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EFETIVIDADE DO MANEJO DA CARDIOPATIA ISQUÊMICA AGUDA E CRÔNICA: DADOS DE REGISTROS LOCAIS

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Esta tese começou a ser escrita no ano de 2000, durante o LV Congresso da Sociedade Brasileira de Cardiologia. Na época, eu ainda era aluna de graduação da Faculdade de Medicina da Universidade Federal do Rio Grande do Sul (UFRGS) e fazia parte do Grupo de Hipertensão do Hospital de Clínicas de Porto Alegre (HCPA), como bolsista de iniciação científica. Fui apresentar o meu primeiro tema livre oral em um congresso nacional, estava muito ansiosa, mas radiante. O palco era o Rio Centro na cidade maravilhosa do Rio de Janeiro. O primeiro impacto foi de surpresa com a grandiosidade do evento. A primeira palestra, do *Professor Dr. Braunwald*. Genial. Eu não conseguia acreditar que estava fazendo parte daquele mundo.

Me preparei muito para minha apresentação, a expectativa era grande, estaria em uma apresentação formal diante do Professor Flávio Fuchs, representando o seu grupo. Mas a tensão aumentou, descobri que antes de mim a Dra. Carísi Polanczyk apresentaria o seu tema livre sobre custos na doença cardiovascular. Na plateia, o Prof. Jorge Pinto Ribeiro. Como uma aluna de graduação poderia apresentar algo depois da Dra. Carísi? Apresentei. Recebi cumprimentos e elogios de meu orientador, Prof. Fuchs, da Dra. Carísi e do Prof. Jorge. Mais do que nunca tive a certeza de que queria fazer parte daquele time. Me apaixonei pela cardiopatia isquêmica e migrei de grupo, carregando comigo o aprendizado do Grupo de Hipertensão.

Desde então, 13 anos se passaram, muitas coisas foram construídas e consolidadas. Me formei médica, fiz residência em Medicina de Emergência, Mestrado em Cardiologia pela UFRGS, Título de Especialista em Cardiologia, ingressei como contratada do HCPA e hoje defendo o doutorado. Muitos temas livres, orientações de alunos no ambulatório, capítulos de livros, artigos. Mas o mais importante da caminhada foi o convívio e as oportunidades diante de meus professores. Pessoas que me ajudaram a crescer, descobrir o novo e apreender que podemos querer sempre mais, sem perder o afeto e o prazer de se fazer o que gosta.

Nesta trajetória perdemos o convívio do Prof. Jorge Pinto Ribeiro, mas ficamos com sua incansável obstinação pelo conhecimento e crescimento. Após sua morte, a Profa. Carísi me disse: “o Jorge era a pessoa que colocava o sarrafo mais alto, para sempre pularmos mais alto”. Carísi, também colocas o sarrafo no alto, mas com a vantagem de fazer isso sem provocar medo, mas sim, inspiração. Muito obrigada por permitir e me ajudar a fazer parte deste time.

Na trama da minha vida, meus sonhos e realizações profissionais só foram possíveis pelo amor e carinho da minha família. Em uma aula do mestrado, o Prof. Manfroi me disse que fiz a melhor e mais bonita metáfora sobre o que é ensinar: “aprendi com meu pai, nas noites quentes da praia de Cidreira, que ensinar é procurar satélites entre as estrelas”. Assim eu cresci, com meu pai, minha mãe e meus irmãos, juntos no prazer e amor do convívio, respeitando a capacidade de cada um em descobrir o seu mundo. A medicina também me proporcionou encontrar o Érico, o homem que me ensinou a cantar e amar, e despertou em mim o desejo de construir a nossa própria família. Há um ano nasceu a nossa Isadora, que me ensinou a mais difícil das lições da vida, ser mãe. A vida e os projetos passaram a ter outro sentido, significado.

Um projeto só acaba quando decidimos que é o seu fim. Este é o fim do meu doutorado, não é exatamente o que planejamos nem o que sonhamos. Mas cito Jorge Drexler, não é um autor científico, apesar de ser médico, mas sim um compositor especialista em metáforas: “... *amar la trama más que al desenlace*...”

A história foi escrita por muitos autores, obrigada por fazerem parte deste caminho. O ponto final está longe de ser encontrado.

SUMÁRIO

LISTA DE ABREVIATURAS - Português

AAS: Ácido acetil salicílico

ACCF/AHA: Sociedades de Cardiologia Americanas

ACTP: Angioplastia Coronariana Transluminal Percutânea

AVC: Acidente Vascular Cerebral

CAPES: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior

CDI: Cardiodesfibrilador Implantável

CNPq: Conselho Nacional de Desenvolvimento Científico e Tecnológico

DAC: Doença Arterial Coronariana

ECA: Enzima conversora de angiotensina

ECR: Ensaios clínicos randomizados

ESC: Sociedade de Cardiologia Européia

FIPE-HCPA: Fundação de Incentivo a Pesquisa do Hospital de Clínicas de Porto Alegre

HCPA: Hospital de Clínicas de Porto Alegre

IAM: Infarto Agudo do Miocárdio;

IAMCSST: Infarto agudo do miocárdio com supradesnível de ST

IAMSSST: Infarto agudo do miocárdio sem supradesnível de ST

IATS: Instituto de Avaliação em Tecnologia em Saúde

IC: Insuficiência cardíaca

NRMI: Registro Nacional de Infarto do Miocárdio

SCA: Síndrome coronariana aguda

SUS: Sistema Único de Saúde

LISTA DE ABREVIATURAS - Inglês

ACCEPT: Brazilian Registry of Clinical Practice in Acute Coronary Syndromes of the Brazilian Society of Cardiology

ACCESS: ACute Coronary Events - a multinational Survey of current management Strategies

ACE: Angiotensin-converting enzyme

ACEi: Angiotensin-converting enzyme inhibitors

ACS: Acute coronary syndrome

AMI: Acute myocardial infarction

ARB: Angiotensin receptor blocker

ARTS: Arterial Revascularization Therapies Study

BARI 2D: Bypass Angiosplasty Revascularization Investigation with type 2 Diabetes study

CABG : Coronary artery bypass grafiting surgery

CAD: Coronary artery disease

CARDia: Coronary Artery Revascularization in Diabetes

CER: Comparative Effectiveness Research

CI: Confidence interval

CK: Creatine kinase

CK-MB: Creatine kinase MB

COPD: Chronic obstructive pulmonary disease

COURAGE: Clinical Outcomes Utilizing Revascularization and Agressive Drug Evaluation

DBP: Diastolic blood pressure

DES: Drug-eluting stents

ECG: Eletrocardiogram

FREEDOM: Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease

HF: Heart failure

HR: Hazard ratio

IATS: Health Technology Assessment Institute

IQR: Interquartile range

LVEF: Left ventricular ejection fraction

MACE: Major adverse cardiovascular event

MASS II: Medical, Angioplasty, or Surgery Study

MI: Myocardial infarction

MT: Medical therapy

NCDR: National Cardiovascular Data Registry

OR: Odds ratio

PCI: Percutaneous coronary intervention

RIKS-HIA: Swedish Register of Cardiac Intensive Care

SAMU: Emergency Medical Service Transport

SBP: Systolic blood pressure

SD: Standard deviation

STEMI: ST-elevation myocardial infarction

STICH: Surgical Treatment for Ischemic Heart Failure trial

SYNTAX: SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery trial

SUS: Brazilian Public Health System

UA: Unstable angina

BASE CONCEITUAL

A cardiopatia isquêmica é uma das principais causas de mortalidade de nossa população, atingindo taxas de 46% no Brasil, já tendo ultrapassado as doenças cerebrovasculares em alguns Estados. Na faixa etária entre 45 e 64 anos é a principal causa de mortalidade e sua prevalência aumenta consideravelmente com a idade. Estima-se que mais de 60.000 brasileiros morrem por ano por doença arterial coronariana (DAC), com uma taxa de mortalidade de 47 por 100.000 habitantes no ano de 2010. [1]

A DAC caracteriza-se pelo seu amplo espectro de apresentação clínica, que engloba desde a doença ateroesclerótica assintomática, até sua forma mais grave, a morte súbita. A evolução da doença não necessariamente percorre um caminho linear e muitos pacientes irão apresentar a morte súbita como primeiro sintoma. Por outro lado, diversos pacientes permanecem com a doença estável por muitos anos, sem nunca manifestar quadros de instabilização. [2]

Esta heterogeneidade pode ser explicadas, em parte, por diferenças na morfologia e remodelamento vascular entre a DAC estável e as síndromes coronarianas agudas (SCA). As placas ateroescleróticas responsáveis pelas SCAs, ditas vulneráveis, tendem a ter uma capa fibrosa fina, grandes centros lipídicos, poucas células musculares lisas, mais macrófagos e menos colágeno quando comparadas às placas estáveis. As placas estáveis são caracterizadas por capas fibrosas espessas, pequeno centro lipídico, mais células musculares lisas, poucos macrófagos e mais colágeno e estão associadas ao remodelamento constritivo, provocando estenose do lume coronariano, resultando em isquemia e sintomas anginosos, sendo menos propensas a resultarem em uma SCA. Por outro lado, placas vulneráveis geralmente não causam estenoses significativas, provocando sintomas quando há ruptura da placa. Assim, lesões coronarianas instáveis que causam o infarto do miocárdio não são necessariamente angiograficamente graves (com mais de

70% de estenose da luz do vaso) e lesões angiograficamente graves não são necessariamente instáveis.[3]

O processo de ruptura da placa aterosclerótica pode evoluir para formação de um trombo oclusivo da luz do vaso, manifestando-se clinicamente, na maioria dos casos, como síndrome coronariana com supradesnível do seguimento ST (SCACSST). Por outro lado, quando o mesmo processo de ruptura de placa resulta na formação de um trombo não oclusivo, mas que obstrui a luz do vaso, estamos diante do diagnóstico de angina instável ou infarto agudo do miocárdio (IAM) sem supradesnível do seguimento ST, diagnósticos agrupados na chamada síndrome coronariana aguda sem supradesnível do seguimento ST (SCASSST). [2]

Estes conceitos patofisiológicos são importantes no entendimento do manejo das diferentes manifestações da doença e o porque determinadas terapias são mais efetivas num contexto do que no outro.

Manejo do Infarto agudo do miocárdio com supradesnével do seguimento ST

Sabe-se que o tratamento efetivo e precoce do IAM, através da instituição de terapia de reperfusão é o componente mais importante do tratamento, sendo crucial para o seu desfecho clínico, com redução do tamanho do infarto, preservação da função ventricular e diminuição importante de morbimortalidade, sendo que o benefício de qualquer tipo de tratamento diminui na medida em que aumenta o tempo decorrido do início dos sintomas. Análises de estudos demonstram o benefício associado ao início precoce da terapêutica, estimando uma mortalidade de 1,6 por 1000 pacientes a cada hora de atraso do início de tratamento [4].

Atualmente estão disponíveis diferentes estratégias efetivas em restabelecer o fluxo coronariano e reduzir a morbidade e mortalidade do IAM com supradesnível de ST, incluindo a trombólise intra-vascular e a angioplastia primária [4-6].

Por muitos anos, a terapia de restauração da perfusão miocárdica foi realizada unicamente por administração sistêmica de droga trombolítica em nível hospitalar.

Esta estratégia foi testada por diversos ensaios clínicos randomizados, mostrando reduzir em 14 a 47% a mortalidade de pacientes atendidos com até 6 horas de evolução dos sintomas [4,5]. Segundo uma meta-análise que incluiu os 9 principais estudos da época, o tratamento com fibrinolítico instituído nas primeiras 6 horas do início da dor reduz 30 mortes a cada 1000 pacientes tratados e entre 6 e 12 horas de evolução, a redução é de 20 mortes a cada 1000 pacientes tratados, deixando de haver benefício significativo após este período [6].

Além disso, a terapia com fibrinolítico possui acesso universal, com tempo curto necessário para início do tratamento, com resultados menos dependentes da experiência do médico, refletindo menor custo para o sistema. Entretanto, apesar de seu incontestável benefício, a trombólise não é específica da circulação coronariana, havendo risco aumentado de sangramentos, sendo contra-indicada em alguns pacientes [7,8].

Neste contexto, a angioplastia primária foi introduzida como opção terapêutica para tratamento do IAM com supradesnível de ST e quando foi comparada, através de ensaios clínicos randomizados, mostrou ser superior à trombólise tanto na redução de mortalidade, quanto na recorrência de IAM: mortalidade em 30 dias de 4,4% nos pacientes que realizaram angioplastia primária e 6,5% nos pacientes que receberam trombolítico (P = 0,02), com redução absoluta de eventos combinados (óbito e recorrência de IAM) de 4,7% [9]. Além disso, o declínio de benefício quando realizada mais tardiamente é menor quando comparada à trombólise [6]. Assim, criou-se o conceito de transferência do paciente atendido com IAM com supradesnível de ST em hospitais sem infra-estrutura para centros que realizem angioplastia primária, apesar da recomendação de que a angioplastia primária deva ser realizada em 90 minutos após o primeiro atendimento do paciente (tempo porta-balão), para atingir o seu maior benefício [10]. Especificamente, pacientes com tempo porta-balão superior a 2 horas possuem um risco de mortalidade 40 a 60% maior do que os pacientes tratados em 1 hora [11].

A estratégia de transferência foi avaliada em uma meta-análise que comparou a utilização de trombolítico, em hospitais sem hemodinâmica, com a transferência para hospitais de referência para a realização de angioplastia primária, sem administração de trombolítico, observando-se benefício da transferência na redução de morte e re-infarto. O atraso relacionado à transferência do paciente foi de 100-120 minutos [12]**.** É importante salientar, entretanto, que ensaios clínicos randomizados mostraram não haver diferença de mortalidade entre angioplastia primária e trombólise nos pacientes tratados precocemente, com até 3 horas de início de apresentação dos sintomas [13, 14].

Mais recentemente, foi introduzida a trombólise pré-hospitalar, realizada pelo serviço de atendimento médico pré-hospitalar, reduzindo assim o tempo para início da instituição de tratamento efetivo. A trombólise pré-hospitalar, quando realizada em pacientes com até 2 horas de apresentação de sintomas, e com posterior realização de cineangiografia em 24 horas, possui resultados similares ou até mesmo superiores à angioplastia primária, devendo ser então considerada para aqueles pacientes em que a transferência para centros com angioplastia retarde mais do que 4 horas [13, 15].

Em inúmeros países o uso de trombólise permanece como a terapia de reperfusão mais utilizada, devido à limitada disponibilidade de laboratórios de hemodinâmica. Apesar de sua eficácia, a trombólise possui taxa de sucesso em restaurar o fluxo epicárdico (patência arterial) em torno de 50 a 70%, inferior às taxas de 70 a 90% atingidas com a angioplastia primária, determinantes diretos de maior risco de mortalidade e IAM recorrente [14]. Assim, passou-se a discutir a necessidade de encaminhar todos os pacientes que recebem terapia fibrinolítica para a realização de cineangiocoronariografia (estratégia fármaco-invasiva), ou encaminhar apenas aqueles que apresentam evidências de falha terapêutica com sinais e sintomas de isquemia recorrente. Em uma meta-análise que avaliou 5 ensaios clínicos contemporâneos (com emprego de stents), incluindo 1.235 pacientes, observou-se menor mortalidade e incidência de re-infarto quando realizada estratégia fármaco-

invasiva, comparada à realização de procedimento invasivo guiado apenas por evidências de isquemia (OR=0,60; IC95% 0,39-0,92) [16].

A prática clínica, em nosso contexto de atendimento no Sistema Único de Saúde (SUS), diverge, entretanto, da realidade de ensaios clínicos. Muitos hospitais que recebem pacientes com IAM com supradesnível de ST não possuem um serviço de hemodinâmica com angioplastia primária disponível 24 horas por dia e 7 dias por semana, a transferência para hospitais de referência muitas vezes não é factível, por contexto de superlotação e retardo na realização de transporte adequado. Determinar qual estratégia de tratamento fornece o melhor benefício ao nosso paciente de acordo com a disponibilidade de recursos torna-se fundamental.

Desenvolvimento de Sistemas de Atendimento

Apesar da superioridade da angioplastia no cenário ideal dos ensaios clínicos, o manejo do IAM com supradesnível do segmento ST na prática apresenta inúmeras considerações. Dados de grandes registros americanos e europeus mostram que 60 a 70% dos pacientes com IAM com supradesnível de ST são atendidos em hospitais sem hemodinâmica e que a instituição de terapia de reperfusão é insuficientemente implementada em muitos países, sendo estimado que aproximadamente um terço dos pacientes não recebe nenhum tipo de terapia de reperfusão [17-20]. Além disso, mesmo para os pacientes que recebem a terapia de reperfusão, atrasos no atendimento pré-hospitalar ou intra-hospitalar podem resultar em um pior prognóstico, sendo o risco relativo para óbito de 1,08 para cada 30 minutos adicionais de atraso [21]. O tempo médio de transferência para realização de angioplastia primária estimado em registros é de 180 minutos, sendo que apenas 4% dos pacientes transferidos atingem tempo menor do que 90 minutos [17].

