Bayesian Analysis
A Practical Approach to Interpret Clinical Trials and Create Clinical Practice Guidelines

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Abstract—Bayesian analysis is firmly grounded in the science of probability and has been increasingly supplementing or replacing traditional approaches based on *P* values. In this review, we present gradually more complex examples, along with programming code and data sets, to show how Bayesian analysis takes evidence from randomized clinical trials to update what is already known about specific treatments in cardiovascular medicine. In the example of revascularization choices for diabetic patients who have multivessel coronary artery disease, we combine the results of the FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) with prior probability distributions to show how strongly we should believe in the new Class I recommendation ("should be done") for a preference of bypass surgery over percutaneous coronary intervention. In the debate about the duration of dual antiplatelet therapy after drug-eluting stent implantation, we avoid a common pitfall in traditional meta-analysis and create a network of randomized clinical trials to compare outcomes after specific treatment durations. Although we find no credible increase in mortality, we affirm the tradeoff between increased bleeding and reduced myocardial infarctions with prolonged dual antiplatelet therapy, findings that support the new Class IIb recommendation ("may be considered") to extend dual antiplatelet therapy after drug-eluting stent implantation. In the decision between culprit artery-only and multivessel percutaneous coronary intervention in patients with ST-segment elevation myocardial infarction, we use hierarchical meta-analysis to analyze evidence from observational studies and randomized clinical trials and find that the probability of all-cause mortality at longest follow-up is similar after both strategies, a finding that challenges the older ban against noninfarct-artery intervention during primary percutaneous coronary intervention. These examples illustrate how Bayesian analysis integrates new trial information with existing knowledge to reduce uncertainty and change attitudes about treatments in cardiovascular medicine. **(*Circ Cardiovasc Qual Outcomes*. 2017;10:e003563. DOI: 10.1161/CIRCOUTCOMES.117.003563.)**

Key Words: Bayes theorem ■ diabetes mellitus ■ probability ■ statistical distributions ■ statistics

"The past is prologue."

—William Shakespeare, in *The Tempest*

Two prominent schools of thought exist in statistics: the Bayesian and the classical (also known as the frequentist). The Bayesian approach, which is based on a noncontroversial formula that explains how existing evidence should be updated in light of new data,[1] keeps statistics in the realm of the self-contained mathematical subject of probability in which every unambiguous question has a unique answer—even if it is hard to find.[2] The classical approach, which relies on a frequency definition of probability based on long-run properties of repeated events, is grounded in the concept of the *P* value and may sometimes entail several reasonable approaches that yield different answers based on the question at hand.[1,3–5]

Meaning of the *P* Value

The concept of the *P* value dates to the 1920s and 1930s, when statisticians recognized that the bell-shaped curve can represent the distribution of a test statistic for all possible outcomes of an experiment, given that the null hypothesis H_0 is true. Sir Ronald Fisher reasoned that a small *P* value corresponding to the tail under the frequency-distribution curve meant that either an exceptionally rare outcome of an experiment had occurred, or the H_0 was not true.[6]

To many practitioners and some statisticians, a *P* value of 0.05 means that there is a 95% chance that the null hypothesis H_0 is false. This is understandable but wrong because the *P* value is calculated on the assumption that the H_0 is true.[4] The upshot is that the *P* value is NOT the probability that H_0 is true, and $1-P$ is NOT the probability that the alternative hypothesis H_A is true.[1,7] Instead, the *P* value is the proportion of times an observed event, or a more extreme event, will occur in a series of repetitions, given that the null hypothesis is true. In practice, the *P* value defines an error limit that prevents a statistician from wrongly rejecting a true H_0 only ≈5% of the time in the long run in, say, his or her career.[1]

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Re-Emergence of Bayesian Analysis

Bayes' rule predated the use of *P* values by ≈150 years, but frequentist approaches have predominated statistical analysis for most of the past century. During the past 30 years, several scientific disciplines like engineering,[2] astrophysics,[8] and genetics[9] have supplemented or replaced frequentist statistics with Bayesian approaches.

In clinical reasoning, Bayes' rule is crucial for explaining how the probability of disease depends on both pretest probability and a test result (Appendix A in the Data Supplement).[3] Bayesian analysis is now appearing in clinical trials, and in a major shift, the American College of Cardiology and American Heart Association have recently proposed using Bayesian analysis to create clinical practice guidelines.[10] In an early exercise, Bayesian methods supported the usefulness of percutaneous coronary intervention (PCI) for left main coronary artery disease (Appendix B in the Data Supplement).[11]

Bayesian Methods for Clinical Trial Analysis

If we suppose that θ is a theoretical parameter denoted by the log odds ratio (OR), $\log_e \mathrm{OR}$, which summarizes the mortality difference between a new therapy and control, prior knowledge about θ from existing randomized clinical trials (RCTs) is denoted by $p(\theta)$. The prior probability $p(\theta)$ may take the form of a bell-shaped curve to show that some values of θ are more probable than others. When we observe some new trial evidence y, which is commonly presented in the form of an OR but for mathematical consistency analyzed as $\log_e(\mathrm{OR})$ and presumed to be conditional on θ, we represent the relation by $p(y|\theta)$ and call it the likelihood.[1–3,12,13]

In Bayesian analysis, θ is a random variable, but in frequentist statistics, the parameter θ is a fixed but unknown value.[1,12] In both statistical approaches, y depends on θ, but in a Bayesian framework, the likelihood $p(y|\theta)$ describes the conditional probability of y for each possible value of θ. The likelihood may assume any mathematical function, but continuous data are commonly represented with a normal distribution (N):

$$\log_e(\mathrm{OR}) \sim \mathrm{N}[\theta, V], \tag{1}$$

where θ represents the underlying hypothesis about the treatment effect and V is its variance (Appendix B in the Data Supplement).[1–3,12,13]

To see how a new trial updates our understanding of θ, we need to move from the probability of the new data y given the underlying hypothesis θ to the probability of the underlying hypothesis θ given the new data y,[13] and this is achieved by using Bayes' theorem[2,3]:

$$\begin{aligned} p(\theta|y) &= \frac{p(y|\theta)\cdot p(\theta)}{p(y)}, \\ &= \frac{p(y|\theta)\cdot p(\theta)}{\sum p(y|\theta)\cdot p(\theta)}, \\ &= \frac{p(y|\theta)\cdot p(\theta)}{\int p(y|\theta)\cdot p(\theta)\cdot d\theta}. \end{aligned} \tag{2}$$

The posterior $p(\theta|y)$ on the left-hand side of the equation increases when there is a strong pre-existing belief in the hypothesis θ or strong new evidence y. The denominator, given by various forms of $p(y)$, plays a normalizing role so that $p(\theta|y)$ integrates to 1. The importance of normalization emerges in a familiar example from clinical reasoning when the number of true positives is divided by the sum of true and false positives to calculate $p(\theta|y)$, which is the probability of disease θ given a test result y (Appendix A in the Data Supplement).

Bayesian analysis often entails complex computations. Until recently, user-friendly software had been scarce, but the availability of high-speed laptop computers and Markov chain Monte Carlo modeling has made the approach more accessible. For the practitioner considering Bayesian analysis, minimal requirements include a dim knowledge of basic calculus,[13] the ability to think in logarithms, and the allure of writing code for statistical programs like [R],[14] an open-source program that links applications running Bayesian inference Using Gibbs Sampling (BUGS). As a benefit, [R] is free of charge, capable of generating stunning graphics, and ready to install (Appendix B in the Data Supplement).

The present review starts with a simple example that uses normal probability distributions to illustrate how Bayesian analysis combines information from various sources. This is followed by gradually more complex examples that use hierarchical, network, and cross-design analyses to tackle issues that may not be amenable to traditional statistics. The aim of the review is (1) to identify parallels between Bayesian and traditional approaches and (2) to describe statistical tools firmly grounded in probability that help to discover what works in cardiovascular medicine.

