Bayesian Inference Supports the Use of Bypass Surgery Over Percutaneous Coronary Intervention To Reduce Mortality in Diabetic Patients with Multivessel Coronary Disease

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Abstract: *Background*: Coronary artery bypass graft (CABG) surgery may confer a survival advantage over percutaneous coronary intervention (PCI) in diabetic patients with multivessel coronary artery disease (CAD), but results of individual studies have been mixed. The primary aim of the current study was to compare mortality rates in diabetic patients with multivessel CAD randomized to either or CABG or PCI at 5 years or longest follow-up.

Methods: Using a Bayesian approach, we updated a prior probability distribution elicited from 8 clinical trials (*N*=2024) with the likelihood obtained from the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) (*N*=1460) to determine whether clinical trial evidence supports the underlying hypothesis that CABG is superior to PCI for diabetics with multivessel CAD.

Results: A conjugate normal model comparing mortality rates favored the use of CABG (posterior mean odds ratio [*OR*] = 0.58, 95% Bayesian credible interval [BCI] = 0.48–0.71). Models weighted by the use of drug-eluting stents also favored the use of CABG over PCI (*OR* = 0.61, 95% BCI 0.48–0.78), as did models weighted by study age (*OR*=0.64, 95% BCI 0.52–0.80) or use of arterial conduits (*OR*=0.64, 95% BCI 0.51–0.81). The results were supported by a Bayesian hierarchical meta-analysis using a non-informative prior distribution (*OR*=0.55, 95% BCI 0.37–0.76).

Conclusions: By integrating evidence from various studies, Bayesian methods directly support the underlying hypothesis that revascularization with CABG improves survival compared with PCI in diabetic patients with multivessel CAD.

Keywords: Health policy and outcome research, catheter-based coronary interventions, stents, CV surgery, coronary artery disease, diabetes mellitus.

Patients with diabetes mellitus (DM) have more diffuse coronary artery disease (CAD) than nondiabetics and stronger evidence of a prothrombotic state and vascular inflammation. These factors may impair the response to percutaneous coronary intervention (PCI) [1], as compared with surgical revascularization. A subgroup analysis from the Bypass Angioplasty Revascularization Investigation (BARI) [2] reported that diabetic patients treated with coronary artery bypass graft (CABG) surgery had lower mortality rates at 5 years than those treated with PTCA (5.8% versus 20.6%, *P*=0.0003).

Randomized controlled trials (RCTs) comparing CABG with PCI for diabetic patients with multivessel CAD have produced mixed findings, though none have suggested a survival advantage of PCI. The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial randomized diabetic patients with multivessel CAD to either CABG or PCI and reported lower 5-year mortality after surgical revascularization (11.0% vs. 16.3%; *P*=0.049) [3]. Although the FREEDOM trial was the first large trial in diabetic patients with multivessel CAD, it was not powered to detect a difference in all-cause mortality [3].

A meta-analysis of 8 trials [4], including FREEDOM, suggested that revascularization with CABG compared with PCI in diabetic patients with multivessel CAD decreased all-cause mortality by one third at 5 years or longest follow-up (relative risk [*RR*] 0.67, 95% confidence intervals [CI] 0.52–0.86). After most of the older studies contained in the meta-analysis were reported, several advances in surgical and interventional practice have appeared. To determine whether newer stents have an advantage over older interventional approaches, Bangalore and colleagues [5] performed a network meta-analysis and reported that the use of cobalt–chromium everolimus-eluting stents may narrow the mortality gap between CABG and PCI (*RR* = 0.90, 95% CI 0.54–1.49). On the other

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hand, Hakeem and colleagues [6] performed a meta-analysis of contemporary trials and reported that CABG in diabetic patients with multivessel CAD was associated with lower mortality than the use of drug-eluting stents (DES, *RR* = 0.66, 95% CI 0.48–0.21).