Em publicação recente, os dados do Registro Nacional Americano (NRMI) foram analisados, comparando os períodos de 1990 a 2006. No total, 2.515.106 pacientes foram incluídos em 2.157 hospitais, sendo 54,6% pacientes com IAM com supradesnível de ST. O emprego de terapia fibrinolítica apresentou queda de 52,5%

em 1990 para 27,6% em 2006, deixando de ser a terapia de reperfusão mais frequentemente utilizada, enquanto a realização de angioplastia primária cresceu de 2,6% em 1990 para 43,2% em 2006. A proporção de pacientes elegíveis para terapia de reperfusão, mas que não receberam nenhum tipo de reperfusão, permaneceu alta, apesar da queda de 44,9% em 1990 para 28,1% em 2006. O tempo para inicio da terapêutica fibrinolítica apresentou melhora, com média de 29 minutos em 2006, dentro do alvo recomendado por diretrizes, comparado aos 59 minutos em 1990. Em relação à angioplastia primária, em pacientes transferidos de outros hospitais, a média de tempo porta-dispositivo reduziu de 226 minutos em 1994 para 139 minutos, enquanto que em pacientes atendidos em serviços com laboratório de hemodinâmica, o tempo porta-balão caiu de 111 minutos em 1994 para 79 minutos em 2006. Entre os pacientes transferidos, apenas 8,8% atingiram tempo porta-dispositivo < 90 minutos no ano de 2006. Estes achados foram acompanhados de uma redução de mortalidade de 7% em 1994 para 6% em 2006 (P<0,001) para pacientes que receberam terapia fibrinolítica, e de 8,6% em 1994 para 3,3% em 2006 (P<0,001) para pacientes submetidos à angioplastia primária [21]. Estes resultados reforçam a proposta inicial do Registro que tinha como objetivo coletar dados uniformes de maneira prospectiva que poderiam ser utilizados pelos centros participantes como indicadores de desempenho, guias para atingir as metas propostas por diretrizes e ajudar a identificar áreas com maior necessidade de melhorias [22].

Ao mesmo tempo, os dados de outros registros são conflitantes em mostrar a superioridade de angioplastia primária em relação à trombólise. Em um registro Francês que incluiu 1.714 pacientes, não houve diferença entre mortalidade intra-hopitalar, IAM recorrente e mortalidade em 30 dias, entre os pacientes tratados com angioplastia primária e trombólise. Entretanto, é importante ressaltar que 96% dos pacientes tratados com trombólise foram submetidos à cineangiocoronariografia durante a internação hospitalar, sendo 75% realizada nas primeiras 24 horas após a administração do trombolítico. A mediana de tempo para transferência do paciente de

um hospital sem hemodinâmica para a realização de angioplastia primária foi de 425 minutos (Amplitude Interquartis [AIQ] 279-701) [18].

Assim, baseado nas evidências que dispomos, não é possível afirmar que uma terapia é mais efetiva para todos os pacientes, em todos os cenários, em todos os momentos. O uso apropriado e no tempo adequado provavelmente é mais importante do que o tipo de reperfusão. Na existência de um laboratório de hemodinâmica, com disponibilidade de realizar uma angioplastia em 90 minutos, o paciente deve ser encaminhado para a realização desta estratégia. Por outro lado, se a angioplastia não é disponível em 90 min, a administração de droga fibrinolítica o mais precoce possível é o recomendado, devendo o paciente ser posteriormente encaminhado para realização de cineangiocoronariografia em até 24 horas [20].

Neste contexto, tem sido difundido, em vários países do mundo, os chamados Sistemas de Atendimento (*Systems of Care*) ao paciente com IAM com elevação do segmento ST, sendo definidos como um grupo integrado de entidades separadas, localizadas em uma determinada região, fornecendo um serviço específico. Estas entidades podem incluir serviços de emergência, hospitais comunitários, hospitais terciários, serviço de atendimento pré-hospitalar, entre outros. É esperado que através de uma gerência central do sistema, possa ser coordenada a prestação de serviço, direcionando o fluxo de atendimento, escolhendo a melhor estratégia terapêutica, melhorando a qualidade dos serviços e o desfecho dos pacientes [23]. Este sistema proporciona que os recursos humanos e de tecnologias previamente disponíveis em cada hospital, comunitário ou de referência, possam ser utilizados de maneira otimizada, sem a necessidade de gerar grandes custos institucionais adicionais, principalmente para hospitais sem laboratório de hemodinâmica que necessitariam de alto investimento para manter um programa de angioplastia primária nas 24 horas do dia [8]. A criação de sistemas de atendimentos está baseada em acordos pré-definidos de transferência e protocolos (fluxogramas) entre os hospitais comunitários e hospitais com centros de angioplastia [24-26].

No Brasil, a rede de saúde caracteriza-se pela heterogeneidade de complexos hospitalares no que diz respeito à incorporação de tecnologias e complexidade de serviços, com concentração de recursos financeiros e de pessoal nas grandes cidades e desequilíbrio regional [27]. Em São Paulo, maior cidade brasileira, com mais de 11 milhões de habitantes, um projeto piloto de rede de atendimento ao IAMCSST foi instituído e organizado pelo Hospital São Paulo da Universidade Federal de São Paulo. A implementação da rede e sistematização do atendimento ocorreu através da definição e utilização de fluxogramas de atendimento, capacitação das equipes de atendimento inicial, constituição de central de leitura de eletrocardiograma a ser transmitidos via celular ou internet, utilização de ambulâncias avançadas com disponibilidade de administração de fibrinolítico (tenecteplase) e transferência para hospital terciário com cineangiocoronariografia sistemática [28].

Por outro lado, encontramos registros de atendimento sub-ótimo em outras cidades e regiões do Brasil. Em um estudo conduzido em Feira de Santana, Bahia, em 2009, demonstrou-se em uma análise de pacientes com IAMCSST atendidos em 3 hospitais, uma grande diferença nos tempos de chegada ao atendimento, espera para terapia adequada e desfechos entre aqueles atendidos em hospitais privados e públicos daquela cidade [29].

Recentemente foi publicado um Registro Brasileiro (ACCEPT) de síndrome coronariana aguda, abrangendo todo o território nacional. O estudo inclui 2.584 pacientes, dos quais 827 (33,4%) apresentaram IAMCSST. Destes, 729 (88,1%) receberam terapia de reperfusão, 107 (12,9%) fibrinolítico e 622 (75,2%) angioplastia primária. Além disso, descrevem taxas de reperfusão diferentes de acordo com a região Brasileira, com maiores taxas na Região Sul e menores na Região Norte [27].

Manejo da síndrome coronariana aguda sem supradesnível de ST

Nos últimos 15 anos, ensaios clínicos randomizados comprovaram a eficácia e segurança de novos tratamentos disponíveis para o manejo das síndromes coronarias

agudas, evidenciando que o uso de dupla agregação plaquetária, β-bloqueadores, estatinas e inibidores da enzima conversora da angiotensina (i-ECA) reduzem a morbidade e mortalidade desta população. Apesar destas evidências, estudos apontam para discrepâncias entre a terapêutica preconizada por diretrizes internacionais e o que realmente é prescrito na prática clínica. [30]

Portanto, cresceu no mundo a necessidade de um entendimento do que acontece no mundo real dos atendimentos à SCA. Grandes registros internacionais foram instituídos com o objetivo de coletar dados uniformes prospectivos que possam ser utilizados pelos centros participantes como indicadores de desempenho, para atingir as metas propostas por diretrizes e ajudar a identificar áreas com maior necessidade de melhorias. Estes registros confirmaram a baixa taxa de adesão a algumas terapias e seu impacto no prognóstico dos pacientes. [30-34]

O estudo CRUSADE (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with early implementation of the ACC/AHA Guidelines), uma iniciativa americana para melhorar a qualidade de atendimento de pacientes com SCA sem supradesnível de ST, avaliou 350 hospitais, com um total de 64.775 pacientes, quanto à adesão às recomendações das diretrizes internacionais. Foi observada uma redução na taxa de mortalidade intra-hospitalar quanto maior a adesão aos protocolos assistenciais, 6,36% para hospitais com taxa de adesão no primeiro quartil e 4,17% para hospitais com taxa de adesão no quarto quartil. Considerando toda a população, a porcentagem da prescrição de AAS foi de 92% , β-bloqueador de 79%, heparina de 82% e de clopidogrel de 41% [35].

O ensaio clínico randomizado brasileiro (BRIDGE), avaliou se, em hospitais terciários que atendem pelo SUS, uma estratégia multifacetada para melhoria de prática clinica é mais eficaz do que o atendimento usual em relação ao padrão de prescrição no atendimento de pacientes com SCA. O estudo incluiu 1.150 pacientes de 34 instituições brasileiras, incluindo hospitais de referência, universitários e de periferia. Foi demonstrado que o uso de ferramentas de melhoria da qualidade

assistencial aumentou a prescrição de terapias baseadas em evidência (AAS, estatina, beta-bloqueadores e i-ECA), independente do tipo de centro: 67,9% dos pacientes do grupo intervenção receberam todas as terapias preconizadas em comparação com 49,5% do grupo controle. Entretanto, a melhor adesão às diretrizes não repercutiu em melhores desfechos intra-hospitalares. [36]

Manejo da cardiopatia isquêmica estável

A cirurgia de revascularização miocárdica (CRM) foi introduzida em 1968 e rapidamente difundiu-se como opção terapêutica para pacientes sintomáticos com DAC [37]. Em 1977, com o desenvolvimento da angioplastia coronariana transluminal percutânea (ACTP), ampliou-se as possibilidades terapêuticas com um procedimento menos invasivo para revascularização coronariana [38]. Inicialmente realizada somente com dilatação por balão intra-luminal, a terapia apresentava resultados inferiores à CRM [39], mas era uma alternativa àqueles pacientes que não podiam ser submetidos a cirurgias de grande porte. O desenvolvimento dos stents mudou a perspectiva do tratamento percutâneo auxiliado pelo desenvolvimento de drogas antiplaquetárias mais eficazes [40,41]. Com o aprimoramento da expertise e avanços tecnológicos, a ACTP passou a ser uma opção terapêutica também para pacientes multi-arteriais.[41-45]. Frente a esta nova perspectiva, surgiram uma série de novos estudos de comparação entre ACTP e CRM, mostrando superioridade da CRM principalmente em prevenção de novas intervenções, sem diferenças significativas em relação a desfechos primários. Sub-análises de grandes estudos e análises de estudos menores mostraram que quanto maior o número de vasos afetados, pior o desempenho da ACTP em relação à CRM [42-46].

O desenvolvimento de stents com eluição de drogas (stent envolvido por fármacos de liberação lenta com propriedades antiinflamatórias e antiproliferativas) foi um avanço do procedimento percutâneo [47-49], demonstrando taxas menores de reestenose em relação aos stents convencionais (em torno de 15%, contra

aproximadamente 30% dos stents não-farmacológicos) [50-52], além de melhora em desfechos clínicos desde que acompanhados de forte terapia antiplaquetária nos meses subseqüentes à angioplastia [53,54]. Porém, o dispositivo apresentou aumento da taxa de trombose intra-stent nos pacientes sem adequado tratamento anti-plaquetário [55,56].

A terapia cirúrgica também evoluiu ao longo do tempo. Melhora na quantificação do risco pré-cirúrgico, do cuidado pós-cirúrgico e da técnica de anestesia diminuíram a morbi-mortalidade hospitalar [57]. O maior conhecimento da técnica cirúrgica e utilização de enxertos arteriais também reduziram a taxa de oclusão dos enxertos, aumentando o sucesso da CRM [58].

Entretanto, nos últimos anos, as evidências cietíficas têm restringido a indicação de procedimentos de revascularização em pacientes com DAC estável, decorrente de resultados conflitantes sobre o impacto destas terapias em morbi-mortalidade neste contexto [49,59-64]. Estudos têm demonstrado que o tratamento com ACTP reduz sintomas de angina e aumenta a capicidade funcional, mas não possue impacto em melhora de sobrevida, mesmo quando comparada à terapia medicamentosa isolada [58]. O estudo COURAGE, demonstrou taxa de eventos primários de 19% nos pacientes submetidos à ACTP e 18,5% naqueles em terapia medicamentosa (HR 1,05 IC95% 0,87-1,27; P = 0,62) [59]. O sub-estudo de avaliação nuclear do estudo COURAGE, publicado posteriormente, demonstrou que pacientes com isquemia moderada a grave (>10%), documentada por cintilografia miocárdica, submetidos à ACTP tiveram maior redução da isquemia em relação àqueles submetidos a tratamento medicamentoso (33% versus 19%; P=0,0004) [60].

Estudos recentes têm confirmado a superioridade da CRM em previnir eventos cardíacos maiores em pacientes com doença multiarterial, especialmente em pacientes com doença coronariana complexa e em diabéticos [61-63]. Porém, os mesmos estudos apontam para resultados similares das duas estratégias em pacientes com lesões coronarias menos complexas [62,64] . O estudo SYNTAX procurou avaliar o

melhor procedimento de revascularização para DAC, em pacientes com lesão do tipo de novo tri-arterial ou em tronco de coronária esquerda (isolada ou acompanhada de doença de outros vasos). Os pacientes foram randomizados para tratamento com ACTP com stent em droga ou para CRM. Os objetivos do estudo foram, além de definir o papel da ACTP com stent com eluição de droga e da CRM, desenvolver um escore (SYNTAX score) capaz de guiar a tomada de decisão do médico cardiologista, optando entre ACTP e CRM de acordo com as características angiográficas das lesões. Os resultados mostraram 17.8% de eventos primários em pacientes submetidos à ICP e 12.4% nos pacientes submetidos à CRM (P = 0.002). Entretanto, em sub-análise desde estudo, observou-se que pacientes com escore SYNTAX mais baixo (<22) submetidos à terapia percutânea teriam taxa de eventos semelhante aos pacientes submetidos à cirúrgica, sendo esta última preferencial em pacientes com escore mais alto [62]. Neste contexto, a determinação do escore SYNTAX tornou-se de grande valia na indicação de procedimento de revascularização em pacientes com lesão de três vasos ou com lesão de tronco de coronária.

As diretrizes nacionais e internacionais para manejo de pacientes com DAC estável recomendam, com objetivo de melhora em sobrevida, a revascularização com CRM para pacientes sintomáticos com doença de tronco de coronária esquerda, doença de 3 vasos com ou sem o comprometimento da artéria coronária descendente anterior proximal ou doença de 2 vasos com acometimento da artéria coronária descendente anterior proximal (Recomendação Classe I). Para os mesmos pacientes, indicam ACTP com Recomendação Classe IIa. Entretanto, todas as recomendações de revascularização para melhora de sobrevida estão baseadas em Níveis de Evidência B ou C. As diretrizes enfatizam a importância da decisão de estratégia terapêutica estar baseada na opinião de um grupo de especialistas (Heart Team), incluindo hemodinamicistas, cirurgiões cardíacos e cardiologistas clínicos, demonstrando que a opção da melhor terapêutica nem sempre é um concenso e deve ser tomada com base em múltiplos aspectos [65-67].

A maneira de avaliação da complexidade da DAC ainda não está bem estabelecida. Em pacientes estáveis, o manejo focal com terapia de reperfusão de lesões coronarianas graves não implica necessariamente em impacto de redução de mortalidade e na taxa de infarto do miocárdio, provavelmente porque a lesão a ser tratada não é a única suscetível em desencadear um evento agudo. Portanto, identificar aquele paciente com maior propensão a desfechos é um desafio diário da prática clínica.

JUSTIFICATIVA

Estudos de efetividade clínica têm ajudado na construção das evidências científicas, principalmente no que diz respeito ao entendimento da prática clínica no mundo real e identificação de pontos críticos. Conhecer a prática local permite ações de melhorias tanto institucionais quanto a criação de modelos a serem disseminados. A hierarquia da evidência avança para a consolidação da importância dos estudos de custo-efetividade e avaliações de tecnologia, ampliando, aos gestores de saúde, a definição de melhores práticas para implementação de políticas de saúde.

OBJETIVO GERAL

Avaliar a efetividade do manejo da cardiopatia isquêmica aguda e crônica através de dados de registros locais.

Objetivos específicos

Artigo 1: Estudar o conceito e processo de desenvolvimento de estudos de efetividade clínica e seu papel na medicina baseada em evidência.

Artigo 2: Avaliar a tendência temporal, ao longo de 11 anos, do uso de terapias médicas baseadas em evidência e indicadores de qualidade assistencial em pacientes com síndrome coronariana aguda, em uma instituição pública de referência do Brasil.

Artigo 3**:** Descrever o atendimento e desfechos de pacientes com infarto agudo do miocárdio com supradesnível de ST em hospital terciário de referência no Sul do Brasil, permitindo uma reflexão do status do cuidado a estes pacientes na América Latina.

Artigo 4**:** Avaliar o prognóstico a longo prazo de pacientes com doença arterial coronariana estável tratados inicialmente com terapia medicamentosa isolada, comparado com pacientes submetidos à terapias de revascularização.

CONFLITOS DE INTERESSE

Os autores declaram não haver conflitos de interesse relacionados aos artigos aqui apresentados.

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REFERÊNCIAS

1. Ministério da Saúde. DATASUS. (Departamento de Informática do SUS). [Acess on 2013 mar 19]. Available from http://www2.datasus.gov.br

2. Canty Jr. JM. Coronary blood flow and myocardial ischemia. In: Libby P, Bonow R, Mann P, Zipes DP, eds Braunwald's Heart Disease. A textbook of cardiovascular medicine. 8th ed. Philadelphia: WB Saunders. 2008. p.1167-1194.

3. Naghavi M, Libby P, Falk E, et al. From vulnerable plaque to vulnerable patient: a call for new definitions and risk assesmentstrategies. Circulation 2003;108:1664-72.

4. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988;2:349-60.

5. Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Lancet 1986;1:397-402.

6. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.

7. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994;343:311-22.

8. Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction: a comprehensive review of contemporary management options. J Am Coll Cardiol 2007;50:917-29.

9. Weaver WD, Simes RJ, Betriu A, et al. Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. JAMA 1997;278:2093-8.

10. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation 2004;110:e82-292.

11. Moyer P, Feldman J, Levine J, et al. Implications of the Mechanical (PCI) vs Thrombolytic Controversy for ST Segment Elevation Myocardial Infarction on the Organization of Emergency Medical Services: The Boston EMS Experience. Crit Pathw Cardiol 2004;3:53-61.