Methods

To perform traditional meta-analyses, we use the open-source statistical program [R] 3.0.3[14] and library package meta 3.8-0.[15] To generate conjugate-normal models, we combine normal probability distributions from older trial data (prior) and new trial results (likelihood) to generate the posterior (Appendix C in the Data Supplement).[3] To perform more complex computations, we use a version of BUGS called OpenBUGS[13,16] that allows Markov chain Monte Carlo modeling to specify the posterior distribution (Appendixes D and E in the Data Supplement). In the Data Supplement, we show how BRugs[16] connects [R] with OpenBUGS to draw samples from any posterior distribution. When we use Markov chain Monte Carlo modeling, we base the posterior inference on 10 000 draws of the Gibbs chain.[3,13]

Results

What Form of Revascularization Is Preferred for Diabetic Patients With Multivessel Coronary Artery Disease?

Conjugate-Normal Analysis

For patients with diabetes mellitus and multivessel coronary artery disease (CAD) requiring revascularization, the 2011 guideline stated that,[17] "Coronary artery bypass graft (CABG) surgery is probably recommended in preference to PCI to improve survival in patients with multivessel CAD and diabetes mellitus, particularly if a LIMA graft can be anastomosed to the LAD artery (Class IIa; Level of Evidence B)."

In 2012, the results of the FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes

Mellitus: Optimal Management of Multivessel Disease) appeared.[18] Although FREEDOM was a dedicated trial of diabetic patients with multivessel CAD, the finding of borderline lower mortality after CABG than after PCI at 5 years (relative risk, 0.63; P=0.049) was not considered definitive, because a P value of 0.044 was predefined as the cutoff for the primary end point, and the trial was not powered for mortality.[18]

A traditional meta-analysis of 8 trials including FREEDOM suggested that CABG was superior to PCI, but only 2 of 8 trials had significant P values favoring surgery.[19] To show how strongly the borderline results from FREEDOM changed the probability of surgical superiority, we use Bayesian analysis to establish[20,21]:

- the plausibility of a surgical advantage based on evidence from older RCTs (the prior distribution),[22–29]
- support for a surgical advantage from the FREEDOM trial itself (likelihood),[18] and a
- final opinion about the advantage of CABG over PCI (the posterior distribution).

As outlined in the Table and detailed in Appendix C in the Data Supplement, Bayesian methods combine information from different sources and generate a posterior inference that is a compromise between the prior and the data.[1] As shown in Figure 1, the posterior inference contains a maximum (mode) at 0.58 with a 95% Bayesian credible interval (BCI) that extends from 0.48 to 0.71.

Compared with traditional statistics, which uses a frequency definition of probability for the null hypothesis H_0, Bayesian analysis generates direct probability statements about the treatment hypothesis, which is arguably more interesting than the null. In this instance, the Bayesian approach identifies with 95% probability that mortality is 29% to 52% lower after CABG than it is after PCI. More precisely, the Bayesian approach identifies with 99.9%, 99.9%, and 96.8% probabilities that mortality rates are at least 10%, 20%, or 30% lower after CABG than they are after PCI. The strength of evidence for CABG can also be expressed by the Bayes factor, which uses small values close to 0.00 to simultaneously provide strong evidence against the H_0 and for the H_A (Appendix C in the Data Supplement).[3,31] In this exercise, the Bayes factor is 0.01, a value that is defined as decisive evidence favoring CABG.[3]

Skeptical and Noninformative Priors

Some critics are concerned that selecting a prior for Bayesian analysis is a subjective process, but 8 RCTs are the source of evidence for the prior in the present example (Figure 1A). If we think that this prior is too enthusiastic, we can repeat the analysis using a skeptical prior centered at a θ of 0.00 to

Table. Components of Analysis

	Clinical Example		
	Revascularization Choices in Diabetic Patients	Duration of DAPT After DES Implantation	Primary PCI Strategies in Patients With STEMI
Intervention	CABG vs PCI	DAPT for 3–12 mo, 12 mo, or 18–48 mo	Culprit vessel-only vs multivessel PCI
Population	Diabetic patients with multivessel CAD	Patients undergoing DES implantation	Patients with STEMI and multivessel CAD
Evidence source	RCT and RCT subgroups	RCTs	RCTs and observational studies
Outcome measure	Mortality at longest follow-up	Mortality, bleeding, MI, and ST	Mortality at longest follow-up
Prospective analysis?	No	No	No
Bayesian model	Conjugate normal	Network meta-analysis	Cross-design meta-analysis
Data tables and programming code	Appendix C in the Data Supplement	Appendix D in the Data Supplement	Appendix E in the Data Supplement
Prior specification	External evidence	Noninformative: $N\left[0, 10^3\right]$	Vague: $\theta \sim N[0, 10]$, $\tau_k \sim HN\left[0.36^2\right]$, and $\sigma \sim HN\left[0.18^2\right]$
Statistical model	Approximate normal distribution of $\log_e$(OR)	3-node network	3-level hierarchical
Estimation approaches	Conjugate normal[3]	MCMC modeling[3,13]	MCMC modeling[3,13]
Interpretation	Confirmatory for a preference of CABG over PCI	Reduced concern for increased mortality with prolonged DAPT	Reduced concern for mortality difference between strategies
Sensitivity analysis	Skeptical and noninformative prior[21]	None	Different weights for RCTs and observational studies[30]

CAD indicates coronary artery disease; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; $HN\left[0.18^2\right]$, half-normal distribution, based on a 95% belief that the underlying risk ratio for a particular study type will <2× or >½ the overall population effect[3]; $HN\left[0.36^2\right]$, half-normal distribution, based on 95% belief that the true underlying OR for a study of a particular type will be <4x or >1/4 the overall OR of that type[3], MCMC, Markov chain Monte Carlo; $N\left[0, 10^3\right]$, normal distribution centered on 0 with variance (1/precision) of 10^3; OR, odds ratio; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; ST, stent thrombosis; and STEMI, ST-segment–elevation myocardial infarction.