The primary aim of the current study was to compare mortality rates in diabetic patients with multivessel CAD after treatment with CABG or PCI. Beyond the standard techniques used for statistical analysis, the current study incorporated Bayesian methods to establish inferences based on probability functions [7]. The first step in the analysis defined a prior probability distribution elicited from 8 clinical trials [2,8-14]. The next step updated the prior with a likelihood distribution obtained from the FREEDOM trial [3] to generate the posterior distribution, which contained the parameter governing the probability that CABG is superior to PCI for diabetic patients with multivessel CAD. A sensitivity analysis was then developed to study the influence of stent type, study age and use of arterial conduits on the treatment effect in the posterior distribution. A final analysis used a Bayesian hierarchical approach to generate conclusions about whether CABG is superior to PCI in reducing mortality in diabetic patients with multivessel CAD.

METHODS

Prior Distribution

The studies for the prior distribution appeared in the data supplements accompanying the 2011 clinical guidelines for revascularization [15]. The evidence base included dedicated RCTs of diabetic patients and diabetic-subgroup analyses of RCTs.

In the current report, the comparison of CABG with PCI is represented by the odds ratio (*OR*), which is the odds of death following CABG divided by the odds of death following PCI. An *OR* <1 favors CABG.

Because 8 previous studies are available (Table **1**) [2,8-14], they can be used as a basis for a prior distribution, with the understanding that the Bayesian concept of the term "prior" is not a literal chronological prerequisite [7]. In the prior studies, we have data $y_1, \ldots, y_H$, each of which is assumed to follow a normal distribution

$$yh \sim N[\theta h, \sigma_h^2], \quad (1)$$

governed by an underlying treatment parameter θ_h and its variance σ_h^2 for h = 1,2, …, 8 trials. If we are willing to assume that the studies are exchangeable [16], this leads to the use of a meta-analysis (Figure **1**). It is common practice to make the assumption that the prior distribution $p(\theta)$ takes the form of a normal distribution [7]

$$p(\theta) = N\left[\theta \middle| \mu, \frac{\sigma^2}{m_0}\right], \quad (2)$$

where θ is the unknown underlying treatment effect, μ is the prior mean, σ is the standard deviation, and m_0 is the implicit sample size.

If y_1 observations in trial 1 have been cross-classified according to treatment received in a *2 x 2*

Table 1: Data for Pooled Bayesian Model

Reference	All	Total N		Deaths		Summary statistics			
	Patient Age (yrs)	*CABGPCI*	*PCI*	*CABG*	*PCI*	*OR*	*$\log_e$(OR)*	*V(θ)*	*m (σ=2)*
BARI [2]	62	180	173	16	47	0.267	-1.320	0.093	43
ARTS [8]	61	96	112	8	15	0.604	-0.504	0.201	20
ERACI II [9]	62	39	39	4	4	1.000	0.000	0.495	8
MASS II [10]	60	59	56	9	9	0.941	-0.061	0.245	16
SoS [11]	62	74	68	1	7	0.167	-1.788	0.828	5
CARDia [12]	64	248	254	32	37	0.871	-0.138	0.065	61
SYNTAX [13]	65	202	227	26	44	0.616	-0.485	0.070	58
VA CARDS [14]	62	97	101	5	21	0.223	-1.502	0.248	16
FREEDOM [3]	63	761	699	83	114	0.629	-0.463	0.023	171

The *m*'s are the "effective number of events" in a balanced trial, obtained from setting the estimated variances of the $\log_e(OR)$ to σ^2/m. The pooled results are obtained by adding the *m*'s and weighting the $\log_e(OR)$ by their respective *m*'s and labeled n_o and used as the basis for the prior distribution for FREEDOM.