12. Dalby M, Bouzamondo A, Lechat P, Montalescot G. Transfer for primary angioplasty versus immediate thrombolysis in acute myocardial infarction: a meta-analysis. Circulation 2003;108:1809-14.

13. Steg PG, Bonnefoy E, Chabaud S, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. Circulation 2003;108:2851-6.

14. Widimsky P, Bilkova D, Penicka M, et al. Long-term outcomes of patients with acute myocardial infarction presenting to hospitals without catheterization laboratory and randomized to immediate thrombolysis or interhospital transport for primary percutaneous coronary intervention. Five years' follow-up of the PRAGUE-2 Trial. Eur Heart J 2007;28:679-84.

15. Stenestrand U, Lindback J, Wallentin L. Long-term outcome of primary percutaneous coronary intervention vs prehospital and in-hospital thrombolysis for patients with ST-elevation myocardial infarction. JAMA 2006;296:1749-56.

16. Collet JP, Montalescot G, Le May M, Borentain M, Gershlick A. Percutaneous coronary intervention after fibrinolysis: a multiple meta-analyses approach according to the type of strategy. J Am Coll Cardiol 2006;48:1326-35.

17. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation 2005;111:761-7.

18. Danchin N, Coste P, Ferrieres J, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data from the french registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation 2008;118:268-76.

19. Fassa AA, Urban P, Radovanovic D, et al. Trends in reperfusion therapy of ST segment elevation myocardial infarction in Switzerland: six year results from a nationwide registry. Heart 2005;91:882-8.

20. Bassand JP, Danchin N, Filippatos G, et al. Implementation of reperfusion therapy in acute myocardial infarction. A policy statement from the European Society of Cardiology. Eur Heart J 2005;26:2733-41.

21. De Luca G, Suryapranata H, Ottervanger JP, Antman EM. Time delay to treatment and mortality in primary angioplasty for acute myocardial infarction: every minute of delay counts. Circulation 2004;109:1223-5.

22. Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008;156:1035-44.

23.Jacobs AK, Antman EM, Faxon DP, Gregory T, Solis P. Development of systems of care for ST-elevation myocardial infarction patients: executive summary. Circulation 2007;116:217-30.

24. Henry TD, Atkins JM, Cunningham MS, et al. ST-segment elevation myocardial infarction: recommendations on triage of patients to heart attack centers: is it time for a national policy for the treatment of ST-segment elevation myocardial infarction? J Am Coll Cardiol 2006;47:1339-45.

25. Van de Werf F, Bax J, Betriu A, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2008;29:2909-45.

26. Bradley EH, Herrin J, Wang Y, et al. Strategies for reducing the door-to-balloon time in acute myocardial infarction. N Engl J Med 2006;355:2308-20.

27. Piva e Mattos LA, Berwanger O, Santos ES, et al. Desfechos Clínicos aos 30 dias do Registro Brasileiro das Síndromes Coronárias Agudas (ACCEPT). Arq Bras Cardiol 2013;100:6-13.

28. Caluza AC, Barbosa AH, Gonçalves I, et al. Rede de Infarto com Supradesnivelamento de ST: Sistematização em 205 Casos Diminui Eventos Clínicos na Rede Pública. Arq Bras Cardiol 2012;99:1040-1048.

29. Ferreira GM, Correia LC, Reis H, et al. Increased mortality and morbidity due to acute myocardial infarction in a public hospital in Feira de Santana, Bahia. Arq Bras Cardiol 2009;93:97-104.

30. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA1999;282:1458- 1465.

31. Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes: variations in practice and outcome: findings from the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2002; 23:1177-1189.

32. Hoekstra JW, Pollack CV Jr, Roe MT, et al. Improving the care of patients with non−ST-elevation acute coronary syndromes in the emergency depart- ment: the CRUSADE initiative. Acad Emerg Med 2002; 9:1146-1155.

33. Carruthers KF, Dabbous OH, Flather MD, et al. The Global Registry of Acute Coronary Events (GRACE). Contemporary management of acute coronary syndromes: does the practice match the evidence? Heart 2005; 91:290-8.

34. The ACCESS Investigators. Management of acute coronary syndromes in developing countries: acute coronary events - a multinational survey of current management strategies. Am Heart J 2011;162:852-859.

35. Peterson E D, Roe M T, Mulgund J, et al. Association Between Hospital Process Performance and Outcomes Among Patients with Acute Coronary Syndromes. JAMA 2006; 296: 1912-1920.

36. Berwanger O, Guimarães H, Laranjeira, et al. Effect of a Multifaceted Intervention on Use of Evidence-Based Therapies in Patients With Acute Coronary Syndromes in Brazil. The BRIDGE-ACS Randomized Trial. JAMA 2012;307:2041-9.

37. Favaloro RG. Saphenous vein autograft replacement of severe segmental coronary artery occlusion: operative technique. Ann Thorac Surg 1968;5:334-9.

38. Grüntzig A. Transluminal dilatation of coronary-artery stenosis. Lancet 1978;1: 263.

39. Hoffman SN, TenBrook JA, Wolf MP, et al. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: one- to eight-year outcomes, J Am Coll Cardiol 2003;41:1293–1304.

40. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of baloon-expandable-stent implantation with baloon angioplasty in patients with coronary artery disease. Benestent group study. N Engl J Med 1994; 331:489-95

41. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent reestenosis study investigators. N Engl J Med 1994; 331:496-501

42. Pursnani S, Korley F, Gopaul R, et al. Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: a systematic

review and meta-analysis of randomized clinal trials. Percutaneous Cardiovasc Interv 2012;5:476-90.

43. Rodriguez A, Bernardi V, Navia J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple Vessel Disease (ERACI II): 30 days results and one-year follow-up results. J Am Coll Cardiol 2001; 3:51–58.

44. Booth J, Clayton T, Pepper J, et al. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation 2008;118:381-8.

45. Serryus PW, Unger F, Souza JE, et al. Comparison of Coronary-Artery Bypass Surgery and Stenting for the Treatment of Multivessel Disease. N Eng J Med 2001; 344:1117-24.

46. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (The stent or surgery Trial): a randomised controlled Trial. Lancet 2002; 360:965-70.

47. Serruys P, Daemen J, Morice MC, et al. Three-year follow-up of the ARTS-II — sirolimus-eluting stents for the treatment of patients with multivessel disease. EuroInterv 2007;3:450–9.

48. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass graft ing in multivessel coronary disease. N Engl J Med 2008;358:331-41.

49. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes D, Mack MJ, et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. N Eng J Med 2009; 360:961-72.

50. Morice MC, Serruys PW, J.E. Sousa JE, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization, N Engl J Med 2002; 346:1773–1780.

51. Grube E, Silber S, Hauptmann KE, et al. TAXUS I: six- and twelve-month results from a randomized, double-blind trial on a slow-release paclitaxel-eluting stent for de novo coronary lesions, Circulation 2003; 107:38–42.

52. Babapulle MN, Joseph L, Belisle P, et al. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents, Lancet 2004; 364:583–91.

53. Kastrati A, von Beckerath N, Joost A, Pogatsa-Murray G, Gorchakova O, Schoming A. Loading with 600 mg clopidogrel in patients with coronary artery disease with and without chronic clopidogrel therapy. Circulation 2004; 110:1916-9

54. Moliterno DJ, Steinhubl SR. Clopidogrel for percutaneous coronary revascularization: time for more pretreatment, retreatment, or both? JAMA 2005; 294:1271-3.

55. Mauri L, Hsieh WH, Massaro JM, Ho KK, D'agostino R, Cutlip DE. Stent thrombosis in randomized clinical trails of drug-eluting stents. N Eng J Med 2007; 356:1020-9.

56. Wenaweser P, Daemen J, Zwahlen M, van Domburg R, Juni P, Vaina S, et al. Incidence and correlates of drug-eluting stent thrombosis in routine clinical practice: 4-year results from a large 2-institucional cohort study. J Am Coll Cardiol 2008; 52:1134-40.

57. Flynn M, Reddy S, Shepherd W, et al. Fast-tracking revisited: routine cardiac surgical patients need minimal intensive care, Eur J Cardiothorac Surg 2004; 25:116–22

58. Tavilla G, Kappetein AP, Braun J, et al. Long-term follow-up of coronary artery bypass grafting in three-vessel disease using exclusively pedicled bilateral internal thoracic and right gastroepiploic arteries, Ann Thorac Surg 2004; 77:794–9

59. Boden WE, O'Rourke RA, Teo KK, Hartigan PM, Maron DJ, Kostuk WJ, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-1516.

60. Shaw LJ, Berman DS, Maron DJ, Mancini J, Hayes SW, Hartigan PM, et al. Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden: Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear substudy. Circulation 2008;117:1283-1291.

61. Hueb W, Soares PR, Gersh BJ, César LAM, Luz PL, Puig LB, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol 2004;43:1743–51.

62. Mohr FW, Morice MC, Kappetein, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.

63. The BARI 2D Study Group. A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. N Engl J Med 2009;360:2503-15.

64. Farkou ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.

65. Guimarães JI, César LAM, Mansur AP, et al. Diretriz de Angina Estável da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol 2004;83: Supl II.

66. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/ SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012;60:e44-e164.

67. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–2555.

ARTIGO 1

O papel dos estudos de efetividade clínica nas doenças cardiovasculares

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Palavras chaves: estudos de efetividade, doenças cardiovasculares

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Inúmeros estudos são publicados diariamente, trazendo novas evidências para a prática médica, tornando um desafio ao médico manter-se atualizado. O olhar crítico das publicações e a avaliação de sua aplicabilidade é crucial para a boa prática da medicina baseada em evidências. Com a disseminação de conceitos da medicina baseada em evidência e avaliação de tecnologia em saúde, muitos atores indiretos do processo de saúde, como gestores, definidores de políticas públicas não entendem os motivos pelos quais as evidências não são adotadas diretamente na prática clínica. A lacuna entre os ensaios clínicos, as diretrizes e os dados reais da prática clínica tem sido constantemente questionada, tornando o cenário por vezes confuso. Parte disto se deve a interpretação simplista e literal de muitos dados da literatura científica. Tem se tornado cada vez mais claro que as lacunas da prática são também lacunas do nosso conhecimento sobre o que é efetivo ou não para os nossos pacientes.

Ensaios clínicos randomizados: o ideal e a prática

Os ensaios clínicos randomizados são considerados a metodologia padrão ouro para estabelecer relação causa e efeito entre uma terapia e um desfecho, pois garantem que os grupos intervenção e controle sejam similares tanto nos aspectos que conhecemos, mas, principalmente, naqueles que não conhecemos e que podem influenciar os desfechos. Quando bem delineados, possuem validade interna e estabelecem a eficácia de novas tecnologias [1,2]. Entretanto, mesmo com eficácia comprovada, não podemos ter a certeza de que os seus resultados podem ser generalizados para a rotina da prática clínica devido, principalmente, aos rígidos protocolos dos estudos e as populações incluídas muito selecionadas. Em geral, existem discrepâncias entre as características das populações de ensaios clínicos randomizados em relação às populações descritas por registros, principalmente quanto ao gênero e presença de comorbidades [3,4]. Esta diferença de populações está exemplificada na Tabela 1, na qual avaliamos o perfil de pacientes com síndrome

coronariana aguda (SCA) atendidos em um hospital terciário do sul do país e comparamos com as populações incluídas em grandes ensaios clínicos [5,6].

A partir disso, surgem alguns questionamentos quanto a validade externa de muitos ensaios clínicos publicados: como os novos tratamentos funcionam fora de circunstâncias ideais? As novas terapias se comportam de maneira diversa em diferentes populações em relação às populações dos ensaios clínicos randomizados?

Um exemplo é o caso da terapia de reperfusão miocárdica, nos quais ensaios clínicos randomizados demonstraram a superioridade da angioplastia primária em relação aos fibrinolíticos em pacientes com infarto agudo do miocárdio com supradesnível de ST (IAMCSST) [7]. Entretanto, estes ensaios clínicos foram conduzidos em centros de referência, onde é realizado um grande volume de cineangiocoronariografias por profissionais experientes. Além disso, geralmente são centros onde há um sistema de saúde integrado e os tempos ótimos de tratamento são atingidos. Registros americanos demonstram que mais de 25% de seus hospitais não possuem serviço de hemodinâmica, assim, uma grande proporção de pacientes atendidos com IAMCSST são transferidos para a realização de angioplastia primária com resultantes atrasos nos tempos de reperfusão. Apenas 5% a 18% dos pacientes transferidos atingem a meta de reperfusão de 90 minutos, sendo a média de tempo de 150 minutos [8]. Em publicação de 2008, o registro francês FAST-MI demonstrou não haver diferença de mortalidade em 30 dias em pacientes com IAMCSST tratados com angioplastia primária e fibrinolítico [9]. Analisando as evidências observamos que os benefícios da angioplastia primária sobre os fibrinolíticos é dependente do tempo de reperfusão atingido e a aplicabilidade dos resultados dos ensaios clínicos varia de acordo com a realidade do centro em que o paciente é atendido [8,9].

Em uma sub-análise do estudo PLATO, que comparou o uso de ticagrelor e clopidogrel em pacientes com SCA, foi demonstrado uma interação significativa entre o efeito do tratamento do estudo e a região em que os pacientes foram alocados, com menor benefício do ticagrelor em relação ao clopidogrel nos pacientes incluídos nos

Estados Unidos, o que foi atribuído à dose de manutenção de aspirina utilizada nos pacientes destes centros [10].

Um modelo sugerido de como generalizar os resultados de ensaios clínicos está representado na Figura 1. Geralmente quanto menor o tamanho do ensaio clínico e maior a sua complexidade, maior a eficácia comprovada, mas menor a sua efetividade[11].

Além da validade externa, outra questão a ser apontada é o surgimento de inúmeros novos medicamentos. A decisão de incorporação de novas tecnologias torna-se um desafio aos gestores de saúde e comunidade médica que devem avaliar se os resultados de ensaios clínicos poderão ser aplicados em sistemas de saúde amplos, nos quais são considerados custos e viabilidade. Muitas vezes a recomendação de uso de novas medicações não é consenso, mesmo dentro de grupo de especialistas. Em 2011 e 2012 foram publicadas as diretrizes para o manejo de SCA sem supradesnível do seguimento ST pela Sociedade de Cardiologia Européia (ESC) [11] e Sociedades de Cardiologia Americanas (ACCF/AHA) [13], com base nas mesmas evidências, a leitura e recomendação para uso de novos antiagregantes plaquetários, inibidores do receptor P2Y12, em adição ao ácido acetil salicílico (AAS), não é a mesma. A ESC recomenda uso de ticagrelor para todos os pacientes de moderado a alto risco de eventos isquêmicos e prasugrel para pacientes virgens de tratamento com inibidores de P2Y12 (especialmente diabéticos) em que a anatomia coronariana é conhecida e angioplastia esta planejada, a menos que haja alto risco de sangramento maior ou contra-indicações para uso desta medicação. O uso de clopidogrel é recomendado para aqueles pacientes que não podem receber ticagrelor ou prasugrel [12]. Por outro lado, a ACCF/AHA não endossa o uso de um dos inibidores do receptor P2Y12 como superior aos outros, recomendando o uso de clopidogrel ou ticagrelor para pacientes de moderado a alto risco quando administrado antes da angioplastia e clopidogrel ou ticagrelor ou prasugrel quando administrado durante a angioplastia. Discutem que a decisão sobre qual inibidor do receptor de P2Y12

escolher deve ser individualizada ao paciente com base na eficácia, riscos de sangramento e na experiência de uso das medicações. Ressaltam que há pouca informação sobre o uso de estratégias para selecionar quais os pacientes mais se beneficiam do uso dos novos inibidores do receptor P2Y12 [13]. Até o momento, não há uma atualização da diretriz da Sociedade Brasileira de Cardiologia. Não existem ensaios clínicos randomizados que comparem o uso dos três inibidores do receptor de P2Y12 na mesma população.

Pesquisa de Efetividade Comparativa

Na prática existe, portanto, uma lacuna entre a produção científica e as necessidades dos consumidores e provedores de cuidados em saúde. Assim, os chamados estudos de efetividade ampliam seu papel e espaço na medicina baseada em evidências, com o objetivo de avaliar como as novas tecnologias de eficácia comprovada se comportam no mundo real. Na literatura internacional podemos encontrar o termo pesquisa de efetividade comparativa (*Comparative Effectiveness Research - CER*), apontada como prioridade nacional nos Estados Unidos em 2009, recebendo grande parte dos recursos destinados à pesquisa. Possui como definição a produção e síntese de evidência que compara os benefícios e malefícios de métodos alternativos de tratamento, prevenção e diagnóstico, com o objetivo de fornecer informações para facilitar a tomada de decisão médica e melhorar os desfechos em saúde e sistemas de cuidado [14].

Os estudos de efetividade clínica não apresentam uma metodologia específica, podendo incluir tanto desenhos experimentais quanto não experimentais. A efetividade pode ser avaliada através de ensaios clínicos pragmáticos; síntese de estudos disponíveis por revisões sistemáticas e meta-análises com utilização de estudos de simulação e modelos de decisão; e a realização de estudos observacionais de alta qualidade, conhecidos como os registros clínicos [11].

