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

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IMPORTANCE 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.

Invited Commentary

Related article

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Left main coronary artery disease (LMCAD) is a serious manifestation of coronary artery disease and has long been known to have an improved prognosis with coronary artery bypass surgery (CABG) compared with medical therapy.[1] More recently, with improved technological advancements, percutaneous coronary interventions (PCIs) have also been investigated as a revascularization procedure to treat LMCAD. The first large multicenter randomized clinical trial comparing CABG with PCI that included patients with LMCAD was published in 2009,[2] and subsequent longer-term follow-up has been reported.[3-5] Post hoc analyses have suggested that LMCAD results with PCI were inferior to CABG in the subgroups with a high anatomical complexity but otherwise suggested that both treatments were valid options for patients with LMCAD.[5] Other studies examining the question of the best technique for outcomes in patients with LMCAD have now been completed.[5-7] Most recently, the 5-year follow-up of the EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) randomized clinical trial, which compared PCI with CABG for treating patients with LMCAD of low or intermediate anatomical complexity, has been published.[8] Although there are many strengths inherent in that trial, including its ability to recruit a large number of patients and to have almost complete follow-up, its interpretation has generated extensive controversy, with the lead surgical investigator withdrawing his name from the final publication.[9]

Bayesian methods[10] have been proposed as a means to provide additional insights into data interpretation by providing probability estimates of direct clinical interest and by allowing the consideration of prior evidence to provide posterior probabilities that mirror natural sequential learning and therefore facilitate medical decision-making. These methods have been recommended to assist in the interpretation of clinical trials for more than 20 years.[11] Because bayesian methods allow the use of direct probability statements, overall clarity and study interpretability is enhanced. Consequently, the present study used bayesian methods to further explore the clinical question concerning optimal revascularization choice for patients with LMCAD. The EXCEL trial is first analyzed in isolation, as presented in its original publication[8] and also within a bayesian framework. Next, bayesian methods are used to incorporate pertinent past knowledge from other trials with the EXCEL data to synthesize the totality of the available evidence for maximally informed decision-making.

Key Points

Question A randomized clinical trial (EXCEL; Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) of patients with left main coronary artery disease reported no significant difference between percutaneous coronary intervention and coronary artery bypass surgery in the composite outcome rate of death, stroke, or nonfatal myocardial infarction at 5 years; however, this interpretation is controversial, and whether bayesian analyses may assist resolution is unknown.

Findings This bayesian reanalysis of EXCEL data suggested that the mean difference for the primary composite outcome was 3% less and for mortality was 1% less with coronary artery bypass surgery than with percutaneous coronary intervention at the 5-year follow-up; the estimated probability of more primary composite events with percutaneous coronary intervention was 95% (virtually 100% when including repeated revascularization) and of more deaths was 99%. Similar results were observed when the totality of prior studies, based on a systematic review, was included.

Meaning Bayesian analysis provided additional insights into the interpretation of randomized trial results, suggesting that percutaneous coronary intervention provides long-term results inferior to coronary artery bypass surgery for patients with left main coronary artery disease.

Methods

An electronic systematic review of all randomized clinical studies was executed using the PubMed database with the query string "(left main disease) and (PCI or CABG) and (5-year follow-up) and (clinical trial)" from January 1996 to January 2020. For studies with multiple publications, only the study reporting the most complete 5-year results was retained. Abstracted data included a standardized composite primary outcome composed of death, nonfatal myocardial infarction, or stroke (the primary end point in EXCEL[8]) as well as a secondary composite outcome of death, nonfatal myocardial infarction, stroke, or repeated revascularization (the primary end point in other similar trials[5-7] and a secondary outcome in EXCEL[8]) and isolated total mortality (a secondary outcome in all of the included trials[5-8]). These outcome events were represented by binomial distributions, which were parameterized by the number of outcomes in a sequence of independent yes or no experiments. This study was exempted from obtaining formal institutional review board approval and the requirement to obtain informed patient consent because it is secondary research of publicly available data sets.

Direct probability statements can only be made if the objective data are conditioned on previous beliefs. This assertion is the correlate of clinical decision-making in which test results are only sensibly interpreted in a clinical context. To estimate the final (posterior) probability of differences in outcomes between the PCI and CABG arms, the objective data (binomial likelihood) for each study must be combined with previous beliefs according to Bayes theorem:

$$\textit{Posterior Distribution} = \frac{\textit{Likelihood of Data} \times \textit{Prior Distribution}}{\textit{Normalizing Constant}}.$$

This formula follows the formal rules of probability in an uncontested and irrefutable mathematical manner, with the only difficulty being the choice of the prior distribution.