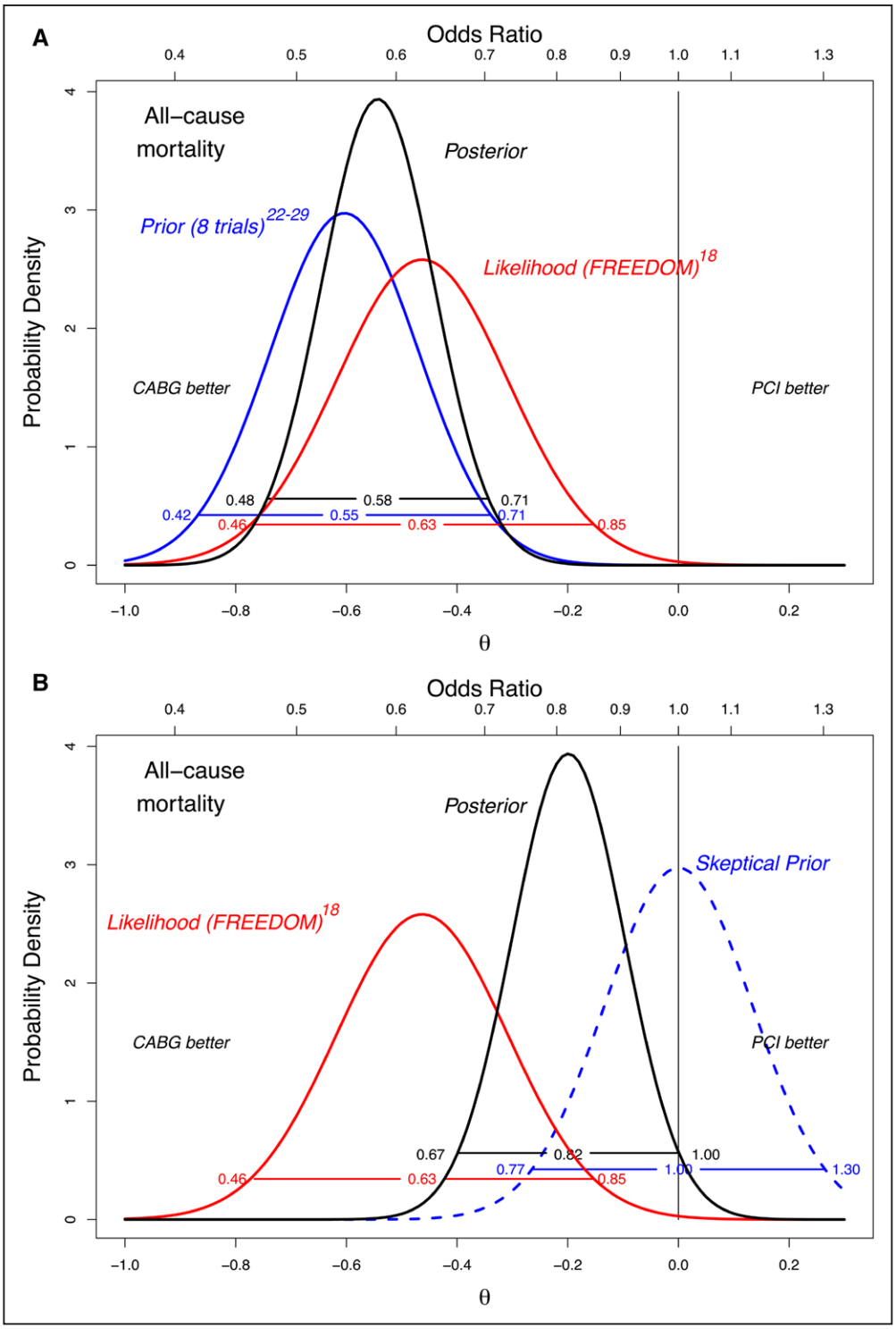

Figure 1. Bayesian triplot of mortality risk after percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in diabetic patients with multivessel coronary artery disease. **A**, Each triplot contains 3 normal distributions and thus illustrates a conjugate-normal analysis, plotted on the odds ratio (OR) scale and on the θ, or $\log_e$(OR), scale. The prior distribution (blue), represented by a bell-shaped curve derived from evidence from 8 older trials,[22–29] strongly suggests a mortality advantage for CABG over PCI. The likelihood (red), representing the results from FREEDOM trial (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease),[18] still favors CABG but less so than the prior. Bayesian methods, which combine the likelihood with the prior to produce the posterior distribution (black), confirm a mortality advantage for CABG. **B**, A skeptical prior (dashed blue), which is centered on an OR of 1.00, results in a posterior distribution that shifts to the right and provides borderline support for a surgical advantage. All curves normalized to 1. Part figure (**A**) is adapted with permission from the American Heart Association.[20,21] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

simulate the null hypothesis and find weaker (posterior OR, 0.82; 95% BCI, 0.67–1.00) but credible support for CABG over PCI (Figure 1B).

If we start with even greater indifference about the superiority of CABG and use a noninformative prior to reflect the belief that all values of θ are equally likely (ie, equipoise), we let the likelihood of the data dominate the posterior inference. When this happens, we get a remarkable result. As shown in Figure 2, a Bayesian hierarchical meta-analysis that starts with a noninformative prior generates a posterior inference (posterior OR, 0.55; 95% BCI, 0.37–0.76) that converges with the result obtained in a traditional meta-analysis (OR, 0.54; 95% confidence interval, 0.38–0.76). Such coincidences are expected when the traditional random-effects model uses an empirical Bayesian approach to estimate between-trial variation.[32] The similarity turns out to be a convenience for practitioners who erroneously use Bayesian language to describe traditional confidence intervals.[3]

Strength of Evidence

In a normal distribution, the strength of evidence is represented by curve width. Narrower curves exclude more values for θ and thus represent stronger sources of evidence than broader curves.[1] Compared with a noninformative prior or a traditional meta-analysis (Figure 3), an informative prior usually produces tighter intervals in the posterior inference, because the posterior borrows information from the prior.[3]

The present example illustrates strengths and limitations of Bayesian analysis. Although a conjugate-normal model is not fully Bayesian, and a narrower interval does not automatically signify a superior approach,[3] an approach based on probability distributions overcomes the reliance on *P* values. Additional strengths include the ability to obtain direct probability statements about the treatment hypothesis and to see how changes in existing knowledge influence the interpretation of new data. Although this may not seem novel when the Bayesian result converges with the frequentist,[19] Bayesian analysis in this instance supports the new Class I recommendation in the American College of Cardiology/American Heart Association guideline update for a preference for CABG over PCI.[33] In the next section, we show how a Bayesian mixed-treatment analysis compares treatments indirectly when direct comparisons do not exist.

What Is the Optimal Duration of Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation?

Bayesian Network Meta-Analysis

Although aspirin and a platelet $P2Y_{12}$ inhibitor may prevent thrombotic complications after drug-eluting stent (DES) implantation, the combined use of 2 antiplatelet agents may increase bleeding. After an authoritative trial[34] found a borderline increase in all-cause mortality with prolonged dual antiplatelet therapy (DAPT), several investigators performed traditional meta-analyses to determine whether prolonged DAPT was associated with increased mortality using the pooled evidence from multiple RCTs, but results were mixed.[35–37] Because each individual RCT compared pairwise DAPT durations that varied widely (Figure 4),[34,38–50] with a DAPT duration of 12 months being defined as short in 4 trials[34,44–47] and long in 7 trials,[38–44] the traditional meta-analyses[35–37] contained several 12-month-versus-12-month comparisons.

Relative Differences

To compare outcomes using a coherent separation of DAPT durations, we define a network (Figure 4).[3] When the network is analyzed using methods outlined in the Table and Appendix D in the Data Supplement, we show in Figure 5 that mortality is not increased when DAPT increased from 3–6 to 12 months (OR, 1.06; 95% BCI, 0.76–1.40), from 12 to 18–48 months (OR, 1.19; 95% BCI, 0.88–1.63), or from 3–6 to 18–48 months (OR, 1.25; 95% BCI, 0.89–1.81). However, bleeding increases, and the risk of myocardial infarctions falls as the duration of DAPT increases (Figure 5).

The network findings provide reassurance that DAPT does not increase all-cause mortality. Furthermore, no differences in outcomes are seen after 3 to 6 months as compared with 12 months of DAPT in stable patients undergoing drug-eluting stent implantation (Figure 5). Together, these findings support the new Class I recommendation for using DAPT for 6 months after drug-eluting stent implantation in stable patients.[51]

Absolute Differences

To provide a practical perspective for the clinician, we calculate absolute event rates and numbers needed to treat (NNTs).[52] For every 1000 patients treated with 18 to 48 months compared with 3 to 6 months of DAPT, there are 6 more major bleeds (95% BCI, 4–14) but 9 fewer myocardial

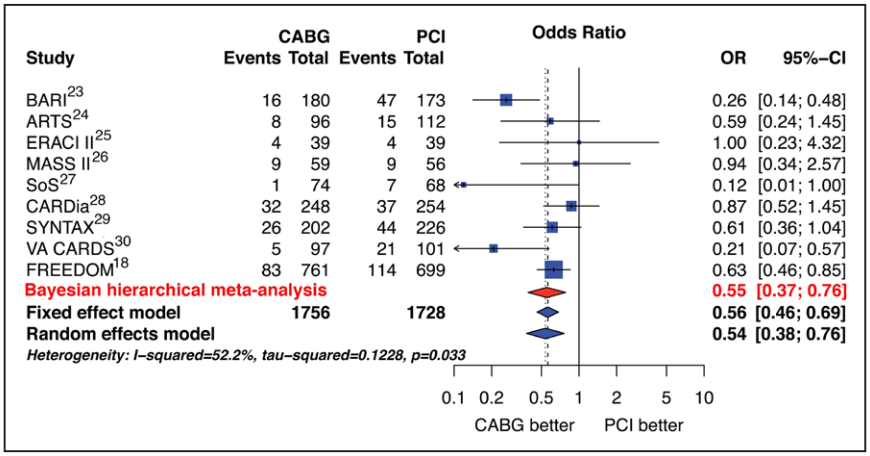

Figure 2. Traditional and Bayesian hierarchical meta-analysis of subgroup and trial evidence comparing percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery in diabetic patients with multivessel coronary artery disease. Adapted with permission from the American Heart Association.[21] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. CI indicates confidence interval; and OR, odds ratio.