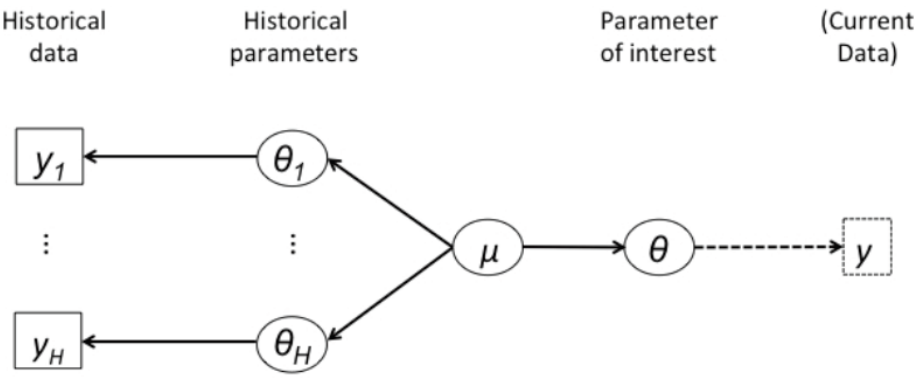

Figure 1: Exchangeable Model. The figure illustrates the assumptions relating parameters (θ_1, …, θ_H) underlying historical data (y_1, …, y_H) to the parameter of current interest (θ). μ represents the pooled log odds ratio from the historical studies, and arrows represent normal distributions.

table, and the odds of death after CABG is *a/c* (the number of deaths divided by the number of survivors) and the odds of death after PCI *b/d*, then the *OR* describing the trial results is given by (*a*/*c*)/(*b*/*d*). Because some trials have small numbers of events, we add 0.5 to both the numerator and denominators, and the trial result μ on the $\log_e$ scale is the estimator of choice for the treatment effect [7],

$$\mu_m = \log_e \left[\frac{(a+\frac{1}{2})(d+\frac{1}{2})}{(b+\frac{1}{2})(c+\frac{1}{2})} \right]. \quad (3)$$

The estimator has an approximate variance

$$V(\mu_m) = \frac{1}{a+\frac{1}{2}} + \frac{1}{b+\frac{1}{2}} + \frac{1}{c+\frac{1}{2}} + \frac{1}{d+\frac{1}{2}}. \quad (4)$$

In order to put the variance into a workable form for the prior distribution, some experts recommend calculating the standard error $\sigma/\sqrt{m}$ for each study using a term *m* to reflect the "effective number of events" in balanced trials, which is obtained from setting the variance of the $\log_e(OR)$ to σ^2/m [7]. In a *2 x 2* table for a balanced randomized trial, it can be assumed that the sample sizes for each treatment are approximately equal, the number of deaths $a \approx b$ are very small compared with the number of surviving patients $c \approx d$ in each treatment group, so that Eq. 4 simplifies to:

$$V(\mu_m) \approx \frac{2}{a} \approx \frac{4}{m}, \quad (5)$$

where m = a + b is the number of events, allowing σ = 2 to be an appropriate choice [7].

After calculating m_h for each y_h, we can obtain the "pooled" results by summing the *m*s for the *h* = 1, 2, …, 8 trials. The pooled *m* can be relabeled m_0 to represent the overall "effective number of events" in the prior distribution. We can use this value to calculate a pooled $\log_e(OR)$ for the prior distribution by weighting the individual $\log_e(OR)$s by their respective *m*s divided by the sum m_0 [17], using the standard approach:

$$\mu_0 = \frac{\sum_{h=1}^{8} m_h y_h}{m_0}$$

In the evaluation of evidence comprising the prior distribution, it is reasonable to down-weight early trials by adjusting the prior "number of events" from *m* to αm, where α is a normalizing factor [18]. With this approach, α can be set to 0, 0.1, 0.5 and 1.0, to discount earlier trials that did not use, for example, drug-eluting stents (DES) or a high proportion of left internal mammary artery (LIMA) grafts:

$$\mu_{weighted} = \frac{\sum_{h=1}^{8} \alpha_h m_h y_h}{\sum_{h=1}^{8} \alpha_h m_h} \quad (6)$$

Likelihood

In the context of a contemporary randomized clinical trial such as FREEDOM [3], it is reasonable to assume that the data can be summarized by a statistic, $y_n = \log_e(OR_n)$, after *n* observations and will assume a normal distribution given by:

$$y_n \sim N\left[\theta, \frac{\sigma^2}{n}\right], \quad (7)$$

where θ is the underlying treatment effect that governs the trial observation. The study-specific trial result y_n

can estimate the true underlying treatment effect with standard error $\sigma/\sqrt{n}$ [7]. Similar to the prior discussion for the prior distribution, we can derive the equations for the likelihood (Supplemental Appendix).

