1984 — 27 Anos — 2011

MASS

5 Trials

52 Publicações

Um Estudo Temático

INCOR·HC FUNDAÇÃO ZERBINI
CIÊNCIA E HUMANISMO

São Paulo

PREFÁCIO

O Projeto MASS (Medicine, Angioplasty and Surgery Study) foi criado em 1984 como resultados de experiências iniciais de um estudo de seguimento clínico em longo prazo de pacientes portadores de obstruções coronarianas graves e que recusaram o tratamento cirúrgico. Nesse estudo observou-se que nesses pacientes, portadores de comprometimento coronariano multiarterial, angina estável e com função ventricular preservada exibiram excelente prognóstico clínico e baixos percentuais de eventos coronarianos e também de morte. Depois de divulgados esses resultados, criamos um grupo de trabalho para planejar e executar uma estratégia de estudos focando a evolução clínica em longo prazo, de pacientes portadores de Doença Arterial Coronária (DAC) que se submetessem às diferentes formas terapêuticas e, compará-las entre si. A organização estrutural reuniu para o seu planejamento, pesquisadores multiprofissionais incluindo: médicos, enfermeiros, estatísticos, psicólogos, nutricionistas, biólogos, digitadores de banco de dados, entre outros. A base operacional do projeto está localizada nas dependências dos ambulatórios da Unidade Clínica de Doenças Coronárias onde os pacientes foram recrutados. O segmento clínico dos pacientes é realizado em salas de atendimento do ambulatório, pelos médicos e também pela equipe multiprofissional e, as informações, obtidas dos pacientes alimentam o nosso banco de dados.

Até o presente momento estão registrados aproximadamente 23.000 pacientes que tiveram o diagnóstico presuntivo de DAC e que foram encaminhados para estudo cinecoronariográfico. Nessa amostra estão incluídos; além de pacientes com artérias coronárias angiograficamente normais, com discreto grau de obstruções, com obstrução importante em uma ou mais artérias, com valvopatias ou aneurismas ventriculares associados e, também, pacientes submetidos previamente à intervenções de revascularização miocárdica. Depois de examinadas todas as condições para inclusão nos estudos, as informações dos pacientes foram fornecidas para um banco de dados, ficando

então disponíveis para várias formas de tratamentos e também para futuras análises.

Por causa da diversidade de apresentação clínica e angiográfica de uma mesma doença e também, pela associação com outras enfermidades, o banco de dados do projeto MASS gerou uma série de sub estudos que permitiu analisar os resultados das diferentes formas clínicas e terapêuticas, das alterações hematológicas em diferentes condições, de processos inflamatórios sub-celulares, do material genético e da biologia molecular.

Com estes dados, o projeto MASS permitiu ampliar as discussões para futuras pesquisas possibilitando assim, considerá-lo como um projeto temático.

Assim, esse banco de dados gerou então, uma amostra representativa de pacientes com comprometimento isolado da Artéria Coronária Descendente Anterior com angina estável em ausência de infarto prévio. Além disso, nessa amostra, a função ventricular estava preservada e, as demais artérias estavam normais. Após três anos de seguimento foi observado que o resultado dos tratamentos clínico, cirúrgico ou percutâneo, indicados de maneira randomizada, revelou mortalidade semelhante para os três grupos. Todavia quando se analisou a incidência de eventos e/ou a necessidade de intervenções, observou-se que os pacientes submetidos previamente ao tratamento percutâneo necessitaram de significativo número de novas intervenções, quando comparado com pacientes do grupo cirúrgico ou clínico.

Essa mesma amostra, acompanhada por cinco anos, revelou resultados semelhantes quando avaliados os mesmos quesitos do estudo anterior. Porém, a incidência de sintomas anginosos e isquemia miocárdica esforço-induzido, foram significativamente maiores nos pacientes tratados clinicamente. Esse estudo recebeu o acrônimo de MASS I.

Com esses resultados buscou-se avaliar, com os mesmos objetivos, os efeitos dos três tipos de tratamentos, indicados de maneira randomizada, nos pacientes portadores de comprometimento multiarterial angina estável e função ventricular preservada. Criou-se assim, o MASS II e, os resultados observados após um ano de seguimento revelaram que a incidência de morte foi semelhante nas três formas terapêuticas aplicadas.

Quando se analisou a necessidade de novas intervenções, observou-se também, que os pacientes submetidos ao tratamento percutâneo tiveram

significativa necessidade de novas intervenções. A mesma análise realizada nesses pacientes após cinco anos de seguimento revelou resultados semelhantes.

Ainda que os resultados terapêuticos tenham revelado similaridade, em relação à mortalidade, observou-se no final do estudo que, os pacientes submetidos ao tratamento cirúrgico, revelavam melhor qualidade de vida em todos os domínios quando comparado com pacientes que receberam outras formas terapêuticas. Esses resultados foram obtidos com a aplicação de um questionário, o Short-Form Health Survey (SF36) com avaliação do componente mental e físico.

A análise dos custos comparativos relativos aos tratamentos aplicados nessa amostra revelou que os custos efetivos do tratamento percutaneo foram semelhantes aos custos do tratamento cirúrgico. Isto se deveu ao grande número de novas intervenções nesses pacientes. O tratamento clínico foi o de menor custo.

Todavia observou-se que, nesses pacientes, uma curva progressiva de aumento nos custos ao longo do seguimento. Também nessa amostra estudada, buscou-se correlacionar o polimorfismo da glicoproteína PIA2 plaquetária com a incidência de eventos. Observou-se que apenas os pacientes fumantes e que apresentavam o polimorfismo evoluíram com aumento de eventos cardiovasculares quando comparados aos fumantes sem a presença do polimorfismo. Por outro lado, nos pacientes não fumantes tal associação não foi encontrada. Pode-se revelar, então, que houve uma interação genético/meio ambiente na população do MASS. Todavia, não se observou diferença na incidência de eventos cardiovasculares independentemente do tipo de tratamento empregado, quando se analisou o aplótipo plaquetário P2Y12.

Pacientes diabéticos também foram contemplados com uma análise em separado. Observou-se no final do estudo, que o tratamento percutâneo ou cirúrgico diminuiu significativamente a incidência de eventos cardiovasculares comparados com pacientes que receberam tratamento clínico.

Além disso, nesses pacientes diabéticos, observou-se que, após testes ergométricos sequenciais, instalava-se o que se denomina pré-condicionamento isquêmico, ou seja: maior tolerância ao exercício após novo

teste ergométrico repetido. O uso de hipoglicemiantes orais aboliu de maneira significativa o pré-condicionamento isquêmico o que seguramente contribuiu para o pior prognóstico do paciente diabético portador de doença coronária.

Todos os pacientes estudados tiveram a randomização, como princípio de análise estatística.

Esse modelo estatístico é usado na grande maioria dos ensaios terapêuticos comparativos com seguimento em longo prazo. Dessa forma, a decisão médica para determinada opção terapêutica fica prejudicada por esse modelo.

Em nosso estudo, a conduta terapêutica foi aplicada através da randomização bem como na análise final dos dados. Além disso, elaboramos uma opção informal de tratamento, baseada na experiência de três observadores da equipe na qual se propunha, hipoteticamente, um possível tratamento independente da randomização. Essa opção informal ficou guardada sob sigilo, sendo liberada após o término do estudo. Após o conhecimento dos resultados da terapêutica randomizada, observamos que; quando a opção informal hipotética foi semelhante á opção randomizada os resultados foram melhores que naqueles que houve discordância entre a hipotética e a randomizada.

Esses resultados permitem concluir que a decisão médica, para determinada opção terapêutica é superior que modelos matemáticos de randomização.

Outro desafio da terapêutica cirúrgica da enfermidade coronariana, diz respeito à cirurgia sem circulação extracorpórea. Esse novo desafio permitiu criar fundamentos para um novo estudo o qual recebeu o nome de MASS III.

Vantagens e desvantagens são enumeradas em favor de uma ou outra opção técnica. A grande maioria dos trabalhos tem revelado similaridade das duas técnicas relativas á segurança, perviabilidade dos enxertos ou incidência de eventos. Todavia a maioria dos estudos tem mostrado resultados imediatos ou de curto prazo.

Nossos resultados imediatos têm apresentado as mesmas semelhanças, e acrescentando que, os pacientes operados sem circulação extracorpórea têm tempo reduzido de permanência na sala de operação, na sala de UTI, e também de internação hospitalar. Além disso, ainda em andamento, com proposta para cinco anos, nosso estudo, poderá confirmar ou não, a similaridade das duas técnicas, buscando avaliar, a incidência de eventos, morte ou necessidade de novas intervenções. Estudos dessa amostra, ainda

em andamento, para avaliar os custos comparativos entre as duas técnicas, têm exibido resultados surpreendentes. Remuneração aplicada com recursos governamentais e metodologia especifica baseada em recursos do sistema nacional de saúde podem estar interferindo nos resultados. Resultados em andamento de qualidade de vida, comparando as duas técnicas cirúrgicas, têm revelado similaridade entre essas técnicas.

Pacientes com diabetes tipo 2 têm frequentemente fatores de risco cardiovascular que podem influenciar o prognóstico da doença. Esses fatores de risco somados podem compor a síndrome metabólica as quais incluem: a pressão arterial elevada dislipidemia e, obesidade, relatados como participantes da patogênese e de eventos cardiovasculares pela possível ação sobre a função endotelial coronariana. Além disso, foi levantada a hipótese de que a alta taxa de excreção urinária de albumina como um indicador adicional de disfunção endotelial, é associada a maior taxa de eventos cardiovasculares e renais.

Outros potenciais fatores de risco tais como: idade, sexo tabagismo, controle glicêmico, distúrbios dos lipídios e terapias de reposição hormonal foram consideradas.

Estudos direcionados ao conhecimento em profundidade da patogênese do diabetes no sistema vascular têm mostrado que endotélio saudável inibe a adesão de plaquetas e leucócitos na superfície do vaso e mantém o equilíbrio da atividade pró-fibrinolítica e pró-trombótico. No entanto, com a ocorrência de disfunção, o endotélio se torna um potencial ator na patogênese da doença vascular no diabetes mellitus e aterosclerose. Em condições fisiológicas, há um delicado equilíbrio de fatores relaxantes e também de fatores derivados do endotélio atuando na contração vascular que aparentemente é desequilibrada na presença de diabetes e pode colaborar para o desenvolvimento da aterosclerose, contribuindo assim para a progressão da lesão vascular em diferentes órgãos. A hiperglicemia tem sido implicada como o principal fator causal no desenvolvimento da aterosclerose coronariana em pacientes diabéticos. No entanto, os mecanismos associados com esse transtorno são susceptíveis de seremmultifatoriais. Entre estes estão relacionados à hipertensão, obesidade abdominal e síndrome pluri-metabólica. Além destes, destacamos a presença de diminuição da lipoproteína de alta densidade (HDL)

e níveis elevados de lipoproteína de baixa densidade (LDL), acompanhados de triglicerídeos elevados, e VLDL aumentado. Além disso, destaca-se anefropatia, distúrbio da coagulação e disfunção plaquetária. Resistência à insulina, outra condição existente no diabetes, tem sido descrito como responsável pelo risco aumentado de morte por doença arterial coronariana (DAC). Admite-se que pacientes com DAC e sem diabetes em comparação com aqueles com diabetes são portadores de aterosclerose coronária mais avançada, com maiores taxas de da disfunção ventricular e eventos cardíacos.

Além disso, o prognóstico dos pacientes com DAC é menos favorável nos pacientes com diabetes do que naqueles não diabéticos. Ao mesmo tempo, a mortalidade dos pacientes no pós-infarto é maior em pacientes diabéticos e é particularmente elevado entre as mulheres.

Muitas vezes, pacientes com diabetes podem ser portadores de DAC sem manifestação de sintomas. Nesses casos, o primeiro sinal da DAC pode ser a ocorrênciade um infarto do miocárdio ou morte cardíaca.

Dados relatados por Haffnere cols. mostraram que pacientes com diabetes, mas sem DAC têm a mesma incidência de ataque cardíaco como pacientes não diabéticos com DAC. Além disso, 79% dos pacientes com diabetes morrem de complicações cardíacas após um infarto agudo do miocárdio.

Além disso, pacientes encaminhados à cirurgia eletiva de revascularização miocárdica tem a necessidade de nova CRM ou PCI que é significativamente maior em indivíduos com diabetes do que aqueles sem a doença. Essa condição levou o National Cholesterol Education Program (NCEP) para considerar o diabetes como um risco equivalente ao do DAC. No entanto, embora a ocorrência de diabetes seja um dos principais determinantes das lesões vasculares, somente uma pequena série de estudos retrospectivos tem abordado o compartimento endotelial nos pacientes diabéticos com doença coronária angiograficamente normais.

Por outro lado, poucos estudos têm sido direcionados a discutir em profundidade a ocorrência de eventos cardiovasculares em longo prazo em pacientes com diabetes mellitus tipo 2 cujas artérias coronárias são angiograficamente normais. Assim esse desafio estimulou a criação de um novo estudo denominado MASS IV-DM.

Dessa forma, nossa hipótese é testar, em que pacientes diabéticos, apesar da ausência de obstrução nas artérias coronárias, com base em critérios angiográficos, se existem mecanismos protetores da doença na macro e micro circulação vascular. Além disso, planejamos avaliar a ocorrência de eventos cardiovasculares e progressão da doença vascular ao longo de cinco anos de seguimento.

O objetivo principal do estudo é identificar os possíveis mecanismos de proteção do envolvimento vascular neste grupode pacientes com diabetes, e as possíveis correlações com eventos cardiovasculares. Além disso, os objetivos secundários do estudo é comparar os dados clínicos, perfil laboratorial e angiográfico, evolução dos dados na admissão, e em 5 anos de seguimento em pacientes com diabetes tipo 2 portadores de artérias coronárias angiograficamente normais.

Nesse cenário de intervenções coronárias, cirúrgica ou percutânea, e os possíveis danos ao miocárdio, há que se estabelecer o grau de agressão ao miocárdio isquêmico e os possíveis danos á partir desses procedimentos.

Objetivando estudar o grau de insulto miocárdico por meio de liberação de enzimas, marcadoras de necrose, após intervenções cirúrgicas ou percutâneas e correlacionar com a imagem Ressonância Nuclear Magnética sem infarto agudo do miocárdio manifesto, criou-se o MASS V.

Admite-se que liberação de marcadores de enzimas de necrose das célulasmiocárdicas após um insulto isquêmico, permite o diagnostico de IAM, quando os níveis de CK-MB ou Troponina estão aumentados em até 3 vezes o estabelecido como normal, para intervenções percutâneas (PCI) e, até 5 vezes para cirurgia de revascularização miocárdica (CRM) mesmo em ausência de alterações eletrocardiográficas ou sintomas clínicos.

Nessas condições, o prognostico desse evento pode estar relacionado com o grau de elevação dos bio-marcadores liberados, e, com o tipo de intervenção aplicada.

Por outro lado, a simples identificação da CK-MB no soro não define completamente a necrose miocárdica em condições adversas como a cirurgia de revascularização miocárdica. O musculo esquelético tem até quatro vezes mais CPK que o musculo cardíaco. Assim, a liberação de CPK do músculo esquelético pode acumular 10% de CK-MB o que pode “contaminar” a análise.

Ainda que os dados disponíveis sobre liberação de enzimas cardíacas após cirurgia de revascularização seja rotineiro, existem evidencias, ainda que empíricas, que apoiam que a isquemia perioperatória ocorre com menor gravidade comparada ao IAM.

Os mecanismos potenciais de necrose miocárdica transoperatória são muitos e ocorrem principalmente por condições técnicas.

Nesse cenário está incluído o pinçamento intermitente da Aorta, intervenção com oclusão na artéria coronária nativa ou no enxerto venoso e embolia gasosa.

Além disso, é considerada a isquemia de todo o órgão, por causa de cardioplegia não protetora.

Em analogia, entre a cirurgia de revascularização miocárdica e a intervenção percutânea, esses dados sugerem uma necessidade semelhante de obtenção de dados de alta confiabilidade para definir o significado da elevação dos marcadores bioquímicos e possíveis morbidades cardíacas subsequentes.

Embolização do material da placa de ateroma submetido à intervenção percutânea foi detectada por estudos com ultrassom intracoronariano. Todavia, essa embolização pode ocorrer em diferentes fases da intervenção essa embolização é mais importante durante a implantação da endoprótese.

Além disso, o material liberado pela placa pode influenciar na extensão da mio-necrose peri-procedimento. Vale lembrar que placas com núcleo necrótico provocam maiores graus de mio necrose enquanto que placas fibrosas têm menor poder de dano miocárdico.

Ainda que a intensidade da micro embolização esteja correlacionada com á necrose microvascular, existe uma somatória considerável entre a grandeza da micro embolização da placa em pacientes submetidos ou não ao procedimento.

Esses dados sugerem que outros fatores, independentes da micro-embolização tais como liberação de substancias vaso ativas, ativação plaquetária ou vulnerabilidade miocárdica podem influenciar na ocorrência de necrose peri-procedimento.

Assim, esse estudo visa avaliar o grau de liberação de enzimas cardíacas durante os procedimentos cirúrgicos ou percutâneos em ausência de infarto manifesto do miocárdio.

O conhecimento da liberação de enzimas sem infarto manifesto, também será comparado entre as cirurgias de revascularização miocárdica com ou sem circulação extracorpórea.

Após identificar a liberação das enzimas e a magnitude desses biomarcadores, objetivamos identificar o prognóstico em longo prazo desses pacientes portadores de doença arterial coronária estável com função ventricular preservada, submetidos aos tratamentos cirúrgicos e percutâneos. .

Resultados esperados: admitindo-se que durante os procedimentos intervencionistas ambos, cirúrgico ou percutâneo, a liberação de biomarcadores de necrose seja mínima, e que, determinados limites de 3 vezes para angioplastia e 5 vezes para cirurgia não configura o Infarto do miocárdio, esperamos encontrar ausência de dano miocárdio após as intervenções.