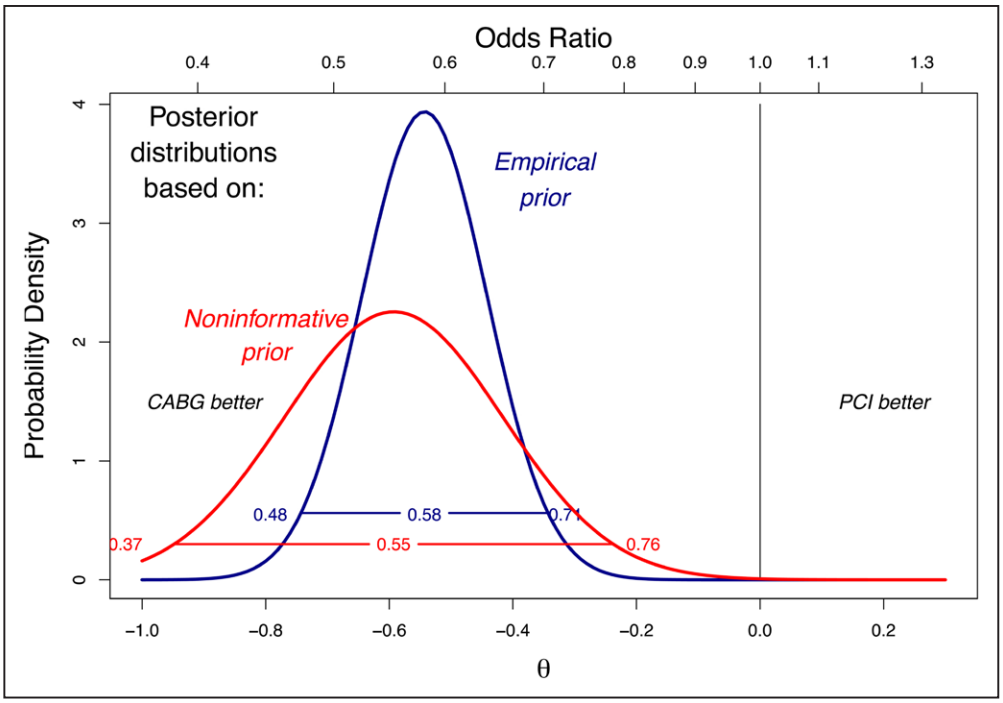

Figure 3. Comparison of posterior probability distributions derived from different prior probabilities distributions. CABG indicates coronary artery bypass graft; and PCI, percutaneous coronary intervention.

infarctions (4–16) and 4 fewer stent thromboses (3–8) for each additional 12 months of therapy.[52] As DAPT is prolonged, the corresponding NNT_{harm} for major bleeding is 165 (95% BCI, 65–537), the $NNT_{benefit}$ for preventing myocardial infarction is 117 (77–726), and the $NNT_{benefit}$ for preventing stent thrombosis is 282 (213–514). The findings support a Class IIb recommendation to prolong DAPT >12 months.[51]

The foregoing analysis uses evidence from RCTs, but in most areas of cardiovascular investigation, RCT evidence is limited or absent. In the next section, we illustrate how Bayesian methods synthesize evidence from disparate sources.

Should Noninfarct PCI Be Performed During ST-Segment–Elevation Myocardial Infarction?

Bayesian Cross-Design Meta-Analysis

Outcomes after culprit vessel-only or multivessel-vessel PCI in patients with ST-segment–elevation myocardial infarction and multivessel CAD have been compared in studies of multiple designs: RCTs, matched cohort, and observational studies.[53] RCTs are commonly viewed as having the highest quality, but cohort studies may be more representative of clinical practice.[10]

Traditional approaches using stratified meta-analyses can determine whether treatment outcomes are sensitive to study type. In stratified analyses,[53] observational studies tend to show that the culprit vessel-only arm has lower mortalities than the multivessel arm, although confounding cannot be excluded, whereas RCTs tend to show that the multivessel arm has lower event rates than the culprit vessel-only arm. A strategy using stratified meta-analyses may not yield a single inference for the overall treatment effect, however, because study designs are different and a power problem might arise from inclusion of small RCTs. Another approach is to use Bayesian cross-design methods.[3,30,54]

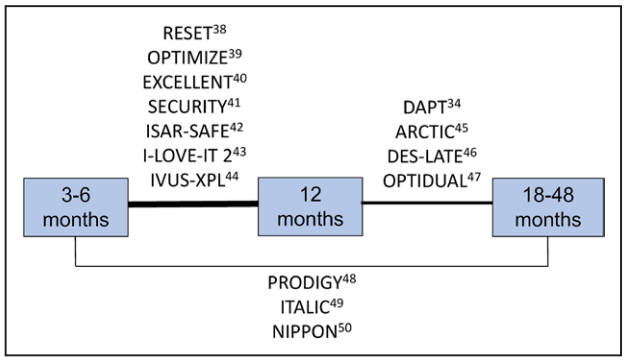

Figure 4. Network meta-analysis of dual antiplatelet therapy (DAPT). Each node represents a different DAPT duration and each line a different pairwise comparison.

Hierarchical Model for Analyzing Evidence From Different Study Designs

To compare mortality outcomes from all sources, we create a 3-level hierarchical model illustrated in Figure 6 and detailed in Appendix E in the Data Supplement that analyzes overall outcome as a function of treatment effect and study type. In the model, we assume[3]:

$$\begin{aligned} \log_e\left[\mathrm{OR}_{i(k)}\right] \mid \theta_{i(k)}, s^2_{i(k)} &\overset{\text{independent}}{\sim} \mathrm{N}\left[\theta_{i(k)}, s^2_{i(k)}\right], \\ \theta_{i(k)} \mid \theta_k, \tau^2_k &\overset{\text{independent}}{\sim} \mathrm{N}\left[\theta_k, \tau^2_k\right], \\ \theta_k \mid \theta, \sigma^2 &\overset{\text{independent}}{\sim} \mathrm{N}\left[\theta, \sigma^2\right], \end{aligned} \tag{3}$$

where $\theta_{i(k)}$ and $s^2_{i(k)}$ denote the study-level treatment effect and its variance, θ_k is the study-type average effect,

