bypass grafting.

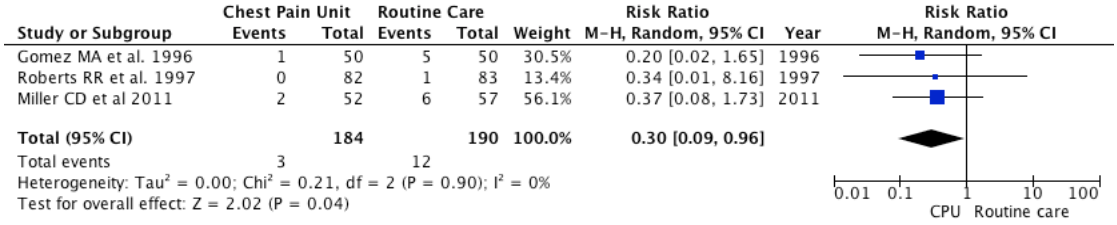

Figure 16: The forest plot of relative risks of overall myocardial revascularization procedures. Sizes of data markers are proportional to the weight of each study in the meta-analysis (random effect. Horizontal bars indicate 95% CIs; CPU, chest pain unit.

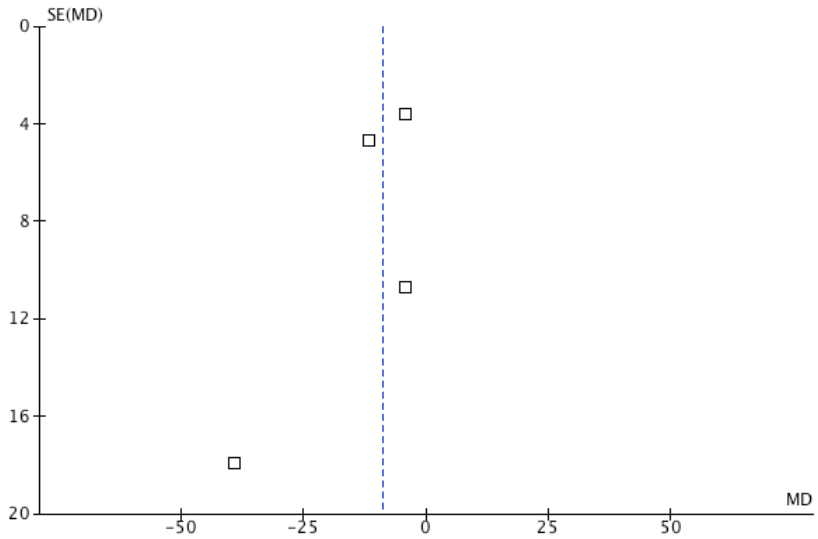

Figure 17: Funnel plot for length of hospital stay

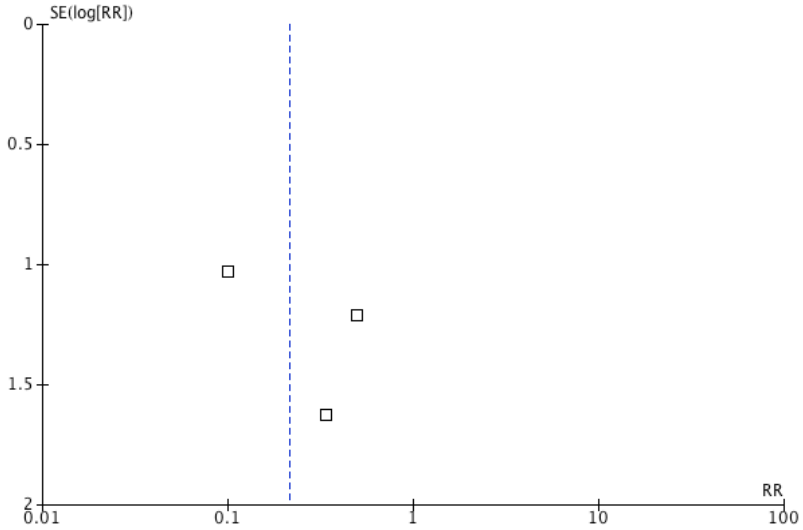

Figure 18: Funnel plot for coronary angiography during follow-up

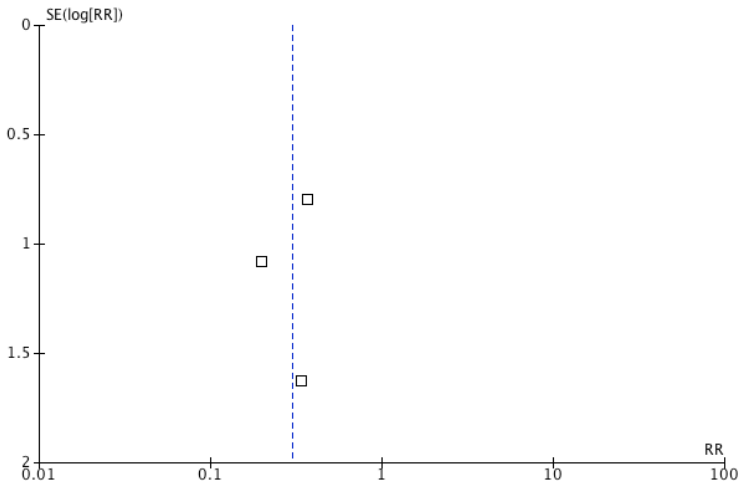

Figure 19: Funnel plot for combined revascularization procedures in the overall study period

Anexo 3 - Versão preliminar de um modelo de simulação de eventos discretos para avaliação da custo-efetividade de unidades de dor torácica em comparação ao atendimento no setor de emergência convencional

Economic assessment of dedicated units for acute coronary syndrome care: development of a discrete event simulation

Avaliação econômica de unidades dedicadas para o atendimento à síndrome coronariana aguda: desenvolvimento de uma simulação de eventos discretos

André Luis Ferreira da Silva, Doutorando em Epidemiologia pela UFRGS;

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

Economic assessment of dedicated units for acute coronary syndrome care: development of a discrete event simulation

André Luis Ferreira-Da-Silva[1,2], MD, MSc; Fred Fink[3]; João Antônio Paim Rodrigues[4]; Caroline Ziane Dalla Pozza Valente[4]; Mariana Vargas Furtado[5,6], MD MSc; Carisi Anne Polaczyk[1,5,6], MD, ScD.