Para que isso seja possível é necessária uma correlação com exames bioquímicos e também de imagem

Toda essa atividade de pesquisa e, também de assistência, gerou publicações em revistas internacionais arbitradas de alto impacto.

Após a divulgação destes resultados em publicações, o projeto MASS recebeu inúmeros convites para formar parcerias com vários centros internacionais os quais se destacam os estudos norte-americanos: BARI-2D, FREEDOM, CORONARY,EXCEL, ISCHEMIA financiados por: National Heart Lung and Blood Institute (NHLBI) EUA.

Neste mesmo ambiente, nosso grupo de estudos mantém parcerias acadêmicas com a Universidade de Pittsburgh, Universidade de Toronto, Mayo ClinicFoundation-(Mayo Medical School) Hospital Mont Sinai – (School of Medicine), Universidade de Stanford dentre outras.

Projetado também para servir como campo de pesquisas acadêmicas, o Projeto MASS recebe sistematicamente alunos de pós-graduação para suas pesquisas e respectivas teses. Assim, nosso projeto gerou 22 teses de Doutorado publicadas nas melhores revistas internacional. Além disso, outras 8 teses estão em andamento nas dependências do projeto MASS.

Os números da produção acadêmica e também de publicações em periódicos arbitrados, bem como, divulgações em congressos estão disponíveis na Tab. 1.

TAB.1 Pesquisa documentada **MASS**

Publicações Nacionais e Internacionais	52
Publicações em andamento	06
Teses defendidas	22
Teses em andamento	08
Teses em planejamento	07
Apresentação em Congressos Nacionais e Internacionais	216

Desnecessário enfatizar que todo esse acervo acadêmico e científico só foi alcançado graças ao apoio de um grupo diversificado de pessoas idealistas direcionados a um objetivo maior que é contribuir, sem interesses subalternos, ou por compensação material. À esse grupo, listado no final da apresentação, deixo registrado meus sinceros agradecimentos.

Whady A. Hueb

Principal Investigador

ÍNDICE

MASS-I

Estudo Comparativo entre os Tratamentos Clinico, Cirúrgico ou Percutâneo em Pacientes Portadores de Angina Estável, com Função Ventricular Preservada, e Lesão única na Artéria Descendente Anterior
Evolução De Curto e Longo Prazo

The Medicine, Angioplasty or Surgery Study (MASS): A Prospective, Randomized Trial of Medical Therapy, Balloon Angioplasty or Bypass Surgery for Single Proximal Left Anterior Descending Artery Stenosis

Whady A. Hueb, Giovanni Bellotti, Sergio Almeida De Oliveira, Shiguemituzo Arie, Cicero Piva De Albuquerque, Adib D. Jatene, Fulvio Pileggi. J Am Coll Cardiol 1995; 26:1600-1605

OBJECTIVES: This study sought to evaluate, in a prospective and randomized trial, the relative eflicacies of three possible therapeutic strategies for patients with a single severe proximal stenosis of the left anterior descending coronary artery and stable angina.

BACKGROUND: Although percutaneous transluminal coronary angioplasty and coronary artery bypass surgery are often performed in patients with a single proximal stenosis of the left anterior descending coronary artery, it is unclear whether revascularization offers greater clinical benefit than medical therapy alone.

METHODS: At a single center, 214 patients with stable angina, normal ventricular function and a proximal stenosis of the left anterior descending coronary artery >80% were randomly assigned to undergo mammary bypass surgery (n = 70), balloon angioplasty (n = 72) or medical therapy alone (n = 72). Angioplasty had to be considered technically feasible in every case. The predefined primary study end point was the combined incidence of cardiac death, myocardial infarction or refractory angina requiring revascularization.

RESULTS: At an average follow-up period of 3 years, a primary end point had occurred in only 2 patients (3%) assigned to bypass surgery compared with 17 assigned to angioplasty (24%) and 12 assigned to medical therapy 117%) (p = 0.0002, angioplasty vs. bypass surgery; p = 0.006, bypass surgery vs. medical treatment; p = 0.28, angioplasty vs. medical treatment, all by log-rank test). There was no difference in mortality or infarction rates among the groups. However, no patient allocated to bypass surgery needed revascularization, compared with eight and seven patients assigned, respectively, to coronary angioplasty and medical treatment (p = 0.019). Both revascularization techniques resulted in greater symptomatic relief and a lower incidence of ischemia on the treadmill test; however, all three strategies eventually resultedin the abolition of limiting angina.

CONCLUSIONS: The more aggressive therapeutic approach with initial bypass surgery for patients with a single severe proximal stenosis of the left anterior descending coronary artery is associated with a lower incidence of medium-term adverse events than coronary angioplasty or medical treatment. However, all three strategies resulted in a similar incidence of death and infarction during an average follow-up period of 3 years. This information should be taken into consideration when physicians and patients make therapeutic choices in this setting.

Meta-Analysis of Randomized Trials Comparing Coronary Angioplasty with Bypass Surgery

Pocock SJ, Henderson RA, Rickards AF, Hampton Jr, King SB 3rd, Hamm CW, Puel J, **Whady A. Hueb,** Goy JJ, Rodriguez A. London School of Hygiene and Tropical Medicine, UK. *Lancet* 1995 Nov; 4; 346(8984):1184-9.

ABSTRACT. A patient with severe angina will often be eligible for either angioplasty (PTCA) or bypass surgery (CABG). Results from eight published randomised trials have been combined in a collaborative meta-analysis of 3371 patients (1661 CABG, 1710 PTCA) with a mean follow-up of 2.7 years. The total deaths in the CABG and PTCA groups were 73 and 79, respectively, with a relative risk (RR) of 1.08 (95% CI 0.79-1.50). The combined endpoint of cardiac death and non-fatal myocardial infarction occurred in 169 PTCA patients and 154 CABG patients (RR 1.10 [0.89-1.37]). Amongst patients randomised to PTCA 17.8% required additional CABG within a year, while in subsequent years the need for additional CABG was around 2% per annum. The rate of additional non-randomised interventions (PTCA and/or CABG) in the first year of follow-up was 33.7% and 3.3% in patients randomised to PTCA and CABG, respectively. The prevalence of angina after one year was considerably higher in the PTCA group (RR 1.56 [1.30-1.88]) but at 3 years this difference had attenuated (RR 1.22 [0.99-1.54]). Overall there was substantial similarity in outcome across the trials. Separate analyses for the 732 single-vessel and 2639 multivessel disease patients were largely compatible, though the rates of mortality, additional intervention, and prevalent angina were slightly lower in single vessel disease. The combined evidence comparing PTCA with CABG shows no difference in prognosis between these two initial revascularisation strategies. However, the treatments differ markedly in the subsequent requirement for additional revascularisation procedures and in the relief of angina. These results will influence the choice of revascularisation procedure in future patients with angina.

Five-Year Follow-Up of the Medicine, Angioplasty, or Surgery Study (MASS) A Prospective, Randomized Trial of Medical Therapy, Balloon Angioplasty, or Bypass Surgery for Single Proximal Left Anterior Descending Coronary Artery Stenosis

Whady A. Hueb, MD; Paulo Rogério Soares, MD; Sérgio Almeida de Oliveira, MD; Shiguemituzo Ariê, MD; Rita Helena A. Cardoso, MSc; Dalia Ballas Wajsbrot, MSc; Luiz A.M. Cesar, MD; Adib D. Jatene, MD; José Antonio F. Ramires, MD. (Circulation. 1999; 100[suppl II]:II-107–II-113.)

BACKGROUND: Although coronary angioplasty and myocardial bypass surgery are routinely used, there is no conclusive evidence that these interventional methods offer greater benefit than medical therapy alone. This study is intended to evaluate, in a prospective, randomized, and comparative analysis, the benefit of the 3 current therapeutic strategies for patients with stable angina and single proximal left anterior descending coronary artery stenosis.

METHODS AND RESULTS: In a single institution, 214 patients with stable angina, normal ventricular function, and severe proximal stenosis (.80%) on the left anterior descending artery were selected for the study. After random assignment, 70 patients were referred to surgical treatment, 72 to angioplasty, and 72 to medical treatment. The primary end points were the occurrence of acute myocardial infarction or death and presence of refractory angina. After a 5-year follow-up, these combined events were reported in only 6 patients referred to surgery as compared with 29 patients treated with angioplasty and 17 patients who only received medical treatment (P50.001). However, no differences were noted in relation to the occurrence of cardiac-related death in the 3 treatment groups (P50.622). No patient assigned to surgery needed repeat operation, whereas 8 patients assigned to angioplasty and 8 patients assigned to medical treatment required surgical bypass after the initial random assignment. Surgery and angioplasty reduced anginal symptoms and stress-induced ischemia considerably. However, all 3 treatments effectively improved limiting angina.

CONCLUSIONS: Bypass surgery for single-vessel coronary artery disease is associated with a lower incidence of medium-term and long-term events as well as fewer anginal symptoms than that found in the patients who underwent angioplasty or medical therapy. In this study, coronary angioplasty was only superior to medical strategies in relation to the anginal status. However, the 3 treatment regimens yielded a similar incidence of acute myocardial infarction and death. Such information should be useful when choosing the best therapeutic option for similar patients.

MASS-II

Estudo Comparativo entre os Tratamentos Clinico, Cirúrgico ou Percutâneo em Pacientes Portadores Doença Coronária Multiarterial Estável e com Função Ventricular Preservada. Evolução de Curto, Médio e Longo Prazo.

Sub-Análises Comparativas das Principais Características Demográficas, Clínicas Laboratoriais e Angiográficas.

Sub-Estudos Comparativos Sobre Qualidade de Vida e Custo-Efetividade.

Sub-Estudos de Genética e Atividade Inflamatória

MASS II (Medical, Angioplasty and Surgery Study)

Whady A. Hueb, Heart Institute (InCor), University of Sao Paulo Medical School, Sao Paulo, Brazil. *Clin Cardiol.* Vol 24 May 2001: 94.

PATIENT POPULATION: Stable angina patients (n = 611) eligible for medical therapy alone (n = 203), surgery (n = 203), or angioplasty (n = 205) with double- or triple-vessel disease and preserved left ventricular function (LVEF ≤ 50%) comprised the patient population. Eligibility was determined by agreement of two out of three physicians.

METHODOLOGY: Patients were randomized to one of the three strategies. After randomization and procedures, patients were referred to out-patient follow-up every 3 months in the first year, with angioplasty patients having repeat angiograms at 6 months. The primary endpoint was the combined occurrence of unstable angina, myocardial infarction (MI), and cardiac death.

RESULTS: Na average of 3.1 vessels was grafted among coronary artery bypass graft (CABG) patients and an average of 2.0 vessels were dilated among angioplasty patients. Stents were placed in 70% of angioplasty patients. Analysis showed freedom from nonfatal MI to be significantly higher (p = 0.0015) for surgery or medical therapy patients compared with the angioplasty group. More patients in the angioplasty group required further revascularization or crossover to surgery than did patients in the other groups (angioplasty 14%, medical therapy 8%, surgery 0%, p = 0.000015). In addition, freedom from angina at one year was most frequent among CABG patients (angioplasty 75%, medical therapy 8%, surgery 94%, p – 0.00002). While survival at 12 months was similar for the three groups, freedom from major combined cardiac events (the primary endpoint) was much greater for the surgery group than for the angioplasty group (p = 0.00002). The rate for medical therapy was not significantly lower than that of surgery.

CONCLUSION: Medical therapy alone was associated with low incidence of the combined occurrence of unstable angina, MI, and cardiac death, and was better than percutaneous transluminal coronary angioplasty (PTCA) for both the primary and anginal endpoints. Surgical revascularization was better than medical therapy only in relation to anginal status. Patients in the PTCA group were more likely to need further interventions.

Relative Cost Comparison of Treatments for Coronary Artery Disease: The First Year Follow-Up of Mass II Study

Favarato D, **Whady A. Hueb,** MD; Gersh BJ, Soares PR, César LAM, Luz PL, Oliveira SA, Ramires JAF. *Circulation* 2003; 108 [suppl II]: II-21II-23.

BACKGROUND: Prior comparisons of costs following CABG and PTCA have demonstrated higher initial costs after CABG but following PTCA, recurrent symptoms and repeat revascularization result in increased late costs and over time their costs equilibrate. The MASS II trial provides an opportunity to compare the costs of CABG and PTCA in addition to a strategy of medical therapy.

METHODS: We studied the 611 patients of MASS II [Medical (203), Angioplasty (205), or Surgery (203) Study], a randomized study to compare treatments for multivessel CAD and preserved left ventricle function. The costs were: CABG US$ 10650.00; PTCA US$ 6400.00; new AMI hospitalization AMI U$ 2550; angiography not fol1owed-up of PTCA US$ 1900.00; and medication US$ 1200.00 for medical, and US$ 1000.00 for the other groups. We did adjustment for average event-free time, and angina-free proportion. The statistical analysis carried out was chi-square, t test, and analysis of variance.

RESULTS: After year, 49%) Medical, 79(% PTCA, and 88% CABG became angina-free; p < O.OOO1. There were 26 coronary angiograms (5 medical, 17 PTCA, and 4 CABG), 23 AMI (8 medical, 17 PTCA, and 6 CABG; p = 0.03); PTCA was performed in 7 Medical] 7 PTCA, and 1 CABG, (p = O.OO03), CABG was performed in 15 Medical, 8 PTCA, and zero CABG; p = 0.002. The event-free and event and angina-free-costs in the first year were US$ 2453.50 and US$5006.32 for Medical; US$ 10348, 43; and US$ 13099.31 for PTCA; and US$ 12404.21 and US$ 14095.09 for CABG group. An increase from expected costs of 317%, 77%, and 21 %, respectively.

CONCLUSION: PTCA effective costs were similar to CABG costs, Medical treatment presented the lowest cost, and however, the greatest increment, and CABG presented the most stable costs.

The Medicine, Angioplasty, or Surgery Study (Mass-II): A Randomized, Controled Clinical Trial of Three Therapeutic Strategies for Multivessel Coronary Artery Disease One- Year Results

Whady A. Hueb, Soares PR, Gersh BJ, César LAM, Luz PL, Puig LB, Martinez EM, Oliveira SA, Ramires JAF. *J Am Coll Cardiol* 2004; 43:1743-51.

OBJECTIVES: We sought to evaluate the relative efficacies of three possible therapeutic strategies for patients with multivessel coronary artery disease (CAD), stable angina, and preserved ventricular function. Despite routine use of coronary artery bypass graft surgery (CABG) and percutaneouscoronary intervention (PCI), there is no conclusive evidence that either one is superior to medical therapy (MT) alone for the treatment of multivessel CAD. The primary end point was defined as cardiac mortality, Q-wave myocardial infarction (MI), or refractory angina requiring revascularization. All data were analyzed according to the intention-to-treat principle.

METHODS: A total of 611 patients were randomly assigned to either a CABG (n = 203), PC I (n = 205), or MT (n = 203) group. The one-year survival rates were 96.0% for CABG, 95.6% for PCI, and 98.5% for MT.

RESULTS: The rates for one-year survival free of Q-wave MI were 98% for CABG, 92% for PC I, and 97% for MT. After one-year follow-up, 8.3% of MT patients and 13.3% of PC I patients underwent to additional interventions, compared with only 0.5% of CABG patients. At one-year follow-up, 88% of the patients in the CABG group, 79% in the PC I group, and 46% in the MT group were free of angina ($p < 0.0001$).

CONCLUSIONS: Medical therapy for multivessel CAD was associated with a lower incidence of short-term events and a reduced need for additional revascularization, compared with PCI. In addition, CABG was superior to MT for eliminating anginal symptoms. All three therapeutic regimens yielded relatively low rates of cardiac-related deaths.

Effect of Glycoprotein IIIa Pi^{a2} Polymorphism on Outcome of Patients with Stable Coronary Artery Disease and Effect of Smoking

Lopes NHM, Pereira AC, **Whady A. Hueb,** Soares PR, Lanz JR, Gersh BJ, Oliveira SA, César LAM, Ramires JAF, Krieger JE. *Am J Cardiol* 2004; 93:1469-1472.

OBJETIVES: A polymorphism of glycoprotein IIb/IIIa has been associated with myocardial infarction and restenosis after percutaneous coronary intervention. The influence on outcome and the interaction of the PIA] genotype with classic risk factors for coronary artery disease (CAD) were characterized in patients with chronic CAD followed prospectively for 3 years.

METHODS: PI^{A1} genotypes were assessed in 592 patients enrolled in the Medical, Angioplasty, or Surgery Study 11, a randomized trial comparing treatments for patients with CAD and preserved left ventricular function.

RESULTS: The incidence of the composite end point of cardiac death, myocardial infarction, and refractory angina requiring revascularization were determined in each genotype group. Risk was assessed with the Cox proportional-hazards model. The clinical characteristics and treatment of each genotype were similar. Although the composite end point tended to be more common in patients with the PI^{A2} allele, only smokers with the PI^{A2} allele had a significantly increased incidence of the composite end point ($p = 0.01$). Moreover, a 2.2-fold increased risk was apparent in smokers with the PI^{A2} allele ($p = 0.03$).

CONCLUSION: Thus, taken together, these data provide support for the interaction effect between smoking and the PIA] gene variant. Smokers with the PIA2 polymorphism of platelet glycoprotein IIIa are at greater risk for subsequent cardiac events in stable coronary disease.

Cardiac Outcomes Occurred More Frequently with PCI than CABG or Medical Therapy in Coronary Artery Disease

Whady A. Hueb, Soares PR, Gersh BJ, et al. The Medicine, Angioplasty, or Surgery Study (MASS-II): A Randomized controlled clinical trial for three therapeutic strategies for multivessel coronary artery disease: one-year results. *ACP Journal Club* 2004; 141:3, 57-58.

QUESTIONS: In patients with multivessel coronary artery disease (CAD), how do percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, and medical therapy (MT) compare for reducing cardiac outcomes?

METHODS: Randomized controlled trial (Medicine, Angioplasty, or Surgery Study [MASS-II]). *FOLLOW-UP PERIOD:* 1 year. Patients: 611 patients (mean age 60y, 85% men) with angiographically documented, visually assessed, proximal, multivessel coronary stenosis > 70% and ischemia (documented by either stress testing or the Canadian Cardiovascular Society class II or III). Exclusion criteria included unstable angina or acute myocardial infarction (MI) requiring emergency revascularization.