The estimates of interest in the present analysis were absolute risk differences, a measure of both clinical and public health importance. Posterior risk differences were calculated for EXCEL data alone and for EXCEL data combined with evidence from the previously identified prior studies. To calculate the isolated EXCEL posterior distribution of the risk dif-

ference, we used noninformative Beta(1, 1) prior distributions for each treatment arm. This method essentially means that the posterior distribution was uniquely defined by the observed EXCEL data. This choice of prior information is also mathematically convenient because it is the conjugate family for the binomial likelihood and permits closed-form solutions. We then sampled 100 000 times from the posterior distribution for each arm to obtain posterior samples for the differences between the 2 revascularization strategies. The posterior distribution difference curves that are displayed in **Figure 1** and **Figure 2** were computed from gaussian kernel density estimates, which provide a smoothed version of the sampled difference histograms.

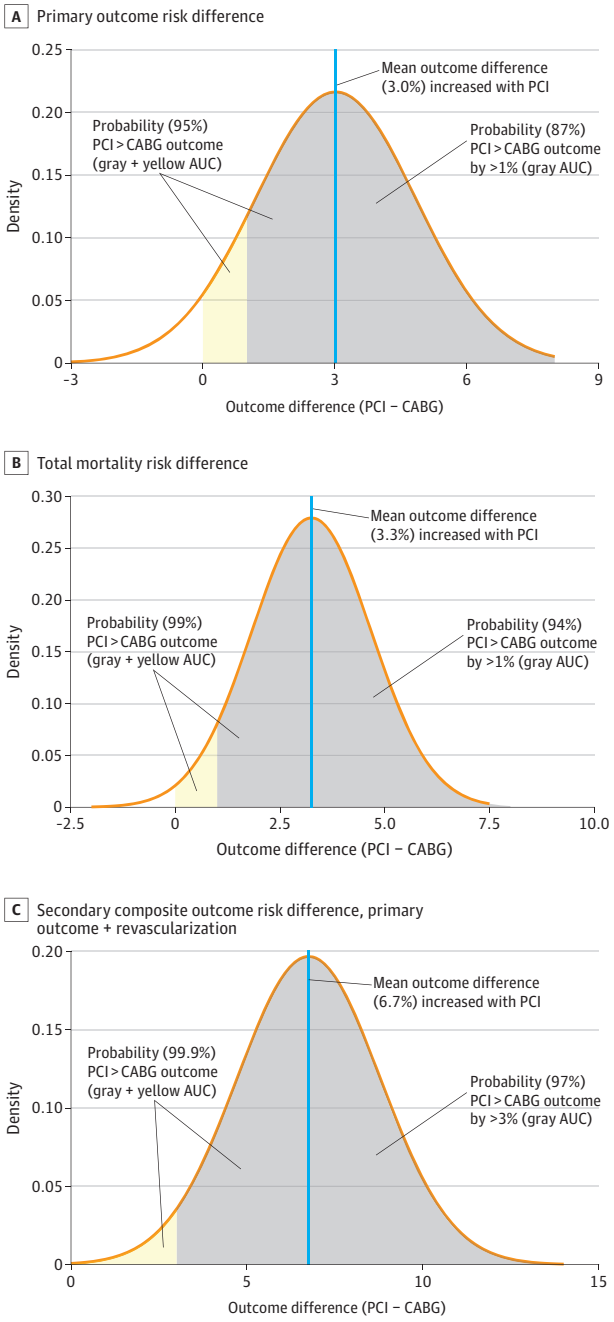
To calculate a maximally informed posterior distribution for the risk differences, we next combined the EXCEL data with informative prior information of all comparable previous studies as identified in the systematic review[5-7] and synthesized them with a random-effects model using a restricted maximum-likelihood estimator.[12] The EXCEL and prior data from previous studies were combined using bayesian normal conjugate analysis[13] of the risk differences. In this closed-form analysis, both the prior mean and the sample mean provide information about the posterior mean. The signals are combined linearly, but more weight is given to the signal that has higher precision (smaller variance).[13] The flexibility of bayesian analyses permits a straightforward calculation of the posterior probability function exceeding any given threshold by a simple calculation of the area under the curve (AUC) to the right of the selected threshold. The visualization of these posterior probability functions greatly assists data interpretation. All computations were conducted using the R programming language,[14] and the code is available online.[15]