1. Graduate Program in Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre

2. Internal Medicine Department of Hospital de Clinicas de Porto Alegre

3. Information Technology Department of Hospital de Clinicas de Porto Alegre

4. Administrative Coordination of Hospital de Clinicas de Porto Alegre

5. Graduate Program in Cardiology and Cardiovascular Sciences, Federal University of Rio Grande do Sul, Porto Alegre, Brazil

6. Cardiovascular Division of Hospital de Clínicas de Porto Alegre.

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Abstract

Background: Chest pain unit (CPU) and Vasculat unit (VU) represents models care for suspected or confirmed acute coronary syndrome (ACS) patients. Discrete Event Simulation (DES) is as a flexible modeling method characterized by the ability to represent complex systemst. Such models are particularly useful in circumstances that involve a series of associated events and to evaluate the optimum allocation of limited resources. **Objective:** To develop a DES model for the evaluation of the CPU and VU strategies incomparison to emergency department (ED) care of ACS patients. **Methods:** CPU effectiveness was estimated from a systematic review of published clinical trials. VU effectiveness was estimated from administrative and clinical datasets from a tertiary public hospital in Brazil. Both strategies were compared to an ED simulated from data of the same hospital. Simulated patients circulated through 9 modules that represented ACS process of care: (1) patient generator; (2) triage; (3) hemodynamic laboratory; (4) unit of care; (5) non-invasive testing; (6) hospital admission; (7) community; (8) death; and (9) patient exit. Resources utilization, costs, events frequency and duration were recorded in 100 replications. **Results:** Total system cost was virtually the same for ED and CPU care (Int$ 260,488 and Int$259,436, respectively). CPU strategy dominates the ED strategy, with reduced rates of hospitalization, coronary angiography and revascularization procedures. However, it was associated with a 3 fold increase in the need for non-invasive testing. VU strategy was associated to an incremental one-year budget impact of Int$ 229,190. **Conclusion:** A functional DES model for process analysis of ACS care was created. CPU care of low-to-intermediate risk ACS patients is likely to be cost-saving and resource sparing in the Brazilian context. VU care is likely to be

associated to an increased budget impact, the magnitude of which might be overestimated in this preliminary economic evaluation.

Keywords: chest pain unit, vascular unit, acute coronary syndrome, discrete event simulation

Introduction

Chest pain units (CPUs) have evolved since the 80's as an alternative to conventional hospital admission for patients with low- and intermediate-risk non-ST elevation acute coronary syndrome (NSTEACS).[1] Such units have incorporated progresses in chest pain evaluation and management, such as protocol oriented drug administration, cardiac monitoring, serial ECG, serial measurements of cardiac biomarkers and systematic use of non-invasive tests for indeterminate cases.

Both observational studies and clinical trials have assessed CPUs' safety and efficacy in comparison to routine hospitalization, the first randomized clinical trials dating from the decade of 1990.[2] Based on the results of individual studies, it is generally accepted that CPU care is capable of reducing resource utilization without adversely affecting the outcomes of such patients.[3-5]

It has been recently proposed an alternative form of dedicated unit for the initial evaluation and management of acute vascular conditions, including NSTEACS and higher risk coronary syndromes, the vascular unit (VU) strategy.[6] VU shares many features with CPUs and stroke units, including a dedicated physical area, a 24-h dedicated medical and nursing staff, a 2:1 nurse-patient ratio, protocol-oriented care, patient monitoring systems, mechanical ventilation, rapid access to specialists and diagnostic imaging, a hemodynamic laboratory and a surgical area. It is adjacent to the ED and functions as a "crowding-proof" area to allow better quality care.

The CPU strategy has been submitted to economic evaluations, however, no full economic evaluation has been based on data from a systematic review of literature. As for the VU strategy, no economic evaluation has been conducted to date.[7-10]

Discrete event simulation (DES) is defined as a flexible modeling method characterized by the ability to represent complex behavior within, and interactions between individuals, populations and their environment. Such models are particularly useful in circumstances that involve a series of associated events and to evaluate the optimum allocation of limited resources.[11-13] Models of this kind may be based on either primary or secondary data (from a systematic review of literature), depending on model purpose. We aimed at developing a generic model to make possible to perform economic evaluations of different interventions for acute coronary syndromes. Two base-case analyses are presented: the first one was based on a systematic review o literature to evaluate CPU care in comparison to ED care; the other one was based on primary historical data regarding an ED system performance before and after the implementation of the VU. Thus, hypothetical cohorts were generated to emulate the performance of different systems of care for suspected or confirmed ACS patients.

The mains objective of the present work is to develop the base-case model for the economic evaluation of dedicated units in the care of acute coronary syndromes using discrete event simulation. The secondary objective is to present a preliminary economic analysis of CPU-care and VU-care in comparison to ED-care for ACSs. This work is academic in nature and it was developed in the interest of public health. No grants were received by the authors to develop this model, and the model is not intended to be used commercially.

Methods

The present study represents a preliminary economic evaluation of dedicated units in the care of suspected or confirmed ACS. A discrete event simulation (DES) model was built to estimate budget impact and cost-effectiveness.