INTERVENTION: All patients received MT (including nitrates, aspirin, β-blockers, calcium-channel blockers, angiotensin-converting enzyme inhibitors, or a combination of these drugs unelss contraindicated). Patients were allocated to continue aggressive MT alone (n = 203), PCI (residual stenosis of < 50% reduction in luminal diameter) with-in 3 weeks (n = 205), or CABG within 12 weeks (n = 203). *OUTCOMES:* Composite endpoint of cardiac mortality, MI, or refractory angina requiring revascularization (event-free survival); therapeutic PCI or CABG during an episode of unstable angina at any time during following-up; and angina status. Patient follow-up: All patients were included in the intention-to-treat analysis.

MAIN RESULTS: The composite endpoint occurred in more patients who received PCI, than in those who received MT or CABG, and in more MT patients than in the CABG group. The groups did not differ for cardiac death (4.5%, 1.5%, and 4.0%, respectively; p = 0.23). Fewer patients who received CABG or MT had MI than did those who received PCI (2% or 5% vs 8.3%, respectively; p = 0.01). Additional revascularizations were required in fewer patients in the CABG group (0.5%) compared with the MT (8%) or PCI group (12%) (p < 0.001). Angina was more frequent with MT than PCI or CABG (64% vs 45% or 39%, respectively; p < 0.001).

CONCLUSIONS. In patients with multivessel coronary artery disease, the combined endpoint of cardiac death, myocardial infarction (MI), and refractory angina occurred more frequently with percutaneous coronary intervention (PCI) than with coronary artery bypass grafting (CABG) or medical therapy (MT).

Commentary

Whady A. Hueb, Lopes Neuza. *Evidence-based Cardiovascular Medicine,* 2005(9):54.

This study found no clear advantage of complete revascularisation over culprit vessel revascularisation in people with multivessel disease. Complete revascularisation was initially associated with lower success rates. More stents were used in this group, 50 there was also a greater incidence of in-stent restenosis. However, people who received culprit lesion revascularisation were more likely to undergo repeat percutaneous coronary interventions during follow up. This was predominantly due to recurrent angina symptoms in an initially untreated artery. Consequently, overall costs equalised between groups. Clinical implicatlons: Drug-eluting stents and optimal pharmacological management may minimise the need for repeat percuatenous coronary intervention and in-stent restenosis. A larger study incorporating these technologies would provide more evidence of the relative benefits of complete and culprit vessel revascularisation in multivessel coronary artery disease. At present, there is insufficient evidence to recommend one strategy over another. Decisions about whether to use culprit vessel or complete revascularisation should be made on an individual basis, taking into account clinical aspects, psychological implications, and quality of life.

Caveats: Although this study addressed an important issue, the implications are limited by the advent of newer methods and medications. Stents, GP IIb/IIIa inhibitors, and statins were used in relatively few people in both study groups. Methodological problems also limit the generalisability of findings. For instance, the sample comprised only 5% of the 4468 people undergoing percutaneous coronary interventions in one centre. Ninety-four percent of people in the sample had two-vessel disease, which has better prognosis than other multivessel disease, and 50% more people in the culprit revascularisation group had involvement of the left anterior descending artery.

The Effects of Glibenclamide, A K (Atp) Channel Blocker, on The Warm-Up Phenomenon

Ferreira BM, Moffa PJ, Falcao A, Uchida A, Camargo P, Pereyra P, Soares PR, **Whady A. Hueb,** Ramires JA. *Annals of Noninvasive Electrocardiology* 2005; 10(3):356-62.

BACKGROUND: The warm-up phenomenon observed after the second of two sequential exercise tests is characterized by an increased time to ischemia and ischemic threshold, and the latter is related to ischemic preconditioning. Previous studies have demonstrated that a single dose of glibenclamide, a cardiac ATP-sensitive K (K(ATP)) channel blocker, prevents ischemic preconditioning. This study aimed to investigate the effects of chronic treatment with glibenclamide during two sequential exercise tests.

METHODS: Forty patients with angina pectoris were divided into three groups: 20 nondiabetics (NDM), 10 patients with diabetes in treatment with glibenclamide (DMG) and 10 diabetic patients with other treatments (DMO). All patients underwent two consecutive exercise tests.

RESULTS: Heart rate and rate-pressure product at 1.0 mm ST-segment depression significantly increased during the second exercise test in NDM group (121.3±16.5 vs 127.3±15.3 beats/min, p <0.001, and 216.7+43.1 vs 232.1±43.0 beats.min^{-1}.mmHg.10^{2}, p <0.001), and in DMO group (114.1±19.6 vs 119.6±18.1 beats/min, p = 0.001, and 199.8±36.6 vs 222.2±29.2 beats.min^{-1}.mmHg.10^{2}, p = 0.019), but it did not change in patients in DMG group (130.7±14.5 vs 132.1±4.7 beats/min, p = ns, and 251.7±47.2 vs 250.3±42.8 beats.min^{-1}.mmHg.10^{2}, p = ns). In the three groups, NDM, DMO, and DMG, the time to 1.0 mm ST-segment depression during the second exercise test was greater than during the first (225.0±112.5 vs 267.0±122.3 seconds, p = 0.006; 187.5±54.0 vs 226.5±74.6 seconds, p = 0.029 and 150.0±78.7 vs 186.0±81.9 seconds, p <0.001).

CONCLUSION: The chronic use of glibenclamide may have mediated the loss of preconditioning benefits in the warm-up phenomenon, probably through its KATP channel-blocker activity, but without acting upon the tolerance to exercise.

One-Year Outcomes of Coronary Artery Bypass Graft Surgery versus Percutaneous Coronary Intervention with Multiple Stenting for Multisystem Disease: A Meta-Analysis of Individual Patient Data from Randomized Clinical Trials

Mercado N, Wijns W, Serruys PW, Sigwart U, MD, Flather MD, Stables RH, O'Neill WW, Rodriguez A, Lemos PE, **Whady A. Hueb,** Gersh BJ, Booth J, Boersma E. *J Thorac Cardiovasc Surg* 2005;130:512-9.

BACKGROUND: We aimed to provide a quantitative analysis of the 1-year clinical outcomes of patients with multisystem coronary artery disease who were included in recent randomized trials of percutaneous coronary intervention with multiple stenting versus coronary artery bypass graft surgery.

METHODS: An individual patient database was composed of 4 trials (Arterial Revascularization Therapies Study, Stent or Surgery Trial, Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty Versus Coronary Artery Bypass Surgery in Multivessel Disease 2, and Medicine, Angioplasty, or Surgery Study 2) that compared percutaneous coronary intervention with multiple stenting (N = 1518) versus coronary artery bypass graft surgery (N = 1533). The primary clinical end point of this study was the combined incidence of death, myocardial infarction, and stroke at 1 year after randomization. Secondary combined end points included the incidence of repeat revascularization at 1 year. All analyses were based on the intention-to-treat principle.

RESULTS: After 1 year of follow-up, 8.7% of patients randomized to percutaneous coronary intervention with multiple stenting versus 9.1% of patients randomized to coronary artery bypass graft surgery reached the primary clinical end point (hazard ratio 0.95 and 95% confidence interval 0.74'1.2). Repeat revascularization procedures occurred more frequently in patients allocated to percutaneous coronary intervention with multiple stenting compared with coronary artery bypass graft surgery (18% vs 4.4%; hazard ratio 4.4 and 95% confidence interval 3.3'5.9). The percentage of patients who were free from angina was slightly lower after percutaneous coronary intervention with multiple stenting than after coronary artery bypass graft surgery (77% vs 82%; p = 002).

CONCLUSIONS: One year after the initial procedure, percutaneous coronary intervention with multiple stenting and coronary artery bypass graft surgery provided a similar degree of protection against death, myocardial infarction, or stroke for patients with multisystem disease. Repeat revascularization procedures remain high after percutaneous coronary intervention, but the difference with coronary artery bypass graft has narrowed in the era of stenting.

Estudo Comparativo dos Resultados da Intervenção Cirúrgica e da Angioplastia na Revascularização do Miocárdio em Portadores de Comprometimento Multiarterial Equivalente

Silva PRD, **Whady A. Hueb,** César LAM, Oliveira LAM, Ramires JAF. *Arq Bras Cardiol,* 2005; vol 84 (nº 3), 214-21.

OBJETIVO: Investigar a relativa eficácia de estratégias terapêuticas em pacientes com doença coronariana multiarterial sintomática, com função ventricular preservada. Os objetivos primários foram definidos com a combinação de: morte por origem cardíaca, infarto agudo do miocárdio (IAM) ou angina refratária que necessitasse de revascularização e, os secundários, estados anginoso e isquemia esforço-induzido.

MÉTODOS: De 20.769 pacientes avaliados por cineangiocoronariografia no InCor, 210 foram escolhidos para o estudo e randomizados para revascularização miocárdica (RCM) (n = 105) e angioplastia transluminal coronariana (ATC) (n= 105).

RESULTADOS: Médias de 3,2 ± 0,8 vasos receberam anastomoses e 2,1±0,8 foram dilatados com sucesso nos grupos RCM e ATC, respectivamente. Em cinco anos de seguimento as respectivas taxas de eventos para RCM e ATC foram: 9,52% e 12,38% para mortalidade, 2,85% e 8,57% (p=0,0668) para IAM, 2,85% e 24,76% (p< 0,001) para uma intervenção adicional; a taxa de sobrevivência de 88,39% para RCM e de 84,93% para ATC; os respectivos porcentuais livres de IAM, 84,40 e 77,40%. Os pacientes estavam livres de angina em 62% do RCM e 60% do grupo ATC e os testes de esforço foram considerados não-isquêmicos em 62,5% e 62,1%, nos grupos cirúrgicos, e angioplastia.

CONCLUSÃO: Comparada com a angioplastia para pacientes multivasculares, a revascularização miocárdica foi associada a uma baixa incidência de eventos em longo prazo e reduzida necessidade de novas intervenções (p=0,001).

Estudo Comparativo entre os Efeitos Terapêuticos da Revascularização Cirúrgica do Miocárdio e Angioplastia Coronária em Situações Isquêmicas Equivalentes: Análise Através da Cintilografia do Miocárdio com 99mTc-Sestamibi

Moreira AELC, **Whady A. Hueb,** Soares PR, Meneghetti JC, Jorge MCP, Chalela WA, Martinez Filho EE, Oliveira SA, Jatene FB, Ramires JAF. *Arq Bras Cardiol,* 2005; vol 85 (n° 2), 92-99.

OBJETIVO: Avaliar a carga isquêmica do miocárdio prévia e ulterior à revascularização do miocárdio.

MÉTODOS: Foram avaliados 96 pacientes randomizados, portadores de doença arterial coronariana multivascular, angina estável, função do ventrículo esquerdo preservado e isquemia miocárdica esforço-induzido tratados com revascularização cirúrgica (RCM) ou angioplastia coronariana (ATC). Cintilografia do miocárdio com 99mTc-Sestamibi foi realizada antes e 6 meses após a revascularização do miocárdio.

RESULTADOS: A RCM determinaram índice significantemente maior de revascularização completa (p=0,001), aumento no número de testes ergométricos máximos (p=0,001) e redução no número de testes ergométricos positivos com angina de esforço (p=0,018). Ambos os procedimentos ofereceram melhora importante na classe funcional da angina (p=0,001), aumento no valor médio do duplo produto de pico (p=0,009), e do tempo de tolerância ao esforço (p<0,001), além de redução no valor médio da somatória do escore do esforço (p<0,001) e da diferença da somatória dos escores (p<0,001) nos dois grupos.

CONCLUSÃO: ATC e RCM não diferiram quanto à redução da carga isquêmica do miocárdio 6 meses após o procedimento. A revascularização do miocárdio foi mais completa com a RCM do que com a ATC, mas não representou fator para redução da carga isquêmica do miocárdio.

Exercise Stress Testing Before and After Succesful Multivessel Percutaneous Transluminal Coronary Angioplasty

Challela WA, Kreling JC, Falcão AM, **Whady A. Hueb,** Moffa PJ, Pereyra PLA, Ramires JAF.
Braz J Med Biol Res 2006; 39:475-482.

OBJECTIVES: Controversy exists regarding the diagnostic accuracy, optimal technique, and timing of exercise testing after percutaneous coronary intervention. The objectives of the present study were to analize variables and power exercise testing to predict restenosis or a new lesion, 6months after procedure.

METHODS: High-four coronary multi-artery diseased patients with preserved ventricular function were studied (66 males, mean age of all patients: 59 ± 10 years). All underwent angiography and exercise testing with the Bruce protocol, before and 6 months after percutaneous coronary intervention. The following parameters were measured: heart rate, blood pressure, rate-pressure product (heart rate x systolic blood pressure), presence of angina, maximal ST-segment depression, and exercise duration.

RESULTS: On average, 2.33 lesion/patient were treated and restenosis or progression of disease occurred in 46 (55%) patients. Significant increases in systolic blood pressure (p = 0.022), rate-pressure product (p = 0.045) and exercise duration (p = 0,003) were detected after the procedure. Twety-seven (32%) patients presented angina during the exercise test before the procedure and 16 (19%) after the procedure. The exercise test for the detection of restenosis or new lesion presented 61% sensitivity, 63% specifity 62% accuracy and 67 and 57% positive and negative predictive values, respectively.

CONCLUSION: In patients without restenosis, the exercise duration after percutaneous coronary intervention was significantly longer (460±154 vs.381± 145. p = 0.008). Only the exercise duration permited us to identify patients with and without restenosis or a new lesion.

Coronary Revascularization (Surgical or Percutaneous) Decreases Mortality after the First Year in Diabetic Subjects but Not In Non Diabetic Subjects With Multivessel Disease: An Analysis from the Medicine Angioplasty or Surgery Study (Mass II)

Soares PR, **Whady A. Hueb,** Lemos PA, Lopes N, Martinez EE, César LAM, Oliveira SA, Ramirez JAF. *Circulation* 2006; 114[suppl]: I-420-I-424.

BACKGROUND: It is currently unknow whether revascularization procedures are associatedwith an improvement in mortalyty among diabetic subjects, as compared with a more conservative medical treatment.

METHODS: In MASS II, a total of 611 patients with stable multivessel coronary disease were randomly assigned to medical treatment, surgery or angioplasty. From these, 190 patients had diabetes (medical, 75patients; angioplasty, 56 patients; surgery, 59 patients) and comprised the present study population. Mortality retes were analyzed for the entire 5 years of follow-up. Separate analyzes were also performed for mortality at 2 time intervals: during the first year and after the first year of follow-up.

RESULTS: We calculated the probability of death conditionalon surviving to the start of the interval analyzed. The cumulative 5-year mortality as well as the mortality during the first year of follow-upwasnot significantly different among treatment groups, both for diabetic and nondiabetic subjects. Also, during years 2 to 5, the mortality of the 3 treatment groups was not different for nondiabetic subjects. Among diabetic subjects, however, patients randomized to angioplasty or surgery hada significantly lower mortality between years 2 and 5 than those allocated to medical treatment ($p = 0.039$).

CONCLUSION: Surgery, angioplasty and medical treatment appear to be associated with similar mortality rates for nonbiabetic subjects. For diabetic subjects, however, coronary revascularization (percutaneous or surgical) significantly decreased the risk of death after the first year and up to 5 years, compared with medical treatment alone.

Clinical Judgment and Treatment Options in Stable Multivessel Coronary Artery Disease. Results from the One-Year Follow-Up of the MASS-II (Medicine, Angioplasty, or Surgery Study) trial

Pereira AC, Lopes N, Soares PR, Krieger JE, Oliveira SA, César LAM, Ramires JAF, **Whady A. Hueb.** *J Am Coll Cardiol* 2006; 48:948-953.

OBJECTIVES: This study examined the predictive power of clinica judgment in the incidence of cardiovascular end points in a group of individual with multivessel coronary artery disease (CAD) followed up in the MASS II (Medicine, angioplasty, or suegery study II. ***BACKGROUND:*** There is no consensus on the best treatment for patients with stable multivessel CAD and preserved left ventricular function.

METHODS: Preferred treatment allocation was reccrded for each of the 611 randomized patients in the MASS II trial before randomization. We have divided our sample according to physician-guide decision and randomizationresult into two categories: concordant or discordant. The incidence of the poits of cardiacdeath myocardial infarction and refrafctory angina was compared between concordant and discordant patients.

RESULTS: The numbers of concordant individuals was 292 (48.2%), and this number was not different between the three studied treatments (p = 0.11). A significant difference (p = 0.02) was disclosed because of an increased incidence of combined end point events in discordant patients. In the multivariate Cox hazard model, clinical judgment was powerful predictor of outcome (p = 0.01) even after adjustment for other covariates. The main subgroup explaining this difference was a significant shift toward a worse outcome in the subgroup of discordant patients who underwet percutaneous coronary intervention (PCI) (p = 0.003).

CONCLUSION: Angiographic variables were more often used in making clinical decision regarding PCI than clinical variables, and the only independent predictor of concordance status in the PCI group was the numbere of diseased vessels (p=0.01). Our data are a reminder that physician judgment remains an important predictor of outcomes.

Association Between Platelet P2y12 Haplotype and Risk of Cardiovascular Events in Chronic Coronary Disease

Schettert IT, Pereira AC, Lopes NH, **Whady A. Hueb,** Krieger JE.*Thrombosis Research* 2006; 118:679-683.

INTRODUCTION: Apositive association was recently described between P2Y12 platelet receptor H1 and H2 haplotypes and peripheral aratery disease. We tested the described P2Y12 receptor haplotypes in a group of patients with coronary artery disease. ***STUDY DESIGNED***

METHODS: The P2Y12 platelet receptor H1 and H2 haplotypes wass tested in a group of 540 patients enrolled in the Medical, Angioplasty, or Surgery Study II (MASS II) a randomized trial comparing treatments for patients with coronary artery disease (CAD) and preserved left ventricular function. After a 3-year follow-up period, the incidence of the composite end-point of cardiac death, myocardial infarction, and refractory angina requiring revascularization was determined in the H1/H1, and H2/H2 haplotype groups.we used Student's t test and the chi-square test to analyse the differences among groups and Kaplan-Meier method to calculate survival curves.Risks was assessed with the use of a Cox proportiona-hazard model.