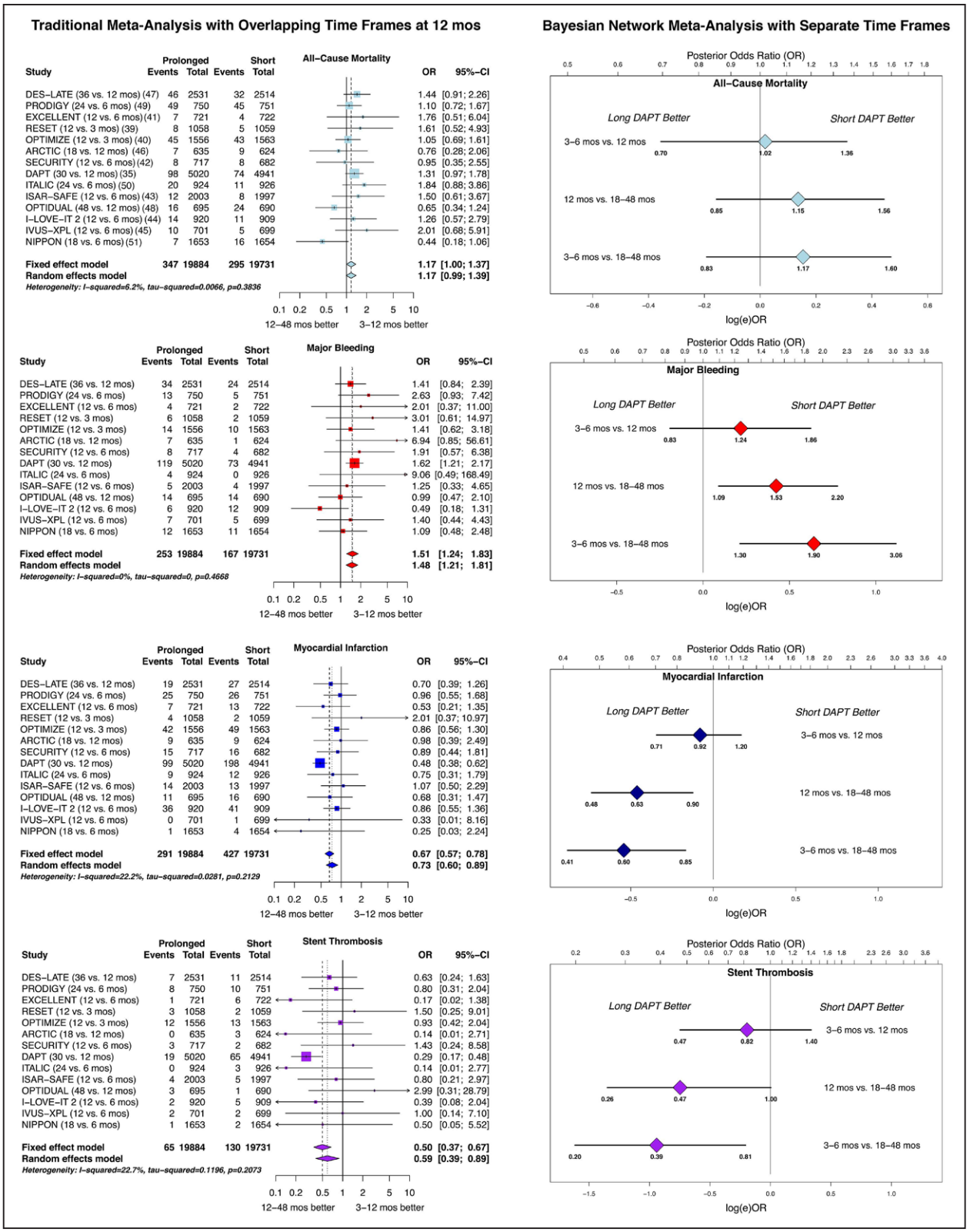

Figure 5. Traditional network meta-analyses of prolonged dual antiplatelet therapy (DAPT). The forest plots (**left**) contain several 12-mo-versus-12-mo comparisons of outcomes, whereas the caterpillar plots (**right**) compare outcomes after DAPT durations that do not overlap. All studies identified and referenced in Figure 4. CI indicates confidence interval.

τ_k^2 is the between-study variance for each design, θ is the global treatment effect viewed as an average across all possible studies (nested within all possible designs), and σ^2 is the between-study type variance for RCTs (k=1), matched cohort (k=2), and unmatched cohort (k=3) studies. The first 2 equations define the random-effects meta-analysis models

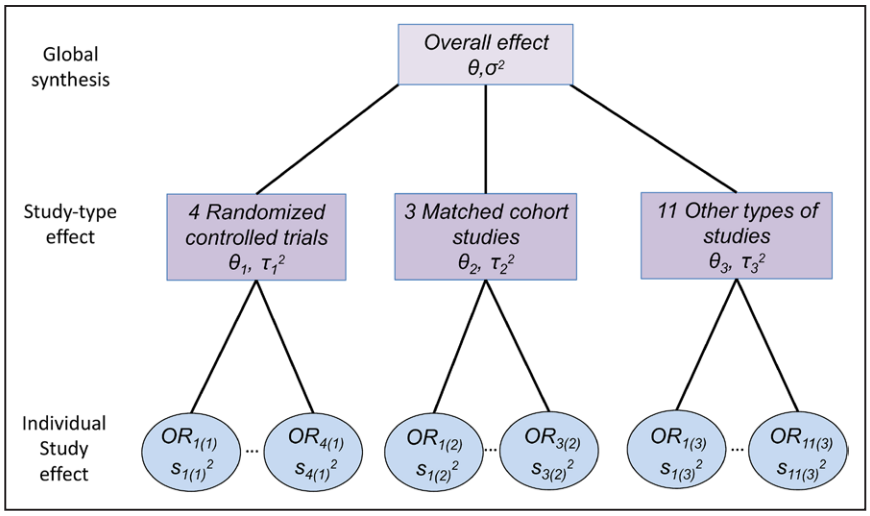

Figure 6. Hierarchical model. At the individual study level in the **bottom** row, the parameters include $OR_{i(k)}$ and variances s^2 from each study i=1,…, 18; in the **middle** level, the mean study-type effects θ_j and variances τ_k^2 from each study type k=1,…, 3; and, in the **top** level, the overall treatment effect θ and its variance σ^2. OR indicates odds ratio. Adapted with permission from John Wiley and Sons.[30] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

for studies separately within each design. The last equation treats the study-type averages as random effects from a normal distribution centered at the global average. The hierarchical model assumes that the θ_ks are exchangeable and conditional on θ and σ^2, whereas a traditional approach would have assumed that they are fixed and independent parameters.[3,54]

Using published guidance[3,54] to select priors that provide no advantage for 1 treatment strategy or study type over another (Table), we obtain a posterior inference that shows no

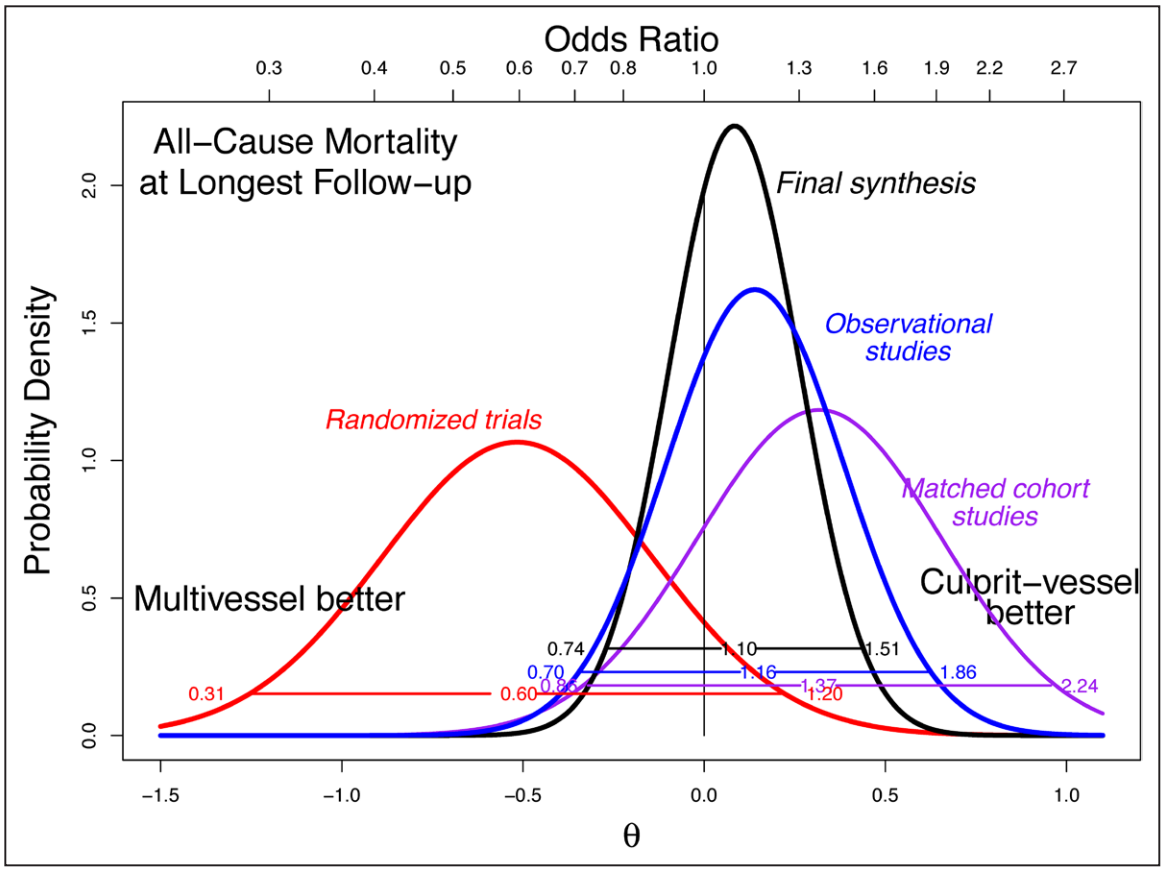

Figure 7. Mortality after multivessel or culprit vessel-only intervention for ST-segment–elevation myocardial infarction. Information sources segregated by study type are plotted on the odds ratio (OR) scale and on the θ scale, which is equivalent to $\log_e$(OR). Data from randomized controlled trials (red), which are represented by a bell-shaped curve to show the distribution of all possible ORs, tend to favor the strategy of multivessel intervention, whereas data from matched cohort studies (purple) and from the unmatched observational studies (blue) tend to favor the strategy of culprit vessel-only intervention. The final synthesis (black), which combines the data from all studies and generates the posterior median OR and 95% Bayesian credible interval (data labels), suggests no plausible difference in mortality rates after a strategy of multivessel or culprit artery-only intervention at the time of primary intervention. All curves are normalized to 1. Adapted with permission from John Wiley and Sons.[30] Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