Context and Vascular Unit

Information on characteristics of target patient-population, time and resource consumption estimates were obtained from published and unpublished primary data from a tertiary public hospital in Brazil. This institution is a referral center for the treatment of acute vascular diseases. Its ED has capacity for 50 patients; however, it is constantly overcrowded, caring for 100 to 150 patients.[6]

Up to the year 2006, suspected ACS patients were initially evaluated and managed in this context of limited resources, constant crowding, inadequate processes, and no specific beds designated. In order to improve the process of care and to remove acute vascular patients from this overcrowded environment, an unit dedicated to the care of acute vascular conditions was created. The Vascular Unit (VU) was implemented to reduce wait time and consolidate the personnel and resources needed for similar emergencies. It is a high acuity area with nine beds that is capable of providing intermediate complexity care. It is located within the hospital's ED. All patients admitted to the VU are treated on evidence-based protocols and evaluated by trained emergency physicians (available 24 h per day) and consulting specialists (on demand).

Compared alternatives and source of effectiveness data

The present model compares 3 alternatives for the initial evaluation and management of suspected and confirmed ACS patients: (1) emergency department care; (2) chest pain unit care (limited to low-to-intermediate risk ACS) and (3) VU care. Detailed information on model parameter estimates of patient characteristics and effectiveness estimates is provided in table 1.

CPU effectiveness

Effectiveness data for CPU care derived from a systematic review of literature. Briefly, 7 full papers were identified and 6 were included in a meta-analysis.[2,5,14-17] Compared to routine hospitalization, CPU care was associated to reductions in hospitalization rates (RR 0.47; 0.29 to 0.77), length of hospital stay (-8.74h; -16.92 to -0.55), need for follow-up coronary angiography (RR 0.22; 0.05 to 0.86) and overall rate of revascularization procedures (RR 0.30; 0.09 to 0.96). There was no difference in mortality or cardiovascular event rates.

VU Effectiveness

The initial impact of VU implementation on ACS patients was reported by Furtado et al.[6] There were observed improved cardiovascular outcomes, quality of healthcare indicators and adherence to clinical protocols comparing the periods before and after VU implementation (years 2000 and 2001 versus 2006 and 2007). This study presents a logistic regression analysis that related the VU period to reduced mortality rates among ACS patients (OR 0.35; 95% CI 0.14 to 0.88). With respect to resources utilization, the VU period

was associated to an increase in coronary angiography rate (60.2% to 77%) and a reduction in PCI rates (39% to 31%).

To confirm and complement these estimates, we conducted a study of ACS mortality rate and resource utilization based on administrative information and on electronic patient records comparing more comprehensive time periods (years 2002 – 2005 and 2007 – 2010). The period prior to VU implementation (2002-2005) included 1649 ACS patients, and the VU period (2007-2010) included 1999 patients. In this analysis, ACS general mortality rate dropped from 6% to 3.8% (p=0.003). Regarding resource utilization, there was a reduction in the length of hospital stay (from 196 to 163h) and an increase in median hospital charges (BRL$ 3062 to 5402) and re-hospitalization rates (11% to 20%) with VU implementation (p<0.001).

ED patient population and effectiveness

The ED care of suspected ACS is the comparator to CPU and VU strategies in this analysis. This was done in order to reflect the context of Brazilian hospitals' ED without dedicated units, which often are constrained in resources, crowded, and unable to provide adequate processes of care for suspected ACS patients.

Incoming chest pain patients' characteristics derived from the period before VU implementation, as reported by Furtado et al. Additional estimates derived from the supplementary analysis based on EPR.

Perspective of analysis, time horizon and costs

The present analysis was performed under the hospital perspective, and the time horizon of 1 year was chosen for the base case. As modeling of systems of care and dedicated units is notoriously challenging, this time horizon was chosen to facilitate face validity and to provide short term economic information to decision makers on implementing a dedicated unit.

Macro costs estimates were obtained from the financial department records. Average values in Brazilian Reais (BRL) from the year 2012 were used. Budget impact and cost effectiveness estimates were converted to 2012 international dollars (Int$) according to purchase power parity index.

Aggregated daily costs for stay in the intensive care unit (ICU) and in the medical ward included expenses with human resources and consumption of supplies. The daily VU and CPU costs were assumed to be equal to daily ICU cost, and daily ED costs were assumed to be equal to daily medical ward costs. These assumptions are believed to be conservative, as VU and CPU costs are likely to be lower than ICU costs in our institution.

Cost differences across scenarios could be explained by three factors: (1) type of unit (ED or CPU/VU); (2) length of stay in ED or CPU/VU; (3) proportion of patients submitted to coronary angiography, non-invasive testing, PCI and CABG. Costs included in the model are presented in table 2.

Considering the developmental nature of the current base-case and the short-term time horizon, we decided not to discount future values or to adjust for inflation.[18] However, such adjustments will be required if this model is to be used for long-term economic evaluations.

Scenarios to be compared

A DES model was built to represent the initial assessment and clinical course of suspected ACS patients from arrival in ED up to six months after hospital discharge. The technology to be evaluated was the evaluation and management system of initial patient assessment. In the main analysis, two scenarios were created to estimate the economic efficiency of CPU and VU care (scenarios CPU–LI and VU–All, respectively). Likewise, two baseline scenarios were created to represent ED simulations comparable to CPU and VU care (ED-LI and ED-All). This was done because CPUs were not developed to manage STEMI and high-risk NSTEACS, thus an ED simulation limited to low-to-intermediate risk patients was generated (ED-LI). On the other hand, ED simulation for comparison to VU comprised patients from all risk categories (ED-All). Incoming patient characteristics was assumed to remain unaffected with CPU or VU implementation in the base-case analysis.

Scenarios ED-LI and ED-All

Data used to represent this setting of care derived from two sources: (1) published prospectively collected data on patient characteristics and incidence of in-hospital clinical events in the period between June 2000 to December 2001 (19 months) and (2) unpublished retrospective data from our institution's electronic patient record (EPR), as well as administrative information from the period prior to VU implementation (January 2002 to December 2005). The scenario ED-LI included only low-to-intermediate risk ACS patients and assumed that higher risk individuals were managed elsewhere (e.g. CCU), with no ED related

resource utilization or costs incurred. The scenario ED-All included patients from all risk categories.