Results

Literature Review

The electronic literature search revealed 24 publications that arose from 4 independent randomized clinical trials (PRECOMBAT [Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease],[7] SYNTAX [Synergy Between PCI With TAXUS and Cardiac Surgery],[5] NOBLE [Nordic-Baltic-British Left Main Revascularization Study],[6] and EXCEL[8]), each with 5-year follow-up data. The main outcomes (death, nonfatal myocardial infarction, and stroke) and the secondary outcomes (death, nonfatal myocardial infarction, stroke, and revascularization) and total mortality are presented for each trial in the **Table**. One additional trial of 105 patients with LMCAD, the Left Main Coronary Artery Stenting (LE MANS) trial,[16] was identified by a hand search but was not included in the present analysis because (1) PCI was not of contemporary standards (ie, it used bare metal and first-generation drug-eluting stents), (2) it had only 10-year results[17] for mortality and no results for our primary composite outcome owing to missing data, and (3) it had no published 5-year follow-up.

Figure 1. Probability Density Functions for the Difference in Outcomes From EXCEL With a Noninformative Prior

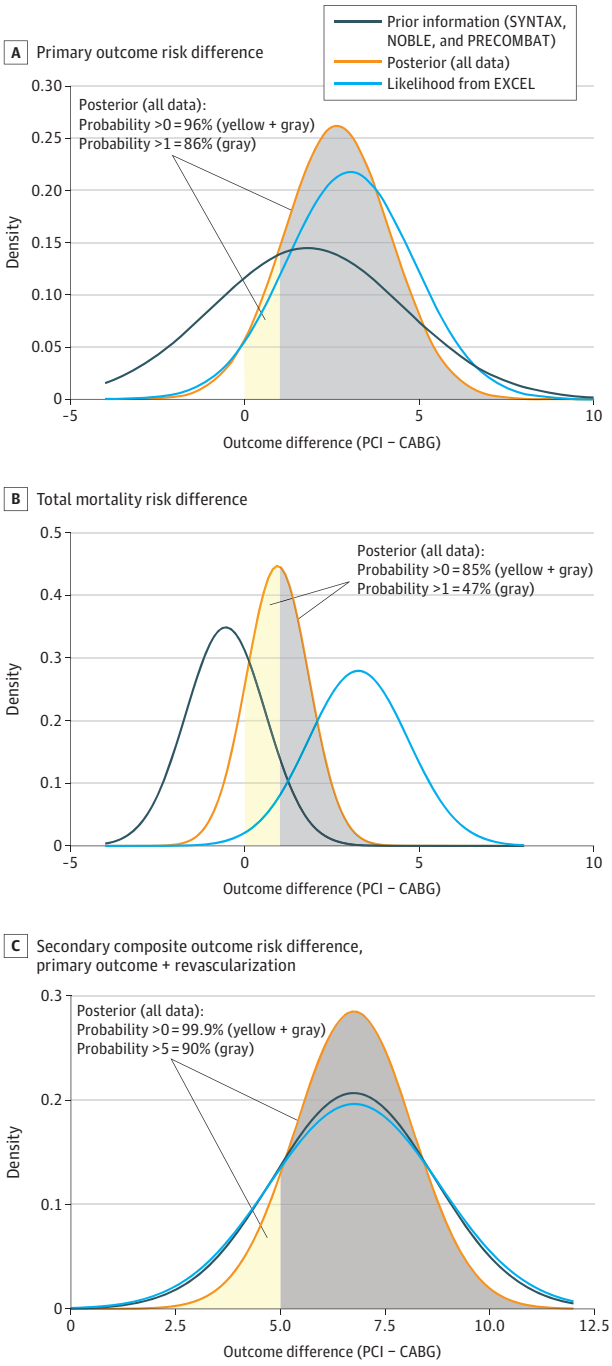


Higher outcome difference (percutaneous coronary intervention [PCI] minus coronary artery bypass graft [CABG]) shown along the abscissa indicated that PCI is inferior. AUC represents area under the curve; EXCEL, Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization.