Conjugate Normal Model

Given that the normal prior $\theta \sim N[\mu_m, \sigma_m^2/m_0]$ (Eq. 2) and the normal likelihood $y_n \sim N[\mu_n, \sigma_n^2/n]$ (Eq. 7) belong to the same family of mathematical functions, we have thus defined a "conjugate normal model" [7]. Derivation of the appropriate equations yields the posterior mean $(m_0\mu + ny_n)/(m_0 + n)$ as an average of the prior mean μ and parameter estimate y_m, weighted by their respective number of observations n and m_0, and is thus a compromise between the 2 [7].

Bayesian Hierarchical Model

Since the initial goal was to compare CABG with PCI described by 9 studies of diabetics with multivessel CAD [2,3,8-14], we believed that a hierarchical model would also be reasonable because the estimates of θ from each study might be related to each other [19]. This is modeled by viewing θ_i from each study as a sample from a common population distribution, which has been described in detail elsewhere [20].

Software

Under specified prior distributions, the posterior distributions of model parameters were obtained by the Gibbs sampling algorithm [21] using [R] 3.0.2 [22], BRugs [23], OpenBUGS 3.2.2 (www.openbugs.net/w/Downloads), and Markov chain Monte Carlo methods [16]. Sample software codes are presented (Supplemental Appendix).

RESULTS

The primary outcome measure of the current study was the comparison of mortality rates at 5 years or longest follow-up after CABG or PCI in diabetic patients with multivessel CAD.

Pooled Conjugate Normal Model

Using a prior distribution elicited from the 8 trials [2,8-14] carried out before the publication of FREEDOM (Table **1**) and using σ = 2 (Eq. 5), we calculate the "pooled" results for the distribution by summing the *m*s from the individual trials (Table **1**) to obtain a total m_0 = 227. The pooled results give rise to a prior distribution with treatment effect μ = -0.604 (Eq. 3), m_0 = 227, a standard error $\sigma/\sqrt{227}$ = 0.133, and