Scenarios CPU–LI and VU–All

The VU–All scenario was designed to reflect the actual performance of our institution's VU, with data derived from the same sources used to model the ED scenarios, reflecting the period after VU implementation (years 2006 and 2007 from Furtado et al and years 2007 to 2010 from the EPR).

The CPU–LI scenario was modeled to represent the expected performance of CPU care in our institution, as reported in the literature, assuming that our institutions' VU functioned as a CPU. To do so, the CPU-LI scenario included only low-to-intermediate risk ACS patients and assumed that higher risk individuals were managed elsewhere (e.g. CCU), with no ED related resource utilization or costs incurred. Cost estimates were the same used for the VU-All scenario.

Model description and assumptions

The current DES model was designed to allow a comprehensive process analysis, considering changes in time and resource utilization that may arise from distinct strategies for the evaluation and management of chest pain patients in the ED. The model is divided in 9 modules: (1) patient generator; (2) triage; (3) hemodynamic laboratory; (4) ED or dedicated unit; (5) non-invasive testing; (6) hospitalization; (7) community; (8) death; and (9) patient exit. An overview of the modules and their interactions is presented in figure 1.

Patient generator module

Patient population is created from the observed frequencies of types of chest pain patients as reported by Furtado et al. There are four possible types of patients: (1) non-ACS chest pain; (2) UA; (3) NSTEMI and (4) STEMI. To each patient are attributed markers of clinical features (e.g. type of ACS) and preset probabilities of being submitted to diagnostic tests, procedures or undergoing clinical events.

Triage module

This module confers to the model the ability to account for duration and resource utilization associated to the triage process. In addition to that, this module may be modified to take into account the consequences of different sensitivity and specificity estimated for the triage process. However, such features were not used in the base-case development, and the only function of this module was to separate STEMI patients, which were sent to primary PCI, from other patients. This was done due to lack of information on triage process. In this analysis, triage duration is assumed to have been accounted for in the length of ED or DU stay and in the duration of primary PCI process.

Hemodynamic laboratory module

This module is divided in 3 process flows: (1) primary PCI; (2) non-primary PCI and (3) coronary angiography. Patients sent to any of these processes incurred costs associated to the applicable procedure. The primary PCI process is the only of these associated to additional time, which comprised STEMI patient initial evaluation, the PCI procedure itself and time in the recovery room. Duration of the other 2 processes is assumed to be included

in the length of stay in the ED or DU. Patients submitted to cardiac catheterization with indication for PCI are assumed to undergo this procedure immediately.

Emergency Department and Dedicated Unit module

This module functions as the main processing unit, where patient evaluation decisions are made according to preset patient probabilities attributed in the generator module. It is split in 3 parts (1) initial medical assessment; (2) first 24h in ED or DU; (3) additional wait time in the ED or VU related to unavailability of hospital beds. This allows the evaluation of constrains related to the initial assessment (e.g. number of physicians and duration of evaluation), estimation of the amount of patients that would have been admitted if there were immediate availability of hospital beds and quantification of additional time spent in the ED or DU in the wait for a hospital bed. The definition of a fixed 24h length for initial evaluation was required to estimate how many patients would have been immediately admitted if this timeframe was the criteria for admission.

According to the preset probabilities, patients could leave this module to undergo coronary angiography or non-invasive testing. Other assumptions related to this module are: 100% of patients with non-ischemic chest pain spend the 24h of evaluation and are then discharged to the exit module without further testing; 100% of high-risk ACS patients (defined as NSTMI in the study by Furtado et al) are submitted to coronary angiography; the remainder of patients were submitted to cardiac catheterization or non-invasive testing according to preset probabilities from the generator module.

Length of stay in the ED or VU derived from a study based on electronic patient records and reflects the wait time for a hospital bed observed in the clinical setting that

originated this estimate. This approach for additional wait time in ED or DU was more feasible then modeling hospital bed dynamic, for which there was no reliable estimate available.

Non-invasive testing

This module allows the consideration of time, resource an costs associated to non-invasive testing for myocardial ischemia. In the current version, it is designed to incur an average cost that represents a generic non-invasive test. However, this can be modified to include 2 or more choices of non-invasive test or to include a more detailed sub-model to permit consideration of accuracy of diagnostic methods.

In the current preliminary analysis, NSTEACS patients not submitted to coronary angiography undergo non-invasive testing according to a preset probability. All non-invasive tests are assumed to be negative for ischemia, as patients with positive tests are assumed to have been captured in the probability of being submitted to coronary angiography.

Hospitalization

This module is divided in clinical and surgical hospitalization. Patients with CABG indication incur costs associated to the procedure added to costs associated to average length of stay in surgical ward and in ICU. Patients with no indication for CABG can be admitted to ICU according to a preset probability from primary hospital data. In the present analyses, the hospitalization module is assumed to behave the same way, irrespective to the kind of unit under evaluation. Differences in costs and resource utilization arise from the proportion of patients with CABG or ICU indication.

Community

This is basically a wait module, were discharged patients spend the time until next day. Each 24h, discharged ACS patients may experience a recurrent ACS. Three conditions exclude patients from the model: (1) having spent 6 months in the community with no event; (2) experiencing 2 or more ACS recurrences; (3) all cases of non-ischemic chest pain. It is possible to set a daily probability of death for patients in the community module, however, as this probability is unknown for the current base-case analysis, it is assumed that no patient dies in this module. Recurring ACS cases have their marker attributes and risk attributes from the previous ACS episode reset before bein re-inserted in the patient generator module. Thus, it is assumed independence between the previous ACS characteristics and the next's.