Isolated EXCEL Results

The EXCEL trial reported a primary outcome event rate difference (PCI − CABG) of 2.8% (95% CI, −0.9% to 6.5%) based on Kaplan-Meier estimates in time-to-first-event analyses. In our analysis, because we did not have time-to-event data, we

Figure 2. Probability Density Functions of Outcomes for Prior Information (SYNTAX, NOBLE, and PRECOMBAT), Likelihood (EXCEL), and Combined Posterior Distributions



CABG represents coronary artery bypass graftt; NOBLE, Nordic-Baltic-British Left Main Revascularization Study; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

calculated only the difference in the proportions of events (3.0%; 95% credible interval [CrI], -0.6% to 6.6%). Similarly, whereas the EXCEL trialists reported an increase in total mortality rate with PCI of 3.1% (95% CI, 0.2%-6.1%), we calculated a mean increase in the proportions of deaths of 3.3% (95% CrI, 0.4%-6.0%).

The probability density function for the difference in the EXCEL primary composite outcomes was centered at the point estimate of the primary outcome mean difference (3.0%) with 95% probability that the primary outcome was increased with PCI compared with CABG (Figure 1A). There was an 87% probability that this difference was at least 1 extra event per 100 patients treated.

The graph of the probability density function for the difference in EXCEL total mortality is centered at the mean of the total mortality difference (3.3%), with 99% probability that the total mortality is increased with PCI compared with CABG (calculated as the AUC to the right of zero on the abscissa) (Figure 1B). There was a 94% probability that this difference was at least as great or greater than 1 extra death per 100 patients treated (calculated as the AUC to the right of 1 on the abscissa). Figure 1A was shifted to the left of Figure 1B owing to increased strokes with CABG and proportionally smaller differences in nonfatal myocardial infarctions compared with deaths.

The EXCEL probability density function for the difference between the treatment arms for their secondary composite outcome (death, myocardial infarction, stroke, or revascularization) was centered at the mean of the difference (6.7%; 95% CrI, 2.8%-10.7%), with 99.9% probability that this composite outcome was increased with PCI (Figure 1C). There was a 97% probability that this difference was greater than 3 extra events per 100 patients treated.

EXCEL Results in the Context of Prior Knowledge

Three other randomized trials have addressed the same question and reported 5-year outcomes (Table). Rather than interpreting EXCEL in isolation, the present bayesian analysis updated the EXCEL 5-year results with the combined prior results from these previous trials. The point estimate differences (PCI − CABG) and SEs obtained from a random-effects model of these 3 previous studies were 1.8% (2.8) for the primary composite, −0.5% (1.1%) for total mortality, and 6.7% (1.9) for the secondary composite.

Figure 2A shows the primary composite outcome probability density functions for the prior data, EXCEL data, and the combined (posterior) data sources. The posterior distribution can be visualized as a weighted mean of the prior and present data. The additional information contained in the posterior is reflected in a narrower distribution than that of the prior data, with a mean posterior difference of 2.6% (95% CrI, −0.33% to 5.6%) fewer primary outcome events with CABG compared with PCI. The probability of more primary events with PCI was 96% (AUC to the right of zero), with 86% probability of exceeding at least 1 event per 100 treated.

Figure 2B shows the total mortality probability density functions for the prior data, EXCEL data, and the combined (posterior) data sources. The posterior distribution, by including previous studies with a smaller mean mortality excess with CABG, consequently shifted the total mortality increase with

Table. Composite Outcomes and Total Mortality for All Trials With a 5-Year Follow-up

	No. of patients							
	Total mortality		MACE		MACCE		Sample size for each arm, No. of patients	
Source	CABG	PCI	CABG	PCI	CABG	PCI	CABG	PCI
PRECOMBAT[7]	23	17	28	25	42	52	300	300
NOBLE[6]	50	54	77	118	110	165	592	592
SYNTAX[5]	48	45	69	67	103	130	348	357
EXCEL[8]	89	119	176	203	228	290	957	948

Abbreviations: CABG, coronary artery bypass graft; EXCEL, Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; MACCE, composite of death, nonfatal myocardial infarction, stroke, and revascularization; MACE, composite of death, nonfatal myocardial infarction, and stroke; NOBLE, Nordic-Baltic-British Left Main Revascularization Study; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery Versus Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; and SYNTAX, Synergy Between PCI With TAXUS and Cardiac Surgery.