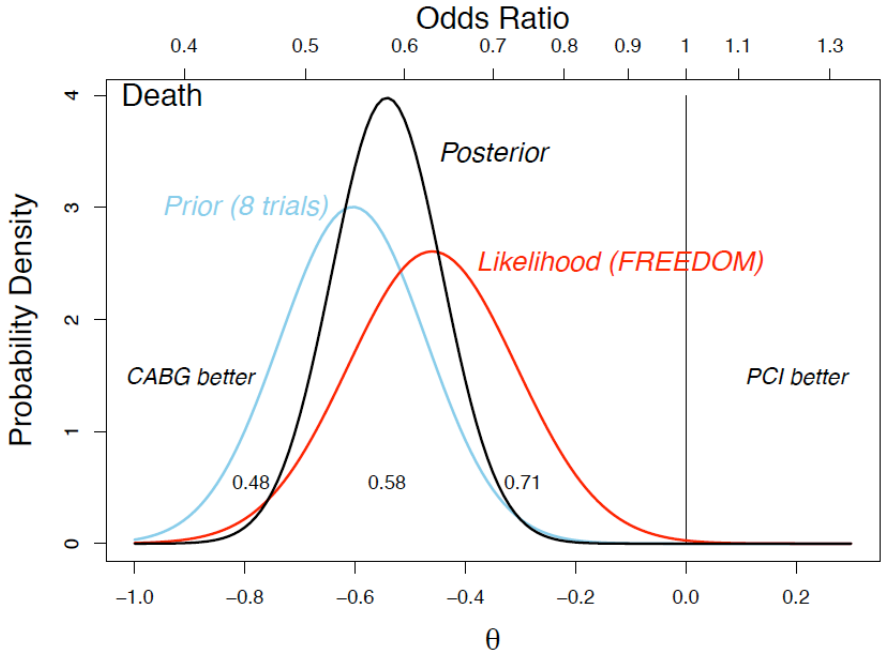

Figure 2: Bayesian Triplot Comparing Death Rates in Diabetic Patients after Coronary Artery Bypass Graft (CABG) Surgery or Percutaneous Coronary Intervention (PCI). A bell-shaped curve represents the prior distribution (blue) of possible odd ratios (ORs) based on evidence elicited from previous trials [2,8-14], and a separate curve represents the distribution of likelihood (red) obtained from the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) [3]. Bayesian methods update the prior with the likelihood in a type of meta-analysis to produce the posterior distribution (black). The posterior is not twice the height of the prior and likelihood, because precision represented by density width is additive. The additional vertical axis intersects the origin (0.00). All probability density functions are normalized to 1. The plot contains an x-axis showing the familiar OR, as well as an axis showing $\log_e$(OR), which equals θ.

variance *V* of 0.018 = 0.133^2 (Eq. 4). The 95% CI for μ of -0.604 are given by $\pm 1.96 \times \sigma / \sqrt{227} = \pm 0.260$, which gives rise to values extending from -0.863 to -0.343. Exponentiation of μ of -0.604 and its 95% CI generates values for the prior *OR* of 0.55 with 95% CI extending from 0.42 to 0.71 (Figure **2**).

The likelihood calculated from FREEDOM (Table **1**) gives rise to values for the *OR* of 0.63 with 95% CI extending from 0.47 to 0.85 (Figure **2**). Because the strength of information in the likelihood is based $n = \sigma^2 / 0.153^2 = 171$ observations, and the strength of information in the prior distribution is based on $m_0 = \sigma^2 / 0.133^2 = 227$ observations, the prior has approximately $m_0 / n = 227 / 171$ or 32% more information than the likelihood.

The posterior distribution (Figure **2**), which is based on the equivalent number of observations in the posterior of $m_0 + n = 398$, yields an *OR* of 0.58 with 95% BCI extending from 0.48 to 0.71. This suggests that in a pooled model, the mortality rate of diabetic patients with multivessel CAD after treatment with CABG has a 95% probability being 29% to 52% lower than that after PCI.

Conjugate Normal Model Weighted by Stent Type

Because early studies did not incorporate newer advances in revascularization that have appeared during the past 10 years, it is reasonable to down-weight older trials by adjusting the prior "number of events" from *m* to αm, where α is a normalizing factor [18]. With this approach, α can be subjectively set to 0, 0.1, 0.5 and 1.0. Assigning α = 0 is equivalent to assessing the results of a previous trial as irrelevant and similar to selecting a uniform prior on the $log_e(OR)$, while assigning α = 1 is equivalent to assessing full weight to the trial in the pooled analysis [18].

In a model that discounts studies by use of DES, α can range from 0.0 for BARI [2] to 1.0 for SYNTAX (Table **2**) [13]. The model (Eq. 6) gives rise to a prior distribution with $\mu_{weighted}$ = -0.54 with 95% CI extending from -0.92 to -0.15. The CI are broader in the weighted model than in the pooled model, because the effective number of observations has decreased from m_0 = 227 to αm_0 = 105. Exponentiation of $\mu_{weighted}$ from the posterior distribution and its 95% BCI generates an $OR_{weighted}$ of 0.61 with 95% BCI extending from 0.48 to 0.78 (Figure **3**).

Conjugate Normal Model Weighted by Study Age

In a model that discounts studies by year of publication, α can range from 0.0 for the BARI trial to 1.0 for contemporary studies (Table **2**). This gives rise to a prior distribution with $\mu_{weighted}$ = -0.42 with 95% CI extending from -0.74 to -0.10, with an effective number of observations of 148. Carrying the prior through the posterior yields an $OR_{weighted}$ of 0.64 with 95% BCI extending from 0.52 to 0.80 (Figure **3**).