Os ensaios clínicos pragmáticos são desenhados para suprir muitas das limitações dos ensaios clínicos randomizados: estudam uma população ampla, sem critérios rígidos de seleção, incluem centros com características diversas, não apenas centros de referência, buscam avaliar uma estratégia terapêutica e não apenas uma droga ou dispositivo, utilizam controles ativos e de comparação relevante e avaliam múltiplos desfechos, incluindo sintomas, qualidade de vida e custos. Entretanto, sua condução é limitada por possuírem, em geral, um alto custo e grande tempo necessário para sua realização [11]. Um exemplo de ensaio clínico pragmático é o estudo brasileiro BRIDGE, ensaio clínico randomizado em cluster que teve como objetivo avaliar se, em hospitais terciários que atendam pelo Sistema Único de Saúde (SUS), uma estratégia multifacetada para melhoria de prática clinica é mais eficaz do que o atendimento usual em relação ao padrão de prescrição no atendimento de pacientes com SCA. Foi demonstrado que o uso de ferramentas de melhoria da qualidade assistencial aumentou o uso da prescrição de terapias baseadas em evidência (AAS, estatina, beta-bloqueadores e inibidores da ECA), independente se fosse centro universitário ou não. O estudo serve aos gestores de saúde como evidência de que práticas de melhoria de qualidade assistencial são eficazes e efetivas [15].

As revisões sistemáticas com realização de meta-análise e modelos de decisão possuem papel importante na avaliação da efetividade. Muitas vezes, achados iniciais de ensaios clínicos randomizados são refutados ao longo dos anos quando testados em diferentes populações [11]. Em estudo publicado em 2005, demonstrou-se que um quarto dos ensaios clínicos mais citados, publicados entre 1990 e 2003, superestimava os efeitos em favor da terapia estudada, ou seja, em estudos publicados posteriormente a magnitude do efeito da terapia era menor [16]. Além disso, muitas vezes ensaios clínicos randomizados que testaram a mesma tecnologia trazem resultados diferentes, sendo difícil estabelecer sua real eficácia. A realização de uma meta-análise permite a avaliação do impacto de uma terapêutica em um número maior

de pacientes, tornando, muitas vezes, possível estabelecer uma conclusão mais precisa sobre dados conflitantes. Outro aspecto a ser considerado é que a eficácia de um tratamento pode variar significativamente de acordo com a característica dos pacientes, como por exemplo idade, sexo e presença de comorbidades, assim em estudos de meta-análise é possível avaliar subgrupos de pacientes em centros diferentes, o que muitas vezes não é factível com um único ensaio clínico pelo número insuficiente de pacientes incluídos e reduzido número de eventos [11].

Em uma meta-análise conduzida no Brasil avaliou-se o impacto da terapia combinada de implante de ressincronizador e cardiodesfibrilador (CDI) na sobrevida de pacientes com insuficiência cardíaca (IC). Como resultado, encontrou-se um benefício significativo com redução de mortalidade e de hospitalizações por IC em adicionar o implante de um ressincronizador para a maioria dos pacientes com IC elegíveis para o implante de um CDI. Além disso, a gravidade da IC foi considerada um importante aspecto que influencia na magnitude do efeito da resposta ao cardiodesfibrilador: pacientes com classe funcional da NYHA III e IV possuem a maior redução de mortalidade [17]. Conclusões essas sobre o impacto em desfechos mais duros que só foram possíveis após agrupar o resultado de estudos, devido ao aumento no número de eventos estudados. Este é um exemplo de avaliação de tecnologia de alto custo, na qual a sua efetividade clínica e identificação de uma população de maior benefício auxilia na incorporação de recomendações para gestores de saúde.

Os registros clínicos têm sido utilizados pela comunidade científica contemporânea para documentar a prática clínica usual, encontrar disparidades nos sistemas de cuidado e avaliar a segurança de terapias e procedimentos. Quando bem conduzidos, podem fornecer dados mais representativos dos benefícios das tecnologias aplicadas na saúde e de como se comportam a expectativa de desfechos na realidade local. Na comunidade internacional cresceram o número de registros nacionais que incluem, cada vez mais, um número maior de centros participantes [8,9,11].

Em 2012, foi publicado no JAMA os dados do Registro Nacional Francês, com um total de 6707 pacientes com IAMCSST incluídos entre 1995 e 2010. Foi identificada uma queda de mortalidade ao longo dos anos (mortalidade em 30 dias em 1995 de 13,7% para 4,4% em 2010) e um maior uso de terapias de reperfusão (49,4% para 74,7%) e prescrição de medicações recomendadas. Além disso, foi observado um aumento no uso de unidades móveis de atendimento de 23,2% para 48,8%. Os resultados observados com impacto na sobrevida dos pacientes foram atribuídos a melhorias instituídas no sistema de cuidado ao IAMCSST no país, que possibilitou uma maior frequência de realização de terapia de reperfusão com angioplastia primária, maior uso de terapias adjuvantes baseadas em evidências, e modificações no comportamento dos pacientes que passaram a procurar atendimento de forma mais precoce e com maior uso de sistema de atendimento pré-hospitalar. Além da reformulação no sistema de cuidado ao IAMCSST, as autoridades de saúde francesas lançaram campanhas nos últimos 10 anos para aumentar o conhecimento dos sintomas iniciais do infarto do miocárdio e estímulo para uso do número de telefone de emergência nacional pela população [18].

Em 1990, foi instituído nos Estados Unidos o Registro Nacional de Infarto do Miocárdio (NRMI), com o objetivo de identificar e monitorar o cumprimento de intervenções que possibilitem a implantação mais rápida de terapias de reperfusão para paciente com IAMCSST. Em 2008, foram publicados os dados de 1990 a 2006, com a inclusão de 1.374.232 pacientes atendidos por IAMCSST em 2.157 hospitais do país. Foi observado um declínio na proporção de pacientes que receberam terapia fibrinolítica de 52,5% em 1990 para 27,6% em 2006 e um aumento na realização de angioplastia primária de 2,6% para 43,2%. Além disso, os tempos para reperfusão diminuíram ao longo dos anos, tanto o tempo porta-agulha (primeiro atendimento do paciente até administração de terapia fibrinolítica) quanto o tempo porta balão (primeiro atendimento até realização da angioplastia coronariana primária). Estes achados foram acompanhados de queda de mortalidade. A melhora relativa de

redução de mortalidade atribuída à melhora no tempo porta-agulha foi de 16,3% e de 7,5% para o tempo porta-agulha [19].

No Brasil, um registro nacional de pacientes atendidos por síndrome coronariana aguda está sendo conduzido pela Sociedade Brasileira de Cardiologia (Registro ACCEPT), incluindo diversos centros do país, com representatividade de todas as regiões brasileiras. Dados de seguimento de 30 dias demonstram uma tendência a menores taxas de mortalidade naqueles pacientes com SCA sem supradesnível do seguimento ST submetidos a procedimento de revascularização (1,9%) em relação aos pacientes sem terapia de revascularização (4,2%) (P=0,070). Da mesma forma, pacientes com IAMCSST apresentaram melhor prognóstico quando submetidos à revascularização, com taxa de mortalidade em 30 dias de 2,0% quando comparados aos sem terapia de reperfusão (8,1%) (P<0,001) [20].

Assim, avaliamos a importância e o papel dos registros clínicos no contexto da medicina baseada em evidência: nos anos 90, ensaios clínicos randomizados comprovaram a superioridade da angioplastia primária em relação aos fibrinolíticos no tratamento do infarto do miocárdio com supradesnível do seguimento ST [7]. Posteriormente, grandes registros internacionais, ou seja, estudos de efetividade, demonstraram que a angioplastia primária no mundo real era, em geral, limitada por atrasos em sua realização, o que gerava piores desfechos, não atingindo o impacto encontrado nos ensaios clínicos randomizados [8,9]. Estes registros serviram, então, de propulsores para o desenvolvimento de estratégias de melhoria dos sistemas de cuidado, com consequente melhora nos tempos de tratamento. A partir de então, foram realizados novos ensaios clínicos que estudaram diferentes estratégias de reperfusão, levando em conta o contexto específico regional [21]. Dessa forma, fecha-se um ciclo de evidências, no qual metodologias de eficácia e efetividade se complementam (Figura 2).

Em conclusão, os estudos de efetividade clínica possuem papel importante na construção da evidência científica e os tipos de estudos não são competitivos. Devemos entender o valor que cada tipo de evidência traz.

Referências

1. Berwanger O, Guimarães HP, Avezum A, Piegas LS. Os dez mandamentos do ensaio clínico randomizado - princípios para avaliação crítica da literatura médica. Rev Bras Hipertens 2006;23:65-70.
2. Stanley K. Desing of randomized controlled trials. Circulation. 2007;115:1164-1169.
3. Gurwitz JH, Col NF, Avorn J. The exclusion of the elderly and women from clinical trials in acute myocardial infarction. JAMA 1992;268: 1417–1422.
4. Brown N, Melville M, Gray D, Young T, et al. Relevance of clinical trial results in myocardial infarction to medical practice: comparison of four year outcome in participants of a thrombolytic trial, patients receiving routine thrombolysis, and those deemed ineligible for thrombolysis. Heart 1999;81:598–602.
5. Yusuf S, Mehta SR, Zhao F, et al. Early and Late Effects of Clopidogrel in Patients With Acute Coronary Syndromes. Circulation 2003;107: 966-972.
6. James S, Akerblom A, Cannon CP, et al. Comparison of ticagrelor, the first reversible oral P2Y12 receptor antagonist, with clopidogrel in patients with acute coronary syndromes: Rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. Am Heart J 2009;157:599-605.
7. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.
8. Boden WE, Eagle K, Granger CB. Reperfusion Strategies in acute ST-segment elevation myocardial infarction. J Am Coll Cariol 2007; 50:917-29.
9. Danchin N, Coste Pierre, Ferrieres J, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary inetervention for ST-segment-elevation acute myocardial infarction. Data from the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI). Circulation 2008;118:268-276.

10. Cannon CP, Harrington RA, James S, Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet 2010; 375: 283–93.

11.Nallamothu BK, Hayward RA, Bates ER. Beyond the Randomized Clinical Trial. The role of effectiveness studies in evaluating cardiovascular therapies. Circulation 2008;1294-1303.

12. Hamm CW, Bassand J-P, Agewall S, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. European Heart Journal 2011;32:2999–3054.

13. Jneid H, Anderson JL, Wright S, et al. 2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update). Circulation 2012;126:875-910.

14. Hlatky MA, Douglas PS, Cook NL, et al. Future directions for cardiovascular disease comparative effectiveness research: report of a workshop sponsored by the National Heart, Lung, and Blood Institute. J Am Coll Cardiol 2012;60:569-80.

15. Berwanger O, Guimarães H, Laranjeira, et al. Effect of a Multifaceted Intervention on Use of Evidence-Based Therapies in Patients With Acute Coronary Syndromes in Brazil. The BRIDGE-ACS Randomized Trial. JAMA. 2012 May 16;307(19):2041-9.

16. Ioannidis JP. Contradicted and initially stronger effects in highly cited clinical research. JAMA 2005;294:218 –228.

17. Bertoldi EG, Polanczyk CA, Cunha V, et al. Mortality Reduction of Cardiac Resynchronization and implantable Cardioverter-Defibrillator Therapy in Heart Failure: An Updated Meta-Analysis. Does Recent Evidence Change the Standard of Care? J Card Fail 2011; 17: 860-866.

18. Puymirant E, Simon E, Steg P. Association of changes in clinical characteristics and management with improvement in survival among patients with ST-elevation myocardial infarction. JAMA 2012;308:998-1006.

19. Gibson M, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-ballon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial infarction from 1990 to 2006. Am Heart J 2008; 156:1035-44.

20. Piva e Mattos LA, Otávio Berwanger O, Santos ES, et al. Desfechos Clínicos aos 30 dias do Registro Brasileiro das Síndromes Coronárias Agudas (ACCEPT). Arq Bras Cardiol 2013;100:6-13.

21. Pinto DS, Frederick PD, Chakrabarti AK, et al. Benefit of Transferring ST-Segment–Elevation Myocardial Infarction Patients for Percutaneous Coronary Intervention Compared With Administration of Onsite Fibrinolytic. Declines as Delays Increase. Circulation 2011;124:2512-2521.

Tabela 1. Comparação entre os pacientes atendidos por SCA na emergência do HCPA e os incluídos nos estudos CURE [5] e PLATO [6]

Características	HCPA	CURE grupo clopidogrel	PLATO grupo ticagrelor
Idade, anos *	64 ± 12,1	64 ± 11,3	61 (53-69)
Sexo feminino	48,5	38,7	25,2
Hipertensão	88,3	59,9	-
Diabetes	44,3	22,4	22,7
Tabagista ativo	19,6	60,6	-
História prévia			
IAM	38,1	32,4	17,1
Revascularização	-	17,7	19,4
AVC	-	4,4	3,1
Diagnóstico na entrada do estudo			
Angina instável	55,7	74,9	13
IAM	44,3	25,1	87

* Média ± desvio padrão

Abreviaturas: AVC, Acidente Vascular Cerebral; HCPA, Hospital de Clínicas de Porto Alegre; IAM, Infarto Agudo do Miocárdio; SCA, Síndrome Coronariana Aguda.

Figura 1. Proposta de como generalizar os resultados de ensaios clínicos randomizados (ECR) com base no tamanho do estudo e na complexidade do tratamento. ECR de grande tamanho e que avaliam tratamentos menos complexos demonstram eficácia, na qual são similares a efetividade - sendo mais fácil sua aplicabilidade na prática clínica. Por outro lado, ECR pequenos e que avaliam tratamentos de alta complexidade comprovam eficácia, mas a efetividade é difícil de ser avaliada. Adaptado de Nallamothu et al.[10]

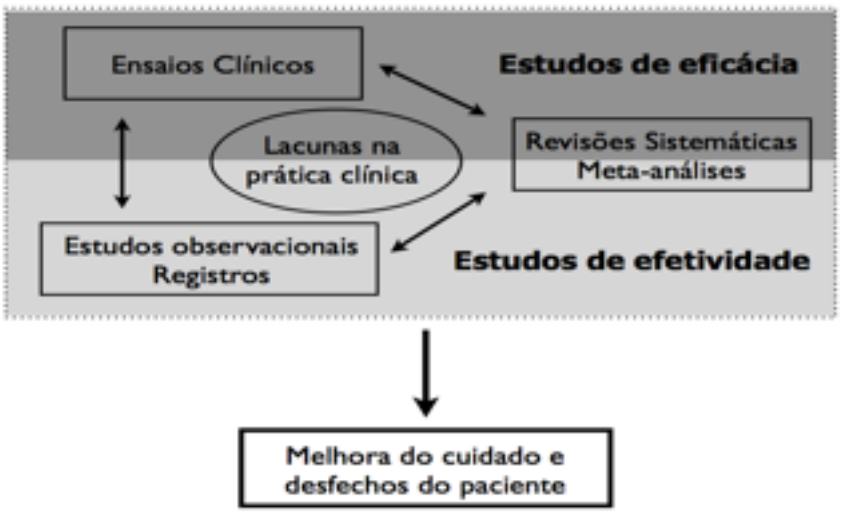

Figura 2. Ciclo de evidências: complementação de estudos de eficácia e efetividade.

ARTIGO 2

Quality of Care in Acute Coronary Syndrome: clinical practice on 11-year follow-up

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Abstract

Background: Global registries indicate the existence of discrepancies between the recommendations for the management of patients with acute coronary syndrome (ACS) and what is actually seen in clinical practice.

Objective**:** To make a contemporary diagnosis of the temporal trend of the care provided to ACS patients and of their clinical indicators in a public tertiary hospital over a period of 11 years.

Methods: Three cohort studies including 669 patients diagnosed with ACS in the emergency department over distinct time periods: 2000 to 2001, after the implementation of a critical pathways for ACS; 2006 to 2007, after opening of a Chest Pain Unit; and from 2010 to 2011, after the Chest Pain Unit was expanded and consolidated. We analyzed the adherence to the recommendations provided by the clinical guidelines for ACS management and the indicators of quality of care: the occurrence of combined events during hospitalization (mortality, heart failure and arrhythmias).

Results: Patient profile changed between periods, with a higher rate of myocardial infarction with ST-segment elevation in the 2010-2011 period. There was a gradual increase in adherence rates to all drugs recommended by the guidelines available at the time: 2000-2001 = 26.4% vs. 2006-2007 = 28.6% vs. 2010-2011 = 49.2% ($p<0.001$). There was a higher rate of combined events in 2010-2011 (21.2%) when compared with 2000-2001 (10%) and 2006-2007 (9%) ($p<0.001$). In the multivariate analysis, adherence to guidelines and time period were not predictors of prognosis. Diabetes (Odds ratio [OR] = 2.1, 95% Confidence Interval [CI] 1.2 to 3.5) and acute myocardial infarction (OR = 4.9, 95% CI 2.8 to 8.9) were the only independent predictors of the combined outcome.

Conclusion: Over the 11 year period, we observed a higher adherence to guideline recommendations, with higher rates of prescription medications having a positive impact on mortality. This reinforces the importance of institutional strategies for the

improvement of quality of care. The consolidation of cardiology practice, however, was not associated with better prognoses, which might be a reflection of the increasing severity of the cases referred to the tertiary sector in our country.

Introduction

Cardiovascular diseases are the leading cause of mortality in Brazil and worldwide. In 2010 they accounted for 31% of all deaths recorded, generating a significant socioeconomic impact in our country [1]. Among cardiovascular diseases, acute coronary syndromes (ACS), including acute myocardial infarction (AMI) and unstable angina (UA), are notable for their heterogeneous presentation and varying severity, which makes ACS a considerable challenge for emergency and cardiology teams [2].

With the advances in the treatment of ACS, over the past 30 years, the mortality and morbidity associated with AMI has dramatic decline in developed countries, with rates of less than 5% in the recent registries [3]. In 2010, the recorded AMI mortality rate was 13% in the Brazilian public system [1]. Over the past 15 years, randomized clinical trials have proven the efficacy and safety of new available treatments for the management of acute coronary syndromes, by demonstrating that the use of dual platelet aggregation, β-blockers, statins, and angiotensin-converting enzyme inhibitors (ACEi) reduce morbidity and mortality in this population [3]. Despite such evidence, studies have revealed discrepancies between the treatment recommended by international guidelines and what is actually prescribed in clinical practice [4-7]. Strategies towards the early recognition and appropriate management of such syndromes are of utmost importance so as to reduce morbidity and mortality and to ensure that treatments proven to be effective are actually administered.