credible difference in the end point of all-cause mortality after culprit artery-only compared with multivessel PCI (OR, 1.10; 95% BCI, 0.74–1.51), as shown in Figure 7. When we use priors that weight RCTs over observational studies by a factor that ranges from 1 to 5, we obtain an estimate closer to 1.00 (OR, 1.05; 95% BCI 0.64–1.48).[30]

The overall findings support the decision made by members of the writing committee to replace the old Class III prohibition against nonculprit PCI[17] with a new Class IIb recommendation allowing nonculprit artery PCI.[55] The process of synthesizing RCT and observational evidence does not change the overall estimate of the mortality difference between the different strategies but rather increases the confidence that no difference likely exists.[3]

Conclusions

Analogous to making a clinical diagnosis, deciding what works in clinical investigation can be challenging. Bayesian analysis quantifies the probability that a study hypothesis is true when it is tested with new data. Although *P* values may ensure that trial results in which we are 95% confident are correct 95% of the time in the long run,[31] *P* values cannot capture the effect size or the evidential meaning of an outcome.[6] Bayesian analysis replaces the dependence on a single number and moves the interpretation of trial results into the world of probabilities based on prior knowledge.[6]

By giving writing committees tools for dealing with the uncertainty of trial results, Bayesian methods are useful for analyzing observational studies,[56] mega-trials,[6] and noninferiority trials by treating H_0 and H_A equivalently by accepting the null rather than failing to reject it. Because many experts rightly demand a higher threshold than 2 SEs in post hoc exercises like meta-analyses, Bayesian methods may raise the bar for declaring that a finding is significant.[31]

In presenting vignettes in this review that illustrate the use of Bayesian approaches for the analysis of trial results, we have tried to strike a balance between the past and the present, between the practical and the academic, and between common sense and the pedantic, in the hope that we can move the search for what works in healthcare from the realm of chance to the science of probability.

Disclosures

None.

References

1. O'Hagan A, Luce BR. *A Primer on Bayesian Statistics in Health Economics and Outcomes Research*. Bethesda, MD: MEDTAP International; 2003.
2. Bertsekas DP, Tsitsiklas JN. *Introduction to Probability*. Belmont, MA: Athena Scientific; 2008.
3. Spiegelhalter DJ, Abrams KR, Myles JP. *Bayesian Approaches to Clinical Trials and Health Care Evaluations*. Chichester, England: Wiley; 2004.
4. Goodman SN. Toward evidence-based medical statistics. 1: the *P* value fallacy. *Ann Intern Med*. 1999;130:995–1004.
5. Carlin JB, Louis TA. *Bayesian Methods for Data Analysis*. Boca Raton, FL: Chapman & Hall/CRC; 2009.
6. Diamond GA, Kaul S. Prior convictions: Bayesian approaches to the analysis and interpretation of clinical megatrials. *J Am Coll Cardiol*. 2004;43:1929–1939. doi: 10.1016/j.jacc.2004.01.035.
7. Greenland S, Senn SJ, Rothman KJ, Carlin JB, Poole C, Goodman SN, Altman DG. Statistical tests, P values, confidence intervals, and power: a guide to misinterpretations. *Eur J Epidemiol*. 2016;31:337–350. doi: 10.1007/s10654-016-0149-3.
8. Gregory PC. A Bayesian Kepler periodogram detects a second planet in HD208487. *Month Notic Royal Astronom Soc*. 2007;374:1321–1333.
9. Fernando RL, Garrick D. Bayesian methods applied to GWAS. *Methods Mol Biol*. 2013;1019:237–274. doi: 10.1007/978-1-62703-447-0_10.
10. Jacobs AK, Kushner FG, Ettinger SM, Guyton RA, Anderson JL, Ohman EM, Albert NM, Antman EM, Arnett DK, Bertolet M, Bhatt DL, Brindis RG, Creager MA, DeMets DL, Dickersin K, Fonarow GC, Gibbons RJ, Halperin JL, Hochman JS, Koster MA, Normand SL, Ortiz E, Peterson ED, Roach WHJ, Sacco RL, Smith SCJ, Stevenson WG, Tomaselli GF, Yancy CW, Zoghbi WA, Harold JG, He Y, Mangu P, Qaseem A, Sayre MR, Somerfield MR. ACCF/AHA clinical practice guideline methodology summit report: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2013;61:213–265.
11. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand SL; American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177–2185. doi: 10.1161/CIRCULATIONAHA.112.000646.
12. Welton N, Sutton AJ, Cooper NJ, Abrams KR, Ades AE. *Evidence Synthesis for Decision Making in Healthcare*. Chichester, West Sussex, United Kingdom: Wiley; 2012.
13. Kruschke JK. *Doing Bayesian Data Analysis: A Tutorial With R and BUGS*. Oxford, England: Elsevier; 2011.
14. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013.
15. Schwarzer G. *Package 'Meta' (version 3.8-0)*. Comprehensive R Archive Network (CRAN). Freiburg, Germany: 2012.
16. Thomas A, O'Hara B, Ligges U, Sturtz S. Making BUGS open. *R News*. 2006;6:12–17.
17. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651. doi: 10.1161/CIR.0b013e31823ba622.
18. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lansky A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S III, Bertrand M, Fuster V; FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375–2384. doi: 10.1056/NEJMoa1211585.
19. Verma S, Farkouh ME, Yanagawa B, Fitchett DH, Ahsan MR, Ruel M, Sud S, Gupta M, Singh S, Gupta N, Cheema AN, Leiter LA, Fedak PW, Teoh H, Latter DA, Fuster V, Friedrich JO. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2013;1:317–328. doi: 10.1016/S2213-8587(13)70089-5.
20. Bittl JA. Percutaneous coronary interventions in the diabetic patient: where do we stand? *Circ Cardiovasc Interv*. 2015;8:e001944. doi: 10.1161/CIRCINTERVENTIONS.114.001944.
21. Lang CD, He Y, Bittl JA. Bayesian inference supports the use of bypass surgery over percutaneous coronary intervention to reduce mortality in diabetic patients with multivessel coronary disease. *Int J Stat Med Res*. 2015;4:26–34.
22. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 1997;96:1761–1769.
23. Abizaid A, Costa MA, Centemero M, Abizaid AS, Legrand VM, Limet RV, Schuler G, Mohr FW, Lindeboom W, Sousa AG, Sousa JE, van Hout B, Hugenholtz PG, Unger F, Serruys PW; Arterial Revascularization Therapy Study Group. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation*. 2001;104:533–538.
24. Rodriguez AE, Baldi J, Fernández Pereira C, Navia J, Rodriguez Alemparte M, Delacasa A, Vigo F, Vogel D, O'Neill W, Palacios IF; ERACI II Investigators. Five-year follow-up of the Argentine randomized

trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol*. 2005;46:582–588. doi: 10.1016/j.jacc.2004.12.081.
25. Hueb W, Gersh BJ, Costa F, Lopes N, Soares PR, Dutra P, Jatene F, Pereira AC, Góis AF, Oliveira SA, Ramires JA. Impact of diabetes on five-year outcomes of patients with multivessel coronary artery disease. *Ann Thorac Surg*. 2007;83:93–99. doi: 10.1016/j.athoracsur.2006.08.050.
26. The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet*. 2002;360:965–970.
27. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, de Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol*. 2010;55:432–440. doi: 10.1016/j.jacc.2009.10.014.
28. Kappetein AP, Head SJ, Morice MC, Banning AP, Serruys PW, Mohr FW, Dawkins KD, Mack MJ; SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg*. 2013;43:1006–1013. doi: 10.1093/ejcts/ezt017.
29. Kamalesh M, Sharp TG, Tang XC, Shunk K, Ward HB, Walsh J, King S III, Colling C, Moritz T, Stroupe K, Reda D; VA CARDS Investigators. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol*. 2013;61:808–816. doi: 10.1016/j.jacc.2012.11.044.
30. Bittl JA, Tamis-Holland JE, Lang CD, He Y. Outcomes after multivessel or culprit-Vessel intervention for ST-elevation myocardial infarction in patients with multivessel coronary disease: a Bayesian cross-design meta-analysis. *Catheter Cardiovasc Interv*. 2015;86(suppl 1):S15–S22. doi: 10.1002/ccd.26025.
31. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. *Ann Intern Med*. 1999;130:1005–1013.
32. Armitage P, Berry G, Matthews JNS. Bayesian methods. *Statistical Methods in Clinical Research*. Malden, MA: Blackwell Science; 2002:165–186.
33. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, Fonarow GC, Lange RA, Levine GN, Maddox TM, Naidu SS, Ohman EM, Smith PK. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749–1767. doi: 10.1161/CIR.0000000000000095.
34. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand SL, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR Jr, Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM; DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155–2166. doi: 10.1056/NEJMoa1409312.
35. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong MK, Kim BK, Jang Y, Kim HS, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Petrou M, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371–2382. doi: 10.1016/S0140-6736(15)60263-X.
36. Bittl JA, Baber U, Bradley SM, Wijeysundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1116–1139. doi: 10.1016/j.jacc.2016.03.512.
37. Food and Drug Administration. Plavix (clopidogrel): long-term treatment does not change risk of death. *Drug Safety Communication*. 2015; 1–6.
38. Kim BK, Hong MK, Shin DH, Nam CM, Kim JS, Ko YG, Choi D, Kang TS, Park BE, Kang WC, Lee SH, Yoon JH, Hong BK, Kwon HM, Jang Y; RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol*. 2012;60:1340–1348. doi: 10.1016/j.jacc.2012.06.043.
39. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto JA, Botelho RV, King SB III, Negoita M, Liu M, de Paula JE, Mangione JA, Meireles GX, Castello HJ Jr, Nicolela EL Jr, Perin MA, Devito FS, Labrunie A, Salvadori D Jr, Gusmão M, Staico R, Costa JR Jr, de Castro JP, Abizaid AS, Bhatt DL; OPTIMIZE Trial Investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310:2510–2522. doi: 10.1001/jama.2013.282183.
40. Gwon HC, Hahn JY, Park KW, Song YB, Chae IH, Lim DS, Han KR, Choi JH, Choi SH, Kang HJ, Koo BK, Ahn T, Yoon JH, Jeong MH, Hong TJ, Chung WY, Choi YJ, Hur SH, Kwon HM, Jeon DW, Kim BO, Park SH, Lee NH, Jeon HK, Jang Y, Kim HS. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) randomized, multicenter study. *Circulation*. 2012;125:505–513. doi: 10.1161/CIRCULATIONAHA.111.059022.
41. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, Oteo Dominguez JF, Steffanon L, Tarantini G, Presbitero P, Menozzi A, Pucci E, Mauri J, Cesana BM, Giustino G, Sardella G. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol*. 2014;64:2086–2097. doi: 10.1016/j.jacc.2014.09.008.
42. Schulz-Schüpke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, Tölg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wöhrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PW, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz KL, Schömig A, Mehilli J, Kastrati A; Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36:1252–1263. doi: 10.1093/eurheartj/ehu523.
43. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, Li X, Zhao X, Wang H, Zhao X, Li X, Yu P, Zang H, Wang Z, Cao X, Zhang J, Pang W, Li J, Yang Y, Dangas GD. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 trial. *Circ Cardiovasc Interv*. 2016;9:e003145. doi: 10.1161/CIRCINTERVENTIONS.115.003145.
44. Hong SJ, Shin DH, Kim JS, Kim BK, Ko YG, Choi D, Her AY, Kim YH, Jang Y, Hong MK; IVUS-XPL Investigators. 6-Month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *JACC Cardiovasc Interv*. 2016;9:1438–1446. doi: 10.1016/j.jcin.2016.04.036.
45. Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, Cuisset T, Elhadad S, Schiele F, Lhoest N, Ohlmann P, Carrié D, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Beygui F, Vicaut E, Montalescot G; ARCTIC investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet*. 2014;384:1577–1585. doi: 10.1016/S0140-6736(14)60612-7.
46. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, Park SW, Han S, Lee SG, Seong IW, Rha SW, Jeong MH, Lim DS, Yoon JH, Hur SH, Choi YS, Yang JY, Lee NH, Kim HS, Lee BK, Kim KS, Lee SU, Chae JK, Cheong SS, Suh IW, Park HS, Nah DY, Jeon DS, Seung KB, Lee K, Jang JS, Park SJ. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. *Circulation*. 2014;129:304–312. doi: 10.1161/CIRCULATIONAHA.113.003303.
47. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, Furber A, Leclercq F, Eltchaninoff H, Falquier JF, Henry P, Cattan S, Sebagh L, Michel PL, Tuambilangana A, Hammoudi N, Boccara F, Cayla G, Douard H, Diallo A, Berman E, Komajda M, Metzger JP, Vicaut E; OPTImal DUAL Antiplatelet Therapy Trial Investigators. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. *Eur Heart J*. 2016;37:365–374. doi: 10.1093/eurheartj/ehv481.
48. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R; Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia Study (PRODIGY) Investigators. Short- versus long-term

duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation*. 2012;125:2015–2026. doi: 10.1161/CIRCULATIONAHA.111.071589.

49. Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B, Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy P, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice MC. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol*. 2015;65:777–786. doi: 10.1016/j.jacc.2014.11.008.
50. Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, Ando K, Anzai H, Tanaka H, Ueda Y, Takiuchi S, Nishida Y, Ohira H, Kawaguchi K, Kadotani M, Niinuma H, Omiya K, Morita T, Zen K, Yasaka Y, Inoue K, Ishiwata S, Ochiai M, Hamasaki T, Yokoi H; NIPPON Investigators. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug-eluting stent implantation. *JACC Cardiovasc Interv*. 2017;10:1189–1198. doi: 10.1016/j.jcin.2017.04.019.
51. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, Granger CB, Lange RA, Mack MJ, Mauri L, Mehran R, Mukherjee D, Newby LK, O'Gara PT, Sabatine MS, Smith PK, Smith SC Jr. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2016;68:1082–1115. doi: 10.1016/j.jacc.2016.03.513.
52. Cates CJ. Simpson's paradox and calculation of number needed to treat from meta-analysis. *BMC Med Res Methodol*. 2002;2:1.
53. Bates ER, Tamis-Holland JE, Bittl JA, O'Gara PT, Levine GN. PCI strategies in patients with ST-segment elevation myocardial infarction and multivessel coronary artery disease. *J Am Coll Cardiol*. 2016;68:1066–1081. doi: 10.1016/j.jacc.2016.05.086.
54. He Y, Bittl JA, Wouhib A, Normand S-LT. Case study in cardiovascular medicine: unprotected left main coronary artery disease. In: Biondi-Zoccai G, ed. *Network Meta-Analysis: Evidence Synthesis With Mixed Treatment Comparison*. New York: Nova Science Publishers, Inc; 2014:285–386.
55. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Lange RA, Mauri L, Mehran R, Moussa ID, Mukherjee D, Ting HH, O'Gara PT, Kushner FG, Ascheim DD, Brindis RG, Casey DE Jr, Chung MK, de Lemos JA, Diercks DB, Fang JC, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2015 ACC/AHA/SCAI focused update on primary percutaneous coronary intervention for patients with ST-elevation myocardial infarction: an update of the 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention and the 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction. *J Am Coll Cardiol*. 2016;67:1235–1250. doi: 10.1016/j.jacc.2015.10.005.
56. Olson WH, Crivera C, Ma YW, Panish J, Mao L, Lynch SM. Bayesian data analysis in observational comparative effectiveness research: rationale and examples. *J Comp Eff Res*. 2013;2:563–571. doi: 10.2217/cer.13.73.