Table 2: Data for Weighted Bayesian Models

Reference	Publication year	CABG	PCI	Study weight (α)		
		IMA Graft (%)	*PTCA/BMS/DES (%)*	*DES*	*Age*	*LIMA*
BARI [2]	1997	81	98/0/0	0.0	0.0	0.1
ARTS [8]	2001	93	11/89/0	0.0	0.1	0.5
ERACI II [9]	2005	89	0/100/0	0.0	0.5	0.1
MASS II [10]	2007	95	19/81/0	0.0	0.5	1.0
SoS [11]	2002	97	0/100/0	0.0	0.1	1.0
CARDia [12]	2010	94	0/31/69	0.5	1.0	0.5
SYNTAX [13]	2013	97	0/0/100	1.0	1.0	1.0
VA CARDS [14]	2013	[a]	0/0/100	1.0	1.0	0.0
FREEDOM [3]	2012	94	0/0/100	—	—	—
Posterior Distribution:						
Odds Ratio				0.61	0.64	0.64
95% BCI				0.48–0.78	0.52–0.80	0.51–0.81
m				105	148	125

The *m*'s are the "effective number of events" in the pooled analysis. [a]Arterial conduit used when possible.

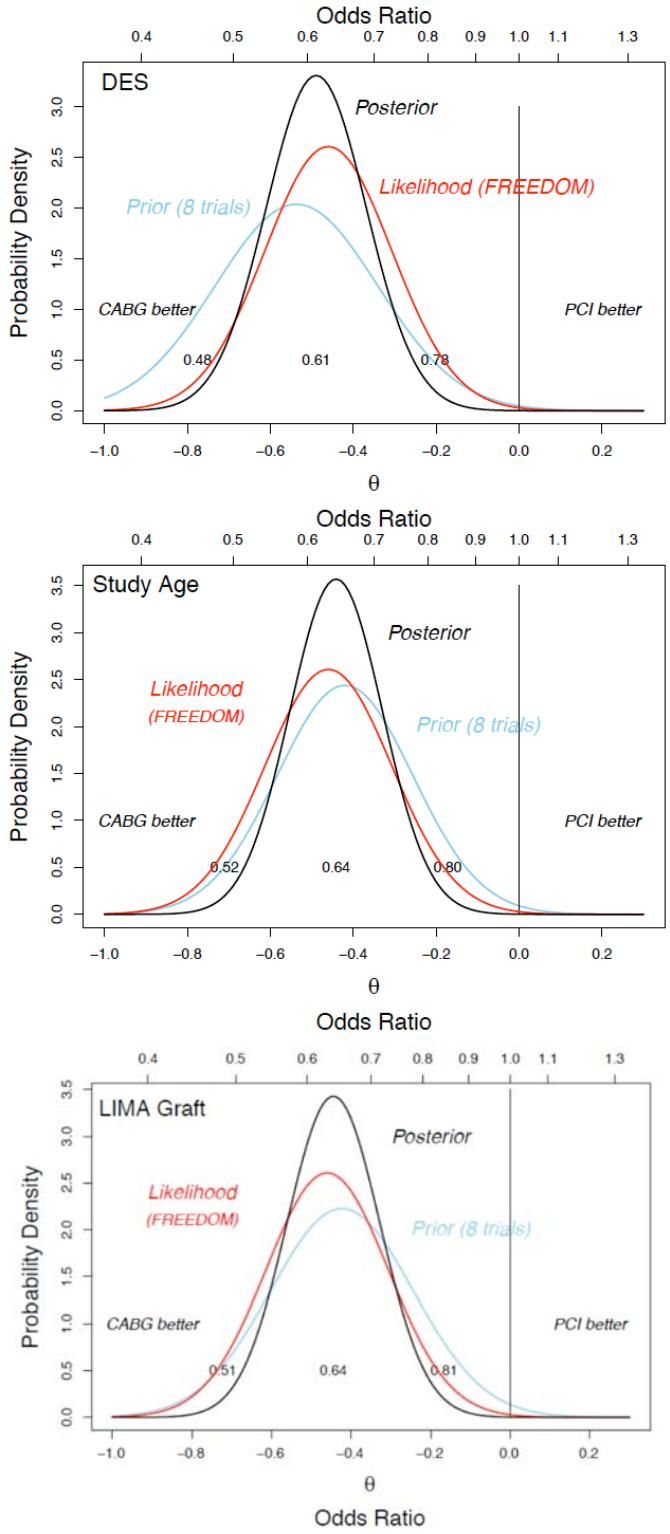

Figure 3: Bayesian Triplots Comparing Death Rates in Diabetic Patients after Coronary Artery Bypass Graft (CABG) Surgery or Percutaneous Coronary Intervention (PCI) in a Weighted Analysis. Prior distributions (solid light blue) are elicited from 8 studies [2,8-14] and weighted by the proportion of patients receiving a drug-eluting stents (DES) during percutaneous coronary intervention, age of study, and proportion of surgical patients treated with left internal mammary (LIMA) graft. The likelihood (solid red) is obtained from the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease trial[3]. The posterior distributions (black) contain the posterior mean odd ratios and their 95% Bayesian credible intervals (data labels). The most obvious difference between traditional frequentist and Bayesian methods is that frequentist statistics uses only unweighted data, whereas Bayesian statistics uses both the likelihood and weighted prior information. Details of weighting are presented in Table **2**. All probability density functions are normalized to 1. The parameter θ is equivalent $\log_e(OR)$.

Conjugate Normal Model Weighted by Use of LIMA Grafts

In a model that discounts by the proportion of LIMA grafts used in surgical patients, α can range from 0.1 for studies with less than 90% use, 0.5 for 90–95% use, and 1.0 for greater than 95% use (Table **2**). This gives rise to a prior distribution with $\mu_{weighted}$ = -0.42 with 95% CI extending from -0.77 to -0.18, with an effective number of observations of 125. Carrying the prior through the posterior yields an $OR_{weighted}$ of 0.64 with 95% CI extending from 0.51 to 0.81 (Figure **3**).