RESULTS: The frequency of haplotypes among studied patients were 410 (75.9%) H1/H1, 119 (22.0%) H1/H2 and 11 (2.1%) H2/H2. The baseline clinical characteristics, mean clinical follow-up time and received treatment of each genotype group were similar. We did not disclose any association between haplotype groups regarding the incidence of any of the studied cardiovascular end-points.

CONCLUSION: This is the first report studying the association of P2Y12 platelet receptor H1 and H2 haplotype and cardiovascular events.

Impact of Diabetes on Five-Year Outcomes of Patients with Multivessel Coronary Disease

Whady A. Hueb, Gersh BJ, Costa F, Lopes N, Soares PR, Dutra P, Jatene F, Pereira A, Góes A; Oliveira AS, Ramires JAF. *Ann Thorac Surg* 2007; 83:93-99.

BACKGROUND: Diabetes melitus is a major cause of coronary artery disease. Despite improvement in the management of patients with stable coronary artery disease, diabetes remains a major cause of increased morbidity and mortality.Although coronary artery bypass grafting surgery (CABG) and percutaneous coronary interventions are widely used, no conclusive evidence exists that either treatment modality is better than medical therapy alone for the treatment of stable single- or multivessel coronary disease in patients with diabetes.

METHODS: We compared medical therapy, percutaneous coronary intervention, and CABG in 499 diabetic patients (38.5%) and nondiabetic patients (61.5%) with single-or multivessel coronary disease. The composite primary end-point was cardiac-related death, Q-wave myocardial infarction, or refractory angina requiring revascularization.

RESULTS: We treated 1,298 patients with either CABG (n=524), percutaneous coronary intervention (n=378), or medical therapy (n=396). More deaths occurred among patients with diabetes than patients without diabetes regardless of which opton was used (p<0.001).When treatment modalities were stratified according to the number of diseasaed vessels, CABG was shown to be more beneficial for patients with diabetes and single-vessel disease (p<o.oo1). However, wen stratified by treatment, patients with diabetes receiving medical therapy had a worse prognosis than patients with diabetes treated with CABG (p<0.005).

CONCLUSION: All three therapeutic regimens resulted in high rates of cardiac-related deaths among patients diabetes compared with patients without diabetes. Moreover, we observed better outcomes among patients with diabetes and multivessel coronary artery disease undergoing CABG regarding the primary endpoint at 5-year follow-up.

Effect of a Hipoglycemic Agent on Ischemic Preconditioning in Patients with Type 2 Diabetes and Stable Angina Pectoris

Whady A. Hueb, Ushida AA, Gersh BJ, Betti RT, Lopes N, Moffa PJ, Ferreira BM, Ramires JA, Wajchemberg BL. *Coronary Artery Disease* 2007; 18:55-59.

OBJECTIVE: Ischemic preconditioning is an increased tolerance to myocardial ischemia during the second of two consecutive exercise tests. ATP-sensitive K+ channel blockers, such as glinides and sulfonil urea drugs, can induce loss of ischemic preconditioning.This study aimed to investigate the effects of repaglinide, a hipoglicemic agent with an affinity for myocardial ATP-sensitive K+channels, on the results of consecutive exercise tests in patients with diabetes and multivessel disease.

METHODS: Forty-two patients with type 2 diabetes and chronic stable angina pectoris, and two-vessel or three-vessel diseased participated in this study.The patients underwent two consecutive treadmill exercise tests (phase 1). On the day after these exercise tests, 2 mg of oral repaglinide was given to the patients. One week later, two exercise tests were repetead consecutively.

RESULTS: All patients achieved 1.0-mmST-segment depression during the four exercise tests (T1, T2, T3 and T4). In fase 2, seven patients improved in time to onset of 1.0-mmST-segment depression. The worsening of the time to onset of 1.0-mmST-segment depression in fhase 2 demonstrated ischemic preconditioning block in 83% of patients (p=0.0001). Even the postexercise electrocardiografic parameters (ST-segment depression morphology and magnitude and arrhythmias) were significantly different between the groups with and withot pharmacologic ischemic preconditioning block (p = 0.031).

CONCLUSION: Repaglinide, an oral Hypoglicemic agent with ATP-sensitive K+ channel blocker activity, eliminated the myocardial ischemic preconditioning in patients with coronary disease and diabetes.

Effects of Epinephrine in Local Dental Anesthesia in Patients with Coronary Artery Disease

Neves RS, Neves IL, Giorgi DM, Grupi CJ, César LA, **Whady A. Hueb,** Grinberg M. *Arq Bras Cardiol,* 2007; 88: 545-551.

BACKGROUND: Vasoconstrictors for local anesthesia in patients with coronary heart disease are controversial in the literature, and there is concern regarding risk of cardiac decompensation.

OBJECTIVE: To evaluate electrocardiographic and blood pressure parameters during restorative dental procedure under local anesthesia with and without a vasoconstrictor in patients with coronary artery disease.

METHODS: Sixty-two patients were included in the study, ages ranging from 39 to 80 (mean 58.7 +/- 8.8), 51 (83.2%) of whom were male. Thirty patients were randomly assigned to receive 2% lidocaine with epinephrine (epinephrine group), and the remaining patients, 2% lidocaine without epinephrine (non-epinephrine group) for local anesthesia. All patients underwent 24-hour ambulatory blood pressure monitoring and dynamic electrocardiography. Three periods were considered in the study: 1) baseline—recordings obtained during the 60 minutes prior to the procedure; 2) procedure--recordings obtained from the beginning of anesthesia to the end of the procedure and 3) 24 hours.

RESULTS: There was an increase in blood pressure in both groups during the procedure, compared with baseline values; but when the two groups were compared no significant difference was detected between them. Heart rate remained unchanged in both groups. No ST-segment depression > 1 mm occurred either at baseline or during the procedure. Seven patients (12.5%) experienced more than ten arrhythmia episodes per hour during the procedure, four (13.8%) in the non-epinephrine group and three (11.1%) in the epinephrine group.

CONCLUSION: No difference was observed in blood pressure, heart rate, or evidence of ischemia and arrhythmias in either group. The use of vasoconstrictor has proved to be safe within the range of the present study.

Quality of Life after Surgical Myocardial Revascularization, Angioplasty or Medical Treatment"

Takiuti ME, **Whady A. Hueb,** Hiscock SB, Nogueira CR, Girardi P, Fernandes F, Favarato D, Lopes N, Borges JC, de Góis AF, Ramires JA. *Arq Bras Cardiol,* 2007; 88: 537-544

BACKGROUND: Although the clinical benefits of coronary interventions seem to be confirmed, their effects on quality of life (QoL) are still scarcely studied.

OBJECTIVE: To assess the QoL in multivessel coronary disease in patients randomly undergoing surgery, angioplasty or medical treatment.

METHODS: The Short-Form Health Survey (SF-36) questionnaire was answered by 483 patients. Of these, 161 underwent surgical revascularization, 166 underwent angioplasty, and 153 were medically treated.

RESULTS: At baseline, 86% of the patients referred angina, 34% referred infarction, and 32% were smokers. Medical Treatment: 12 patients (7.7%) had AMI, 24 (15.3%) underwent surgery, and 19 (12.1%) died. In addition, 5 (3.2%) had stroke, and 40 (25.6%) had angina. As regards the mental component, 64.1% and 30.8% had their condition improved and worsened, respectively. As regards the physical component, 70.5% and 27.6% had their condition improved and worsened, respectively. Surgery: 13 patients (8.1%) had AMI, 2 (1.2%) underwent surgery, and 12(7.4%) died. Also, 9 (5.6%) had stroke and 30 (18.6%) had angina. As regards the mental component, 72.7 % and 25.5% had their condition improved and worsened, respectively. As regards the physical component, 82.6% and 16.1% had their condition improved and worsened, respectively. Angioplasty: 18 patients (10.9%) had AMI, 51 (30.7%) underwent interventions, and 18 (19.9%) died. Additionally, six (3.6%) presented stroke and 35 (21%) reported angina. As regards the mental component, 66.9% and 26.5% had their condition improved and worsened, respectively. As regards the physical component, 77.1% and 20.5% had their condition improved and worsened, respectively.

CONCLUSION: Improvement was observed in all domains and in the three therapeutic modalities. Comparatively, surgery had provided a better quality of life after a four-year follow-up.

Isquemia Silenciosa Na Doença Coronariana Estável em Vigência de Tratamento Medicamentoso

Ferreira JFM, César LAM, Grupi CJ, Giorgi DMA, **Whady A. Hueb**, Ramires, JAF. *Arq Bras Cardiol,* 2007; 89(5): 312-318

FUNDAMENTO: Existem poucos dados sobre comportamento da isquemia miocárdica às atividades habituais na vigência da medicação em pacientes com doença coronariana.

OBJETIVO: Estudar mecanismo gerador da isquemia miocárdica avaliando-se o comportamento da pressão arterial e da freqüência cardíaca em pacientes com doença aterosclerótica estável, medicados e com evidência de isquemia.

MÉTODOS: Cinqüenta pacientes (40 homens) realizaram ambulatorialmente por 24 horas a monitorização eletrocardiográfica sincronizada com a monitorização da pressão arterial.

RESULTADOS: Em 17 pacientes detectaram-se 35 episódios de isquemia miocárdica, com duração total de 146,3 minutos, ocorrendo relato de angina em cinco casos. Houve 29 episódios (100,3 minutos) durante o período de vigília, com 11 episódios (35,3+3,7 min) no período das 11 às 15 horas. A avaliação da pressão arterial e freqüência cardíaca nos três intervalos de 10 minutos posteriores ao momento de isquemia mostraram diferença estatisticamente significante ($p<0,05$), o que não ocorreu nos três intervalos anteriores. Entretanto, durante o momento isquêmico, percebeu-se elevação maior que 10mmHg da pressão arterial e de cinco batimentos por minuto da freqüência cardíaca quando comparado ao intervalo de tempo entre 20 e 10 minutos anterior. A freqüência cardíaca média no início da isquemia durante teste ergométrico prévio ao estudo foi de 118,2+14, 0, e de 81,1+20,8 batimentos por minuto na eletrocardiografia de 24 horas ($p<0,001$).

CONCLUSÃO: A incidência de isquemia silenciosa é freqüente na doença coronária estável, relacionando-se com alterações da pressão arterial e da freqüência cardíaca, com diferentes limiares de isquemia para o mesmo paciente.

Quality of Life in Patients with Symptomatic Multivessel Coronary Artery Disease: A Comparative Post Hoc Analyses of Medical, Angioplasty or Surgery Strategies – MASS II – Trial

Favarato ME, **Whady A. Hueb,** Boden W, Lopes N, Nogueira CR, Takiuti M, Oliveira SA, Ramires JA. *Int J Cardiol* 2007; 116: 364-370.

OBJECTIVES: We sought to evaluate the impact of Coronary Artery Bypass Graft Surgery (CABG), Percutaneous Coronary Intervention (PCI) or Medical Therapy (MT) on self-perceived quality-of-life among patients with stable Coronary Artery Disease (CAD).

BACKGROUND: The Medicine, Angioplasty and Surgery Study (MASS-II) implemented initial policies of CABG, PCI or continued medical treatment in patients which allow assessment of mid-term health consequences.

METHODS: A total of 542 patients were randomly assigned (175 to CABG, 180 to PCI and 187 to MT). The short form 36 (SF-36) self-administrated quality-of-life questionnaires were completed at randomization, 6 months and 12 months later.

RESULTS: The CABG group had significantly greater improvement in physical functioning, vitality and general health when compared with MT or PCI. For the three groups there were also, improvements in ratings of physical and mental role functioning and social functioning, but for these, the superiority of CABG over PCI or MT was less pronounced.

CONCLUSIONS: Coronary bypass surgery substantially improves patient-perceived Quality of Life (QOL), especially physical functioning and vitality as compared with PCI or continued medical therapy. Men had the best QOL at the beginning of the treatment when compared to women, with a progressive improvement after 6 and 12 months, whereas improvement in women occurred after 6 months only, decreasing at 12 months.

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

Whady A. Hueb, Lopes NH, Gersh BJ, Soares P, César LAM, Jatene F, Oliveira SA, Ramires JAF. *Circulation* 2007; 115:1082-1089.

BACKGROUND: Despite routine use of coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI), no conclusive evidence exists that either modality is superior to medical therapy (MT) alone for treating multivessel coronary artery disease (CAD) with stable angina and preserved ventricular function.

METHODS: The primary end-points were total mortality, Q-wave myocardial infarction (MI), or refractory angina requiring revascularization. The study comprised 611 patients randomly assigned to undergo CABG (n=203), PCI (n=205), or MT (n=203). At 5-year follow-up, the primary end-points occurred in 21.2% of patients who underwent CABG compared with 32.7% treated with PCI and 36% receiving MT alone (p = 0.0026).

RESULTS: No statistical differences were observed in overall mortality among the 3 groups. In addition, 9.4% of MT and 11.2% of PCI patients underwent repeat revascularization procedures, compared with 3.9% of CABG patients (p = 0.021). Moreover, 15.3%, 11.2%, and 8.3% of patients experienced nonfatal MI in MT, PCI, and CABG groups, respectively (P<0.001). The pair-wise treatment comparisons of the primary end-points showed no difference between PCI and MT [CI 95%; 0.93 (0.66-1.36)] and a significant protective effect of CABG compared with MT [CI 95%; 0.53 (0.36-0.77)].

CONCLUSIONS: All 3 treatment regimens yielded comparable, relatively low rates of death. Medical therapy was associated with a similar incidence of long-term events and rate of additional revascularization as that for PCI. CABG was superior to MT with regards to the primary end-points, reaching a significant 44% reduction in primary end-points at 5-year follow-up of patients with stable multivessel CAD.

Dinamic Regulation of MTHFR MRNA Expression and C677T Genotype Modulate Mortality in Coronary Artery Disease Patients after Revascularization

Pereira AC, Miyakawa AA, Lopes NH, Soares PR, de Oliveira SA, Cesar LA, Ramires JF, **Whady A. Hueb,** Krieger JE. *Thromb Res.* 2007; 121:25-32.

INTRODUCTION: A large body of evidence links plasma homocysteine (Hcy) concentrations and cardiovascular disease. A common MTHFR polymorphism (C677T) leads to a variant with reduced activity and associated with increased Hcy levels. Coronary surgery precipitates a significant and sustained increase inthe blood concentration of Hcy and elevated levels of plasma Hcy have been associated to saphenous vein (SV) graft disease after CABG. However, theeffects of MTHFR genotypes in the incidence of cardiovascular events afterCABG have not been investigated prospectively. Here, we investigate whether MTHFR gene variants are associated with an increased cardiovascular risk in individuals submitted to CABG. We also propose a molecular mechanism toexplain our findings.

METHODS: We performed MTHFR C677T genotypes in 558 patients with two or three vessel-disease and normal left ventricular function prospectively followed in the MASS II Trial, a randomized study to compare treatments for multivessel CAD and preserved left ventricle function. Follow-uptime was 5 years. Survival curves were calculated with the Kaplan-Meier method, and evaluated with the log-rank statistic. We assessed the relationship between baseline variables and the composite end-point of death, myocardial infarction and refractory angina using a Cox proportional hazards survivalmodel.

RESULTS: There were no significant differences among individuals within each genotype group for baseline clinical characteristics. A statistically significant association between the TT genotype,associated with increased serum levels of Hcy, and cardiovascular mortalityafter 5 years was verified ($p = 0.007$) in individuals submitted to CABG surgery.In addition, MTHFR TT genotype was still significantly associated with a 4.4 fold increased risk in cardiovascular outcomes ($p = 0.01$) even after adjustment of a Cox multivariate model for age, sex, hypertension, diabetes, LDL, HDL,triglycerides, and number of diseased vessels in this population. Finally, asignificant reduction in MTHFR gene expression was demonstrated in human SV when submitted to an arterial hemodynamic condition ($p = 0.02$).

CONCLUSIONS: There is a dynamic regulation of MTHFR gene expression duringthe arterialization process of human saphenous vein grafts resulting in lower levels of gene expression when in an arterial hemodynamic condition. In addition, the C677T MTHFR functional variat is associated with a worse outcome in individuals submitted to CABG. Taken together, these data suggest an important role of Hcy metabolism in individuals after CABG.

Impact of Number of Vessels Disease on Outcome of Patients with Stable Coronary Artery Disease: 5-Year Follow-Up of the Medical, Angioplasty and Bypass Surgery Study (MASS-II)"

Lopes NH, Paulitsch FS, Gois AF, Pereira AC, Stolf NA, Dallan LO, Ramires JA, **Whady A. Hueb.** *Eur J Cardiothorac Surg* 2008; 33:349-354.

OBJECTIVE: To evaluate whether the number of vessels disease has an impact on clinical outcomes as well as on therapeutic results accordingly to medical, percutaneous, or surgery treatment in chronic coronary artery disease.

METHODS: We evaluated 825 individuals enrolled in MASS study, a randomized study to compare treatment options for single or multivessel coronary artery disease with preserved left ventricular function, prospectively followed during 5 years. The incidence of overall mortality and the composite end-point of death, myocardial infarction, and refractory angina were compared in three groups: single vessel disease (SVD n=214), two-vessel disease (2VD n=253) and three-vessel disease (3VD n=358). The relationship between baseline variables and the composite end-point was assessed using a Cox proportional hazards survival model.

RESULTS: Most baseline characteristics were similar among groups, except age (younger in SVD and older in 3VD, $p<0.001$), lower incidence of hypertension in SVD ($p<0.0001$), and lower levels of total and LDL-cholesterol in 3VD ($p=0.004$ and $p=0.005$, respectively). There were no statistical differences in composite end-point in 5 years among groups independent of the kind of treatment; however, there was a higher mortality rate in 3VD ($p<0.001$). When we stratified our analysis for each treatment option, bypass surgery was associated with a lower number of composite end-point in all groups (SVD $p<0.001$, 2VD $p=0.002$, 3VD $p<0.001$). In multivariate analysis, we found higher mortality risk in 3VD comparing to SVD ($p=0.005$, HR 3.14, 95%CI 1.4-7.0).