Thus, it has become essential to truly understand what happens in the real-world of ACS care. Large international registries have been created to collect uniform prospective data to be used by the participating centers as performance indicators in order to achieve the goals proposed by the guidelines and to help identify the areas that are in most need of improvement. These registries confirmed the low adherence rates to some therapies and the impact on prognosis [7-10]. In Brazil, several local initiatives have been described over the years. In 2010, a national registry supported

by the Brazilian Society of Cardiology presented a similar scenario to that found in the rest of the world. However, regional differences and others related to whether the institution was public or private were also observed [11].

On the other hand, there is little data on the evolution of the care provided for ACS patients and the speed in which new therapies are adopted in public hospitals in our country. This study aims to describe a temporal trend over an 11 year period regarding the use of evidence-based medical therapies and indicators of quality of care for ACS patients in a tertiary care university hospital in southern Brazil.

Methods

Patients

The study was conducted at the Adult Emergency Unit of Hospital de Clínicas de Porto Alegre, a public center deemed of excellence for the treatment of acute vascular diseases. The study included all patients referred to the Emergency Unit with confirmed ACS in the following periods: June 2000 to December 2001, after a protocol of care for ACS was implemented (2000/2001 period); April 2006 to October 2007, after the opening of a Chest Pain Unit in the Emergency service (2006/2007 period); and from July 2010 to August 2011 after the Chest Pain Unit was expanded and consolidated (2010/2011 period). In the latter period, for methodological reasons, only patients with less than 24 hours of symptom onset were included. The diagnosis and management of ACS in the three periods was established by the medical staff of the Hospital based on the institution's clinical pathways and without interference from the researchers.

The study was approved by the Ethics Committee of the Hospital and, in all three periods, the patients signed an informed consent.

Data Collection

The information regarding each case was collected using a standardized questionnaire that included the necessary data for the study: demographic characteristics, history of current symptoms, physical examination, time spend and the

procedures employed from the moment the patient arrived at the emergency unit to the moment the patient was discharged, exams requested and the final diagnosis. The approaches used within the emergency unit were the sole responsibility of the attending physicians at the center, without any influence from the researchers.

The diagnosis of AMI was defined using the following criteria: typical rise and fall of the biochemical markers of myocardial necrosis - total creatine kinase (CK) and CK-MB in the 2000/2001 period (at that time, the institution did not have troponin measures), CK-MB and Troponin T in the 2006/2007 period and ultrasensitive troponin I in the 2010/2011 period - with at least one of the following: a) symptoms of myocardial ischemia, b) development of pathologic Q waves on the eletrocardiogram (ECG), and c) changes on the ECG that were indicative of ischemia (elevation or depression of the ST segment) [12,13]. Unstable angina was defined as chest pain at rest accompanied by transient ischemic ST-segment changes or T-wave changes on the ECG, with no markers of myocardial necrosis, and requiring drug treatment and/or a revascularization procedure [14].

Follow-up and Outcomes

Patient evolution and clinical outcomes were prospectively followed during hospitalization and through an active search of the medical records. In-hospital outcomes were defined as death for any reason and associated major complications, which included arrhythmias with hemodynamic repercussion, acute heart failure (HF) and death.

Quality of care considered and analyzed were the adherence to ACS management guidelines and the occurrence of combined in-hospital outcomes. Adherence to guidelines was defined as the prescription, within the first 24 hours of admission, of medications recommended by national and international guidelines for ACS management with an impact on morbidity and mortality in each period of time: hence considering the prescription of aspirin, heparin, beta-blockers and ACEi in the 2000/2001 period [15]; aspirin, heparin, beta-blockers, ACEi and statins in the 2006/2007

period,[16] and aspirin, clopidogrel, heparin, beta-blockers, ACEi and statin in the 2010/2011 period [17].

Statistical Analysis

Baseline characteristics and in-hospital complications were described as percentages and 95% confidence intervals (CI) for categorical variables, and in means and standard deviation for continuous ones. Group comparison was performed using Fisher's exact test for categorical variables, Student-t test for continuous variables with a normal distribution and the Wilcoxon test for non-normally distributed variables. A multivariate logistic regression analysis was carried out in order to establish the effect of the studied periods on hospital outcomes. Variables affecting the variable of interest with p value <0.20 were selected by the manual method and the stepwise effect. Statistical package SPSS 18.0 for Windows was used for the statistical analysis. Differences were considered statistically significant when p value <0.05.

Results

The study included a total of 669 patients, of whom 261 were included in 2000/2001 period, 290 in 2006/2007 and 118 in 2010/2011. Table 1 presents the characteristics of the ACS patients according to the period studied. Significant differences were found among periods, both in age and gender and in some risk factors, such as prior history of systemic hypertension and diabetes, but mainly regarding the final diagnosis established, with a significantly higher rate of AMI in the 2010/2011 period.

The comparison between pharmacological treatment prescribed in the first 24 hours of hospitalization is shown in Table 2. There was an increase in the prescription of aspirin, ACEi, heparin and statins over the years studied. The prescription of β-blockers was the only one that remained constant throughout, with a slight increase in the 2010/2011 period, yet proving no statistical significance. There was also an increase in the prescription of clopidogrel and statins between 2006/2007 and

2010/2011. In the 2000/2001 period, statin and clopidogrel were not standardized in the institution. The full adherence of the medications recommended by the guidelines at the time was markedly more pronounced in the 2010/2011 period. In the multivariate analysis, the 2010/2011 period was an independent predictor of adherence to recommended medications (Odds ratio [OR] = 2.3, 95% CI 1.43 to 3.70).

When analyzing the revascularization procedures, we observed that the number of coronary angiographies performed over the 11-year period increased from 60.2% to 85% ($p < 0.001$) and that the number of percutaneous coronary interventions (PCI) was higher in 2010/2011 when compared with previous periods. The number of coronary artery bypass graft surgeries (CABG) was similar throughout. These data are shown in Figure 1.

Rates of in-hospital events are described in Table 3. Despite the fewer deaths in the 2010/2011 period (but with no statistical difference between periods), we observed more cases of in-hospital HF and severe arrhythmias in this period. The rate of combined events was higher in 2010/2011, posing double the risk in this period (OR = 2.43, 95% CI 1.33 to 4.42). However, when the multivariate analysis was performed to control for factors that increase severity, the study period was not a predictor of prognosis (OR = 1.6, 95% CI 0.8 to 2.9). Diabetes (OR = 2.1, 95% CI 1.2 to 3.5) and AMI (OR = 4.9, 95% CI 2.8 to 8.9) were the only independent predictors of the combined outcome. Full adherence to the guidelines of each time period was not associated with prognosis, with combined event rate of 11.3% in the non-adhering group and 11.9% in the adhering group.

Discussion

The main findings of our study are in agreement with those demonstrated by international registries which characterize the population of patients presenting with ACS [5-10]. We observed a growing trend towards the adoption and incorporation of evidence-based therapeutic strategies as well as a strict/close adherence to the

recommendations developed by national and international guidelines. However, unlike most registries, this increased adherence did not translate into fewer in-hospital complications.

During the period studied, some institutional strategies were adopted at our center aiming at improving the quality of care. The first strategy was implemented in January 2000 through the creation of critical pathways for the management of chest pain and ACS patients in the emergency-room, with improvement of quality indicators right after its implementation [18]. In January 2006, a Chest Pain Unit was inaugurated within the emergency department [19]. In 2009, the unit was further expanded and the use of the critical pathways was consolidated, as was the role of the cardiology consulting team. With proven benefits in care practices, the Chest Pain Unit of our institution has also been shown to have an impact on the adoption of evidence-based therapies.

It is important to point out that our study regards to a single public university hospital, where it comes to be expected that new therapeutic strategies with proven evidence are to be promptly adopted, despite the inherent difficulties experienced by the public sector as to standardization and availability of new drugs. The use of statins and clopidogrel became incorporated over the years encompassed by this study, having had average rates of prescription in 2006/2007, and a clear increase in 2010/2011 when the numbers became similar to those observed in registries from developed countries such as the United States and others in Europe [8,10,20]. Likewise, it can be inferred that the constant rate of β-blocker prescriptions in 2000/2001 and 2006/2007, and the slight increase seen in 2010/2011, also represents the incorporation of new evidence, there being greater restriction in the prescription of this drug in the first 24 hours of hospitalization since the COMMIT study publication in 2005 [21,22]. The same was observed in the analysis of the GRACE registry, which showed that most patients continue receiving β-blockers even after the publication of the study, but without any increase in its prescription over the years, as is observed with other drugs[5].

Improvements in the quality of care and the development of efficient systems of care can be observed worldwide. A Swiss registry (RIKS-HIA) observed patients with acute myocardial infarction with ST-segment elevation over a period of 12 years (1996-2007), and observed that prescription rates for all recommended medications increased over the years, as did the rates of revascularization [8]. In the United States, the National Cardiovascular Data Registry (NCDR), which measures the American quality of care, demonstrated an increase in the use of medications recommended by guidelines between 2005 and 2009, mainly with regard to patients undergoing percutaneous revascularization and the use of new antithrombotic drugs [10]. When we compared our data with the Acute Coronary Events - a multinational Survey of current management Strategies (ACCES), which encompasses 19 developing countries in Africa, the Middle East and Latin America, including Brazil, and involves 11.731 patients with acute coronary syndrome with and without ST-segment elevation [9], we observed that our center had higher rates regarding the prescription of dual antiplatelet aggregation, but especially a greater number of coronary angiographies (84% vs. 58% in ACCES) and angioplasties (55.1% vs. 35% in ACCES), which could be explained by the fact that our center is a reference institution. We expected that long-term results coming from the Brazilian Registry of Clinical Practice in Acute Coronary Syndromes of the Brazilian Society of Cardiology (ACCEPT)[11], which represents the care provided throughout the country, be maintained and published, thereby allowing for a better comparison with international registries.

Despite the improvement in guidelines adherence, our study observed a higher rate of in-hospital complications in recent years, though no increase in mortality, which may be explained by the large difference in populations over the periods studied. We also observed a greater severity of the cases, represented by the rise in the proportion of patients with myocardial infarction, especially with ST-segment elevation and the highest number of diabetic patients compared with the 2000-2001 period. These were the only factors that were independent predictors of the combined outcome in the

multivariate analysis of our study. This finding differs from many international registries which reveal a recent tendency towards a reduction of in-hospital complications, but on the other hand, present lower risk populations being treated over the years, which in turn reflects an improvement in primary and secondary prevention strategies in these countries [8,20].

The increase in the diagnosis of AMI cases also reflects the incorporation of new technologies that have proven beneficial in identifying patients with a poor prognosis: troponin T levels that was incorporated in the 2006/2007 period, following the recommendations of the new universal definition of myocardial infarction and the subsequent switch to Ultra-sensitive cardiac troponin-I kits [13,23]. Moreover, the use of more sensitive and accurate enzymes for the diagnosis of AMI probably resulted in the small number of patients with a final diagnosis of unstable angina in the 2010/2011 period [23,24]. The identification of a greater number of patients with myocardial injury and of patients with worse prognosis possibly accounts for the higher rates of invasive assessments through coronary angiographies and angioplasties found in the last period.

Some methodological considerations should be mentioned, such as the fact that this is an observational study, with the inherent limitation of the method, whereby cause-and-effect relations cannot be proven, only suggested. In addition, in any temporal analysis there is always the possibility that factors external to those evaluated in the study can end up being modified over the years and that these changes may impact the results of the study. Also, the analysis of data from a single center cannot be considered to reflect a national reality, thus the data cannot be generalized to the rest of the country. However, our data is still of cardinal importance as it demonstrates that the indicators of quality of care can be improved in public institutions in developing countries, and be compared to the care provided in developed countries where medical excellence is closer to a fact.

In conclusion, our analysis indicates an increase in the implementation and prescription of new evidence-based therapies, with greater adherence to national and international guidelines, and thus reinforces the importance of institutional strategies for the improvement of the quality of care provided. This improvement in clinical practice, however, was not associated with reduced mortality and in-hospital complications, which may be a reflection of the increasing severity of the cases referred to the tertiary sector in our country.

References

1. Ministério da Saúde. DATASUS. (Departamento de Informática do SUS). [Acess on 2013 mar 19]. Available from http://www2.datasus.gov.br

2. Nicolau JC, Timerman A, Piegas LS, Marin-Neto JA, Rassi A. Jr. Guidelines for Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction of the Brazilian Society of Cardiology (II Edition, 2007). Arq Bras Cardiol 2007; 89: e89-e131.

3. Krumholz HM, Anderson JL, Bachelder BL, et al. ACC/AHA 2008 Performance Measures for Adults With ST-Elevation and Non–ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures (Writing Committee to Develop Performance Measures for ST-Elevation and Non–ST-Elevation Myocardial Infarction). J Am Coll Cardiol 2008; 52:2046–99.

4. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282(15):1458- 1465.

5. Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes: variations in practice and outcome: findings from the Global Registry of Acute Coronary Events (GRACE). Eur Heart J 2002; 23(15):1177-1189.

6. Hoekstra JW, Pollack CV Jr, Roe MT, et al. Improving the care of patients with non−ST-elevation acute coronary syndromes in the emergency depart- ment: the CRUSADE initiative. Acad Emerg Med 2002; 9(11):1146-1155.

7. Carruthers KF, Dabbous OH, Flather MD, et al. The Global Registry of Acute Coronary Events (GRACE). Contemporary management of acute coronary syndromes: does the practice match the evidence? Heart 2005; 91:290-8.

8. Jernberg T, Johason P, Held C, et al. Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction. JAMA 2011; 305:1677-1684.

9. The ACCESS Investigators. Management of acute coronary syndromes in developing countries: acute coronary events - a multinational survey of current management strategies. Am Heart J 2011;162:852-859.

10. Roe MT, Messenger JC, Weintraub WS, et al. Treatments, Trends, and Outcomes of Acute Myocardial Infarction and Percutaneous Coronary Intervention. J Am Coll Cardiol 2010;56:254-63.

11. ACCEPT-SBC Registry Investigators. Rationality and Methods of ACCEPT Registry - Brazilian Registry of Clinical Practice in Acute Coronary Syndromes of the Brazilian Society of Cardiology. Arq Bras Cardiol 2011; 97: 94-99.

12. The Joint European Society of Cardiology/American College of Car- diology Committee. Myocardial infarction redefined: A consensus document of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction. Eur Heart J. 2000;21:1502–1513; J Am Coll Cardiol 2000;36:959–969.

13. Thygesen K, Alpert JS, White HD. Joint ESC / ACCF / AHA / WHF Task force for the redefinition of myocardial infarction. Universal definition of myocardial infarction. Eur Heart J 2007;28:2525-2538.

14. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/Non −ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update): A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. Circulation 2012;126:875-910.

15. Feitosa GS, Nicolau JC, Piegas LS, et al. II Diretriz da SBC para tratamento do IAM. Arq Bras Cardiol 2000;74 (Suplemento II).

16. Piegas LS, Timerman A, Nicolau JC, , et al. III Diretriz sobre tratamento do infarto agudo do miocárdio. Arq Bras Cardiol 2004;83 (Suplemento IV).

17. Nicolau JC, Timerman A, Piegas LS, Marin-Neto JA, Rassi A. Jr. Guidelines for Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction of the Brazilian Society of Cardiology (II Edition, 2007). Arq Bras Cardiol 2007; 89: e89-e131.

18. Polanczyk CA, Biolo A, Imhof BV, et al. Improvement in clinical outcomes in acute coronary syndromes after the implementation of a critical pathway. Crit Pathw Cardiol 2003;2:222-30.

19. Furtado MV, Cardoso A, Patrício MC, et al. Influence of implementation of a chest pain unit on acute coronary syndrome outcomes. J Emerg Med 2011;40:557-64.

20. Peterson ED, Shah BR, Parsons L, et al. Trends in quality of care for patients with acute myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008; 156:1045-55.

21. Chen ZM, Pan HC, Chen YP, et al. COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1622-32.

22. Edwards J, Goodman SG, Yan RT, et al. Has de Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) of early β-blocker use in acute coronary syndromes impacted on clinical practice in Canada? Insights from the Global Registry of Acute Coronary Events (GRACE). Am Heart J 2011;161:291-7.

23. Bonaca M, Scirica B, Sabatine M, et al. Prospective Evaluation of the Prognostic Implications of Improved Assay Performance With a Sensitive Assay for Cardiac Troponin I. J Am Coll Cardiol 2010;55:2118–24.

24. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. J Am Coll Cardiol 2012 Oct 16;60(16):1581-98.

Table 1. Clinical characteristics of acute coronary syndrome patients by study period.

Characteristics	**2000-2001 N=261(%)**	**2006-2007 N=290(%)**	**2010-2011 N=118 (%)**	***P* Value**
Age, years *	61 (±12.4)	64 (±12.1)	60 (±11.8)	0.027
Male sex	143 (54.8)	150 (51.5)	82 (69.5)	0.004
Hypertension	201 (77)	257 (88.3)	91 (77.8)	0.003
Diabetes Mellitus	71 (27.2)	129 (44.3)	40 (34.2)	0.001
Dyslipidemia	147 (56.3)	133 (45.7)	70 (59.8)	0.001
Current smoker	51 (19.5)	57 (19.7)	44 (37.3)	<0.001
Previous Myocardial Infarction	100 (38.3)	111 (38.1)	45 (38.5)	1.000
Prior Revascularization Surgery	30 (11.5)	46 (15.9)	15 (12.8)	0.495
Physical examination on admission				
SBP mmHg *	138 (±32)	142 (±30)	142 (±29)	0.559
DBP mmHg *	83 (±19)	83 (±18)	82 (±19)	0.559
Heart Rate bpm *	76 (±18)	81 (±20)	80 (±19)	0.021
Final Diagnosis				
Acute Myocardial Infarction	99 (37.9)	129 (44.3)	83 (70.3)	<0.001
ST elevation	45 (45.5)	32 (24.8)	46 (55.4)	<0.001
Non-ST elevation	54 (54.5)	97 (75.2)	37 (44.6)	<0.001
Unstable Angina	162 (62.1)	161 (55.5)	34 (28.8)	<0.001

* mean (±SD)
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; SD, standard deviation

Table 2. Pharmacological treatment prescribed within the first 24 hours of admission by period.