PCI seen in EXCEL toward zero. Including all of the studies, the posterior mean total mortality difference was 0.9% excess (9 of 1000) deaths with PCI compared with CABG. The diminished uncertainty in the mean posterior estimate of total mortality is graphically displayed again with the narrowing of the posterior distribution compared with the prior distribution. Numerically, this result was reflected in the shrinking of the uncertainty around the EXCEL trial total mortality estimate (95% CrI, 0.5-6.0 vs 95% CrI, −0.8 to 2.7 for the posterior). The posterior probability of more deaths with PCI was 85%, with 47% probability of exceeding 1 event per 100 treated when the totality of the evidence was considered.

Figure 2C shows the EXCEL secondary composite outcome probability density functions for the prior data, EXCEL data, and the combined (posterior) data sources. All studies uniformly had increased rates of revascularization following PCI, and its inclusion in this composite end point shifted the posterior curve to the right again, with the expected narrower distribution. Although individual end points varied between EXCEL and the previous studies, their composite end points were remarkably similar. The mean posterior difference was 6.8% (95% CrI, 4.0%-9.5%) fewer secondary composite outcome events with CABG compared with PCI. The probability of more composite events with PCI was 99.9%, virtually 100% (AUC to the right of zero), with 98% probability of exceeding 4 events per 100 treated and 90% probability of exceeding 5 events per 100 treated.

Discussion

Had the 5-year EXCEL results been interpreted in alignment with their original primary noninferiority design and prespecified primary outcome margin of 4.2%,[18] a different conclusion would have been reached even within the framework of a standard frequentist analysis. The 5-year primary outcome as reported by the EXCEL authors was a difference of 2.8% (95% CI, −0.9% to 6.5%; P = .13), with the upper 95% CI extending beyond the 4.2% noninferiority margin. This result indicated that the null hypothesis of PCI being inferior to CABG by at least the stated margin could not be rejected. If a margin of 4.2% was judged to represent a clinically meaningful difference at 3 years, would it not also be reasonably considered a meaningful difference at 5 years? Instead, the EXCEL authors interpreted the 5-year results as a superiority trial in which the null hypothesis consisted of no difference and with observed data not being sufficiently extreme to reject this null hypothesis. The recognized limitations of frequentist null hypothesis statistical testing[19] associated with the pernicious mendacities of dichotomized P values[20] can be avoided with the bayesian paradigm.

The present bayesian analysis, conducted via analytical and graphical procedures, enabled a more in-depth examination and interpretation of the original EXCEL conclusion that "there was no significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or myocardial infarction at 5 years."[8(p1820)] Rather than dichotomizing results into statistical significance or not, the bayesian analysis concentrates on estimation of key outcome differences with direct probability measures of their uncertainty. Analyzing EXCEL alone, this bayesian analysis estimated a 3.0% mean difference in the EXCEL primary outcome (death, nonfatal myocardial infarction, and stroke) in favor of CABG, with 95% probability of increased risk with PCI. Moreover, there was 87% probability that this difference was greater than 1 extra event per 100 patients treated. Although the inclusion of the prior studies reduced the estimated mean difference to 2.6% (95% CrI, −0.33% to 5.6%), the probability of more primary events with PCI remained high at 96%, with 86% probability of exceeding at least 1 event per 100 procedures. This analysis is arguably more informative in representing and understanding not only the EXCEL data but also the totality of the evidence.

The inferences from this bayesian analysis for the EXCEL secondary composite outcome of mortality, myocardial infarction, stroke, or revascularization provided further evidence for the advantages of CABG over PCI. Specifically, the composite outcome with revascularization was increased 6.8% (95% CrI, 4.0%-9.5%) with PCI, with 90% probability that this outcome was greater than 5 events per 100 procedures.