Death

The purpose of this module is to account fatalities occurred either in-hospital or in the community. In the current base-case, there is a single general probability of death incurred by patients after each hospitalization. Probabilities from Furtado et al and form the EPR study were appropriately converted to annual probabilities of death, to match the base-case time horizon.

Patient exit

Patients are removed from the model according to the conditions enunciated in the community model, above. This module removes patients from the model in order to avoid and excessive number of circulating entities, which could make each model run too prolonged.

Softwares, pre-processing of information and DES model parameters

The present DES model was built in Arena, version 13.5, Rockwell automation. Statistical distributions for duration of time periods was derived from primary data (see below) with the software Input Analyzer, version 13.5. Statistical treatment of data in estimation of model parameters was done in PASW Statistics, version 18.0. Events probabilities were converted from the original timeframe to rates, and then to the timeframe of interest for the model.

Model parameters assumed to differ between the ED scenario and the dedicated unit-scenario were limited to those for which there was observed statistical significance. Mortality rates, time and resources consumption associated to ACS were compared between the two four-year time periods of interest: (1) the before VU period (2002-2005) and (2) the VU period (2007-2010). Comparisons were performed using the chi-square test with continuity correction. Average length of ED stay of the studied periods were compared with a t-test. Differences were considered statistically significant for p values < 0.05. A Bonferroni correction was applied in order to adjust for multiple comparisons, which rendered an adjusted p value of < 0.005 for statistical significance.

In order to avoid initialization bias, a 180 days warm-up period was used (simulated period of model activity before data collection from the model). One hundred replications

were performed per model run, which is reported to provide reasonable narrow model output estimates.[11,19,20]

Results

Successive model runs were performed to adjust baseline model parameters to the more appropriate format to match actual data from which parameters where estimated. These calibration runs were performed with 60 days of warm-up period and 19 months of time horizon in order to be readily comparable to original results reported by Furtado et al for the period before VU (2000-2001). A comparison of actual and modeled data is provided in table 3. Modeled data approximated actual proportion patient types and events, despite a slightly smaller total number of patients (663 versus 626).

STEMI and high-risk NSTEACS patients were successfully removed from the model for the comparison of ED care with CPU care, as demonstrated by the absence of primary PCI in this analysis (table 4). Total system cost was virtually the same for ED and CPU care (BRL 500,137,00 and 498,117.00, respectively). As the CPU strategy reduced the need for hospitalization, coronary angiography and revascularization procedures, it dominates the ED strategy. However, the CPU strategy was associated with a 3 fold increase in the need for non-invasive testing.

Regarding the economic evaluation of VU care, this strategy was associated with to a one year cost of BRL 1,264,692.00 (Int$ 658,694.80), while the ED strategy cost was BRL 824,650.00 (Int$ 429,505.20). This represents an incremental one-year budget impact of BRL 440,044.00 (Int$ 229,189.6). Considering the impact of VU in ACS case-fatality rate, this

figures correspond to an incremental cost-effectiveness ratio (ICER) of BRL 146,681.3 / death avoided (Int$ 76,396.53 / death avoided). Results for the VU scenario analysis is presented in table 5.

Discussion

The economic evaluation of complex interventions is challenging. Compared to more common health technologies, such as pharmaceuticals, diagnostic tests, procedural interventions and medical devices, the evaluation of systems of care requires additional levels of complexity to be taken into account. This means the use of models with elaborate structure and the consideration of factors such as the consequences of constrained resources and the passage of time. In this preliminary report, we offer a DES model base-case analysis for future evaluation of dedicated units and and systems of care for suspected ACS.

Accepting model assumptions, the budget impact of CPU care implementation in comparison to ED care was negligible. A CPU exclusive to low-to-intermediate risk NSTEACS was the dominant strategy, incurring virtually no additional costs while averting hospitalizations, coronary angiographies and revascularization procedures. This resulted in an increased demand for non-invasive testing, which might not be matched by hospital capabilities. In this base-case analysis, it was assumed no limit for non-invasive testing, so no impact was observed in patient flow and length of stay. This illustrated the usefulness of decision-analytic models, which may demonstrate health technology's unintended consequences emerged from system behavior.[21,22]

However, care must be taken on accepting favorable economic outcomes of CPU care reported in the present study and in previous economic evaluations. It is unclear to which extend the outcomes observed in the clinical trials of CPUs may be successfully reproduced in other contexts. For instance, the 2004 clinical trial by Goodacre et al reported reduced proportion of hospital admissions, improved health utility and cost savings of £78 per patient.[16] However, another clinical trial by the same author (2007) failed to reproduce CPU benefits in 7 other hospitals in the United Kingdom.[17,23,24]

With respect to VU care, its adoption in comparison to ED care for ACS of all risk categories resulted in a one-year incremental budget impact of 53%. Considering the estimated effect of VU care in case-fatality rates for ACS, this additional amount corresponded to an elevated ICER (Int$ 76,396.53 / death avoided). However, this is a preliminary estimate from this model-development analysis, with no cost-utility estimate and within a short time horizon.

Our model has several limitations that must be taken into account. First, this is essentially a process analytic model, with no evolving event risk as a result from simulated events or processes. Second, the macro cost estimate is not accurate enough to permit judgment of specific cost components that might contribute to the observed budget impacts. Third, assuming VU's and CPU's costs to be equal to ICU's is likely to be overestimating the costs of such dedicated units, specially in the case of CPU. We believe this assumption to be conservative. As such, CPU care is likely to be cost saving and VU's budget impact is likely to be lower. Finally, we did perform successive model runs in the development stage for debugging and model calibration, however parameters estimates might be further evaluated in an extensive scenario sensitivity analysis.