Medications	**2000-2001 N (%)**	**2006-2007 N (%)**	**2010-2011 N (%)**	***P* Value**
Aspirin	230 (88.1)	267 (92.1)	118 (100)	<0.001
Clopidogrel	-	195 (67.2)	115 (97.5)	<0.001
β-blocker	190 (72.8)	208 (73.2)	97 (82.2)	0,115
ACE Inhibitor	136 (52.1)	181 (63.7)	88 (74.6)	<0.001
Heparin	183 (70.1)	219 (75.5)	105 (89)	<0.001
IIb/IIIa Inhibitor	-	-	18 (15.3)	
Statin	-	219 (75.5)	109 (92.4)	<0.001
Full adherence to recommended therapies	69 (26.4)	83 (28.4)	58 (49.2)	<0.001

Abbreviations: ACE, angiotensin-converting enzyme

Table 3. In-hospital events by period.

Outcomes	**2000-2001 N = 261(%)**	**2006-2007 N = 290 (%)**	**2010-2011 N = 118 (%)**	***P* Value**
Deaths	14 (5.4)	8 (2.8)	1 (0.8)	0.058
Congestive Heart Failure	15 (5.7)	20 (6.9)	18 (15.3)	0.005
Arrhythmias *	3 (1.1)	4 (1.4)	10 (8.5)	<0.001
Combined events	26 (10.0)	26 (9.0)	25 (21.1)	0.001

* included arrhythmias with hemodynamic repercussion

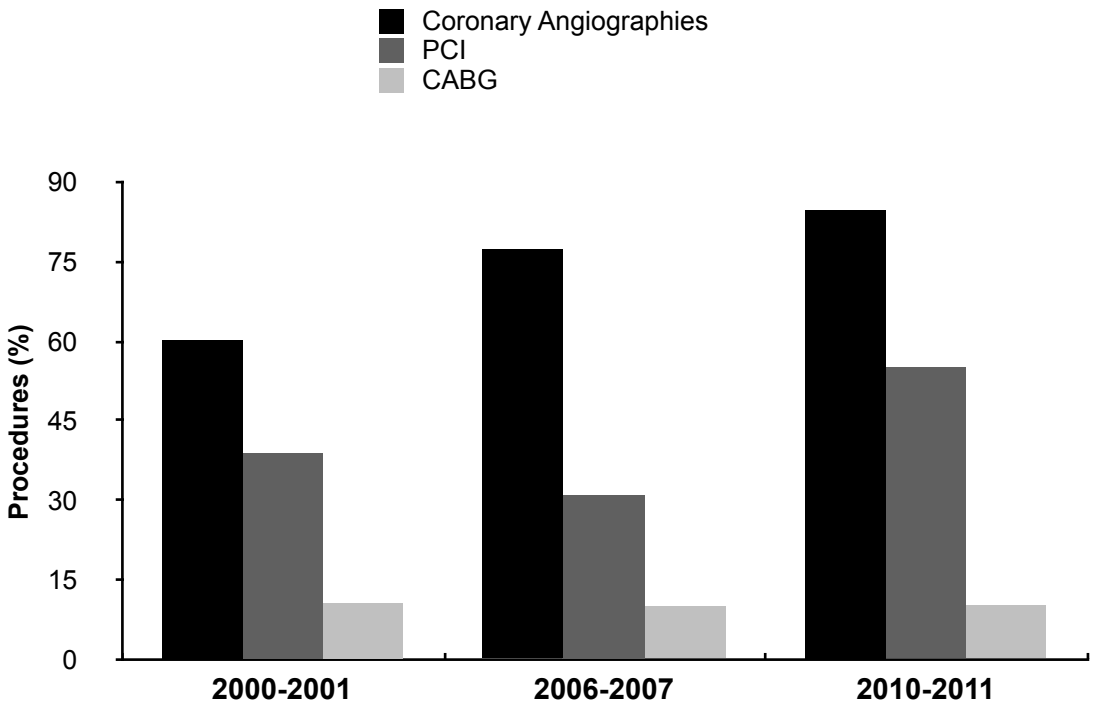

Figure 1. Comparison between periods in percentage of Coronary Angiographies, Percutaneous Coronary Revascularization (PCI) and Coronary Artery Bypass Grafting (CABG)

ARTIGO 3

Delays in reperfusion therapy in the management of ST-segment elevation myocardial infarction patients: report from a Public Hospital in Brazil

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Abstract

Background: The therapeutic benefits of the care provided for ST-segment elevation acute myocardial infarction (STEMI) patients are time-dependent, being exponentially greater the earlier the treatment is initiated. Determining which treatment strategy provides the best benefit to each patient, based on the resources available, becomes crucial. This study aimed to describe the healthcare provided to STEMI patients and the outcomes reached in a tertiary hospital in southern Brazil

Methods: We evaluate a cohort of STEMI patients assisted between October 2009 and July 2011 in our center. All clinical data, prehospital and in-hospital treatment provided were recorded during the hospitalization period. Total mortality rates were assessed at 30 days.

Results**:** One hundred and seventy-eight consecutive patients were included in the study, with a mean age of 60 ± 12 years, 73% were men, 64% had hypertension, 22% had diabetes mellitus, and 17% had a history of prior myocardial Infarction (MI). Primary percutaneous coronary intervention was performed in 70% of patients, thrombolysis in 9%, and no-reperfusion therapy was offered to 21%. The main reason for non-reperfusion was symptom onset more than 12 hours prior to admission. Regarding initial treatment, over half the patients had transferred out of referral hospitals (52%) and 57% of these patients had a symptom onset of more than 6 hours. In a multivariate analysis, independent predictors of non-reperfusion were female gender (HR= 2.95, 95% CI 1.28 - 6.86), chronic renal failure (OR= 4.85, 95% CI 1.04 - 22.6) and initial care in an outsite city (OR= 2.60, 95% CI 1.04 - 6.48). Cardiovascular 30-day mortality was 10.1%.

Conclusion: Initial treatment given in outlying cities was an independent predictor of non-reperfusion, associated with a lower use of thrombolysis and pain lasting over 6 hours. These data reflect the need to develop systems of care for STEMI, which are still incipient in most Brazilian states.

Introduction

Ischemic heart disease is a major cause of mortality in Brazil, affecting 46% of the population and having surpassed cerebrovascular diseases in some Brazilian states [1]. Of the clinical manifestations of the disease, acute myocardial infarction (AMI) has the highest mortality rates and is the one for which different therapeutic strategies have been implemented to reduce its impact over the past years [2]. The crude AMI mortality rates in Brazil have increased in recent years, having risen from 35 per 100,000 inhabitants in 2005 to 39.3 per 100,000 in 2008. In the state of Rio Grande do Sul, AMI mortality rates are higher than the national average, at 52.8 per 100,000 inhabitants [3].

The early and effective treatment of ST-segment elevation AMI (STEMI) through the institution of reperfusion therapy is the most important component of treatment and a crucial factor for outcome [4]. Despite the superiority of primary percutaneous coronary intervention (PCI) in the ideal setting of clinical trials, the management of STEMI in actual practice presents a number of considerations [5]. Data from large registries have shown that 60 to 70% of patients with STEMI are treated at non-PCI-capable institutions and that the use of reperfusion therapy is insufficiently established in many countries. It is estimated that approximately one third of patients do not receive any reperfusion therapy at all. Furthermore, it can be observed that even for those patients who do receive it, there are delays in prehospital and in-hospital care, which may result in a worse prognosis [6-10]. Determining which treatment strategy provides the best benefits to our patients, according to the resources available, is crucial.

Therefore, international guidelines have recommended that systems of care for STEMI patients be created so as to define clinical pathways and management for these cases, while at the same time providing the means for continuous assessment and improvement in quality of care for emergency services. The guidelines reinforce the importance of a comprehensive approach that involves everything from patient education to the establishment of networks between hospitals with (PCI-capable) and

without hemodynamics (non-PCI-capable). This concept has already become widespread in the United States and in European countries, where quality of care indicators have been shown improvements [2,11].

This study aims to describe the management and outcomes of STEMI patients in a tertiary reference hospital in southern Brazil, which is registered in the Brazilian Public Health System (SUS) as a reference for highly complex cardiovascular care. Such data might help better understanding on the patients care provided in the Latin America, where the incorporation of knowledge and technology is also limited by managerial, financial and developmental issues.

Methods

Study Population

This study was conducted at Hospital de Clínicas de Porto Alegre (HCPA), a 740-bed university hospital, and a tertiary reference center for the treatment of acute vascular diseases. All consecutive STEMI patients aged 18 years and above admitted between October 2009, and July 2011 were included in the study. The criteria for the diagnosis of STEMI were adopted in accordance with the European Society of Cardiology/ American College of Cardiologists/ American Heart Association consensus and thus defined as new persistent ST-segment elevation in two contiguous leads with the cut-off points: ≥ 0.2 mV in men or ≥ 1.5 mV in women in leads V2-V3 and/or ≥ 0.1 mV in other leads or a new left bundle branch block, along with symptoms compatible with acute myocardial infarction and detection of a rise and/or fall of troponin with at least one value above the 99th percentile of the upper reference limit[12]. Patients with iatrogenic myocardial infarction were not included.

All patients signed an informed consent to participate in the study. The protocol was reviewed and approved by the Institution's Ethics Committee.

Data Collection

All data were collected on computerized registries by a trained research team. Demographic characteristics including cardiovascular history, risk factors, current use of medication, detailed history of current symptoms, physical examination, time between admission and discharge, tests performed, and the in-hospital clinical course were recorded. Patients were managed solely by their physicians, with no interference of the investigators.

Follow up and end points

Patients were followed up for 30 days, and the data were collected by telephone contact with the patients or their families. When unavailable, vital status was assessed from hospital medical records. The thirty-day follow-up was 89% complete.

Reperfusion time was defined as the time between symptom onset and the arterial puncture for patients treated with primary PCI or intravenous thrombolytic therapy. Primary rescue PCI was defined as primary PCI mandated by persisting symptoms or ST-elevation persisting for 60 minutes or more after the administration of thrombolysis. Recurrent myocardial infarction was defined as recurrent symptoms with a new rise in troponin and major bleeding, as any life-threatening bleeding or bleeding that required transfusion. The primary outcomes of interest were time to reperfusion and non-reperfusion. The secondary outcomes were 30-day death from any cause and occurrence of a major adverse cardiovascular event (MACE), defined as acute coronary syndrome (ACS), stroke and death.

Statistical analysis

Categorical variables were expressed as percentages and a 95% confidence interval (CI), whereas continuous variables were presented as means and standard deviation. The interquartile range (IQR) was selected to define the median hospital length of stay. Group comparison was performed using Fisher's exact test for categorical variables, Student's t test for normally distributed continuous variables and the Wilcoxon test for non-normally distributed variables. A logistic regression analysis was performed to determine the effect of different clinical and demographic

characteristics on non-reperfusion and on patient outcomes. Any variables that had an effect on the variable of interest with $p<0.20$ were selected by manual and stepwise method and included in the model.

Data was analyzed using statistical package SPSS 20.0 for MAC. Differences were considered statistically significant when $p<0.05$.

Results

A total of 178 patients were registered during the studied period. The clinical characteristics and risk profile of STEMI patients are shown in Table 1. The mean age of the patients was 60 years, and they were predominantly white (76%) and male (72%).

Of all the patients, 140 (78.7%) underwent reperfusion therapy. Primary PCI was the reperfusion method in 124 patients (69.7%), whereas 16 patients (9%) received thrombolysis. Seven patients who received thrombolysis were transferred to HCPA for primary rescue PCI. Among the patients with non-reperfusion therapy, 30 patients (17% of the total patients) received the diagnosis of AMI more than 12 hours after symptom onset, 6 patients underwent coronary angiography and had no indication for angioplasty and 2 patients were submitted to coronary artery bypass surgery. None of the patients who arrived at the hospital with more than 12 hours since symptom onset had a prior history of coronary artery disease. There were no other clinical characteristics that differentiated this population.

Among patients who underwent primary PCI, the median door-to-balloon time was 80 minutes (IQR, 51-110) and the percentage of patients with a door-to-balloon time ≤ 90 minutes was 57.3%. The median time from symptom onset to reperfusion was 300 minutes (IQR, 210-425).

Regarding the initial care, 86 (48.3%) received their treatment at HCPA, and only 9 of these patients (10.5%) had been transported to the hospital by the Emergency Medical Service Transport (SAMU), thereby having received some previous primary

care. Over half the patients had transferred out of a non-PCI-capable institution (51.8%): 52 patients (29.2%) came from hospitals and emergency centers in the city of Porto Alegre, 17 (9.6%) from the metropolitan area of this city, and 23 (12.9%) came from hospitals in the countryside of the state. Table 2 shows a comparison between rates of reperfusion and the location where initial care was given as well as time-to-reperfusion. We observed a higher prevalence of non-reperfusion in patients referred from locations outside the city of Porto Alegre, as well as a greater median time and a higher number of patients with over 6 hours to reperfusion. In the multivariate analysis, independent predictors of non-reperfusion were female gender (Odds Ratio [OR]= 2.95, 95% CI 1.28-6.86), chronic renal failure (OR= 4.85, 95% CI 1.04-22.65) and initial care provided in cities outside Porto Alegre (OR= 2.60, 95% CI 1.04-6.48). Concomitant medication and clinical outcomes are presented in Table 3. The prescription of dual platelet aggregation agents was quite significant in the first 24 hours of hospitalization (97.2%). On the other hand, the prescription of angiotensin-converting enzyme inhibitors in the first 24 hours of evolution was low (47.2%), as was that of beta-blockers (26.9%), which may reflect the severity of the cases, as can be seen by the incidence of cardiogenic shock (13.5%) and cardiac arrests (12.9%). Cardiovascular mortality at 30 days was 10.1% and the incidence of major adverse cardiac events (MACE) at 30 days was 15.7%. There were no differences found in mortality rates at 30 days between patients from Porto Alegre (12.7%) and those from other cities in the state (8.6%) or MACE rates at 30 days, 18.4% and 14.7% respectively. In the multivariate analysis, the factors associated with MACE at 30 days were age >75 years (OR= 3.05, 95% CI 1.01 - 9.23) and Killip class >1 at admission (OR= 7.25, 95% CI 2.65 - 19.80). In this analyses, non-reperfusion was not independently associated with a worse prognosis (OR=0.85, 95% CI 0.27-2.70).

Discussion

This study points to the lack of a structure for the management of cases at the time data were collected, as can be seen by the large number of referrals from other cities where the prevalence of thrombolytic therapy was low and by the number of patients reaching the referral hospital with over 6 hours since symptoms onset. Having received initial care in another city was an independent factor related to non-reperfusion, yet we found no association between non-reperfusion and prognosis in this group of patients, which may be partially explained by the fact that more severe patients, such as those with cardiogenic shock and cardiac arrest, may not have been transferred out due to the technical difficulties involved in moving them.

We also observed a low prevalence of patients within the city coming to the hospital using the SAMU, which could represent that the population is not entirely aware of the symptoms of myocardial infarction or of the need for medical assessment and prehospital transportation, as well as a poor network structure in regulating to transfers to referral hospitals, often characterized by overcrowded emergency rooms.

The city of Porto Alegre pioneered the creation of the SAMU in Brazil in 1995, providing to the population a free qualified prehospital healthcare. In 2002, the State's Emergency & Urgent Care Systems were set up so as to regulate the transfer of cases to high complexity hospitals [13]. Up until 2011 there were no clinical pathways in the city that were organized for STEMI patients who were cared for by SAMU.

In Brazil, healthcare network is characterized by the heterogeneity of hospitals with regard to the incorporation of technologies and the complexity of services, there being a concentration of financial resources and personnel in major cities and an overall regional imbalance. In 2003, the SAMU was established nationwide and by late 2011 they covered 60.5% of the population. In December 2011, a decree was issued approving the Line of Care for AMI and the Acute Coronary Syndrome Protocol, which incorporated technologies into the SUS, thereby allowing for medications such as Clopidogrel, Tenecteplase and Alteplase, as well as the troponin testing, to be included

into the SUS. It was after this date that Porto Alegre structured a network system in which SAMU healthcare teams came to perform the prehospital eletrocardiogram (ECG) and send it to the Hospital do Coração de São Paulo (HCor) for interpretation. When patients with STEMI are identified, they are referred to previously defined reference centers, one of which is the HCPA [13].