CONCLUSION: Three-vessel disease was associated with worse prognosis compared to single- or two-vessel disease in patients with stable coronary disease and preserved ventricular function at 5-year follow-up. In addition, event-free survival rates were higher after bypass surgery, independent of the number of vessels diseased in these subsets of patients.

Long-Term Safety and Efficacy of Percutaneous Coronary Intervention with Stenting and Coronary Artery Bypass Surgery for Multivessel Coronary Artery Disease. A Meta-Analysis with 5-Year Patient-Level Data from the ARTS, ERACI-II, MASS-II, and SoS Trials

Daemen J, Boersma E, Flather M, Booth J, Stables R, Rodriguez A, Rodriguez-Granillo G, **Whady A. Hueb,** Lemos PA, Serruys PW. *Circulation* 2008; 118:1146-1154.

BACKGROUND: Randomized trials that studied clinical outcomes after percutaneous coronary intervention (PCI) with bare metal stenting versus coronary artery bypass grafting (CABG) are underpowered to properly assess safety end points like death, stroke, and myocardial infarction. Pooling data from randomized controlled trials increases the statistical power and allows better assessment of the treatment effect in high-risk subgroups.

METHODS: We performed a pooled analysis of 3051 patients in 4 randomized trials evaluating the relative safety and efficacy of PCI with stenting and CABG at 5 years for the treatment of multivessel coronary artery disease. The primary end point was the composite end point of death, stroke, or myocardial infarction. The secondary end point was the occurrence of major adverse cardiac and cerebrovascular accidents, death, stroke, myocardial infarction, and repeat revascularization.

RESULTS: We tested for heterogeneities in treatment effect in patient subgroups. At 5 years, the cumulative incidence of death, myocardial infarction, and stroke was similar in patients randomized to PCI with stenting versus CABG (16.7% versus 16.9%, respectively; hazard ratio, 1.04, 95% confidence interval, 0.86 to 1.27; P=0.69). Repeat revascularization, however, occurred significantly more frequently after PCI than CABG (29.0% versus 7.9%, respectively; hazard ratio, 0.23; 95% confidence interval, 0.18 to 0.29; P<0.001). Major adverse cardiac and cerebrovascular events were significantly higher in the PCI than the CABG group (39.2% versus 23.0%, respectively; hazard ratio, 0.53; 95% confidence interval, 0.45 to 0.61; P<0.001). No heterogeneity of treatment effect was found in the subgroups, including diabetic patients and those presenting with 3-vessel disease.

CONCLUSIONS: In this pooled analysis of 4 randomized trials, PCI with stenting was associated with a long-term safety profile similar to that of CABG. However, as a result of persistently lower repeat revascularization rates in the CABG patients, overall major adverse cardiac and cerebrovascular event rates were significantly lower in the CABG group at 5 years.

Impact of Metabolic Syndrome on the Outcome of Patients with Stable Coronary Artery Disease: 2-Year Follow-Up of the MASS II Study

Lopes NH, Paulitsch FS, Pereira AC, Góis AF, Gagliardi A, Garzillo CL, Ferreira JF, Stolf NA, **Whady A. Hueb.** *Coron Artery Dis.* 2008;19:383-388.

OBJECTIVE: We characterized the impact of the metabolic syndrome (MetS) and its components on cardiovascular adverse events in patients with symptomatic chronic multivessel coronary artery disease, which have been followed prospectively for 2 years.

METHODS: Patients enrolled in the MASS II study were evaluated for each component of the MetS, as well as the full syndrome.

RESULTS: The criteria for MetS were fulfilled in 52% of patients. The presence of MetS ($P<0.05$), glucose intolerance ($P=0.007$), and diabetes ($P=0.04$) was associated with an increased mortality in our studied population. Moreover, despite a clear tendency for each of its components to increase the mortality risk, only the presence of the MetS significantly increased the risk of mortality among nondiabetic study participants in a multivariate model ($P=0.03$, relative risk 3.5, 95% confidence interval 1.1-6). Finally, MetS was still associated with increased mortality even after adjustment for diabetes status. These results indicate a strong and consistent relationship of the MetS with mortality in patients with stable coronary artery disease.

CONCLUSION: Although glucose homeostasis seems to be the major force driving the increased risk of MetS, the operational diagnosis of MetS still has information for stratifying patients when diabetes information is taken into account.

TCF7L2 Variant Genotypes and Type 2 Diabetes Risk in Brazil: Significant Association, but not a Significant Tool for Risk Stratification in the General Population

Marquezine GF, Pereira AC, Sousa AG, Mill JG, **Whady A. Hueb,** Krieger JE. *BMC Med Genet* 2008, 9:106-113.

BACKGROUND: Genetic polymorphisms of the TCF7L2 gene are strongly associated with large increments in type 2 diabetes risk in different populations worldwide. In this study, we aimed to confirm the effect of the TCF7L2 polymorphism rs7903146 on diabetes risk in a Brazilian population and to assess the use of this genetic marker in improving diabetes risk prediction in the general population.

METHODS: We genotyped the single nucleotide polymorphisms (SNP) rs7903146 of the TCF7L2 gene in 560 patients with known coronary disease enrolled in the MASS II (Medicine, Angioplasty, or Surgery Study) Trial and in 1,449 residents of Vitoria, in Southeast Brazil. The associations of this gene variant to diabetes risk and metabolic characteristics in these two different populations were analyzed. To access the potential benefit of using this marker for diabetes risk prediction in the general population we analyzed the impact of this genetic variant on a validated diabetes risk prediction tool based on clinical characteristics developed for the Brazilian general population.

RESULTS: SNP rs7903146 of the TCF7L2 gene was significantly associated with type 2 diabetes in the MASS-II population (OR = 1.57 per T allele, p = 0.0032), confirming, in the Brazilian population, previous reports of the literature. Addition of this polymorphism to an established clinical risk prediction score did not increased model accuracy (both area under ROC curve equal to 0.776).

CONCLUSIONS: TCF7L2 rs7903146 T allele is associated with a 1.57 increased risk for type 2 diabetes in a Brazilian cohort of patients with known coronary heart disease. However, the inclusion of this polymorphism in a risk prediction tool developed for the general population resulted in no improvement of performance. This is the first study, to our knowledge, that has confirmed this recent association in a South American population and adds to the great consistency of this finding in studies around the world. Finally, confirming the biological association of a genetic marker does not guarantee improvement on already established screening tools based solely on demographic variables.

Coronary Artery Bypass Surgery Compared with Percutaneous Coronary Interventions for Multivessel Disease: A Collaborative Analysis of Individual Patient Data from Ten Randomised Trials

Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hamm CW, **Whady A. Hueb,** Kähler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. *Lancet* 2009; 373:1190-1197.

BACKGROUND: Coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) are alternative treatments for multivessel coronary disease. Although the procedures have been compared in several randomised trials, their long-term effects on mortality in key clinical subgroups are uncertain. We undertook a collaborative analysis of data from randomised trials to assess whether the effects of the procedures on mortality are modified by patient characteristics.

METHODS: We pooled individual patient data from ten randomised trials to compare the effectiveness of CABG with PCI according to patients' baseline clinical characteristics. We used stratified, random effects Cox proportional hazards models to test the effect on all-cause mortality of randomised treatment assignment and its interaction with clinical characteristics. All analyses were by intention to treat.

FINDINGS: Ten participating trials provided data on 7812 patients. PCI was done with balloon angioplasty in six trials and with bare-metal stents in four trials. Over a median follow-up of 5.9 years (IQR 5.0-10.0), 575 (15%) of 3889 patients assigned to CABG died compared with 628 (16%) of 3923 patients assigned to PCI (hazard ratio [HR] 0.91, 95% CI 0.82-1.02; p=0.12). In patients with diabetes (CABG, n=615; PCI, n=618), mortality was substantially lower in the CABG group than in the PCI group (HR 0.70, 0.56-0.87); however, mortality was similar between groups in patients without diabetes (HR 0.98, 0.86-1.12; p=0.014 for interaction). Patient age modified the effect of treatment on mortality, with hazard ratios of 1.25 (0.94-1.66) in patients younger than 55 years, 0.90 (0.75-1.09) in patients aged 55-64 years, and 0.82 (0.70-0.97) in patients 65 years and older (p=0.002 for interaction). Treatment effect was not modified by the number of diseased vessels or other baseline characteristics.

INTERPRETATION: Long-term mortality is similar after CABG and PCI in most patient subgroups with multivessel coronary artery disease, so choice of treatment should depend on patient preferences for other outcomes. CABG might be a better option for patients with diabetes and patients aged 65 years or older because we found mortality to be lower in these subgroups.

Mild Chronic Kidney Dysfunction and Treatment Strategies for Stable Coronary Artery Disease

Lopes NH, Paulitsch FS, Pereira A, Garzillo CL, Ferreira JF, Stolf N, **Whady A. Hueb.** *J Thorac Cardiovasc Surg* 2009; 137:1443-1449.

OBJECTIVE: Our objective was to evaluate the association of chronic kidney dysfunction in patients with multivessel chronic coronary artery disease, preserved left ventricular function, and the possible interaction between received treatment and cardiovascular events.

METHODS: The glomerular filtration rate was determined at baseline on 611 patients who were randomized into three treatment groups: medical treatment, percutaneous coronary intervention, and coronary artery bypass surgery. Incidence of myocardial infarction, angina requiring a new revascularization procedure, and death were analyzed during 5 years in each group.

RESULTS: Of 611 patients, 112 (18%) were classified as having normal renal function, 349 (57%) were classified as having mild dysfunction, and 150 (25%) were classified as having moderate dysfunction. There were significant differences among the cumulative overall mortality curves among the three renal function groups. Death was observed more frequently in the moderate dysfunction group than the other two groups ($P < .001$). Interestingly, in patients with mild chronic kidney dysfunction, we observed that coronary artery bypass treatment presented a statistically higher percentage of event-free survival and lower percentage of mortality than did percutaneous coronary intervention or medical treatment

CONCLUSIONS: Our results confirm that coronary artery disease accompanied by chronic kidney dysfunction has a worse prognosis, regardless of the therapeutic strategy for coronary artery disease, when renal function is at least mildly impaired. Additionally, our data suggest that the different treatment strategies available for stable coronary artery disease may have differential beneficial effects according to the range of glomerular filtration rate strata.

In Vitro Simultaneous Transfer of Lipids to HDL in Coronary Artery Disease and in Statin Treatment

Lo Prete AC, Dina CH, Azevedo CH, Puk CG, Lopes NH, **Whady A. Hueb,** Maranhão RC. *Lipids* 2009, 44:917-924.

OBJECTIVE: The exchange of lipids with cells and other lipoproteins is a crucial process in HDL metabolism and for HDL antiatherogenic function.

METHODS: Here, we tested a practical method to quantify the simultaneous transfer to HDL of phospholipids, free-cholesterol, esterified cholesterol and triacylglycerols and to verify the lipid transfer in patients with coronary artery disease (CAD) or undergoing statin treatment.

RESULTS: Twenty-eight control subjects without CAD, 27 with CAD and 25 CAD patients under simvastatin treatment were studied. Plasma samples were incubated with a donor nanoemulsion prepared by ultrasonication of the constituent lipids and labeled with radioactive lipids; % lipids transferred to HDL were quantified in the HDL-containing supernatant after chemical precipitation of non-HDL fractions and the nanoemulsion. The assay was precise and reproducible. Increase of temperature (4-37 degrees C), of incubation period (5 min to 2 h), of HDL-cholesterol concentration (33-244 mg/dL) and of mass of nanoemulsion lipids (0.075-0.3 mg/muL) resulted in increased lipid transfer from the nanoemulsion to HDL. In contrast, increasing pH (6.5-8.5) and albumin concentration (3.5-7.0 g/dL) did not affect lipid transfer.

CONCLUSIONS: There was no difference between CAD and control non-CAD with regard to the lipid transfer, but statin treatment reduced the transfer to HDL of all four lipids. The test herein described is a valid and practical tool for exploring an important aspect of HDL metabolism.

TCF7L2 Polymorphism rs7903146 is Associated with Coronary Artery Disease Severity and Mortality

Sousa AG, Marquezine GF, Lemos PA, Martinez E, Lopes N, **Whady A. Hueb ,** Krieger JE, Pereira AC. *PLoS One,* 2009, 4:e7697.

BACKGROUND: TCF7L2 polymorphisms have been consistently associated with type 2 diabetes mellitus in different populations and type 2 diabetes mellitus is a major risk factor for cardiovascular disease, especially coronary artery disease. This study aimed to evaluate the association between TCF7L2 polymorphism rs7903146 and coronary artery disease in diabetic and non-diabetic subjects.

METHODS: Two populations were studied in order to assess severity of coronary artery disease and cardiovascular events incidence.

RESULTS: Eight-hundred and eighty nine subjects who were referred for cardiac catheterization for coronary artery disease diagnosis were cross-sectionally evaluated for coronary lesions (atherosclerotic burden) and 559 subjects from the MASS-II Trial were prospectively followed-up for 5 years and assessed for major cardiovascular events incidence. As expected, rs7903146 T allele was associated with diabetes. Although diabetic patients had a higher prevalence of coronary lesions, no association between TCF7L2 genotype and coronary lesions was found in this subgroup. However, non-diabetic individuals carrying the T allele were associated with a significantly higher frequency of coronary lesions than non-diabetic non-carriers of the risk allele (adjusted OR = 2.32 95%CI 1.27-4.24, p = 0.006). Moreover, presence of multi-vessel coronary artery disease was also associated with the CT or TT genotypes in non-diabetics. Similarly, from the prospective sample analysis, non-diabetics carrying the CT/TT genotypes had significantly more composite cardiovascular end-points events than CC carriers (p = 0.049), mainly due to an increased incidence of death (p = 0.004).

CONCLUSIONS: rs7903146 T allele is associated with diabetes and, in non-diabetic individuals, with a higher prevalence and severity of coronary artery disease and cardiovascular events. Name of registry site (see list below), registration number, trial registration URL in brackets.

Electrocardiographic Score: Application in Exercise Test for the Assessment of Ischemic Preconditioning

Uchida A, Moffa P, **Whady A. Hueb**, Cesar LA, Ferreira BM, Ramires JA. *Arq Bras Cardiol.* 2010, 95:486-492.

BACKGROUND: The time for 1.0 mm ST-segment depression (T-1.0mm) adopted to characterize ischemic preconditioning (IPC) in sequential exercise tests is consistent and reproducible; however, it has several limitations.

OBJECTIVE: To apply an electrocardiographic score of myocardial ischemia in sequential exercise tests, comparing it to the conventional T-1.0 mm index.

METHODS: Sixty one patients with mean age of 62.2 ± 7.5 years were evaluated; 86.9% were males. A total of 151 tests were analyzed, 116 of which were from patients who completed two assessment phases. The first phase comprised two sequential exercise tests for the documentation of IPC; the second phase, initiated one week later, comprised two more tests carried out under the effect of repaglinide. Two observers who were blind to the tests applied the score.

RESULTS: Perfect inter and intraobserver agreement was found (Kendall tau-b = 0.96, $p < 0.0001$, and Kendall tau-b = 0.98, $p < 0.0001$, respectively). Values of sensitivity and specificity, negative predictive value, positive predictive value and accuracy were 72.41%, 89.29%, 75.8%, 87.5% and 81.0%, respectively.

CONCLUSION: The ischemic score is a consistent and reproducible method for the documentation of IPC, and is a feasible alternative to T-1.0 mm.

Association Between ADAMTS13 Polymorphisms and Risk of Cardiovascular Events in Chronic Coronary Disease

Schettert IT, Pereira AC, Lopes NH, **Whady A. Hueb,** Krieger JE. *Thromb Res.* 2010, 125:61-66.

INTRODUCTION: Association between ADAMTS13 levels and cardiovascular events has been described recently. However, no genetic study of ADAMTS13 in coronary patients has been described.

MATERIAL AND METHODS: Based on related populations frequencies and functional studies, we tested three ADAMTS13 polymorphisms: C1342G (Q448E), C1852G (P618A) and C2699T (A900V) in a group of 560 patients enrolled in the Medical, Angioplasty, or Surgery Study II (MASS II), a randomized trial comparing treatments for patients with coronary artery disease (CAD) and preserved left ventricular function. The incidence of the 5-year end-points of death and death from cardiac causes, myocardial infarction, refractory angina requiring revascularization and cerebrovascular accident was determined for each polymorphim's allele, genotype and haplotype. Risk was assessed with the use of logistic regression and Cox proportional-hazards model and multivariable adjustment was employed for possible confounders.

RESULTS: Clinical characteristics and received treatment of each genotype group were similar at baseline. In an adjusted model for cardiovascular risk variables, we were able to observe a significant association between ADAMTS13 900V variant and an increased risk of death (OR: 1,92 CI: 1,14-3,23, p=0,015) or death from cardiac cause (OR:2,67, CI: 1,59-4,49, p=0,0009). No association between events and ADAMTS13 Q448E or P618A was observed.

CONCLUSIONS: This first report studying the association between ADAMTS13 genotypes and cardiovascular events provides evidence for the association between ADAMTS13 900V variant and an increased risk of death in a population with multi-vessel CAD.

Ten-year Follow-up Survival of the Medicine, Angioplasty, or Surgery Study (MASS II): A Randomized Controlled Clinical Trial of 3 Therapeutic Strategies for Multivessel Coronary Artery Disease

Whady A. Hueb, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. *Circulation.* 2010 ;122:949-957.

BACKGROUND: This study compared the 10-year follow-up of percutaneous coronary intervention (PCI), coronary artery surgery (CABG), and medical treatment (MT) in patients with multivessel coronary artery disease, stable angina, and preserved ventricular function.

METHODS: The primary end points were overall mortality, Q-wave myocardial infarction, or refractory angina that required revascularization. All data were analyzed according to the intention-to-treat principle.