In conclusion, we believe to have developed a valid DES model for process analysis of ACS care in the ED or dedicated units. CPU care of low-to-intermediate risk ACS patients is likely to be cost-saving and resource sparing in the Brazilian context. VU care is likely to be associated to an increased budget impact, the magnitude of which might be overestimated in this preliminary economic evaluation.

This model should be further developed in order to include evolving and interdependent risks and more accurate cost estimates.

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Figure Legends

Figure 1 - Overview of patient flow within the discrete event simulation model

Figure 1

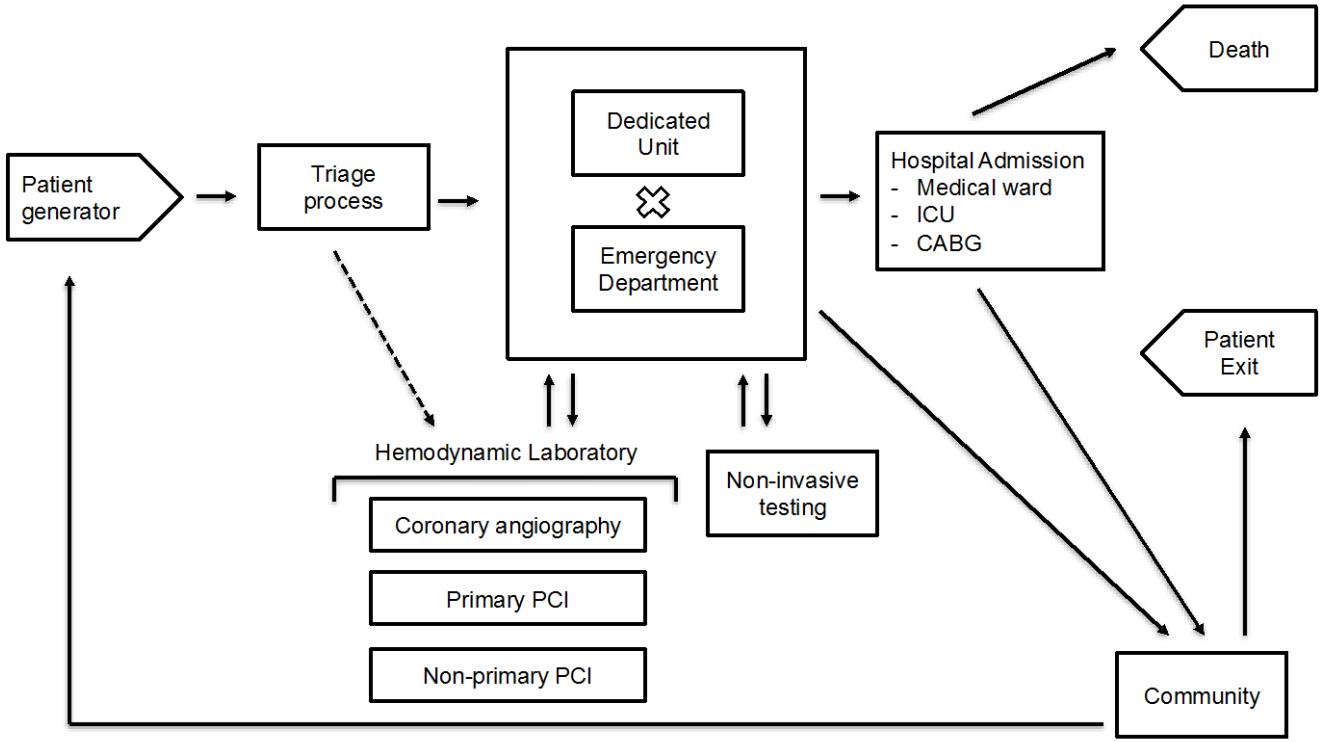
Patient generator
Triage process
Dedicated Unit
Emergency Department
Death
Hospital Admission
- Medical ward
- ICU
- CABG
Patient Exit
Hemodynamic Laboratory
Coronary angiography
Primary PCI
Non-primary PCI
Non-invasive testing
Community

Table 1 - Model input parameters used in the base-case analysis

	Base-case CPU			Base-case VU		
Model Parameter	**Baseline parameters**	**CPU adjusted parameters**	**Source / Comment**	**Baseline parameters**	**VU adjusted parameters**	**Source / Comment**
Age	Assumed to be normally distributed NORM 63.18	Unchanged	Furtado MV et al 2011 (Years 2000-2001)	Assumed to be normally distributed NORM 63.18	Unchanged	Furtado MV et al 2011 (Years 2000-2001)
Probability of ACS among chest pain incoming patients	0.394	Unchanged	Furtado MV et al 2011 (Years 2000-2001)	0.394	Unchanged	Furtado MV et al 2011 (Years 2000-2001)
STEMI probability among ACS patients	0.1724	Unchanged	Furtado MV et al 2011 (Years 2000-2001)	0.1724	Unchanged	Furtado MV et al 2011 (Years 2000-2001)
Proportion of STEMI with time to presentation ≥ 12h)	1	Unchanged	Assumed	1	Unchanged	Assumed
Proportion of intermediate-to-high (≥ 4 TIMI risk score) among NSTEACS patients	0.25	Unchanged	Furtado MV et al 2011 (Years 2000-2001) Proportion of NSTEMI among NSEACSs used as surrogate	0.25	Unchanged	Furtado MV et al 2011 (Years 2000-2001) Proportion of NSTEMI among NSEACSs used as surrogate
Resource use related parameters						
Probability of staying in the hospital more	0.95	0.4465 (0.2755 – 0.7315)	Baseline value: EPR Query (Years 2002-2005 and	0.95	Unchanged	Baseline and VU values: EPR Query (Years 2002-2005 and 2007-2010)