In São Paulo, Brazil's largest city, with over 11 million inhabitants, a pilot STEMI system of care has been organized and established by the Hospital São Paulo of the Federal University of São Paulo. The deployment of the network and the systematization of care occurred through the definition and use of clinical pathways, the training of primary care teams, the establishment of an ECG reading center where ECG is transmitted via cell phone or the internet, and the use of advanced emergency medicine system transport that can provide fibrinolytic management (tenecteplase) and which transfer patients to tertiary hospitals with systematic coronary angiography. Data from the pilot project was published in 2012 showing the reflection of 205 cases treated through the network. The mortality rate was 6.8%, which is lower than that observed in our institution. [14]

On the other hand, we have several reports of suboptimal care in other cities and regions of Brazil. In 2009, in an analysis of patients with STEMI treated at three hospitals in Feira de Santana, Bahia, for instance, Ferreira et al., demonstrated a huge difference in time to reach care, time to appropriate treatment and outcomes between patients treated in private hospitals and those seen in public hospitals. [15]

A Brazilian Registry (ACCEPT) for acute coronary syndrome has recently been published covering the entire national territory. The study included 2584 patients, of whom 827 (33.4%) had STEMI. Of these, 729 (88.1%) received reperfusion, 107 (12.9%) fibrinolytic therapy and 622 (75.2%) underwent primary angioplasty. Different reperfusion rates are described by region, with a higher prevalence in the South and a lower one in the Northern Region. Cardiac mortality rate at 30 days was 3.4%. [16] Our center had higher rates of non-reperfusion and mortality, even with the high prevalence

of recommended medications. Methodological issues may have contributed to these differences, given that only those patients seen within 24 hours since the event were considered eligible for the National Register, and therefore many patients who had transferred out of other hospitals ended up being excluded.

There are few data regarding the management of patients with STEMI in Latin America. In Chile, in 2005, the AUGE plan was implemented. This national policy instituted electrocardiograms conducted through an interpretation center for patients presenting with chest pain, rapid administration of thrombolytic therapy, as well as the incorporation of adjuvant medications and referral for angioplasty. The impact of the plan was analyzed through the records from 9 hospitals, which showed an increase in the use of reperfusion therapy from 52.3% in 2001-2005 (pre-AUGE) to 67.8% in 2005-2006 (post-AUGE), accompanied by a reduction in mortality from 12% to 8.6%, respectively. [17] Argentine records describe in-hospital STEMI mortality at 3-10%, though it is estimated to be even higher since the data available refers to reference hospitals in the country. [18,19] We found no information in the existing literature regarding any healthcare networks and care for AMI in neighboring countries.[20]

We observed differences between data from Latin America and that coming from countries such as the United States and others in Europe, concerning the ability to structure and maintain large national registries which can provide suitable local data and organize healthcare networks. Nevertheless, even in developed countries, the effectiveness of treatment of patients with STEMI is far below ideal. An American Registry demonstrated that even with a reduction in time-to-care, in 2006 alone 8.8% of transferred patients achieved door-to-needle ≤ 90 minutes. [21] In the French Registry, a country characterized as having a well-developed pre-hospital system of care and interventional cardiology, 40% of the patients received no revascularization, and these patients tended to be older and to have a higher risk profile. [22]

The present study has the limitations inherent to observational studies. In addition, it includes data from a single center, a tertiary university hospital, therefore

not representing the reality of most hospitals in the country. However, the study does show a contemporary vision of care provided to patients in the south of the country, which is characterized by the centralization and referencing of cases, and a limited resoluteness of outlying cities. Studies on clinical effectiveness are important in this context as they enable the identification of system failures, thereby assisting health managers at both institutional and state levels to produce effective improvements in patient care.

In conclusion, non-reperfusion rates in patients with STEMI were high, and the initial care provided in outlying cities was an independent predictor of non-reperfusion. The study shows a large number of patients transferred out of other cities from the state having over 6 hours since symptom onset as well as a lower use of thrombolysis. This data reflects the need to organize systems of care for STEMI, a notion which is still incipient in most Brazil's states.

References

1. Ministério da Saúde. DATASUS. (Departamento de Informática do SUS). [Acess on 2013 mar 19]. Caderno de informações de saúde. Secretaria Executiva Ministério da Saúde. 2010. Available from www.datasus.gov.br.

2. O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2013;127:e362-e425.

3. Ministério da Saúde. DATASUS. (Departamento de Informática do SUS). [Acess on 2013 mar 19]. Available from www.datasus.gov.br.

4. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;348:771-5.

5. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13-20.

6. Boden WE, Eagle K, Granger CB. Reperfusion strategies in acute ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2007;50:917-29.

7. Ellrodt G, Sadwin LB, Aversano T, et al. Development of systems of care for ST-elevation myocardial infarction patients. Circulation. 2007;116:e49-e54.

8. Nallamothu BK, Bates ER, Herrin J, Wang Y, Bradley EH, Krumholz HM. Times to treatment in transfer patients undergoing primary percutaneous coronary intervention in the United States: National Registry of Myocardial Infarction (NRMI)-3/4 analysis. Circulation 2005;111:761-7.

9. Danchin N, Coste P, Ferrieres J, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention with primary percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction: data

from the French registry on acute ST-elevation myocardial infarction (FAST-MI). Circulation 2008;118:268-76.

10. Fassa AA, Urban P, Radovanovic D, et al. Trends in reperfusion therapy of ST-segment elevation myocardial infarction in Switzerland: six year results from a nationwide registry. Heart 2005;91:882-8.

11. Bassand JP, Danchin N, Filippatos G, et al. Implementation of reperfusion therapy in acute myocardial infarction. A policy statement from the European Society of Cardiology. Eur Heart J 2005;26:2733-41.

12. Thygesen K, Alpert JS, White HD, et al. Universal definition of myocardial infarction. Circulation 2007;116:2634-53.

13. Relatório de Gestão 2011 [database on the internet] Secretaria de Atenção à Saúde. Brasília, March, 2012. Available at www.datasus.gov.br

14. Caluza AC, Barbosa AH, Gonçalves I, et al. Rede de Infarto com Supradesnivelamento de ST: Sistematização em 205 Casos Diminui Eventos Clínicos na Rede Pública. Arq Bras Cardiol 2012;99:1040-1048.

15. Ferreira GM, Correia LC, Reis H, et al. Increased mortality and morbidity due to acute myocardial infarction in a public hospital in Feira de Santana, Bahia. Arq Bras Cardiol 2009 Aug;93(2):97-104

16. Piva e Mattos LA, Berwanger O, Santos ES, et al. Desfechos Clínicos aos 30 dias do Registro Brasileiro das Síndromes Coronárias Agudas (ACCEPT). Arq Bras Cardiol 2013;100:6-13.

17. Nazzal NC, Campos TP, Corbalán HR, Lanas ZF. Impacto del plan AUGE en el tratamiento de pacientes con infarto agudo al miocardio con supradesnivel ST, en hospitales chilenos. Rev Med Chile 2008; 136:1234-9.

18. Caccavo A. El infarto agudo de miocardio, un problema de salud pública. Rev Argent Cardiol 2010;78:259-263.

19. Piombo AC, Rolandi F, Maurice MF, et al. Registro de calidad de atención del infarto agudo de miocardio en los hospitales públicos de la ciudad de Buenos Aires. Rev Argent Cardiol 2011;79:132-138.

20. Mele EF. Progress in reperfusion after acute myocardial infarction. The situation in Latin America. Rev Esp Cardiol 2010;63 Suppl 2:12-9.

21. Gibson CM, Pride YB, Frederick PD, et al. Trends in reperfusion strategies, door-to-needle and door-to-balloon times, and in-hospital mortality among patients with ST-segment elevation myocardial infarction enrolled in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008;15:1035-44.

22. Danchin N, Coste P, Ferrieres J, et al. Comparison of thrombolysis followed by broad use of percutaneous coronary intervention for ST-segment-elevation acute myocardial infarction. Data from the French Registry on Acute ST-Elevation Myocardial Infarction (FAST-MI). Circulation 2008;118:268-276.

Table 1. Clinical characteristics of the patients.

	N=178 (%)
Age in years *	60 (±12.4)
Male	129 (72.5)
Race	
White	136 (76.4)
Black	17 (9.6)
Mestizo	22 (12.4)
others	2 (1.1)
Systemic Hypertension	113 (63.5)
Diabetes Mellitus	40 (22.5)
Dyslipidemia	52 (29.2)
Active smoking	85 (47.8)
Family history of CAD	45 (25.3)
Prior Myocardial Infarction	30 (16.9)
Prior CAD	22 (12.4)
Prior stroke	14 (7.9)
Peripheral vascular disease	20 (11.2)
Chronic renal failure	8 (4.5)
Prior medication used	
Aspirin	43 (24.2)
β-Blockers	50 (28.1)
ECAi	62 (34.8)
Statins	41 (23.0)
Physical examination on admission	
SBP mmHg *	131 (±32)
DBP mmHg *	78 (±20)
Heart Rate bpm *	82 (±19)
Killip > 1	47 (26.4)

* means (± Standard Deviation)
Abbreviations: CAD, coronary artery disease; ECAi, angiotensin-converting enzyme inhibitor; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 2. Comparison between reperfusion rates by location where first care was provided

	Porto Alegre N=138 (%)	**Other cities N=40 (%)**	***P* value**
Reperfusion therapy	112 (81.2%)	28 (70%)	0.187
pPCI	101 (73.2%)	23 (57.5%)	0.078
Fibrinolytic therapy	11 (8%)	5 (12.5%)	0.363
Median time-to-reperfusion, min (IQR)	275 (210-420)	365 (262-453)	0.184
Symptom onset to reperfusion > 6 hours	36 (36.2%)	16 (57.1%)	0.053
No reperfusion therapy	26 (18.8%)	12 (30)	0.187
Symptom onset to AMI diagnosis > 12 hours	20 (14.5%)	10 (25%)	0.149

Abbreviations: pPCI, primary percutaneous coronary intervention; IQR, Interquartile Range.

Table 3. Concomitant medical therapy and patient outcomes by location

	All N=178 (%)	Porto Alegre N=138 (%)	Other cities N=40 (%)	P Value
Medications during the first 24h				
Aspirin	173 (97.2)	136 (99.3)	37 (94.4)	0.12
Clopidogrel	173 (97.2)	136 (99.3)	37 (94.4)	0.12
Glycoprotein IIb/IIIa inhibitors	35 (19.7)	26 (19.5)	9 (23.7)	0.65
Statins				
β-Blockers	48 (27)	36 (26.9)	12 (31.6)	0.55
ACEi	84 (47.2)	66 (48.9)	18 (47.4)	1.00
In-hospital complications				
In-hospital death	16 (9)	13 (9.4)	3 (7.5)	1.00
Recurrent MI	2 (1.1)	1 (0.7)	1 (2.5)	0.40
Stroke	5 (2.8)	3 (2.2)	2 (5)	0.30
Major bleeding	2 (1.1)	1 (0.7)	1 (2.5)	0.40
Heart Failure	42 (23.6)	29 (21.2)	13 (32.5)	0.14
Cardiogenic shock	24 (13.5)	19 (13.8)	5 (12.5)	1.00
Ventricular fibrillation or Cardiac arrest	23 (12.9)	20 (14.5)	3 (7.5)	0.30

Abbreviations: ECAi, angiotensin-converting enzyme inhibitor; MI, myocardial infarction

ARTIGO 4

Long term prognosis of stable coronary artery disease: effectiveness of medical and revascularization strategies in a cohort study

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Abstract

Background: Coronary artery bypass grafting surgery (CABG) or percutaneous coronary intervention (PCI) are widely used strategies in the management of coronary artery disease (CAD), although recent evidence has restricted its indication in stable patients. This study aimed to describe the prognosis of patients with stable CAD initially treated by medical therapy (MT) compared to the patients who were submitted to CABG and PCI.

Methods: We conducted a prospective cohort study of 560 patients from an outpatient clinic in a tertiary hospital, included between 1998 and 2011, with a mean follow-up of 5 years. Patients were divided into MT (n=288), PCI (n=159) and CABG (n=113) groups according to their initial treatment strategy. Primary endpoints were overall mortality and combined events of death, acute coronary syndrome and stroke.

Results: During the follow-up period, death rates were 11.1% in MT, 11.9% in PCI and 15.9% in CABG patients, similar between interventions and medical groups (hazard ratio [HR] for the PCI, 1.05; 95% confidence interval [CI], 0.59 to 1.84; and HR for the CABG, 1.20; 95% CI 0.68 to 2.15). Combined outcomes were more often among patients initially submitted to PCI compared to MT (HR 1.50, 95% CI 1.05 to 2.14), and did not differ between MT and CABG patients (HR 1.24, 95% CI 0.84 to 1.83). Among patients with diabetes (n=198), PCI was the only therapeutic strategy predictive of combined outcomes (HR 2.14; 95% CI 1.25 to 3.63).

Conclusion: In this observational study of stable coronary artery disease, no difference was found in overall mortality between initial medical or revascularization management strategies. Patients initially treated with PCI had greater chance to present a combined major cardiovascular events.

Introduction

Coronary artery bypass grafting surgery (CABG) and percutaneous coronary intervention (PCI) are widely used strategies in the management of coronary artery disease (CAD), coupled with intensive medical therapy (MT). However, in the last years, evidences has narrowed the indication of revascularization procedures in stable patients, with conflicting results regarding the benefits and impact on mortality when comparing the initial treatment options [1-9]. Prior studies have suggested that PCI decreases symptoms without long-term prognostic effect, even when compared to medical treatment alone [7,8]. More recent data reinforce the superiority of CABG in preventing major cardiac events in patients with multivessel disease, especially in patients with more complex coronary artery disease and diabetes [10-12]. Although, these same studies pointed out to similar results between CABG and PCI when only the subgroup of patients with less complex disease are evaluated [10,12].

Between 2005 and 2008, 166,514 PCI were performed in Brazil by the Brazilian Public Health System (SUS), an annual average of 41,628 procedures or 22/100,000 inhabitants. Of these, 37% were undertaken electively in patients with stable CAD. Drug-eluting stents (DES) are not covered by SUS and the Brazilian population is facing difficulties in access to optimized medical therapy and revascularization procedures, with a significant difference among geographic regions of Brazil [13]. Therefore, the results of many clinical trials my not be generalizable to our real-world clinical practice.

Even in developed countries, there are gaps in the literature regarding the effectiveness of treatment strategies in patients with stable CAD. There are few clinical trials with three arms comparing the therapeutic options and this lack of knowledge brings complexity to the decision-making process. The propose of this study was to evaluate the long-term prognosis of patients with stable CAD treated with medical

therapy alone as initial option of treatment, compared with patients whom had been submitted to PCI or CABG in a public hospital in Brazil.

Methods

Study population

This is a prospective cohort study among cardiovascular patients from an outpatient clinic in a tertiary care university hospital in Southern Brazil. Between 1998 and 2011, consecutive patients with stable CAD were enrolled. All patients had documented CAD, which was defined by the presence of at least one of the following: documented history of myocardial infarction, surgical or percutaneous myocardial revascularization, a lesion >50% in at least one coronary artery assessed by angiography, or the presence of angina and positive noninvasive testing of ischemia [14].

Patients were divided into three groups, according to the baseline intervention strategy: MT, PCI or CABG, which was adopted prior to enrollment in this study. During follow-up, patients were managed by a multidisciplinary team according to current guidelines and at the discretion of attending physicians. Patients who performed PCI or CABG during follow-up were identified, although were analyzed as originally classified. All patients enrolled had complete clinical and laboratory data at baseline, at least three visits and one year of follow-up. This study was approved by the Institutional Research and Ethics Committee.

Follow up and end points

Stable patients were periodically assessed every 3-6 months. At each visit, a standardized register was filled in, which included the current disease history, cardiovascular risk factors control, new cardiac events (including admission data and invasive procedures), laboratorial and cardiac exams and pharmacological and nonpharmacological treatment. Relevant comorbidities were evaluated by questionnaire and chart review.

The primary outcomes of interest were death from any cause and occurrence of a major adverse cardiovascular event (MACE), defined as acute coronary syndrome (ACS), stroke and death. Acute coronary syndrome was defined as a hospital admission for chest pain or related symptoms and a discharge diagnosis by a physician of myocardial infarction or unstable angina. All-cause mortality and need for revascularization (either surgical or percutaneous) were also assessed.

Statistical Analyses

Continuous variables were expressed as mean ± 1 Standard Deviation (SD) and non-continuous were expressed as median an interquartile range (IQR) and were compared by using paired t-test or the Wilcoxon signed-rank test, as appropriate. Categorical data were presented as frequencies and were compared by Qui-square or Fisher's exact test. All tests were two-sided. Long-term outcomes were compared for those who initially underwent medical treatment, with the outcomes for those who underwent CABG and PCI, irrespective of stent type. The primary analysis evaluated the time to the first MACE. Survival curves were derived by Kaplan–Meier analysis and compared using log-rank tests. Multivariate Cox analyses were used to compare event-free survival among groups. In multivariate analyses, parameters clinically or significantly associated with main outcomes were included in the models. Outcomes were adjusted for gender, age, diabetes, smoking, ventricular dysfunction, chronic kidney disease and presence of comorbidities as peripheral vascular disease, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), liver disease and cancer. Variables that had any effect on the variable of interest were selected by the manual and *stepwise* method ($p < 0.10$). All data were analyzed using SPSS (version 11.0.0; SPSS, Chicago, Illinois, USA) and P values less than 0.05 were considered significant.

Results

Characteristics of the study population

A total of 560 patients were included in the study, with a mean follow-up of 5.1 years. Of these, 288 (51.4%) were initially managed with MT, 159 (28.4%) with PCI and 113 (20.2%) with CABG. Baseline characteristics of patients according to the management strategy are shown in Table 1. Patients in PCI group were more likely to have previous acute myocardial infarction than the other two groups. Patients in CABG group had more hypertension, dyslipidemia, left ventricular dysfunction and, as expected, greater proportion of patients with three-vessel coronary disease.

Outcomes

All cause of death occurred in 69 patients (12.3%) and combined major events of death, ACS and stroke in 168 patients (30%). On average, the annual mortality incidence was 2.5%/year (13 events/year). The cumulative survival rates for patients assigned to each group were 89% for MT, 88% for PCI, and 84% for CABG (P=0.82). During follow-up, 115 patients (20.5%) underwent PCI and 56 patients (10%) underwent CABG. The rate of events and comparisons among groups are shown in Table 2. Patients from the PCI and CABG groups had more ACS (22.6% and 23.9% respectively) when compared with MT group (14.9%, P=0.04). On the other hand, the rate of GABG revascularization during the follow-up was higher in MT (14.2%) and PCI (6.9%) groups when compared with CABG (3.5%) (P<0.01).