In response to questions about the overall initial conclusion of no significant difference between PCI and CABG,[9,21] the EXCEL leadership stated that the observed increased all-cause mortality "was a secondary underpowered end point and the modest difference noted between groups was not adjusted for multiplicity and is therefore statistically uncertain."[22(p1)] They

also asserted that their meta-analysis of the same 4 trials show no difference in 5-year mortality between PCI and surgery. Assuming the exchangeability of the 4 studies, this present analysis not only provided an estimate of any mortality risk difference but also measured its associated uncertainty while avoiding the issues of multiplicity and secondary analyses that plague standard frequentist analyses, thereby permitting a deeper dive into statistical inference. The current analysis, which enabled an updating of prior information with EXCEL results, did not show any indisputable mortality risk, ostensibly confirming the EXCEL leadership's opinion and meta-analysis.[22] However, this bayesian analysis was not restricted to the dichotomous world of null hypothesis statistical testing and provided additional quantitative insights into the mortality risk differences. This insight suggested that the probability of increased mortality with PCI was 85%, with almost 50% probability that this increase was greater than 1 extra life lost per 100 treated. The most likely estimate was 9 lives lost per 1000 with 95% confidence that the value was between 8 lives saved per 1000 and 27 lives lost per 1000. By avoiding the dichotomization of results into binary statistical significance bins at an arbitrary threshold, these bayesian inferences arguably provide an enhanced appreciation of the results that may be helpful both to physicians and patients. The transparent and mathematically rigorous bayesian approach reveals the possibility of a mortality signal and underscores that the scientific response should be not to ignore either the previous or the current total mortality findings but rather to systematically integrate them to provide an informed quantifiable estimate with its associated uncertainty.

The question then becomes the following: how did the interpretation of no difference gain its predominant position in the final EXCEL publication?[8] Plausible hypotheses include (1) honest statistical misinterpretations due to confusion regarding study design, superiority vs noninferiority, and dichotomous thinking induced by *P* values; (2) confusion arising from assigning equal weights to periprocedural myocardial infarctions as to other clinically more important events, including death, stroke, and nonprocedural myocardial infarctions; and (3) failure to quantitively synthesize evidence from similar trials and combine it with the current data. The presented bayesian approach has addressed and clarified these statistical issues, thereby enriching understanding of the data and their context.

Finally, a Cochrane review[23] has suggested that sponsorship of drug and device studies by the manufacturing company leads to more favorable results and conclusions that cannot be readily explained by standard "risk of bias" assessments. Fourteen of 34 EXCEL authors, including the first and last authors, had a relationship with the trial sponsor (a stent manufacturer), and the Cardiovascular Research Foundation (which 8 authors list as their affiliation) received a $937 000 donation from the sponsor during the trial.[24] This factor may lead to the entirely speculative hypothesis that conflict of interest contributed to the EXCEL interpretation.

Limitations

Although the present analysis had the strengths noted above, it also had limitations. First, we did not have access to either individual data from EXCEL (their supplemental information explicitly states data will not be shared) or from the other previous trials. By using the aggregated EXCEL data, there appeared to be very small differences between our calculated risk differences and the event rate differences reported in the original publication. Without individual data, we are also unable to explore the increased periprocedural myocardial infarctions noted in the CABG arm of EXCEL. This factor is an intriguing finding because the periprocedural myocardial infarction rates observed in the SYNTAX trial,[5] with recruitment occurring 5 years earlier and involving many of the same sites as in EXCEL, were approximately equivalent between the 2 arms. Recognizing the difficulty in determining the threshold and significance of periprocedural myocardial infarctions, other trials have chosen to exclude them as end points.[6] We were also unable to perform a full bayesian analysis with noninformative priors on the between-study variations because, with only 4 studies to draw on, we had insufficient measures of precision. A traditional bayesian meta-analysis with a semi-informative prior for the between-study variation (half-Cauchy distribution with scale = 0.5) does give approximately the same results as the present analysis. We elected not to present this study as a bayesian meta-analysis because our goal was to illustrate how bayesian principles could be informative when applied to the interpretation of new trial data. Notwithstanding any limitations, it would appear that this bayesian analysis enables a richer interpretation of the EXCEL data and calls into question the original trial interpretation of no significant differences between PCI and CABG.

Conclusions

In conclusion, this bayesian interpretation of the EXCEL results, either considered in isolation or in the context of previous knowledge, suggested with a reasonably high probability that PCI was associated not only with statistical inferiority but also with clinical inferiority to CABG for treatment of patients with LMCAD, ceteris paribus. However, clinicians must also recognize the need for individual personalization and consequently acknowledge that PCI may be an appropriate choice for selected patients, such as those with a reduced overall life expectancy of less than 2 to 3 years or those with very high surgical risk profiles.

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