Bayesian Hierarchical Meta-Analysis

A Bayesian hierarchical meta-analysis using a non-informative prior distribution for all 9 studies produces a posterior mean odds ratio of 0.55 with 95% BCI of 0.37–0.76 (Figure **4**). The broader 95% BCI seen in the hierarchical model than in the normal conjugate model (0.48–0.71) represents the effect of "borrowing" from the informative prior in the normal conjugate model.

It may be instructive to compare the results of the Bayesian hierarchical meta-analysis with a traditional meta-analysis (Figure **4**) of the 9 studies of patients with DM and multivessel CAD (N=3,484 patients). The latter approach using a random effects model produces a pooled odds ratio and 95% confidence interval favoring the use of CABG over PCI to improve survival (0.54, 0.38–0.76), in good agreement with the Bayesian hierarchical meta-analysis using a non-informative prior distribution (0.54, 0.38–0.76)

DISCUSSION

The issue of identifying whether CABG is superior to PCI for diabetic patients with multivessel CAD is larger than the results from an individual trial or a meta-analysis of several trials. A Bayesian approach uses the process of inductive inference, which is similar to the way that clinicians make a diagnosis from clinical evidence at the bedside [24]. Clinicians know, for example, that an elevated troponin does not always equate with myocardial infarction [25]. The Bayesian approach treats clinical trial results like a troponin elevation and puts new trial results (ie, *OR*) into the context of what is already known from previous studies to define the probability distribution for the parameter θ that governs the underlying treatment effect (eg, lower mortality after CABG than after PCI).

Clinical Guidelines

The current American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline states that [26]:

Class I — CABG is generally recommended in preference to PCI to improve survival in patients with diabetes mellitus and multivessel CAD for which revascularization is likely to improve survival (3-vessel