RESULTS: At a single institution, 611 patients were randomly assigned to CABG (n=203), PCI (n=205), or MT (n=203). The 10-year survival rates were 74.9% with CABG, 75.1% with PCI, and 69% with MT (p=0.089). The 10-year rates of myocardial infarction were 10.3% with CABG, 13.3% with PCI, and 20.7% with MT (p<0.010). The 10-year rates of additional revascularizations were 7.4% with CABG, 41.9% with PCI, and 39.4% with MT (p<0.001). Relative to the composite end point, Cox regression analysis showed a higher incidence of primary events in MT than in CABG (hazard ratio 2.35, 95% confidence interval 1.78 to 3.11) and in PCI than in CABG (hazard ratio 1.85, 95% confidence interval 1.39 to 2.47). Furthermore, 10-year rates of freedom from angina were 64% with CABG, 59% with PCI, and 43% with MT (p<0.001).

CONCLUSIONS: Compared with CABG, MT was associated with a significantly higher incidence of subsequent myocardial infarction, a higher rate of additional revascularization, a higher incidence of cardiac death, and consequently a 2.29-fold increased risk of combined events. PCI was associated with an increased need for further revascularization, a higher incidence of myocardial infarction, and a 1.46-fold increased risk of combined events compared with CABG. Additionally, CABG was better than MT at eliminating anginal symptoms.

Five-year Follow-up of Angiographic Disease Progression after Medicine, Angioplasty or Surgery

Borges JC, Lopes N, Soares PR, Góis AF, Stolf NA, Oliveira SA, **Whady A. Hueb,** Ramires JA. *J Cardiothorac Surg.* 2010, 5:91-98.

BACKGROUND: Progression of atherosclerosis in coronary artery disease is observed through consecutive angiograms. Prognosis of this progression in patients randomized to different treatments has not been established. This study compared progression of coronary artery disease in native coronary arteries in patients undergoing surgery, angioplasty, or medical treatment.

METHODS: Patients (611) with stable multivessel coronary artery disease and preserved ventricular function were randomly assigned to CABG, PCI, or medical treatment alone (MT). After 5-year follow-up, 392 patients (64%) underwent new angiography. Progression was considered a new stenosis of ≥ 50% in an arterial segment previously considered normal or an increased grade of previous stenosis > 20% in nontreated vessels.

RESULTS: Of the 392 patients, 136 underwent CABG, 146 PCI, and 110 MT. Baseline characteristics were similar among treatment groups, except for more smokers and statin users in the MT group, more hypertensives and lower LDL-cholesterol levels in the CABG group, and more angina in the PCI group at study entry. Analysis showed greater progression in at least one native vessel in PCI patients (84%) compared with CABG (57%) and MT (74%) patients ($p < 0.001$). LAD coronary territory had higher progression compared with LCX and RCA ($P < 0.001$). PCI treatment, hypertension, male sex, and previous MI were independent risk factors for progression. No statistical difference existed between coronary events and the development of progression.

CONCLUSION: The angioplasty treatment conferred greater progression in native coronary arteries, especially in the left anterior descending territories and treated vessels. The progression was independently associated with hypertension, male sex, and previous myocardial infarction.

Genetic Variants of Diabetes Risk and Incident Cardiovascular Events in Chronic Coronary Artery Disease

Sousa AG, Lopes NH, **Whady A. Hueb**, Krieger JE, Pereira AC. *PLoS One.* 2011, 6(1):e16341.

OBJECTIVE: To determine whether information from genetic risk variants for diabetes is associated with cardiovascular events incidence.

METHODS: From the about 30 known genes associated with diabetes, we genotyped single-nucleotide polymorphisms at the 10 loci most associated with type-2 diabetes in 425 subjects from the MASS-II Study, a randomized study in patients with multi-vessel coronary artery disease. The combined genetic information was evaluated by number of risk alleles for diabetes. Performance of genetic models relative to major cardiovascular events incidence was analyzed through Kaplan-Meier curve comparison and Cox Hazard Models and the discriminatory ability of models was assessed for cardiovascular events by calculating the area under the ROC curve.

RESULTS: Genetic information was able to predict 5-year incidence of major cardiovascular events and overall-mortality in non-diabetic individuals, even after adjustment for potential confounders including fasting glycemia. Non-diabetic individuals with high genetic risk had a similar incidence of events then diabetic individuals (cumulative hazard of 33.0 versus 35.1% of diabetic subjects). The addition of combined genetic information to clinical predictors significantly improved the AUC for cardiovascular events incidence (AUC = 0.641 versus 0.610).

CONCLUSIONS: Combined information of genetic variants for diabetes risk is associated to major cardiovascular events incidence, including overall mortality, in non-diabetic individuals with coronary artery disease.

The Effect of Internal Thoracic Artery Grafts on Long-Term Clinical Outcomes after Coronary Bypass Surgery

Hlatky MA, Shilane D, Boothroyd DB, Boersma E, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hamm CW, **Whady A. Hueb,** Kahler J, Lopes N, Pocock SJ, Rodriguez A, Serruys P, Sigwart U, Stables RH. *J Thorac Cardiovasc Surg.* 2011;142:828-835.

OBJECTIVES: We sought to compare long-term outcomes after coronary bypass surgery with and without an internal thoracic artery graft.

METHODS: We analyzed clinical outcomes over a median follow-up of 6.7 years among 3,087 patients who received coronary bypass surgery as participants in one of 8 clinical trials comparing surgical intervention with angioplasty. We used 2 statistical methods (covariate adjustment and propensity score matching) to adjust for the nonrandomized selection of internal thoracic artery grafts.

RESULTS: Internal thoracic artery grafting was associated with lower mortality, with hazard ratios of 0.77 (confidence interval, 0.62-0.97; P = .02) for covariate adjustment and 0.77 (confidence interval, 0.57-1.05; P = .10) for propensity score matching. The composite end point of death or myocardial infarction was reduced to a similar extent, with hazard ratios of 0.83 (confidence interval, 0.69-1.00; P = .05) for covariate adjustment to 0.78 (confidence interval, 0.61-1.00; P = .05) for propensity score matching. There was a trend toward less angina at 1 year, with odds ratios of 0.81 (confidence interval, 0.61-1.09; P = .16) in the covariate-adjusted model and 0.81 (confidence interval, 0.55-1.19; P = .28) in the propensity score-adjusted model.

CONCLUSIONS: Use of an internal thoracic artery graft during coronary bypass surgery seems to improve long-term clinical outcomes.

MASS-III

Estudo Comparativo Entre a Cirurgia de Revascularização Miocárdica Com e Sem Circulação Extracorpórea em Pacientes Portadores De Doença Coronária Multiarterial Estável e Função Ventricular Preservada.

Sub-Análises Comparativas das Principais Características Demográficas, Clínicas Laboratoriais e Angiográficas.

Sub-Estudos Comparativos Sobre Qualidade de Vida e Custo-Efetividade.

Sub-Estudos de Genética e Atividade Inflamatória

A Randomized Comparative Study of Patients Undergoing Myocardial Revascularization with or Without Cardiopulmonary Bypass Surgery: The MASS III Trial

Whady A. Hueb, Lopes NH, Gersh BJ, Castro CC, Paulitsch FS, Oliveira SA, Dallan LA, Hueb AC, Stolf NA, Ramires JA. *Trials* 2008 Aug 28; 9(1):52-58.

ABSTRACT. The MASS III Trial is a large project from a single institution, The Heart Institute of the University of Sao Paulo, Brazil (InCor), enrolling patients with coronary artery disease and preserved ventricular function. The aim of the MASS III Trial is to compare medical effectiveness, cerebral injury, quality of life, and the cost-effectiveness of coronary surgery with and without of cardiopulmonary bypass in patients with multivessel coronary disease referred for both strategies. The predefined primary end point was the incidence of cardiovascular mortality, cerebrovascular accident, nonfatal myocardial infarction, and refractory angina requiring revascularization. The secondary end points in this trial include noncardiac mortality, presence and severity of angina, quality of life based on the SF-36 Questionnaire, and cost-effectiveness at discharge and at 5-year follow-up. In this scenario, we will analyze the cost of the initial procedure, hospital length of stay, resource utilization, and repeat revascularization events during the follow-up.Exercise capacity will be assessed at 6-months, 12-months, and the end of follow-up. A neurocognitive evaluation will be assessed in a subset of subjects using the Brain Resource Center computerized neurocognitive battery. Furthermore, magnetic resonance imaging will be made to detect any cerebral injury before and after procedures in patients who undergo coronary artery surgery with and without cardiopulmonary bypass. Clinical Trial registration information ISRCTN59539154 Off-pump vs. on-pump surgery in patients with Stable CAD MASS III.

Qualidade de Vida após Revascularização Cirúrgica do Miocárdio com e sem Circulação Extracorpórea

Nogueira C, **Whady A. Hueb,** Takiuti ME, Girardi P, Nakano T, Fernandes F, Paulitsch FS, Góis AFT, Lopes NHM, Stolf NA.. Arq Bras Cardiol, 2008; 91: 238-244.

FUNDAMENTO: Técnicas de cirurgia de revascularização miocárdica (RM) sem o uso de circulação extracorpórea (CEC) possibilitou resultados operatórios com menor dano sistêmico, menor ocorrência de complicações clínicas, menor permanência na sala de terapia intensiva e também no tempo de internação, gerando expectativas de melhor qualidade de vida (QV) dos pacientes.

OBJETIVO: Avaliar a QV em pacientes submetidos à cirurgia de revascularização com e sem CEC.

MÉTODOS: Em pacientes com doença multiarterial coronariana (DAC) estável e função ventricular preservada, aplicou-se o *Short-Form Health Survey (SF-36) Questionnaire* antes da cirurgia e depois de 6 e 12 meses.

RESULTADOS: Entre janeiro de 2002 e dezembro de 2006, foram randomizados 202 pacientes para cirurgia de RM. As características demográficas clínicas laboratoriais e angiográficas foram semelhantes nos dois grupos. Desses pacientes, 105 foram operados sem CEC e 97 com CEC. Na evolução, 22 pacientes sofreram infarto, 29 relataram angina, um reoperou, 3 tiveram AVC e nenhum morreu. A avaliação da QV mostrou similaridade nos dois grupos em relação ao componente físico e mental. Todavia, encontrou-se significativa melhora da capacidade funcional e percepção do aspecto físico nos pacientes do sexo masculino. Além disso, um expressivo número de pacientes dos dois grupos retornou ao trabalho.

CONCLUSÃO: Em todos os pacientes estudados, observaram-se melhora progressiva da qualidade de vida e retorno precoce ao trabalho, independentemente da técnica cirúrgica empregada. Exceto pela melhor percepção da capacidade funcional e do aspecto físico experimentado pelos homens, não houve diferença estatística nos resultados dos demais domínios alcançados pelos dois grupos estudados.

Custos Comparativos entre a Revascularização Miocárdica com e sem Circulação Extracorpórea

Girardi P, **Whady A. Hueb,** Nogueira C, Takiuti ME, Nakano T, Garzillo CL, Paulitsch FS, Góis AFT, Lopes NHM, Stolf NA. Arq Bras Cardiol, 2008; 91:369-376.

FUNDAMENTO: Técnicas cirúrgicas de revascularização miocárdica sem o uso de circulação extracorpórea (CEC) projetaram esperanças de resultados operatórios com menor dano sistêmico, menor ocorrência de complicações clínicas e menor tempo de internação hospitalar, gerando expectativas de menor custo hospitalar.

OBJETIVO: Avaliar o custo hospitalar em pacientes submetidos à cirurgia de revascularização miocárdica com e sem o uso de CEC, e em portadores de doença multiarterial coronariana estável com função ventricular preservada.

MÉTODOS: Os custos hospitalares foram baseados na remuneração governamental vigente. Acrescentaram-se aos custos uso de órteses e próteses, complicações e intercorrências clínicas. Consideraram-se o tempo e os custos de permanência na UTI e de internação hospitalar.

RESULTADOS: Entre janeiro de 2002 e agosto de 2006, foram randomizados 131 pacientes para cirurgia com CEC (CCEC) e 128 pacientes sem CEC (SCEC). As características basais foram semelhantes para os dois grupos. Os custos das intercorrências cirúrgicas foram significativamente menores ($p < 0,001$) para pacientes do grupo SCEC comparados ao grupo CCEC (606,00 ± 525,00 vs. 945,90 ± 440,00), bem como os custos na UTI: 432,20 ± 391,70 vs. 717,70 ± 257,70, respectivamente. Os tempos de permanência na sala cirúrgica foram (4,9 ± 1,1 h vs. 3,9 ± 1,0 h), ($p < 0, 001$) na UTI (48,2 ± 17,2 h vs. 29,2 ± 26,1h) ($p < 0, 001$), com tempo de intubação (9,2 ± 4,5 h vs. 6,4 ± 5,1h) ($p < 0,001$) para pacientes do grupo com e sem CEC, respectivamente.

CONCLUSÃO: Os resultados permitem concluir que a cirurgia de revascularização miocárdica, sem circulação extracorpórea, proporciona diminuição de custos operacionais e de tempo de permanência em cada setor relacionado ao tratamento cirúrgico.

Hemostatic Changes and Clinical Sequelae after On-pump Compared with Off-pump Coronary Artery Bypass Surgery: A Prospective Randomized Study

Paulitsch FS, Schneider D, Sobel BE, Rached R, Ramires J, Jatene F, Stolf N, **Whady A. Hueb,** Lopes NH. Coron Artery Dis 2009; 20:100-105.

OBJECTIVE: To delineate the effects of extracorporeal bypass on biomarkers of hemostasis, fibrinolysis, and inflammation and clinical sequelae.

METHODS: Patients were assigned prospectively and randomly to either on-pump (n=41) or off-pump (n=51) coronary bypass surgery. The concentrations of C-reactive protein, fibrinogen, D-dimer, and plasminogen activator inhibitor type-1 in blood were quantified before and after (1 and 24 h) surgery. Similar surgical and anesthetic procedures were used for both groups. Clinical events were assessed during initial hospitalization and at the end of 1 year.

RESULTS: The concentrations of plasminogen activator inhibitor type-1 and D-dimer were greater compared with preoperative values 1 and 24 h after surgery in both groups, but their concentrations increased to a greater extent 24 h after surgery in the on-pump group ($p < 0.01$). The concentration of C-reactive protein did not change appreciably immediately after surgery in either group but increased in a parallel manner 24 h after either on-pump or off-pump surgery ($p < 0.01$). Bypass surgery in the on-pump group was associated with greater blood loss during surgery and more bleeding after surgery ($p <$ or $= 0.01$). The incidence of all other complications was similar in the two groups.

CONCLUSION: On-pump surgery was associated with biochemical evidence of a prothrombotic state early after surgery but no greater incidence of thrombotic events was observed. The prothrombotic state might be a consequence of extracorporeal bypass, compensation in response to more bleeding, or both in patients undergoing on-pump surgery.

Reduced Expression of Systemic Proinflammatory and Myocardial Biomarkers after Off-Pump versus On-Pump Coronary Artery Bypass Surgery: A Prospective Randomized Study

Serrano CV Jr, Souza JA, Lopes NH, Fernandes JL, Nicolau JC, Blotta MH, Ramires JA, **Whady A. Hueb,** *J Crit Care.* 2010, 305-312.

BACKGROUND: The effects of off-pump (Off PCABG) and on-pump (On PCABG) coronary artery bypass grafting (CABG) on myocardium and inflammation are unclear. ***OBJECTIVE:*** Compare the inflammatory response and myocardial injury from patients (pts) submitted to Off PCABG with those that undergo On PCABG.

METHODS: Patients with normal left ventricular function were assigned to OffPCABG (n = 40) and OnPCABG (n = 41). Blood samples were collected before and 24 hours after surgery for determination of creatine kinase (CK)-MB (CK-MB), troponin I (cTnI), interleukin (IL)-6, IL-8, P-selectin, intercellular adhesion molecule (ICAM)-1 and C-reactive protein (CRP). Mortalities were registered at 12 months.

RESULTS: Preoperative CK-MB and cTnI levels were 3.1 +/- 0.6 IU and 1.2 +/- 0.5 ng/mL for OffPCABG and 3.0 +/- 0.5 IU and 1.0 +/- 0.2 ng/mL for OnPCABG pts. Postoperative CK-MB and cTnI levels were 13.9 +/- 6.5 IU and 19.0 +/- 9.0 ng/mL for OffPCABG vs 29.5 +/- 11.0 IU and 31.5 +/- 10.1 ng/mL for OnPCABG (p < .01). OffPCABG and OnPCABG pts had similar preoperative IL-6 (10 +/- 7 and 9 +/- 13 pg/mL), IL-8 (19 +/- 7 and 17 +/- 7 pg/mL), soluble P-selectin (70 +/- 21 and 76 +/- 23 pg/mL), soluble ICAM-1 (117 +/- 50 and 127 +/- 52 ng/mL), and CRP (0.09 +/- 0.05 and 0.11 +/- 0.07 mg/L). At 24 hours, for OffPCABG and OnPCABG: IL-6 was 37 +/- 38* and 42 +/- 41*(,dagger) g/mL; IL-8, 33 +/- 31* and 60 +/- 15*(,dagger) pg/mL; soluble P-selectin, 99 +/- 26 and 172 +/- 30*(,dagger) pg/mL; soluble ICAM-1, 227 +/- 47 and 236 +/- 87*(,dagger) ng/mL; and CRP, 10 +/- 11* and 14 +/- 13*(,dagger) mg/L (*P < .01 vs preoperation; (dagger)P < 01 vs OffPCABG). Increased 24-hour postoperative CRP levels was the only marker to have significant positive correlations with events and occurred just for the OnPCABG pts. In-hospital and 1-year mortalities for the OnPCABG and OffPCABG pts were 2.0% and 2.2% (P = .1) and 2.7% and 4.7% (P = .06), respectively.

CONCLUSIONS: Thus, the absence of CPB during CABG preserves better the myocardium and attenuates inflammation-however, without improving survival.

Five-year Follow-up of a Randomized Comparison Between Off-pump and On-pump Stable Multivessel Coronary Artery Bypass Grafting. The MASS III Trial

Whady A. Hueb, Lopes NH, Pereira AC, Hueb AC, Soares PR, Favarato D, Vieira RD, Lima EG, Garzillo CL, Paulitch F da S, César LA, Gersh BJ, Ramires JA. Circulation. 2010, 122:S48-52.

BACKGROUND: Coronary artery bypass graft surgery with cardiopulmonary bypass is a safe, routine procedure. Nevertheless, significant morbidity remains, mostly because of the body's response to the nonphysiological nature of cardiopulmonary bypass. Few data are available on the effects of off-pump coronary artery bypass graft surgery (OPCAB) on cardiac events and long-term clinical outcomes.

METHODS: In a single-center randomized trial, 308 patients undergoing coronary artery bypass graft surgery were randomly assigned: 155 to OPCAB and 153 to on-pump CAB (ONCAB).

RESULTS: Primary composite end points were death, myocardial infarction, further revascularization (surgery or angioplasty), or stroke. After 5-year follow-up, the primary composite end point was not different between groups (hazard ratio 0.71, 95% CI 0.41 to 1.22; p=0.21). A statistical difference was found between OPCAB and ONCAB groups in the duration of surgery (240±65 versus 300±87.5 minutes; p<0.001), in the length of ICU stay (19.5±17.8 versus 43±17.0 hours; p<0.001), time to extubation (4.6±6.8 versus 9.3±5.7 hours; p<0.001), hospital stay (6±2 versus 9±2 days; p<0.001), higher incidence of atrial fibrillation (35 versus 4% of patients; p<0.001), and blood requirements (31 versus 61% of patients; p<0.001), respectively. The number of grafts per patient was higher in the ONCAB than the OPCAB group (2.97 versus 2.49 grafts/patient; p<0.001).

CONCLUSIONS: No difference was found between groups in the primary composite end point at 5-years follow-up. Although OPCAB surgery was related to a lower number of grafts and higher episodes of atrial fibrillation, it had no significant implications related to long-term outcomes.

Preoperative B-type Natriuretic Peptide, and not the Inflammation Status, Predicts an Adverse Outcome for Patients Undergoing Heart Surgery

Ganem F, Serrano CV, Fernandes JL, Blotta MH, Souza JA, Nicolau JC, Ramires JA, **Whady A. Hueb**. *Interact Cardiovasc Thorac Surg.* 2011;12:778-783.

OBJECTIVES: B-type natriuretic peptide (BNP) and inflammatory markers are implicated in the pathophysiology of both ischemic cardiomyopathy and complications after cardiac surgery with cardiopulmonary bypass (CPB). The purpose of this study was to assess preoperative and postoperative levels of BNP, interleukin-6 (IL-6), interleukin-8 (IL-8), P-selectin, intercellular adhesion molecule (ICAM), C-reactive protein (CRP) in patients undergoing cardiac surgery with CPB and investigate their variation and ability to correlate with immediate outcome.

METHODS: Plasma levels of these markers were measured preoperatively, 6 and 24 h after CBP in 62 patients. Main endpoints were requirement for intra-aortic balloon pump, intensive care unit (ICU) stay longer than five days, ventilator dependence >24 h, requirement for dobutamine, hospital stay >10 days, clinical complications (infection, myocardial infarction, renal failure, stroke and ventricular arrhythmias) and in-hospital mortality.

RESULTS: Preoperative BNP levels correlate with longer ICU stay (p=0.003), longer ventilator use (P=0.018) and duration of dobutamine use (p<0.001). The receiver-operating characteristic curve demonstrated BNP levels >190 pg/ml as predictor of ICU >5 days and BNP levels >20.5 pg/ml correlated with dobutamine use, with areas under the curve of 0.712 and 0.842, respectively. Preoperative levels of ICAM-1 were associated with in-hospital mortality (P=0.042). In the postoperative period, was found association between CRP, IL-6 and P-selectin with ventilation duration (p=0.013, p=0.006, p<0.001, respectively) and P-selectin with ICU stay (p=0.009).

CONCLUSIONS: BNP correlates with clinical endpoints more than inflammatory markers and can be used as a predictor of early outcome after heart surgery.

MASS-IV DM

Hipóteses, Fundamentos, Desenho e Métodos do Valor Prognóstico de Pacientes diabéticos tipo 2 com Artérias Coronárias angiograficamente Normais.

Sub-análises das principais características Demográficas, Clínicas Laboratoriais e Angiográficas.

Sub-estudos comparativos sobre Qualidade de Vida e Custo-Efetividade.

Sub-estudos de Genética e atividade inflamatória

Hypotheses, rationale, design, and methods for prognostic evaluation in type 2 diabetic patients with angiographically normal coronary arteries. The MASS IV-DM Trial

Whady A. Hueb, Lopes N, Soares PR, Gersh BJ, Lima EG, Vieira RD, Garzillo CL, Garcia RR, Pereira AC, Strunz CM, Meneguetti C, Tsutsui J, Parga J, Lemos P, Hueb AC, Ushida A, Maranhão R, Chamone DA, Ramires JA. *BMC Cardiovasc Disord.,* 2010; 10:47-54.

BACKGROUND: The MASS IV-DM Trial is a large project from a single institution, the Heart Institute (InCor), University of São Paulo Medical School, Brazil to study ventricular function and coronary arteries in patients with type 2 diabetes mellitus.

METHODS: The study will enroll 600 patients with type 2 diabetes who have angiographically normal ventricular function and coronary arteries. The goal of the MASS IV-DM Trial is to achieve a long-term evaluation of the development of coronary atherosclerosis by using angiograms and coronary-artery calcium scan by electron-beam computed tomography at baseline and after 5 years of follow-up.

DESIGN: In addition, the incidence of major cardiovascular events, the dysfunction of various organs involved in this disease, particularly microalbuminuria and renal function, will be analyzed through clinical evaluation. In addition, an effort will be made to investigate in depth the presence of major cardiovascular risk factors, especially the biochemical profile, metabolic syndrome inflammatory activity, oxidative stress, endothelial function, prothrombotic factors, and profibrinolytic and platelet activity. An evaluation will be made of the polymorphism as a determinant of disease and its possible role in the genesis of micro- and macrovascular damage.

DISCUSSION: The MASS IV-DM trial is designed to include diabetic patients with clinically suspected myocardial ischemia in whom conventional angiography shows angiographically normal coronary arteries. The result of extensive investigation including angiographic follow-up by several methods, vascular reactivity, pro-thrombotic mechanisms, genetic and biochemical studies may facilitate the understanding of so-called micro- and macrovascular disease of DM.

MASS-V

Hipóteses, Fundamentos, Desenho e Métodos sobre o Valor diagnóstico da Elevação dos Marcadores de Necrose Miocárdica após Revascularização Cirúrgica e Percutânea em ausência de Infarto do Miocárdio Manifesto.

Elevação dos Marcadores de Necrose Miocárdica após intervenção Coronária percutânea
Análise comparativa entre liberação enzimática e Ressonância Nuclear Magnética em ausência de Infarto do Miocárdio Manifesto.

Elevação dos Marcadores de Necrose Miocárdica após Cirurgia de Revascularização Miocárdica com Circulação Extracorpórea
Análise comparativa entre liberação enzimática e Ressonância Nuclear Magnética em ausência de Infarto do Miocárdio Manifesto.

Elevação dos Marcadores de Necrose Miocárdica após Cirurgia de Revascularização Miocárdica sem Circulação Extracorpórea
Análise comparativa entre liberação enzimática e Ressonância Nuclear Magnética em ausência de Infarto do Miocárdio Manifesto.

Hipóteses, Fundamentos, Desenho e Métodos sobre o Valor diagnóstico da Elevação dos Marcadores de Necrose Miocárdica após Revascularização Cirúrgica e Percutânea em ausência de Infarto do Miocárdio Manifesto. MASS V

Publicações em parceria.

Projeto MASS/BARI 2D.

Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group. Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial

Am Heart J 2008; 156:528-536.

BACKGROUND: The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial was undertaken to determine whether early revascularization intervention is superior to deferred intervention in the presence of aggressive medical therapy and whether antidiabetes regimens targeting insulin sensitivity are more or less effective than regimens targeting insulin provision in reducing cardiovascular events among patients with type 2 diabetes mellitus and stable coronary artery disease (CAD).

METHODS: The BARI 2D trial is a National Institutes of Health-sponsored randomized clinical trial with a 2 x 2 factorial design. Between 2001 and 2005, 49 clinical sites in North America, South America, and Europe randomized 2,368 patients. At baseline, the trial collected data on clinical history, symptoms, and medications along with centralized evaluations of angiograms, electrocardiograms, and blood and urine specimens.

RESULTS: Most of the BARI 2D patients were referred from the cardiac catheterization laboratory (54%) or cardiology clinic (27%). Of the randomized participants, 30% were women, 34% were minorities, 61% had angina, and 67% had multiregion CAD. Moreover, 29% had been treated with insulin, 58% had hemoglobin A(1c) >7.0%, 41% had low-density lipoprotein cholesterol >or=100 mg/dL, 52% had blood pressure >130/80 mm Hg, and 56% had body mass index >or=30 kg/m(2).

CONCLUSIONS: Baseline characteristics in BARI 2D are well balanced between the randomized treatment groups, and the clinical profile of the study cohort is representative of the target population. As a result, the BARI 2D clinical trial is in an excellent position to evaluate alternative treatment approaches for diabetes and CAD.

Factors Related to the Selection of Surgical Versus Percutaneous Revascularization in Diabetic Patients With Multivessel Coronary Artery Disease in the BARI 2D (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes) Trial

Lauren J. Kim, Spencer B. King, III, Kenneth Kent, Maria Mori Brooks, Kevin E. Kip, J. Dawn Abbott, Alice K. Jacobs, Charanjit Rihal, **Whady A. Hueb,** Edwin Alderman, Ivan R. Pena Sing, Michael J. Attubato, Frederick Feit, for the BARI 2D (Bypass Angioplasty Revascularization Investigation Type 2 Diabetes) Study Group. *JACC Cardiovasc Interv* 2009; 2:384-392.

BACKGROUND: Factors guiding selection of mode of revascularization for patients with diabetes mellitus and multivessel CAD are not clearly defined.

METHODS: In the BARI 2D trial, the selected revascularization strategy, CABG or PCI, was based on physician discretion, declared independent of randomization to either immediate or deferred revascularization if clinically warranted. We analyzed factors favoring selection of CABG versus PCI in 1,593 diabetic patients with multivessel CAD enrolled between 2001 and 2005.

RESULTS: Selection of CABG over PCI was declared in 44% of patients and was driven by angiographic factors including triple vessel disease (odds ratio [OR]: 4.43), left anterior descending stenosis 70% (OR: 2.86), proximal left anterior descending stenosis 50% (OR: 1.78), total occlusion (OR: 2.35), and multiple class C lesions (OR: 2.06) (all $p < 0.005$). Nonangiographic predictors of CABG included age 65 years (OR: 1.43, $p = 0.011$) and non-U.S. region (OR: 2.89, $p = 0.017$). Absence of prior PCI (OR: 0.45, $p < 0.001$) and the availability of drug-eluting stents conferred a lower probability of choosing CABG (OR: 0.60, $p = 0.003$).

CONCLUSIONS: The majority of diabetic patients with multivessel disease were selected for PCI rather than CABG. Preference for CABG over PCI was largely based on angiographic features related to the extent, location, and nature of CAD, as well as geographic, demographic, and clinical factors. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes [BARI 2D]; NCT00006305

Prevalence of diabetic peripheral neuropathy and relation to glycemic control therapies at baseline in the BARI 2D cohort

Pop-Busui R, Lu J, Lopes N, Jones TL; BARI 2D Investigators. *J Peripher Nerv Syst.* 2009; 14:1-13.

BACKGROUND: We evaluated the associations between glycemic therapies and prevalence of diabetic peripheral neuropathy (DPN) at baseline among participants in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial on medical and revascularization therapies for coronary artery disease (CAD) and on insulin-sensitizing vs. insulin-providing treatments for diabetes.

METHODS: A total of 2,368 patients with type 2 diabetes and CAD was evaluated. DPN was defined as clinical examination score >2 using the Michigan Neuropathy Screening Instrument (MNSI). DPN odds ratios across different groups of glycemic therapy were evaluated by multiple logistic regression adjusted for multiple covariates including age, sex, hemoglobin A1c (HbA1c), and diabetes duration.

RESULTS: Fifty-one percent of BARI 2D subjects with valid baseline characteristics and MNSI scores had DPN. After adjusting for all variables, use of insulin was significantly associated with DPN (OR = 1.57, 95% CI: 1.15-2.13). Patients on sulfonylurea (SU) or combination of SU/metformin (Met)/thiazolidinediones (TZD) had marginally higher rates of DPN than the Met/TZD group.

CONCLUSION: This cross-sectional study in a cohort of patients with type 2 diabetes and CAD showed association of insulin use with higher DPN prevalence, independent of disease duration, glycemic control, and other characteristics. The causality between a glycemic control strategy and DPN cannot be evaluated in this cross-sectional study, but continued assessment of DPN and randomized therapies in BARI 2D trial may provide further explanations on the development of DPN.

A randomized trial of therapies for type 2 diabetes and coronay artery disease.

BARI 2D Study Group. *N Engl J Med* 2009; 60:2503-2515.

BACKGROUND: Optimal treatment for patients with both type 2 diabetes mellitus and stable ischemic heart disease has not been established.

METHODS: We randomly assigned 2368 patients with both type 2 diabetes and heart disease to undergo either prompt revascularization with intensive medical therapy or intensive medical therapy alone and to undergo either insulin-sensitization or insulin-provision therapy. Primary end points were the rate of death and a composite of death, myocardial infarction, or stroke (major cardiovascular events). Randomization was stratified according to the choice of percutaneous coronary intervention (PCI) or coronary-artery bypass grafting (CABG) as the more appropriate intervention.

RESULTS: At 5 years, rates of survival did not differ significantly between the revascularization group (88.3%) and the medical-therapy group (87.8%, P=0.97) or between the insulin-sensitization group (88.2%) and the insulin-provision group (87.9%, P=0.89). The rates of freedom from major cardiovascular events also did not differ significantly among the groups: 77.2% in the revascularization group and 75.9% in the medical-treatment group (p = 0.70) and 77.7% in the insulin-sensitization group and 75.4% in the insulin-provision group (p = 0.13). In the PCI stratum, there was no significant difference in primary end points between the revascularization group and the medical-therapy group. In the CABG stratum, the rate of major cardiovascular events was significantly lower in the revascularization group (22.4%) than in the medical-therapy group (30.5%, p = 0.01; p = 0.002 for interaction between stratum and study group). Adverse events and serious adverse events were generally similar among the groups, although severe hypoglycemia was more frequent in the insulin-provision group (9.2%) than in the insulin-sensitization group (5.9%, p = 0.003).

CONCLUSIONS: Overall, there was no significant difference in the rates of death and major cardiovascular events between patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin provision.

The prevalence and predictors of an abnormal ankle-brachial index in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial

Singh PP, Abbott JD, Lombardero MS, Sutton-Tyrrell K, Woodhead G, Venkitachalam L, Tsapatsaris NP, Piemonte TC, Lago RM, Rutter MK, Nesto RW; Bypass Angioplasty Revascularization Investigation 2 Diabetes Study Group. *Diabetes Care*. 2011;34:464-467.

OBJECTIVE: To examine ankle-brachial index (ABI) abnormalities in patients with type 2 diabetes and coronary artery disease (CAD).

RESEARCH DESIGN AND METHODS: An ABI was obtained in 2,240 patients in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) Trial. ABIs were classified as: normal, 0.91-1.3; low, ≤ 0.9; high, >1.3; or noncompressible artery (NC). Baseline characteristics were examined according to ABI and by multivariate analysis. RESULTS ABI was normal in 66%, low in 19%, and high in 8% of patients, and 6% of patients had NC. Of the low ABI patients, 68% were asymptomatic. Using normal ABI as referent, low ABI was independently associated with smoking, female sex, black race, hypertension, age, C-reactive protein, diabetes duration, and lower BMI. High ABI was associated with male sex, nonblack race, and higher BMI; and NC artery was associated with diabetes duration, higher BMI, and hypertension.

CONCLUSIONS: ABI abnormalities are common and often asymptomatic in patients with type 2 diabetes and CAD.

MASS-I

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"Estudo da qualidade de vida em portadores de doença arterial coronariana isolada submetidos ao tratamento clínico-cirúrgico-angioplastia: Projeto MASS". **Whady A. Hueb** (Co-autor). In: XLVIII Congresso da Sociedade Brasileira de Cardiologia Recife-PE, Setembro de 1992.

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MASS-II

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Five-year Follow-up of a Randomized Comparison between Off-Pump and On-Pump on Stable Multivessel Coronary Artery Bypass Grafting”. **Whady A. Hueb,** Lopes NH, Gersh BJ, Cesar LAM, Hueb A, Vieira RD, Lima EG, Dallan LAO, Paulitsch FS, Ramires JAF. In: ESC Congress 2009. Barcelona. Journal of the European Society of Cardiology, 2009, v 30, p. 903.

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MASS-IV

Apresentação em Congressos Nacionais e Estrangeiros

Lipid Transfer To HDL In Type 2 Diabetic Patients With And Without Coronary Artery Disease Marília C O Sprandel, **Whady A. Hueb,** Paulo Cury Rezende, Priscyla Girardi, Ana L O Carvalho, Antonio Casella-Filho, Carlos A Segre, Raul C Maranhão, European Heart Journal - Abstract Supplement, 2011

CAPÍTULOS DE LIVROS

High-Risk Cardiac Revascularization and Clinical Trials. The Mass Trials – págs. 203-216.

Machado César L A**, Whady A. Hueb.**

Livro: The Livery House, 7-9 Pratt Street, London Nw1 Oae UK 2002. Martin Dunitz Ltda.

SUMMARY: Coronary artery disease (CAD) has a broad presentations and evolves differently patients. Those presenting with chronic coronary disease may have stable angina or may have no symptoms at all even though they test positive for ischemia or they have stenosis documented by angiography. Patients may experience sudden death or may have stable angina that last for years. Based on the results of non-randomized and necropsy studies, we assume an unfavorable prognosis in patients with proximal left anterior descending artery stenosis.

Therefore more aggressive therapy has been recommended, because this artery supplies blood to an important myocardial area.

The danger of LAD stenosis causes a dilemma for cardiologists who have to choose the best treatment for each individual patient. Since the development of coronary artery bypass graft surgery, in the late 1960s, many patients have been operated on because it was supposed that they would survive longer and have fewer symptoms.

They also have the advantage of needing fewer medications and would thus have a better quality of life. This kind of thinking was reasonable considering what was known about the disease at the time, including single-vessel disease compromising the left anterior descending artery. However, the publication of the results of the Coronary Artery Surgery Study (CASS) raised doubts about the line of thinking and shed new line of pathology and natural history of CAD. In CASS, medical treatment as compared with CABG. Patient undergoing to bypass surgery were more frequently free of symptoms at the five years follow-up but, except for certain sub groups, they had no better survival. We must6 remember that at the time of the study, only beta-blockers and nitrates were prescribed as a rule although aspirin and anti-coagulants also played a role. Patients with poor left ventricular function received great benefits.

Subsequent analysis of CASS revelated that those patients with stenosis of LAD and disease in one other vessel, or those with tree- vessel disease also better mortality rates with surgical treatment but, patients with single-vessel disease without a compromised LAD did not. It is important to point out the patients with vessels >50% stenosed were considered for inclusion in CASS. Similar results were results were also observed especially in patients with multi-vessel disease.

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.

Year Book of Cardiology, Published by Mosby an Elsevier Health Sciences Company has selected the article cited above to be abstracted in the 2005 Year book.

Whady A. Hueb, *et al.*

Myocardial Revascularization with and without Extracorporeal Revascularization" – págs. 278-298.

Whady A. Hueb, Neuza H. Lopes.

Livro: Coronary Artery Bypasses.

Ed.R.T.Hammond, J.B.Alton.Sciences Publishers 2008

Coronary bypass surgery performed without the use of cardiopulmonary bypass (off-pump surgery) has been used sporadically since the beginning of the bypass surgery era in 1967, but the use of this strategy increased substantially during the 1990s. The major reasons for the increased use of off-pimp surgery was the hope that this strategy would decreased perioperative morbidity and possible mortality by eliminating cardiopulmonary bypass (on-pump surgery).The apprehension concerning off-pump surgery has been that the revascularization at the time of surgery and worse long-term outcomes.

The advantages and undergoing off-pump and on-pump surgery, follow-up studies both randomized and observational have sometimes noted inferior long-term outcomes after off-pump surgery compared with on-pump surgery such as decreased patency, increased risk of repeat revascularization or increased mortality. Other studies have shown no long-term differences. When present, these differences usually have not been large and often have been attributed to be the surgeon's lack of experience with off-pump surgery.

Capítulo: Estudos Comparativos entre os Tratamentos Clínico, Percutâneo e Cirúrgico – págs. 225-232.

Garzillo, CL, **Whady A. Hueb**

Livro: Condutas Práticas em Cardiologia. Editora Manole Ltda., 2009. São Paulo.

Editores: José Carlos Nicolau, Flávio Tarasoutchi, Leonardo Vieira da Rosa, Fernando de Paula Machado.

Esse capítulo de livro inclui os principais estudos randomizados sobre os tratamentos clínicos cirúrgicos ou percutâneos Descreve, inicialmente, a metodologia empregada, em todos os "trials" seus principais objetivos primários e secundários, e seus resultados.

Nos resultados de cada estudo discutem-se os resultados esperados e os resultados obtidos. Além disso, compara-os com os resultados esperados e obtidos de cada estudo entre si.

Por fim discorre uma consideração sobre os resultados entre os estudos randomizados e suas aplicações na prática clinica diária.

Enfatiza sobretudo um guia de conduta sobre os tratamentos da Doença Arterial Coronária á luz dos resultados obtidos por estudos randomizados.

TESES

Concluídas
Em andamento
Em planejamento

Teses e Publicações Geradas Pelo Projeto MASS

Teses de Doutoramento Concluídas

Estudo Comparativo Entre Os Efeitos Terapêuticos Da Revascularização Cirúrgica Do Miocárdio E Angioplastia Coronária Em Situações Isquêmicas Equivalentes – Análise Através Da Cintilografia Do Miocárdio De Esforço Com Sestamibi 99mtecnécio.
Autor (a): Anellys Emilia Lourenço Costa Moreira

Estudo Avaliação Dos Episódios Isquêmicos E Dos Determinantes Do Consumo De Oxigênio Em Pacientes Com Ico Estável.
Autor (a): João Fernando Monteiro Ferreira

Os Efeitos Da Glibenclamida Bloqueador Seletivo Dos Canais De Potássio Dependente De Atp No Pré-Condicionamento Isquêmico.
Autor (a): Beatriz Moreira Ayub Ferreira

Estudo Comparativo Da Eficácia De Intervenção Cirúrgica E Da Angioplastia Na Revascularização Miocárdica Em Portadores De Comprometimento Multiarterial Equivalente.
Autor (a): Paulo Roberto Dutra Da Silva

O comportamento do Teste Ergométrico na avaliação de pacientes multiarteriais após angioplastia transluminal coronária percutânea
Autor (a): Júlio César Kreling

Qualidade de vida em portadores de doença arterial coronária submetidos a diferentes tratamentos: comparação entre genêros.
Autor (a): Maria Elenita Favarato

Comportamento Dos Marcadores Inflamatórios Em Humanos Com Disfunção Ventricular Esquerda Submetidos À Revascularização Miocárdica Cirúrgica Com Circulação Extracorpórea: Correlação Com A Evolução E Prognóstico Imediato.
Autor (a): Fernando Ganen

Estudo De Parâmetros Eletrocardiográficos E Pressóricos Durante Procedimento Odontologico Restaurador Sob Anestesia Local Com E Sem Vaso Constritor Em Portadores De Doença Arterial Coronária.
Autor (a): Ricardo Simões Neves

Qualidade De Vida Em Pacientes Com Doença Multiarterial Coronária Sintomática: Estudo Comparativo Entre Os Tratamentos: Clinico, Angioplastia E Cirurgia.
Autor (a): Myrthes Emy Takiuti

Interferência Da Diabete Melito No Prognóstico Dos Pacientes Portadores De Doença Arterial Coronariana (DAC) Que Foram Submetidos Ao Tratamento Clínico, Cirúrgico Ou Através Da Angioplastia: Seguimento A Longo Prazo
Autor (a): Fernando Augusto Alves Da Costa

Progressão Da Aterosclerose Coronária Entre Os Grupos Diabéticos E Não Diabéticos Avaliada Pela Coronariografia, Em Portadores De Doença Multiarterial, Submetidos Ao Tratamento Clínico, Cirúrgico Ou Angioplastia.
Autor (a): Aécio Flavio Teixeira De Góis

Progressão Da Aterosclerose Coronária Avaliada Pela Coronariografia, Em Portadores De Doença Multiarterial, Submetidos Aos Tratamentos: Clínico, Cirúrgico Ou Angioplastia.
Autor (a): Jorge Chiquie Borges

Impacto De Farmaco Hipoglicemiante Oral Sobre O Pré-Condicionamento Isquêmico Em Pacientes Diabéticos Com Doença Multiarterial Coronária Estável
Autor (a): Roberto Tadeu Barcellos Betti

Avaliação Da Qualidade De Vida Em Pacientes Com Doença Multiarterial Coronária Sintomática: Estudo Comparativo Entre Pacientes Submetidos À Cirurgia De Revascularização Miocárdica Com E Sem Circulação Extra Corpórea.
Autor (a): Célia Regina Simões Da Rocha Nogueira

Avaliação Das Variantes Genéticas Relacionadas Ao Metabolismo Lipídico Em Pacientes Diabéticos E Não Diabéticos Com Doença Arterial Coronariana
Autor (a): Letícia De Araújo Funari Ferri

Estudo Comparativo Do Custo Relativo Do Tratamento De Pacientes Portadores De Doença Multiarterial Coronária Submetidos À Revascularização Miocárdica Com Ou Sem Circulação Extra-Corpórea: Mass Iii – 1º Ano De Seguimento
Autor (a): Priscyla Borges Myamoto De Araujo Girardi

Determinação De Marcadores Inflamatórios Em Pacientes Submetidos À Cirurgia Cardíaca Com E Sem Circulação Extracorpórea
Autor (a): Juliana Souza

Estudo Comparativo Entre Os Tratamentos: Clinico, Angioplastia Ou Cirurgia Em Portadores De Doença Coronária Multiarterial Mass Ii -10 Anos De Seguimento.
Autor (a): Antonio Sergio Cordeiro Da Rocha

Estudo Da Cascata De Coagulação E Liberação De Células Progenitoras Em Pacientes Submetidos À Cirurgia De Revascularização Miocárdica Com E Sem Circulação Extracorpórea – Subprojeto Do MASS III
Autor (a): Felipe Da Silva Paulitsch

Valor do teste de dosagem do Dímero - D plasmático no diagnóstico do tromboembolismo venoso agudo.
Autor (a): Luciana Pereira de Almeida de Piano

Estudo do polimorfismo genético C242T no gene da p22phox e a incidência de eventos cardiovasculares na doença arterial coronária.
Autor (a): Alexandre da Costa Pereira

Influência das Variantes Genéticas Funcionais do Sistema Renina Angiotensina na Doença Arterial Coronária
Autor (a): José Ramon Lanz Luces

Teses em andamento

Avaliação da função ventricular em pacientes portadores de coronariopatia crônica, dez anos após serem submetidos a tratamento clínico, cirúrgico ou angioplastia.
Autor (a): Cibele Larrosa Garzillo

Efeito do Inibidor da enzima Dipeptidil Peptidase-IV sobre o pré-condicionamento isquêmico de pacientes com Diabetes Mellitus tipo 2 e angina estável.
Autor (a): Rosa Maria Rahmi Garcia

Estudo comparativo dos custos entre os tratamentos clinico, cirúrgico e angioplastia em portadores de doença multiarterial coronária: MASS II - 5 anos de seguimento.
Autor (a): Ricardo D'Oliveira Vieira

Avaliação Prognóstica em Longo Prazo de Pacientes Diabéticos Portadores de Insuficiência Renal Crônica e Doença Coronária Multiarterial Submetidos aos Tratamentos Clínico, Cirúrgico ou Angioplastia.
Autor (a): Eduardo Gomes Lima

Efeitos do metabolismo e função das lipoproteínas de alta densidade (HDL) na doença arterial coronária (DAC) em portadores de diabetes mellitus tipo 2.
Autor (a): Marília da Costa Oliveira Sprandel

Comportamento do precondicionamento isquêmico em pacientes portadores de doença coronária multiarterial estável com e sem diabetes mellitus.
Autor (a): Paulo Cury Rezende

Qualidade de Vida após Revascularização Cirúrgica do Miocárdio, Angioplastia ou Tratamento Clínico: Seguimento por 10 anos. Avaliação prognóstica da doença estável através de um escore composto com dados clínicos e o revelado do teste de esforço.
Autor (a): Ana Luiza de Oliveira Carvalho

Estudo de parâmetros eletrocardiográficos e pressóricos durante procedimento odontológico restaurador sob anestesia local com e sem vaso constritor em pacientes diabéticos insulino dependentes e portadores de doença arterial coronária.
Autor (a): Marcela Alves dos Santos

Teses em planejamento

Protocolo Clinico sobre a elevação persistente da troponina ultra sensível na ausência de isquêmia miocárdica em pacientes portadores de doença coronariana obstrutiva estável – subestudo MASS II
Autor (a): Carlos Alexandre Wainrober Segre

Elevação dos Marcadores de Necrose Miocárdica após Revascularização Percutânea em ausência de Infarto do Miocárdio Manifesto.
Autor (a): Kamila Staszko

Elevação dos Marcadores de Necrose Miocárdica após Revascularização Cirúrgica com Circulação Extracorpórea Percutânea em ausência de Infarto do Miocárdio Manifesto.
Autor (a): Rodrigo M Melo

Elevação dos Marcadores de Necrose Miocárdica após Revascularização Cirúrgica sem Circulação Extracorpórea Percutânea em ausência de Infarto do Miocárdio Manifesto.
Autor (a): Fernado Ikawa

Elevação dos Marcadores de Necrose Miocárdica em pacientes submetidos á Cirurgia de Revascularização Miocárdica com ou sem Circulação Extracorpórea em ausência de Infarto do Miocárdio Manifesto.
Autor (a): Leandro Costa

Estudo da Lesão isolada de Artéria Descente Anterior
Autor (a): Henrique Barbosa Ribeiro

Avaliação do Syntax Score em pacientes portadores de Doença Arterial Coronariana e diabetes tipo 2
Autor (a): Rodrigo Barbosa Sper

Trabalhos em Andamento

Trabalhos em andamento MASS

The Triglyceride/HDL ratio is the only lipid parameter independently associated with major cardiovascular events in the 10-year Follow-up of the Medicine, Angioplasty or Surgery Study II (MASS II)

Análise da composição e das características funcionais das subfrações da HDL colesterol em pacientes portadores de diabetes mellitus tipo 2 com sem doenças coronarianas obstrutivas avaliada pela angiográficas.

Marcadores de estresse oxidativo em pacientes diabéticos tipo 2 com e sem doença arterial coronária obstrutiva.

Estudos em Parceria

Estudos em Parceria

BARI 2D - **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation **2 D**iabetes
Estudo comparativo entre os tratamentos intervencionistas e clínicos em pacientes diabéticos portadores de doença arterial coronária.

FREEDOM - Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease
Avaliar se intervenções coronárias percutâneas com stents eluidores de medicamentos são mais ou menos eficazes que a cirurgia de revascularização do miocárdio em pacientes diabéticos portadores de doença arterial coronária.

EXCEL - Evaluation of XIENCE PRIME ™ or XIENCE V® versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (the "Study")
Avaliar a segurança e eficácia do Sistema de Stent Coronário com Eluição de Everolimus (EECSS) XIENCE PRIME ou XIENCE V em pacientes portadores de doença do tronco da artéria coronária esquerda não protegida (seja isolada no tronco da artéria esquerda ou associada à doença em outras artérias coronárias) comparando com a cirurgia de revascularização de artéria coronária.

CORONARY - CABG **O**ff o**r On** Pump Revascul**ar**ization Stud**y**
Estudo de revascularização CABG com e sem circulação extracorpórea para avaliar a ocorrência se eventos combinados (morte, IAM fatal ou não fatal, AVE, IRC) após 30 dias de cirurgia.

ISCHEMIA - International Study of Comparative Health Effectiveness with Medical and Invasive Approaches
Comparar duas estratégias para o manejo de pacientes com doença coronariana estável: conduta invasiva de rotina com a intenção de utilizar revascularizar PCI contemporânea ou CRM mais a terapia médica ótima, versus terapia ideal rotina médica isolada.

TRABALHOS PREMIADOS EM PUBLICAÇÕES PERIÓDICAS

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DESTACADOS EM CONGRESSOS

TRABALHOS DESTACADOS EM PUBLICAÇÕES PERIÓDICAS

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Trabalho mereceu destaque em editorial do periódico "Circulation" 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 Disease. **Hueb WA,** Neuza Helena Lopes, Bernard J Gersh, Paulo Soares, Luis M. Cesar, Fabio Jatene, Sergio Almeida Oliveira, José Antonio Franchini. Ramires. *Circulation.* 2007; 115:1082-1089.

Trabalho mereceu destaque como melhor publicação do ano e recebeu prêmio de C$ 4.500,00 em espécie**. "**Estudo Comparativo entre os Efeitos Terapêuticos da Revascularização Cirúrgica do Miocárdio e Angioplastia Coronária em Situações Isquêmicas Equivalentes: Análise Através da Cintilografia do Miocárdio com 99mTc-Sestamibi". Moreira AELC, **Hueb WA,** Soares PR, Meneghetti JC, Jorge MCP, Chalela WA, Martinez Filho EE, Oliveira SA, Jatene FB, Ramires JAF. *Arq Bras Cardiol,* 2005; volume 85 (n° 2), 92-99.

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Trabalho mereceu destaque em “Continuing medical education (CME) credit is available for this article”.Go to take the quiz do periódico “Circulation” 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 Disease. **Hueb WA,** Neuza Helena Lopes, Bernard J Gersh, Paulo Soares, Luis M. Cesar, Fabio Jatene, Sergio Almeida Oliveira, José Antonio Franchini. Ramires. *Circulation.* 2007; 115:1082-1089.

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strategies for multivessel coronary artery disease. **Hueb WA**, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, Favarato D, Rocha AS, Hueb AC, Ramires JA. Circulation. 2010 ;122:949-957.

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Genetic variants related with lipids metabolism genes as a predictor marker of cardiovascular events on stable coronary artery disease.

N H. Lopes, AC. Pereira, LF. Ferri, RDO. Vieira, EG. Lima, CL. Garzillo, JT. Fukushima, JE. Krieger, **Hueb WA**, JAF. Ramires. *Journal of the European Society of Cardiology.* 2010. v.31. p.613 - 613

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PRÊMIOS E HONRARIAS CONCEDIDAS AO PROJETO MASS

Prêmio "American College of Cardiology", durante o 43rd Annual Scientific Session, Atlanta, Georgia, USA, 1994. Trabalho: Randomized trial of surgery angioplasty or medical therapy for single vessel proximal left anterior descending artery stenosis.

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Prêmio Arquivos Brasileiros de Cardiologia - Melhor trabalho publicado no ano de 2007 sobre o tema "Qualidade de Vida após Revascularização cirúrgica do miocárdio e Angioplastia coronária e Tratamento Clinico" autorgado em cerimônia realizada em Dezembro de 2007. Rio de Janeiro.

State of the Art and Featured Research on Coronary Artery Disease - Genetic variants related with lipids metabolism genes as a predictor marker of

cardiovascular events on stable coronary artery disease, European Society of Cardiology.

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