than 24h after ED our VU arrival (surrogate for probability of hospital admission)[d]			2007-2010) CPU values based on Meta-analysis estimate: RR 0.47 (95% CI 0.29 – 0.77)			
Proportion of positive results among non-invasive tests	0	Unchanged	Assumed all positive tests were contemplated in the probability of being submitted to coronary angiography	0	Unchanged	Assumed all positive tests were contemplated in the probability of being submitted to coronary angiography
Proportion of coronary angiography among NSTEACS patients	0.7268	0.1601 (0.0363 – 0.6259)	Baseline value: Furtado MV et al 2011 Excluding STEMI patients, which were assumed to be submitted to primary PCI (Years 2000-2001) CPU values based on Meta-analysis estimate: RR 0.22 (95% CI 0.05 – 0.86)	0.7268	0.8697 (0.7911 – 0.9563)	Baseline and VU values: Furtado MV et al 2011 Excluding STEMI patients, which were assumed to be submitted to primary PCI (Years 2000-2001 and 2006-2007) RR 1.195 (95% CI 1.087 – 1.314)
Proportion of revascularization procedures among NSTEACS patients	0.5286	0.1585 (0.0475 – 0.5074)	Baseline value: Furtado MV et al 2011 (Years 2000-2001) Excluding STEMI patients, which were assumed to be	0.5286	0.3890 (0.3124 – 0.4841)	Baseline and VU values: Furtado MV et al 2011 (Years 2000-2001 and 2006-2007) Excluding STEMI patients, which were assumed to be submitted to primary PCI

			submitted to primary PCI CPU values based on Meta-analysis estimate: RR 0.3 (95% CI 0.09 – 0.96)			RR 0.73 (95% CI 0.591 – 0.916)
Proportion of PCI among patients submitted to e revascularization procedure, excluding primary PCI	0.6868	Unchanged	Furtado MV et al 2011 (Years 2000-2001)	0.6868	Unchanged	Furtado MV et al 2011 (Years 2000-2001)
Proportion of CABG among patients submitted to e revascularization procedure, excluding primary PCI	0.3132	Unchanged	Furtado MV et al 2011 (Years 2000-2001)	0.3132	Unchanged	Furtado MV et al 2011 (Years 2000-2001)
P admission CABG	1	Unchanged	EPR Query (Years 2007-2010)	1	Unchanged	EPR Query (Years 2007-2010)
Proportion of STEMI patients submitted to CABG	0.026	Unchanged	EPR Query (Years 2002-2005)	0.026	Unchanged	EPR Query (Years 2002-2005)
Probability of ICU admission after	1	Unchanged	Assumed 100% probability	1	Unchanged	Assumed 100% probability of admission to the

CABG			of admission to the ICU after CABG			ICU after CABG
Clinical outcomes related parameters						
Daily probability of readmission among ACS patients	0.0001875 /day	Unchanged	EPR Query (Years 2002-2005)	0.0001875 /day	0.0002261 /day	EPR Query (Years 2007-2010)
Probability of death	0.054 in 19 months (0.0342 in 1 year)	Unchanged	Furtado MV et al 2011 (Years 2000-2001)	0.054 in 19 months (0.0342 in 1 year)	0.0119 / year (0.005 – 0.03) 0.0191 / year (0.0143 – 0.0253)	Furtado MV et al 2011 (Logistic Regression Analysis) RR 0.35 (95% CI 0.14 – 0.88) Administrative system query (Years 2002-2005 and 2007-2010) RR 0.56 (95% CI 0.42 – 0.75)
Time estimates parameters						
Time between chest pain patients arrivals (h)[c]	Poisson distribution POIS (20.6)	Unchanged	Monthly average inter-arrival time estimated from Furtado et al 2011	Poisson distribution POIS (20.6)	Unchanged	Monthly average inter-arrival time estimated from Furtado et al 2011

Overall time spent from arrival to primary PCI	Lognormal distribution LOGN (3.01,6.95)	Unchanged	EPR Query (Years 2002-2005)	Lognormal distribution LOGN (3.01,6.95)	Unchanged	EPR Query (Years 2002-2005)
Duration of non-primary PCI and diagnostic coronary angiography	0	Unchanged	Assumed to be included in overall ED or VU length of stay	0	Unchanged	Assumed to be included in overall ED or VU length of stay
Non-invasive test duration	0	Unchanged	Assumed to be included in ED or VU length of stay	0	Unchanged	Assumed to be included in ED or VU length of stay
Length of stay in ED or VU	Beta distribution 298*BETA(0.784,3.26)	Beta distribution 298*BETA(0.784,3.26) - TRIA (8.74;16.92,0.55)	Baseline value: EPR Query (Years 2002-2005) CPU values based on Meta-analysis estimate: Mean difference -8.74 (95% CI -16.92 to -0.55)	Beta distribution 298*BETA(0.784,3.26)	309*BETA(0.728, 3.53)	EPR Query (Years 2007-2010)
Length of stay in medical ward, excluding time in ED/VU and time in ICU, excluding CABG patients	Beta distribution 1+715*BETA(0.462,2.6)	Unchanged	EPR Query (Years 2002-2005)	Beta distribution 1+715*BETA(0.462,2.6)	Unchanged	EPR Query (Years 2002-2005)

Length of ICU stay - clinical and surgical patients (h)	1+ERLA(37.9,2)	Unchanged	EPR Query (Years 2002-2005)	1+ERLA(37.9,2)	Unchanged	EPR Query (Years 2002-2005)
Additional duration of hospitalization in patients submitted to CABG (excluding time in ED/VU and ICU)	Beta distribution -0.001 + EXPO (148)	Unchanged	EPR Query (Years 2002-2005) Distribution of the difference between total length of hospitalization and the sum of time from arrival to surgery and time spent in ICU	Beta distribution -0.001 + EXPO (148)	Unchanged	EPR Query (Years 2002-2005) Distribution of the difference between total length of hospitalization and the sum of time from arrival to surgery and time spent in ICU

EPR Query, electronic patient records query comprising the period from 2002 to 2005 for general ED estimates and 2007 to 2010 for VU estimates. Unpublished data; ED, emergency department; VU, vascular unit; NSTEACS, no-ST elevation acute coronary syndrome; NSTEMI, no-ST elevation myocardial infarction; SA, sensitivity analysis.

a. Base-case analysis was based preferably on estimates from prospective data reported by Furtado MV et al 2011. Missing parameters were estimated from the EPR query.

b. Alternative estimates were mostly derived from the EPR query

c. Time estimates were captured considering the hospitalization as unit of analysis, as opposed to individual patients.

d. All patients with length of hospital stay greater then 24h were assumed to have been admitted to the hospital, as opposed to being discharged directly from the ED or VU.