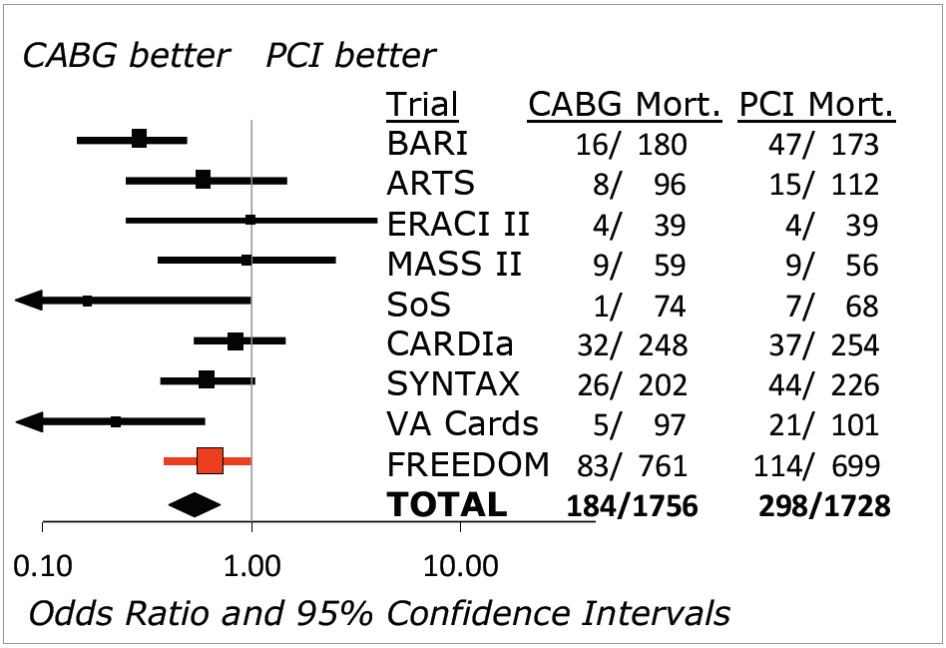

Figure 4: Forest Plot of Studies Comparing Coronary Artery Bypass Graft (CABG) Surgery with Percutaneous Coronary Intervention (PCI) in Diabetic Patients with Multivessel Coronary Artery Disease.

CAD or complex 2-vessel CAD involving the proximal LAD), particularly if a LIMA graft can be anastomosed to the LAD artery, provided the patient is a good candidate for surgery. (Level of Evidence: B)

A Class I recommendation for CABG in diabetics with multivessel coronary artery disease suggests that the benefits clearly outweigh risk in most, if not all, diabetic patients with multivessel CAD. A suggestion of a positive result in overall survival in FREEDOM [3] signifies that CABG appeared to confer greater survival than did PCI in a single cohort of patients at a single point in time.

FREEDOM

The FREEDOM trial was a dedicated trial in a diabetic population with multivessel CAD designed test the hypothesis that CABG is superior to PCI. The primary endpoint of all-cause death MI, or stroke occurred less frequently in the CABG group than in the PCI group (18.7% vs. 26.6%, $P = 0.005$). The benefit of CABG was driven by differences in rates of both myocardial infarction ($P < 0.001$) and death from any cause ($P = 0.049$). The significance of the survival advantage for CABG has remained controversial, however, because a final P value of less than 0.044 was considered to indicate statistical significance for the primary outcome after 3 interim analyses had been performed [3].

Current Analysis

The current analysis used several Bayesian approaches. The results of the normal conjugate model favored the use of CABG over PCI for diabetic patients with multivessel CAD. In a sensitivity analysis, models weighted by the use of DES, study age and use of arterial conduits also favored the use of CABG over PCI for diabetic patients with multivessel CAD.

LIMITATIONS

Limitations of the current study include the possibility of "hindsight bias," because we assessed the prior distribution after seeing the report of Verma and colleagues [4] and the 2011 clinical guidelines for revascularization [15]. However, we carried out the current analysis prospectively and concurrently with the creation of the 2014 focused update of the guidelines for the diagnosis and management of patients with stable ischemic heart disease [26]. To complete the analysis, we assumed that the RCTs were exchangeable [29], because the studies were of the same fundamental design and all trial and subgroups analyses dealt with diabetic patients with multivessel CAD. Another potential limitation of the current analysis involves the changes in treatments introduced during the past 20 years in which the various RCTs were conducted. For example, BARI used PTCA [2], 4 studies used bare-metal stents (BMS) [8-11], and 4 studies used DES [3, 7, 12-14]. We dealt with the issue of multiplicity of treatments by performing sensitivity analysis. The subjective nature of the weighting parameter α used in the sensitivity analysis is also recognized. Accordingly, we recognize that the sensitivity analyses involving DES, study age and the use of the LIMA grafts must be considered exploratory.

SUPPLEMENTAL MATERIALS

The supplemental materials can be downloaded from the journal website along with the article.

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