At the end follow-up, there was no significant difference in adjusted mortality between groups (hazard ratio [HR] for the PCI group, 1.05; 95% confidence interval [CI], 0.59 to 1.84; and HR for the GABG group, 1.20; 95% CI 0.68 to 2.15), with survival curves virtually identical (Figure 1 - A). In the multivariate Cox-model, age, male gender, diabetes and cerebrovascular disease were predictive of overall mortality (Table 3). Considering occurrence of combined major events, PCI was independently associated with worse prognosis (HR 1.50, 95% CI 1.05 to 2.14) with no difference between MT and CABG (HR 1.24, 95% CI 0.84 to 1.83) (Figure 1 - B). Ventricular dysfunction, diabetes and cerebrovascular disease were also predictive of major events (Table 3).

Both groups of MT and PCI were more likely to require further revascularization (PCI or CABG) during the follow-up, after multivariate adjusting analysis (HR =1.55, 95% CI 1.01 to 2.41 and HR = 1.85, 95% CI 1.13 to 3.02, respectively) (Figure 1 - C). The median time to subsequent revascularization was 32 months (IQR 11 to 79) in the MT, 32 months (IQR 8 to 79) in the PCI and 38 months (IQR 24 to 83) in the CABG group (P=0.019). Ventricular dysfunction and diabetes were also predictive of additional revascularization and previous acute myocardial infarction was inversely associated with this outcome (Table 3).

Subgroup analyses

We also analyzed rates of combined major events in specific subgroups of patients with diabetes and three-vessel coronary disease, factors identified as determinants in the choice of therapy in patients with stable angina. There was no significant difference in outcome between initial management strategy among patients with 3-vessel coronary disease (HR =1.22, 95% CI 0.36 to 4.15 in PCI group and HR = 1.05, 95%, CI 0.40 to 2.73 in CABG group). However, when analyzed patients with diabetes, the only variable predictor of combined major events in multivariate analyses was PCI group (HR = 2.14, 95% CI 1.26 to 3.63).

Discussion

The present data report the results of an observational study from an outpatient clinic in a tertiary care university hospital in southern Brazil. The development countries are characterized by the restrict access to therapies and difficulties in incorporating new technologies, where the gap in applying the results of clinical trials is even more evident.

National and international guidelines for the management of patients with stable CAD recommend revascularization with CABG for symptomatic patients with unprotected left main disease, 3-vessel disease with or without proximal left anterior descending artery disease or 2-vessel disease with proximal left anterior descending

(Class I of recommendation). For the same patients, recommend PCI with Class IIa of recommendation to improve survival. However, all revascularization recommendations to improve survival are based on level of evidence B or C [14-16]. Guidelines emphasize the importance of using a Heart Team approach in choosing which therapy is best for each patient, demonstrating that the optimal therapeutic strategy in stable CAD patients is not straightforward [15].

The Second Medical, Angioplasty, or Surgery Study (MASS II) was the first randomized clinical trial with stable multivessel CAD comparing the 3 current therapeutic strategies, PCI with bare-metal stents versus CABG versus MT alone, in a long-term follow-up [9]. The 5-year and 10-year follow-up data showed no differences in overall mortality among the three groups of treatment. CABG was superior to MT and PCI for the combined endpoints of myocardial infarction, additional revascularization, and mortality [17,18]. Our study results were consistent with MASS II findings regarding overall mortality and subsequent revascularization, suggesting that the initial strategy with MT can be considered, recognizing that during a long-term follow-up a revascularization procedure may be necessary. However, 10-year follow-up MASS II study showed a higher incidence of myocardial infarction in MT and PCI patients than CABG patients, which demonstrates the better prognosis of surgical patients [18].

The lack of difference in mortality between MT and PCI strategies in our study corroborate the finds of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial which showed death rates of 7.6% in PCI group and 8.3% in MT group [8]. The COURAGE nuclear substudy, however, observed a graded relationship between risk of events and the extent and severity of residual ischemia in the end of follow-up. In addition, revascularization with PCI resulted in more effective reduction of ischemia than MT alone. Although not evidenced by the clinical trial, the pragmatic interpretation of these data has been to indicate revascularization for patients with more than 10% of ischemia during stress testing [19]. Our study did not evaluate data from stress testing and not considered the degree of

ischemia in the analysis, limiting the ability to identify a subgroup of patients with worse prognosis in MT group. On the other hand, the Surgical Treatment for IsChemic Heart Failure (STICH) trial showed that in patients with CAD with severe left ventricular dysfunction (ejection fraction ≤ 35%) inducible myocardial ischemia did not identify patients with worse prognosis or those with greater benefit from CABG revascularization over MT alone [20].

Similar results concerning the overall mortality were observed in Bypass Angioplasty Revascularization Investigation in patients with type 2 Diabetes study (BARI 2D), in which cumulative survival did not differ significantly between the revascularization group (88.3%) and the medical-therapy group (87.8%, P=0.97) [11]. These rates are very similar to those found in our study. However, we observed a worse prognosis in PCI group when analyzed combined events, especially in the subgroup of diabetic patients. This difference may be attributable to the use of bare-metal stent in our patients, the only device available in the public health system in our country. In BARI 2D study the majority of patients received drug-eluting stent. The significantly reduced major cardiovascular events among patients who were select to undergo CABG compared with MT differ from our results. In the BARI 2D study CABG was not compared to PCI [11]. Yet, in the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial the combined events of death, myocardial infarction and stroke occurred more frequently in the PCI group, with 5-year rates of 26.6% in the PCI group and 18.7% in the CABG group [12]. These findings are consistent with reports from Arterial Revascularization Therapies Study (ARTS) (historical control) [21], the Coronary Artery Revascularization in Diabetes (CARDia) [22], and SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery (SYNTAX) trials (subgroup analysis)[10], in which they observed excess rates of major adverse cardiovascular events in diabetic patients assigned to undergo PCI rather than CABG. These findings were primarily the result of a higher rate of revascularization in PCI group. In these

studies there is no MT group. Our results showed the same worse prognosis and the needs for additional revascularization in patients undergoing PCI.

The subgroup analysis of 3-vessel disease patients showed no difference in combined events between initial management strategy. Although multivessel disease is considered a complex CAD, results of the SYNTAX trial demonstrated the importance of estimating the severity of the lesions, and showed that major cardiac events did not significantly differ between PCI and CABG in patients with low SYNTAX score [10]. The present study did not use a measure of coronary disease severity, limiting its ability to provide a comparative data regarding better optimum revascularization strategy for multivessel disease patients. In a large American observational study sponsored by the National Heart, Lung, and Blood Institute, patients older than 65 years with multivessel coronary disease had a long-term survival advantage while submitted to CABG as compared with patients who underwent PCI [23]. Our results demonstrated a worse prognosis in PCI group of patients but do not found difference among patients managed with MT or CABG.

Our study has some limitations inherent to observational studies. Besides, is a single institution data in a reference hospital, in which the results may not be generalizable to many others centers of our country. However, our results represent the real-world practice in a public health system.

In conclusion, the present study showed that in patients who had been treated with medical therapy for stable coronary artery disease as initial strategy instead of coronary revascularization had similar rates of death from any cause and major cardiovascular events compared to those submitted to these procedures.

References

1. Pursnani S, Korley F, Gopaul R, et al. Percutaneous coronary intervention versus optimal medical therapy in stable coronary artery disease: a systematic review and meta-analysis of randomized clinal trials. Percutaneous Cardiovasc Interv 2012;5:476-90.

2. Serruys P, Daemen J, Morice MC, et al. Three-year follow-up of the ARTS-II—sirolimus-eluting stents for the treatment of patients with multivessel disease. EuroInterv 2007; 3:450–9.

3. Rodriguez A, Bernardi V, Navia J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multiple Vessel Disease (ERACI II): 30 days results and one-year follow-up results. J Am Coll Cardiol 2001; 3:51–58.

4. Booth J, Clayton T, Pepper J, et al. Randomized, controlled trial of coronary artery bypass surgery versus percutaneous coronary intervention in patients with multivessel coronary artery disease: six-year follow-up from the Stent or Surgery Trial (SoS). Circulation 2008;118:381-8.

5. Hannan EL, Wu C, Walford G, et al. Drug-eluting stents vs. coronary-artery bypass graft ing in multivessel coronary disease. N Engl J Med 2008;358:331-41.

6. Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes D, Mack MJ, et al. Percutaneous Coronary Intervention versus Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease. N Eng J Med 2009; 360:961-972.

7. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med 2007;356:1503-1516.

8. Shaw LJ, Berman DS, Maron DJ, et al. Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden: Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear substudy. Circulation 2008;117:1283-1291.

9. Hueb W, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol 2004;43:1743–51.

10. Mohr FW, Morice MC, Kappetein, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.

11. The BARI 2D Study Group. A Randomized Trial of Therapies for Type 2 Diabetes and Coronary Artery Disease. N Engl J Med 2009;360:2503-15.

12. Farkou ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.

13. Piegas LS, Haddad N. Intervenção Coronariana Percutânea no Brasil. Resultados do Sistema Único de Saúde. Arq Bras Cardiol 2011;96:317-324.

14. Guimarães JI, César LAM, Mansur AP, et al. Diretriz de Angina Estável da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol 2004;83: Supl II.

15. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/ SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2012 Dec 18;60 (24):e44-e164.

16. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–2555.

17. Hueb W, Lopes NH, Gersh BJ, et al. Five-Year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II). A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2007;115:1082-1089.

18. Hueb W, Lopes NH, Gersh BJ, et al. Ten-Year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II). A randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation 2010;122:949-957.

19. Shaw LJ, Berman DS, Maron DJ, et al. Optimal Medical Therapy With or Without Percutaneous Coronary Intervention to Reduce Ischemic Burden : Results From the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) Trial Nuclear Substudy. Circulation 2008;117:1283-1291.

20. Julio A, Panza JA, Holly TA, et al. Inducible Myocardial Ischemia and Outcomes in Patients With Coronary Artery Disease and Left Ventricular Dysfunction. J Am Coll Cardiol 2013;61:1860–70.

21. Serruys PW, Ong AT, van Herwerden LA, et al. Five-year outcomes after coronary stenting versus bypass surgery for the treatment of multivessel disease: the final analysis of the Arterial Revascularization Therapies Study (ARTS) randomized trial. J Am Coll Cardiol 2005;46:575-81.

22. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneouscoronary intervention with coronary artery bypass grafting in diabetic patients: 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432-40.

23. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies. N Engl J Med 2012;367(5):476-7.

Table 1. Baseline Characteristics of the Patients

	Total n= 560 (%)	**MT n= 288 (51.4%)**	**PCI n=159 (28.4%)**	**CABG n=113 (20.2%)**	**P Value**
Age, years	62 ±11	62 ±11	61 ±12	63 ±10	0.16
Male	329 (58.8)	170(59)	85 (53.5)	74 (65.5)	0.14
History of					
Diabetes Mellitus	198 (35.4)	110 (38.2)	47 (29.6)	41 (36.3)	0.18
Hypertension	438 (78.2)	226 (78.5)	114 (71.7)	98 (86.7)	0.01
Dyslipidemia	355 (63.4)	178 (61.8)	96 (60.4)	81 (71.7)	0.05
Smoking (current)	83 (14.8)	45 (15.6)	31 (19.5)	7 (6.2)	0.02
Smoking (previous)	264 (47.1)	132 (45.8)	67 (42.1)	65 (57.5)	0.02
Myocardial infarction	289 (51.6)	130 (45.1)	108 (67.9)	51 (45.1)	<0.001
Cerebrovascular disease	58 (10.4)	33 (11.5)	15 (9.4)	10 (8.8)	0.67
Renal failure	86 (15.4)	36 (12.5)	25 (15.7)	25 (22.1)	0.06
LVEF (%)	54 ±13	55 ±14	54 ±13	50 ±11	0.01
LVEF <50%	188 (33.6)	94 (32.6)	43 (27)	51 (45.1)	<0.01
Three-vessel disease	81 (14.5)	30 (17.3)	14 (10.8)	37 (41.6)	<0.001

Data are expressed as means ± Standard Deviation or as a number (%)

Abbreviations:LVEF, left ventricular ejection fraction.

Table 2. Primary and secondary outcomes

	Total n= 560 (%)	**MT** n= 288 (51.4%)	**PCI** n=159 (28.4%)	**CABG** n=113 (20.2%)	**P Value**
Combined Outcomes	168 (30)	77 (26.7)	52 (32.7)	39 (34.5)	0.21
Death	69 (12.3)	32 (11.1)	19 (11.9)	18 (15.9)	0.41
ACS	106 (18.9)	43 (14.9)	36 (22.6)	27 (23.9)	0.04
Stroke	14 (2.5)	9 (3.1)	5 (3.8)	0	0.16
Cardiovascular death	40 (7.1)	23 (9)	7 (4.4)	10 (8.8)	0.27
Heart failure	24 (4.3)	10 (3.5)	6 (3.8)	8 (7.1)	0.26
Subsequent revascularization*					
PCI	115 (20.5)	54 (18.8)	37 (23.3)	24 (21.2)	0.51
CABG	56 (10)	41 (14.2)	11 (6.9)	4 (3.5)	<0.01

ACS, acute coronary syndrome; MT, medical therapy; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

Some patients had a nonfatal myocardial infarction or stroke before their subsequent death, so the number of combined events is lower than the sum of each single event. In the survival analyses, it was use the time until the first event.

* Values represent the first revascularization procedure in patients who were originally assigned to the medical therapy

Table 3. Multivariate Cox regression analyses comparing event-free survival between groups, adjusted for clinical parameters.

Outcome	HR	95%CI	P
Death			
Age	1.04	1.01 - 1.07	0.005
Male gender	2.17	1.14 - 4.13	0.018
Diabetes	2.22	1.28 - 3.86	0.005
Cerebrovascular disease	5.07	2.89 - 8.90	<0.001
Renal failure	1.65	0.93 - 2.91	0.086
Death, myocardial infarction, and stroke			
Ventricular dysfunction	1.43	1.06 - 1.95	0.022
Diabetes	1.58	1.16 - 2.15	0.004
Cerebrovascular disease	1.73	1.16 - 2.59	0.008
PCI group	1.50	1.05 - 2.14	0.026
CABG group	1.24	0.84 - 1.83	0.270
Revascularization			
Ventricular dysfunction	1.46	1.05 - 2.05	0.025
Diabetes	1.88	1.37 - 2.59	<0.001
Previous myocardial infarction	0.58	0.42 - 0.82	0.002
PCI group	1.85	1.13 - 3.02	0.015
Medical therapy group	1.55	1.01 - 2.41	0.049

HR, Hazard Ratio; 95% CI, 95% confidence interval; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting

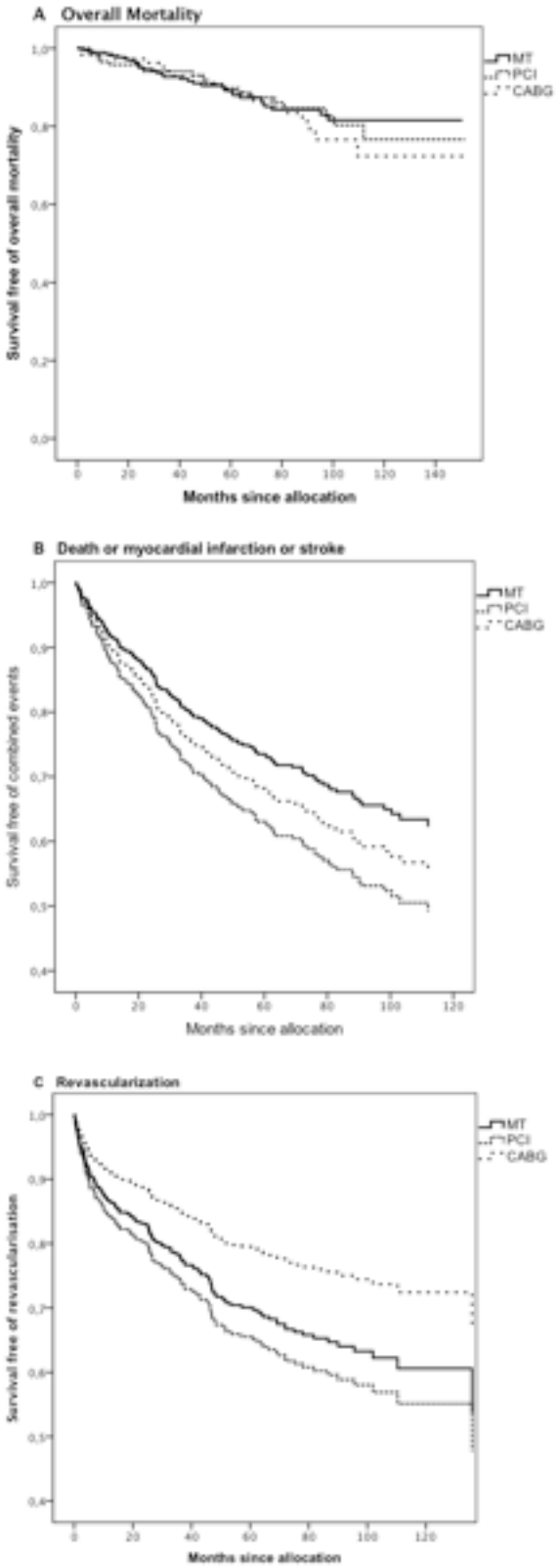

Figure 1. Probability of survival free of events among patients in the MT, CABG, and treatment groups, adjusted for clinical parameters. **A**: overall mortality; **B**: combined events of death, myocardial infarction, and stroke; **C**: revascularization.