Table 2 - Cost parameters adopted in the modeling of ED, CPU and VU strategies

Resource	Cost	Resource availability in the model	Type of use in the base-case model
General hospitalization			
Aggregated costs of routine hospitalization in medical ward	239.30 BRL/day (9.97 BRL/h)	50	Busy hours
Aggregated costs of ICU hospitalization	990.56 BRL/day (41.2733 BRL/h)	10	Busy hours
Non invasive testing	100 BRL	infinite	Per use
Cardiac catheterization laboratory			
Interventionist cardiologist	88 BRL/patient	1	Busy hours
Aggregated human resources cost, except interventionist cardiologist	148.9 BRL/patient	1	Busy hours
PCI supplies, including one bare metal stent	3542.80 BRL/patient	infinite	Per use
Coronary angiography supplies	486.38 BRL/patient	infinite	Per use
CABG			
CABG with extracorporeal circulation	5432.52 BRL / patient	1	Per use
CPU and VU			
Aggregated costs of dedicated unit stay	990.56 BRL/day (41.2733 BRL/h)	9	Busy hours
Emergency Department			
Aggregated costs of ED stay	239.30 BRL/day (9.97 BRL/h)	50	Busy hours

BRL, Brazilian Real (R$); CPU, chest pain unit; ED, emergency department; VU, vascular unit; ICU, intensive care unit; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 3 - Comparison of prospectively collected data and modeled data

Result	Furtado et al 2011 (years 2000 and 2001)	Model generated data (average of 100 replications)
Chest pain patients	663	626
Not ACS	402	378.12
ACS	261	247.95
STEMI	45	43.84
NSTEMI	54	53
UA	162	151.11
Deaths	14	13.01
Readmissions	NR	7.06
Coronary angiography	157	153.44
PCI	102	99.9
CABG	26	26.67

STEMI, ST elevation myocardial infarction; NSTEMI, no-ST elevation myocardial infarction; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; NR, not reported.

Table 4 - Model results for the comparison of ED care to CPU care for low-to-intermediate risk ACS patients in one year (100 replications). CPU effectiveness based on a systematic review of literature.

	Scenario ED-LI			Scenario CPU-LI		
	Average	**Maximum average**	**Minimum average**	**Average**	**Maximum average**	**Minimum average**
Costs						
Total system cost	BRL 498,117.00	-	-	BRL 502,137.00	-	-
Busy cost	BRL 267,163.00	-	-	BRL 469,059.00	-	-
Per-patient cost	BRL 1,172.04	-	-	BRL 1,181.49	-	-
Clinical outcomes						
Primary cases	425	416	436	426	414	439
STEMI*	29	15	41	30	18	43
NSTEACS*	136	118	164	139	110	172
Non-cardiac chest pain	260	241	282	257	230	288
Deaths	3	0	9	1	0	6
Hospital admissions	113	84	137	52	30	73
Hospital readmissions	3	0	8	4	0	8
Length of hospital stay (h)	180.67	141.92	212.73	167.06	115.81	230.47
Resource utilization						
Coronary angiography	75	57	95	18		
PCI	28	16	45	2	0	5
Primary PCI	0	-	-	0	-	-
CABG	13	4	21	1	0	3
Non-invasive test	29	16	53	90	62	109

* In this analysis, STEMI and NSTEMI patients are assumed to be transferred to another hospital unit, with no costs incurred to ED or CPU.

BRL, Brazilian Reais; ED-LI, emergency department - low-to-intermediate risk patients; CPU-LI, chest pain unit - low-to-intermediate risk patients; STEMI, ST elevation myocardial infarction; NSTEACS, no-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

Table 5 - Model results for the comparison of ED care to VU care for ACS patients of all risk categories in one year (100 replications). VU effectiveness based primary data.

	Scenario ED-All			Scenario VU-All		
	Average	**Maximum average**	**Minimum average**	**Average**	**Maximum average**	**Minimum average**
Costs						
Total system cost	BRL 824,650.00	-	-	BRL 1,264,694.00	-	-
Busy cost	BRL 394,295.00	-	-	BRL 845,923.00	-	-
Per-patient cost	BRL 1,940.35	-	-	BRL 2,975.75	-	-
Clinical outcomes						
Primary cases	425	412	436	425	413	436
STEMI	30	18	42	31	18	41
NSTEACS	136	116	164	135	118	166
Non-cardiac chest pain	259	236	285	259	235	283
Deaths	6	2	12	3	0	8
Hospital admissions	182	146	216	181	148	224
Hospital readmissions	6	1	12	7	1	15
Length of hospital stay (h)	184.9	157.08	261.67	178.93	151.44	219.30
Resource utilization						
Coronary angiography	103	79	125	124	101	152
PCI	67	38	97	64	40	84
Primary PCI	30	18	42	30	18	41
CABG	18	9	28	16	7	30
Non-invasive test	38	27	52	18	9	28

BRL, Brazilian Reais; ED-LI, emergency department - low-to-intermediate risk patients; CPU-LI, chest pain unit - low-to-intermediate risk patients; STEMI, ST elevation myocardial infarction; NSTEACS, no-ST elevation acute coronary syndrome; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting