

Boletim Científico

03/2020

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EDITORIAL

Novas evidências reacendem polêmica do caso EXCEL. Revelações alarmantes que distorcem e desvirtuam nossa prática clínica

O Boletim Científico da SBCCV neste número traz artigos publicados nas melhores revistas científicas mundiais, com notícias que alarmam a comunidade médica e leiga, sobre a possibilidade de graves distorções na geração e divulgação de resultados de evidências científicas, que servem de referência para o tratamento dos pacientes com doenças cardiovasculares e guiam nossa prática clínica.

Na esteira da controvérsia sobre a manipulação de dados e possível fraude no estudo EXCEL, o artigo publicado no *JAMA Internal Medicine* do professor James M. Brophy, professor de Medicina, Epidemiologia e Bioestatística da Universidade McGill University, em Montreal no Canadá, reanalisa o desenho e resultados do estudo EXCEL e outros recentes ensaios clínicos randomizados no campo do tratamento da lesão de tronco da artéria coronária esquerda, utilizando métodos bayesianos.

O artigo mostra aspectos e detalhes sutis de análise estatística, não descobertos anteriormente, que foram usados para dissimular e burlar os resultados do estudo EXCEL, permitindo a conclusão desejada. Revela que o método de análise estatística usado na interpretação dos dados em 5 anos, foi diferente daquele utilizada na publicação de 3 anos, e em não-conformidade com o protocolo originalmente estabelecido. Se os resultados de 5 anos do EXCEL tivessem sido interpretados em alinhamento com seu projeto original de não-inferioridade primária, e margem de resultado primário pré-especificada de 4,2%, uma conclusão diferente teria sido alcançada, mesmo dentro da estrutura de uma análise padrão. Em vez disso, os autores do EXCEL interpretaram os resultados de 5 anos como um estudo de superioridade, no qual a hipótese nula não consistia em nenhuma diferença e os dados observados não eram suficientemente extremos para rejeitar essa hipótese nula.

Essa percepção sugeriu que a probabilidade de aumento da mortalidade por ICP era de 85%, com quase 50% de probabilidade de que esse aumento fosse superior a 1 vida extra perdida por 100 tratados. A estimativa mais provável foi de 9 vidas perdidas por 1000, com 95% de confiança de que o valor era entre 8 vidas salvas por mil e 27 vidas perdidas por mil.

A análise bayesiana auxiliou na interpretação dos dados, seja com base nos resultados do EXCEL isoladamente, ou na totalidade das evidências de que a ICP estava associada a resultados inferiores em longo prazo em todos os eventos, incluindo mortalidade, em comparação com CRM em pacientes com lesão de tronco.

O professor Brophy, embora reconhecendo que essas falhas de análise pelos autores do estudo EXCEL possam ter sido somente por incompetência e irresponsabilidade, sugere que o patrocínio pela empresa fabricante do stent utilizado no estudo, levou a resultados e conclusões mais favoráveis. Reforça que 14 dos 34 autores do EXCEL, incluindo o primeiro e o último autores, tiveram um relacionamento com o patrocinador do estudo (o fabricante do stent), e a *Cardiovascular Research Foundation* (que 8 autores listam como afiliados) recebeu uma doação de US \$ 937.000 do patrocinador durante o estudo.

Inferre que este fator pode levar à hipótese inteiramente especulativa de que o conflito de interesses contribuiu para a interpretação enviesada do EXCEL.

Isso traz à tona o assunto de como pode a revista *New England Journal of Medicine* aceitar publicar um artigo com tantos desvios, que é uma comunicação incorreta de ciência e claramente um desserviço aos pacientes. Quem foram os revisores desse artigo? Qual o conflito de interesse deles? Eles não notaram a diferença significativa na mortalidade? Eles não informaram o editor? Por que o editor concordou em proceder com a publicação dessa maneira?

No outro artigo do *JAMA Internal Medicine*, o comentário do professor Sanjay Kaul, professor de medicina no Cedars-Sinai Medical Center in Los Angeles, mostra que é incontestável que encontrar uma diferença significativa num estudo seja baseada em testes formais de hipóteses, que no EXCEL foram pré-especificados como demonstração de não-inferioridade aos 3 anos, e não de superioridade, que foi avaliada pelos pesquisadores aos 5 anos. A justificativa para essa mudança não é clara porque não foi pré-especificada no protocolo e não foi declarada no artigo do EXCEL. Ressalta que, se os autores tivessem mantido a análise de não-inferioridade que foi realizada em 3 anos, ela não atenderia aos critérios porque o limite superior da diferença de 95% é de 6,5%, o que excede a margem de não inferioridade pré-especificada em 3 anos, de 4,2%.

Reitera que a conclusão no EXCEL, de que a ICP e a CRM foram similares, apesar de uma diferença de 3,1% na mortalidade que favorece a CRM, é um exemplo clássico de viés de interpretação, também conhecido como *spin*. O *spin* ocorre frequentemente associado ao patrocínio comercial de estudo. Reforça que os resultados gerais de mortalidade da reanálise do Brophy favorecem claramente a CRM em comparação com o uso de ICP.

Valor econômico da cirurgia de revascularização miocárdica é reforçada

Avaliando o valor econômico, que pode ser definido como o custo relativo por ano adicional de vida útil para as operações mais custosas realizadas em um centro médico acadêmico urbano (o Hospital Monte Sinai em Nova Iorque), os autores encontraram que entre os procedimentos mais caros realizados na instituição, a cirurgia de revascularização miocárdica foi a mais econômica, com o menor custo por ano de vida economizado (US \$ 1.345,45) e a maior expectativa de vida pós-procedimento (17,6 anos).

Um achado relevante para os pacientes, assim como para as fontes pagadoras tanto pública como privada, que corrobora a efetividade da cirurgia de revascularização miocárdica como o único método que diminui o risco de infarto do miocárdio e aumenta a sobrevida em pacientes de maior risco, como também propiciando melhor qualidade de vida em longo-prazo com redução do sintoma anginoso.

O conflito de interesse econômico interferindo com a melhor prática médica

Os dois artigos adicionais do Boletim enfocam o conflito de interesse econômico interferindo com a melhor prática médica.

As relações financeiras entre os líderes das mais influentes associações médicas profissionais dos EUA e a indústria de medicamentos e dispositivos médicos, foram analisadas no artigo de Moynihan et al. Dentre 328 líderes das sociedades American College of Cardiology, Orthopaedic Trauma Association, American Psychiatric Association, Endocrine Society, American College of Rheumatology, American Society of Clinical Oncology, American Thoracic Society, North American Spine Society, Infectious Diseases Society of America, e American College of Physicians, 235 tinham relacionamento financeiro direto com a indústria.

Durante o período de 2017-19, líderes das 10 mais influentes associações médicas profissionais americanas receberam quase US \$ 130 milhões da indústria durante seu ano de liderança, nos quatro anos anteriores e no ano seguinte. 80% dos médicos norte-americanos que lideram associações médicas profissionais influentes mantinham relações financeiras com a indústria, com grande variação no valor médio dos pagamentos por associação, desde US \$ 212.000 a US \$ 518.000. Em um cenário de crescente pleito por independência financeira em relação aos interesses comerciais, essas descobertas mostram que, para alguns grupos de médicos, isso exigirá grande reforma de comportamento.

As maiores somas de pagamentos foram para os líderes da Sociedade Americana de Oncologia Clínica (US \$ 54 milhões) e do American College of Cardiology (US \$ 21 milhões).

Como observou o autor, dado seu papel essencial na “manutenção e promoção da qualidade da assistência médica” e para mostrar “independência e integridade”, os líderes de associações médicas profissionais devem estar “livres de todos os laços financeiros com a indústria”, o que ele argumenta ser viável. Como outros observaram, as diretrizes dessas associações médicas profissionais “frequentemente exigem maior uso dos serviços de saúde” e a independência financeira de interesses comerciais é duplamente desejável, se quisermos enfrentar os problemas de uso excessivo e superdiagnóstico. Embora os membros do conselho das sociedades raramente escrevem diretrizes, sua liderança e influência orientam o tom e a abordagem de todo o trabalho este trabalho. Os autores recomendam que os líderes de sociedades e os autores de diretrizes se tornem livres de relações financeiras com a indústria.

No outro artigo, Gaudino e cols investigaram as principais características dos estudos randomizados controlados contemporâneos de intervenções cardiovasculares invasivas, e sua associação com a fonte de financiamento.

Mais da metade dos estudos randomizados controlados teve apoio comercial. Os ensaios patrocinados comercialmente apresentaram características distintas, incluindo registro de protocolo mais frequente, uso de análise de não inferioridade, maior tamanho de amostra, inclusão de maior porcentagem de pacientes rastreados, maior número de pacientes perdidos no acompanhamento, publicação em periódicos com fatores de impacto mais altos e maior número de citações após publicação. O patrocínio comercial foi associado a achados estatisticamente significativos, favorecendo o tratamento patrocinado. Esses dados contemporâneos parecem mostrar que os incentivos que envolvem organizações com fins lucrativos têm o potencial de influenciar os resultados de estudos clínicos. Tentativas anteriores de explicar esse fenômeno se concentraram amplamente no viés de design, viés de interpretação, supressão de dados e qualidade diferencial dos dados.

Walter José Gomes, Luciano Cabral Albuquerque

Revisão sistemática contendo uma reanálise do EXCEL Trial, demonstra pior mortalidade na angioplastia de lesões de TCE, comparada à revascularização do miocárdio

Bayesian Interpretation of the EXCEL Trial and Other Randomized Clinical Trials of Left Main Coronary Artery Revascularization

BACKGROUND

Patients with left main coronary artery disease have improved outcomes with coronary revascularization compared with medical therapy, but the choice of optimal revascularization technique is unresolved.

OBJECTIVE

To use bayesian methods to analyze the risk differences for patients with left main coronary artery disease randomized to treatment with coronary artery bypass surgery (CABG) compared with those randomized to percutaneous coronary intervention (PCI) in recent randomized clinical trials (RCTs).

DESIGN, SETTING, AND PARTICIPANTS

A systematic review using the PubMed database with the query string “(left main disease) and (PCI or CABG) and (5-year follow-up) and (clinical trial)” identified all RCTs from January 1996 to January 2020 comparing CABG to PCI for treatment of patients with left main coronary artery disease and with 5-year follow-up data. With the use of bayesian methods, the largest and most publicized RCT (EXCEL; Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; 2019) was reanalyzed (1) as an isolated entity using noninformative priors and (2) in the context of previous knowledge using informative priors derived from similar trials. Published aggregate data were used with assignments from each trial following the original intention-to-treat principle. Combining EXCEL data with varying levels of prior information using Bayes theorem provided final (posterior) probability distributions for primary and secondary outcomes.

MAIN OUTCOMES AND MEASURES

A composite end point of death, nonfatal myocardial infarction, and stroke was the primary EXCEL outcome and was accordingly the primary outcome for this reanalysis. Secondary analyses were performed for isolated all-cause mortality and for the composite outcome along with repeated revascularization procedures.

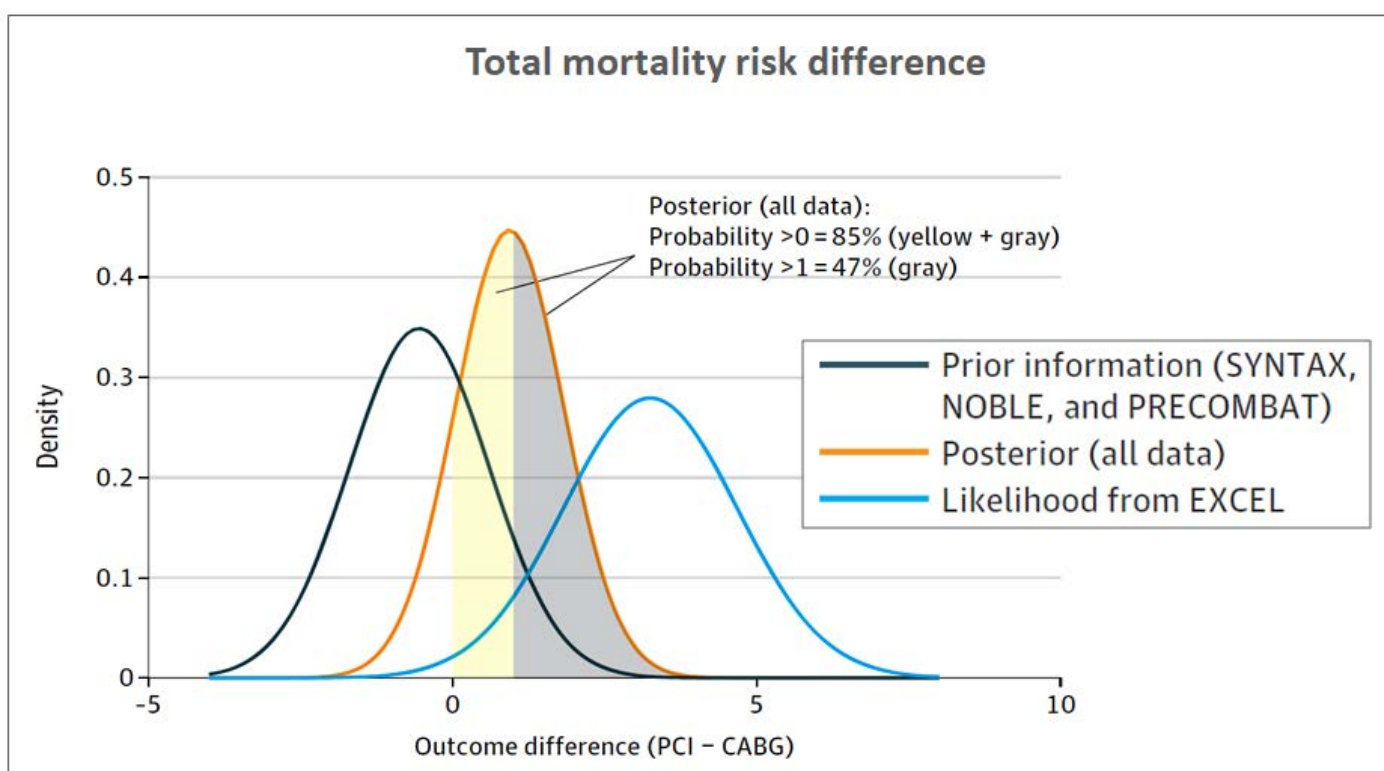
RESULTS

When EXCEL data were analyzed using the originally stated noninferiority design, the 5-year primary outcome difference reported (2.8%; 95% CI, -0.9% to 6.5%) exceeded the predefined 4.2% noninferiority margin; thus, the null hypothesis of PCI inferiority could not be rejected. By contrast, the present bayesian analysis of the EXCEL primary outcome estimated 95% probability that the 5-year primary outcome difference was increased with PCI compared with CABG and 87% probability that this difference was greater than 1 extra event per 100 patients treated. Bayesian analyses also suggested 99% probability that EXCEL total mortality

was increased with PCI and 94% probability that this absolute difference exceeded 1 extra deaths per 100 treated. A systematic review identified 3 other RCTs that studied the same question. The incorporation of this prior knowledge reduced the estimated probability of any excess mortality with PCI to 85%. For the secondary composite end point, which also included repeated revascularizations, there were estimated probabilities of 98% for at least 4 extra events and of 90% for at least 5 extra events per 100 patients treated with PCI.

CONCLUSIONS AND RELEVANCE

Bayesian analysis assisted in RCT data interpretation and specifically suggested, whether based on EXCEL results alone or on the totality of available evidence, that PCI was associated with inferior long-term results for all events, including mortality, compared with CABG for patients with left main coronary artery disease.



Should Percutaneous Coronary Intervention Be Considered for Left Main Coronary Artery Disease? Insights From a Bayesian Reanalysis of the EXCEL Trial.

In this issue of JAMA Internal Medicine, Brophy presents a bayesian analysis of randomized clinical trials comparing revascularization strategies for treatment of left main coronary artery disease (LMCAD). This article is important because of the recent publication of the 5-year results of the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG) in patients with LMCAD of low or intermediate anatomical complexity. The EXCEL trial has ignited a firestorm of controversy. The investigators concluded that there was no significant difference between PCI and CABG in the primary outcome of death or myocardial infarction (MI) or stroke (major adverse cardiac events, MACEs) (difference, 2.8%; 95%CI, -0.9% to 6.5%), even though the odds ratio for mortality was 38% higher in the PCI arm (difference, 3.1%; 95% CI, 0.2%-6.1%).

This conclusion highlights the perils of misinterpreting differences that do not reach statistical significance. The 95% CI estimate of the difference in MACE rates between PCI and CABG ranges from 0.9% absolute reduction to 6.5% increase with PCI. Thus, to state that EXCEL showed these interventions were comparable is misleading because it discounts altogether the clinically relevant effect size and a 95%CI that lies mostly above 0%. Absence of evidence is not evidence of absence.

The MI criterion used in EXCEL (creatinine kinase–myocardial band elevation >10 times the upper limit of normal) underestimates the number of PCI related MIs and overestimates the MIs related to CABG because the more invasive surgery causes greater release of cardiac enzymes than PCI.

The study by Brophy highlights the advantage of the bayesian approach in providing a wider and more informative set of interpretations than that typically provided by frequentist analysis. The results suggest high probability of a clinically important benefit with CABG over PCI especially in terms of MACCE, revascularization, and even mortality. Thus, the suggestion by EXCEL investigators that the treatment strategies are comparable is questionable at best, and at worst risks unnecessary and avoidable deaths of patients with LMCAD.

The current European revascularization guidelines, issued in 2018, endorse PCI as a Class IA recommendation in patients with LMCAD with low anatomical complexity. This recommendation was, in large part, driven by the 3-year results of EXCEL, which showed PCI to be noninferior to CABG.

As summarized in the study by Brophy, the quality and the quantity of evidence is insufficient to support this recommendation. The treatment of choice for LMCAD should be CABG regardless of anatomical complexity. Therefore, the guideline recommendation for PCI for low-complexity LMCAD should be downgraded in alignment with the new evidence.

Características dos ensaios clínicos contemporâneos em intervenções cardiovasculares, e sua associação com a fonte de financiamento do estudo

Characteristics of Contemporary Randomized Clinical Trials and Their Association with the Trial Funding Source in Invasive Cardiovascular Interventions

IMPORTANCE

Changes in evidence-based practice and guideline recommendations depend on high-quality randomized clinical trials (RCTs). Commercial device and pharmaceutical manufacturers are frequently involved in the funding, design, conduct, and reporting of trials, the implications of which have not been recently analyzed.

OBJECTIVES

To evaluate the design, outcomes, and reporting of contemporary randomized clinical trials of invasive cardiovascular interventions and their association with the funding source.

DESIGN, SETTING, AND PARTICIPANTS

This cross-sectional study analyzed published RCTs between January 1, 2008, to May 31, 2019. The trials included those involving coronary, vascular and structural interventional cardiology, and vascular and cardiac surgical procedures.

MAIN OUTCOMES AND MEASURES

We assessed (1) trial characteristics, (2) finding of a statistically significant difference in the primary end point favoring the experimental intervention, (3) reporting of implied treatment advantage in trials without significant differences in primary end point, (4) existence of major discrepancies between registered and published primary outcomes, (5) number of patients whose outcomes would need to switch from a nonevent to an event to convert a significant difference in primary end point to nonsignificant, and (6) association with funding source.

RESULTS

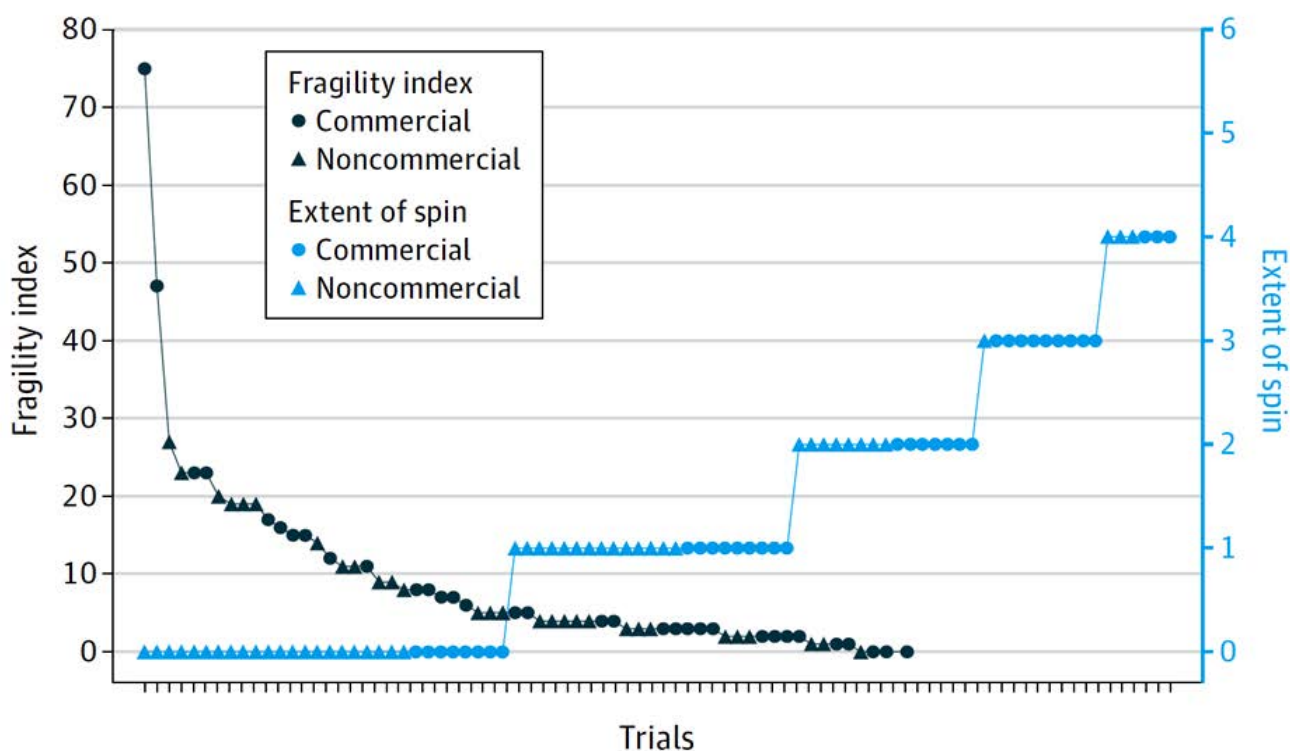
Of the 216 RCTs analyzed, 115 (53.2%) reported having commercial sponsorship. Most trials had 80% power to detect an estimated treatment effect of 30%, and 128 trials (59.3%) used composite primary end points. The median (interquartile range [IQR]) sample size was 502 (204-1702) patients, and the median (IQR) follow-up duration was 12 (1.0-14.4) months. Overall, 123 trials (57.0%) reported a statistically significant difference in the primary outcome favoring the experimental intervention; reporting strategies that implied an advantage were identified in 55 (65.5%) of 84 trials that reported nonsignificant differences. Commercial sponsorship was associated with a statistically significantly greater likelihood of favorable outcomes reporting (exponent of regression coefficient, 2.80; 95% CI, 1.09-7.18; $P=.03$) and with the reporting of findings that are inconsistent with the trial results. Discrepancies between the registered and published primary outcomes were found in 82 trials (38.0%), without differences in trial sponsorship. A median (IQR) number of 5 (2.8-12.5) patients experiencing a different outcome would have change statistically significant results to nonsignificant. Commercial spon-

sponsorship. A median (IQR) number of 5 (2.8-12.5) patients experiencing a different outcome would have change statistically significant results to nonsignificant. Commercial sponsorship was associated with a greater number of patients (exponent of regression coefficient, 1.29; 95% CI, 1.00-1.66; P =.04).

CONCLUSIONS AND RELEVANCE

These results suggest that contemporary RCTs of invasive cardiovascular interventions are relatively small and fragile, have short follow-up, and have limited power to detect large treatment effects. Commercial support appeared to be associated with differences in trial design, results, and reporting.

The Fragility Index and Extent of Spin According to Funding Source



Meaning Findings of this study suggest that contemporary trials in invasive cardiovascular treatments may be small and fragile, have short follow-up, and have limited power to detect large treatment effects.

Laços financeiros entre líderes influentes das associações médicas nos EUA e a indústria: potenciais consequências na formação da evidência e no cuidado com os pacientes

Financial Ties Between Leaders of Influential US Professional Medical Associations and Industry: Cross Sectional Study

OBJECTIVE

To investigate the nature and extent of financial relationships between leaders of influential professional medical associations in the United States and pharmaceutical and device companies.

SETTING

Professional associations for the 10 costliest disease areas in the US according to the US Agency for Healthcare Research and Quality. Financial data for association leadership, 2017-19, were obtained from the Open Payments database.

POPULATION

328 leaders, such as board members, of 10 professional medical associations: American College of Cardiology, Orthopaedic Trauma Association, American Psychiatric Association, Endocrine Society, American College of Rheumatology, American Society of Clinical Oncology, American Thoracic Society, North American Spine Society, Infectious Diseases Society of America, and American College of Physicians.

MAIN OUTCOME MEASURES

Proportion of leaders with financial ties to industry in the year of leadership, the four years before and the year after board membership, and the nature and extent of these financial relationships.

RESULTS

235 of 328 leaders (72%) had financial ties to industry. Among 293 leaders who were medical doctors or doctors of osteopathy, 235 (80%) had ties. Total payments for 2017-19 leadership were almost \$130m (£103m; €119m), with a median amount for each leader of \$31 805 (interquartile range \$1157 to \$254 272). General payments, including those for consultancy and hospitality, were \$24.8m and research payments were \$104.6m—predominantly payments to academic institutions with association leaders named as principle investigators. Variation was great among the associations: median amounts varied from \$212 for the American Psychiatric Association leaders to \$518 000 for the American Society of Clinical Oncology.

CONCLUSIONS

Financial relationships between the leaders of influential US professional medical associations and industry are extensive, although with variation among the associations. The quantum of payments raises questions about independence and integrity, adding weight to calls for policy reform.

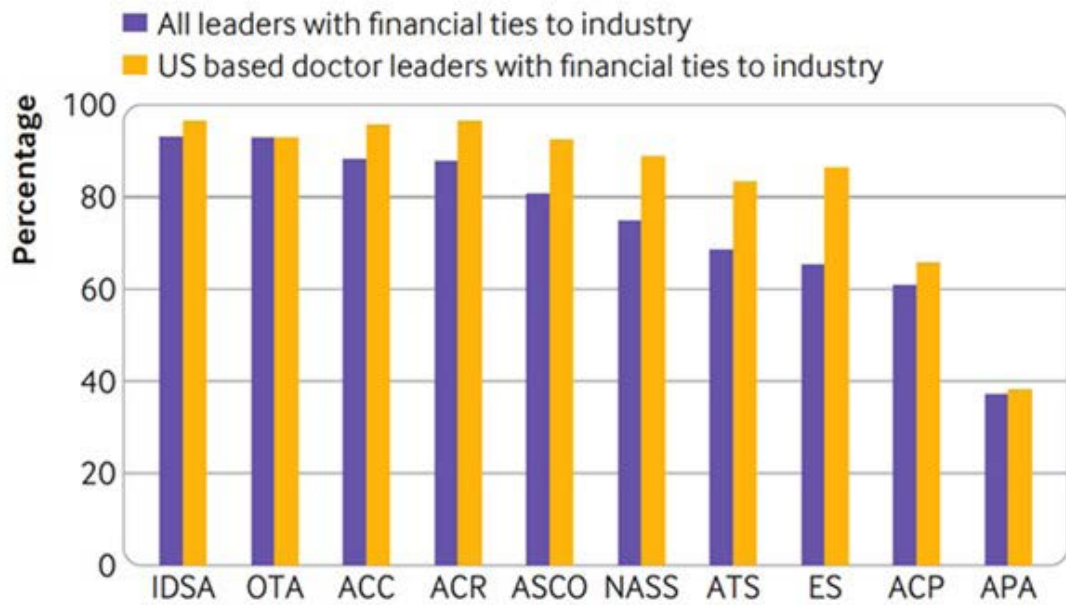


Fig 1 | Proportion of leaders of professional medical associations with financial ties to industry. IDSA=Infectious Diseases Society of America; OTA=Orthopaedic Trauma Association; ACC=American College of Cardiology; ACR=American College of Rheumatology; ASCO=American Society of Clinical Oncology; NASS=North American Spine Society; ATS=American Thoracic Society; ES=Endocrine Society; ACP=American College of Physicians; APA=American Psychiatric Association

Dentre todos os procedimentos de alto custo nos EUA, a cirurgia de revascularização miocárdica (CRM) foi o mais econômico, com o menor custo por ano de vida economizado e o de maior expectativa de vida pós-procedimento

Value Analysis of the Costliest Elective Lifesaving Procedures at an Academic Medical Center

INTRODUCTION

When evaluating the cost of a lifesaving operation, one must consider the economic value, which can be defined as the relative cost per additional year of life lived. This evaluation might provide useful information for the application of costly procedures. The objective of this study was to determine the cost per year of life saved for the costliest operations performed at an urban academic medical center.

METHODS

Total hospital expenditures were categorized by diagnosis related group (DRG) between January 1, 2015 and December 31, 2016. Average cost and patient age for each procedure were calculated. Average lifespan following successful outcome was determined based upon published benchmarks. Cost per year of life saved was calculated for each procedure. Only those elective procedures necessary to prolong life and enhance health were analyzed.

RESULTS

114,448 hospital admissions were reviewed. The 12 costliest procedures were identified and ranked according to cost per year of life saved: Coronary bypass (\$1,345.45), portacaval shunt procedure (\$2,261.70), cardiac valve/other major cardiothoracic procedure (\$2,733.78), major bladder procedure (\$2,733.78), cardiac defibrillator implant (\$5,047.65), bone marrow transplant (\$5,181.80), intracranial vascular procedures (\$8,572.05), kidney transplant (\$9,024.87), liver transplant (\$11,112.73), endovascular cardiac valve replacement (\$12,842.25), simultaneous pancreas/kidney transplant (\$14,087.50), and heart transplant (\$20,472.11).

CONCLUSIONS

Among the costliest procedures, coronary bypass was the most economic, having the lowest cost per year of life saved (\$1,345.45) and longest post-procedure life expectancy (17.6 years). These findings combined with further analysis of the identified procedures may allow us to better determine their relative value.

Most Costly Elective Invasive Procedures

Elective Invasive Procedure	Average Cost/Case	Additional Years of Life (Reference Number)	Quality of Life Utility Score (Reference Number)	Additional QALYs*	Cost/QALY* Saved
Coronary Bypass	\$23,679.93	17.6 [21]	0.83 [7]	14.61	\$1,621.02
Cardiac Valve/other Major Cardiothoracic Procedure	\$32,805.39	12 [23]	0.76 [9]	9.12	\$3,597.08
Portacaval Shunt Procedure	\$13,954.70	6.17 [22]	0.61 [33]	3.76	\$3,707.71
Major Bladder Procedure	\$18,207.73	5 [24]	0.65 [12]	3.25	\$5,602.38
Cardiac Defibrillator Implant	\$30,285.91	6 [25]	0.88 [13]	5.28	\$5,735.97
Allogenic and Autologous Bone Marrow Transplant	\$67,363.41	13 [26]	0.52 [15]	6.76	\$9,965.00
Kidney Transplant	\$90,248.69	10 [28]	0.76 [17]	7.60	\$11,874.83
Intracranial Vascular Procedures	\$55,718.34	6.5 [27]	0.67 [16]	4.36	\$12,794.11
Liver Transplant	\$166,690.88	15 [29]	0.8 [18]	12.00	\$13,890.91
Endovascular Cardiac Valve Replacement	\$51,369.01	4 [30]	0.73 [10]	2.92	\$17,592.13
Simultaneous Pancreas/Kidney Transplant	\$192,998.70	13.7 [31]	0.52 [19]	7.12	\$27,091.34
Heart Transplant	\$225,193.19	11 [32]	0.57 [20]	6.27	\$35,915.98

*QALY = Quality adjusted life year.

Ranking of the 12 most costly elective invasive procedures based on the cost per quality adjusted life-year (QALY) saved for each procedure. Cost per QALY saved is defined as the procedural cost distributed across each additional QALY lived following the procedure.

Cost Per Quality Adjusted Life Year Saved