Bayesian Analysis: A Practical Approach to Interpret Clinical Trials and Create Clinical Practice Guidelines

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Contents

Supplemental Appendix A: Bayesian Approach to Diagnostic Testing

To show how Bayesian analysis has become a crucial part of clinical reasoning,[1] we start with a familiar example. A common question is: What is the chance that a patient has a disease when he or she has an abnormal result on screening test that is accurate 80% to 90% of the time? To put the question into the context of cardiovascular medicine, we ask: What is the predictive value of an abnormal stress test that has a sensitivity of 85% and a specificity of 80% in a healthy 40-year old person who has a 1% prior probability of having coronary artery disease (CAD)? The answer is 4%. This result may seem low, but it is based on a straightforward application of Bayes rule[2, 3]:

$$p(H_1|y) = \frac{p(H_1) \cdot p(y|H_1)}{p(y)} = \frac{p(H_1) \cdot p(y|H_1)}{p(H_1) \cdot p(y|H_1) + p(H_0) \cdot p(y|H_0)},$$

where H_1 is the presence of obstructive CAD, H_0 the absence of disease, y is an abnormal stress test, $p(y)$ is the probability of getting a true or false positive test result, and $p(H_1|y)$ is the probability of having CAD given an abnormal stress test y.[*]

Plugging a value of 0.01 for the prior probability of having CAD $p(H_1)$, 0.99 for the prior probability of not having CAD $p(H_0)$, 0.85 for the sensitivity $p(y|H_1)$ of stress testing, and 0.20 (ie, 1 – specificity) for the false positive rate of stress testing $p(y|H_0)$ into Bayes' formula yields a posterior probability $p(H_1|y)$ of 0.041.

To better understand how Bayesian analysis improves diagnostic thinking, we simply calculate that for every 10,000 low-risk patients, only 100 will have obstructive CAD (0.01·10,000). Of 10,000 low-risk patients undergoing screening stress tests, 85 with CAD will have true positive tests (0.85·100) and 1980 without CAD will have false positive tests (0.20·9900). When we compute the posterior probability $p(H_1|y)$ by dividing the number of true positives $p(H_1) \cdot p(y|H_1)$ by the sum of true positives $p(H_1) \cdot p(y|H_1)$ plus false positives $p(H_0) \cdot p(y|H_0)$, we obtain 85/(85+1980), or 4.1%, which agrees with the result above and illustrates how the number of false positives overwhelms the number of true positives. To improve the accuracy of stress testing in the clinical setting and reduce the number of false positives, many experts include factors like maximum exercise time and the degree of ST depression.[4, 5]

Using a similar line of thinking for an asymptomatic patient who has received a drug-eluting stent (DES) and has a 5% risk of restenosis,[6] we calculate that the positive predictive value of an abnormal screening stress test is 18%. This surprising result is obtained by setting the risk of restenosis of 5% as the prior probability $p(H_1)$. In a theoretical sample of 1000 patients

[*] | is the symbol from probability theory that denotes conditional, or "given," as in $p(H_1|y)$, which refers to the presence of disease H_1 *given* a positive test result y.

after DES implantation, 50 (0.05·1000) will have restenosis, 950 (1000 – 50) will not, 43 (0.85·50) will have a true positive test result, and 190 (0.20·950) will have a false positive test result. Substituting 50, 950, 43, and 190 for $p(H_1)$, $p(H_0)$, $p(H_1) \cdot p(y|H_1)$, and $p(H_0) \cdot p(y|H_0)$ in Bayes' Equation yields a posterior probability $p(H_1|y)$ of 0.18, which is same as that obtained by dividing the true positives by the sum of true and false positives, 43/(43+190).

Similar examples discussed during the revision of the 2011 PCI guideline prompted members of the writing committee replace an older recommendation for routine screening stress testing with a Class III ("no benefit") recommendation: "Routine periodic stress testing of asymptomatic patients after PCI without specific clinical indications should not be performed (Level of Evidence: C)."[7]

Supplementary Appendix B:
Doing Bayesian Analysis on Your Computer Using Open-Source Software

Running OpenBUGS and [R] On a Macintosh Computer Using a Native Windows Platform (Preferred)[3]:

1. Because OpenBUGS and WinBUGS are Windows-based, you will need to be able to run Windows programs on your Mac. First, download and open WINE (Windows Not an Emulator). Get the file WineBottlerCombo_1.6.1.dmg, or latest version compatible with your operating system (OS), from winebottler.kronenberg.org.
2. To run WINE in an older Mac OS environment such as OS X El Capitan version 10.11.6 or earlier, download and run XQuartz 2.7.11. Get the file from xquartz.org. To run WINE in OS X Sierra version 10.12.1, you do not need XQuartz.
3. If you have trouble loading WINE, check the security settings on your Mac. Under the **Apple logo**, select **System Preferences…** and click on **Security and Privacy**. Under the **General** menu, select ⦿Allow apps downloaded from … App store and identified developers. If this fails, go to the **Applications** folder, open the **Utilities** folder, and double-click on **Terminal.** At the prompt, type sudo spectl –master-disable, and then find under the **General** pane in **Security and Privacy** a new radio button ⦿**Anywhere.** After you successfully open WINE, remember to go back into **Terminal** and reset the security settings by typing sudo spctl –master-enable.
4. To perform statistical analyses using [R], you will need to load R-3.0.3-win.exe. To run [R] using WINE on your Mac, download the Windows version of the file from cran.r-project.org. You can get any of the previous versions by clicking on the "Old" button and scrolling, for example, to R-3.0.3.pkg 2014-03-06 16:47 66M.
5. To edit code in [R], you need an editing program like Tinn-R. You can get Tinn-R_3.0.3.6_setup.exe from https://sourceforge.net/projects/tinn-r/files/Tinn-R setup/3.0.3.6/.
6. To get the [R] code in this Supplemental Appendix to work, you will need to copy it to Tinn-R or similar program, save it as a file on your computer and access it directly from [R]. Copying and pasting from the Supplemental Appendix directly into [R] will probably not work.
7. To find [R] on your Mac, click on the Wine icon, which is the shape of a tiny wineglass and may be in your applications folder but should be moved to the task bar for easy accessibility. In the Wine submenu on the menu bar, scroll down to **File Manager**. Double click on the folder **Program Files**, double click on the folder **R**, double click on the folder **R 3.0.3**, double click on folder **bin**, double click on folder **i386**, double click on file **Rgui.exe**, and watch [R] start.
8. To perform Markov chain Monte Carlo (MCMC) modeling, get and run OpenBUGS323setup.exe or the latest version compatible with your OS. Download the file from www.openbugs.net/w/**Downloads.** Under the Wine icon on the menu bar, scroll

down to **File Manager**. Double click on the folder **Program Files**, double click on the folder **OpenBUGS**, double click on the folder **OpenBUGS323**, double click on file **OpenBUGS.exe**, and watch OpenBUGS start.

9. In [R], scroll down from **File** to **Change dir…** to browse for a folder that you intend to use for data files, code files and figures.
10. To run OpenBUGS in the background with [R], you must install the package BRugs. To do this, open both [R] and OpenBUGS. In [R], scroll down from the **Packages** to **Install package(s)…** and select CRAN mirror **USA (CA 1)** or any other familiar source. Then, scroll down from **Packages** to **Load package…** and select **BRugs.** In [R], type `install.packages("BRugs")` and then type `library(BRugs)`. In future [R] sessions, simply type `library(BRugs)`.
11. To run meta-analyses, type `install.packages("meta")` and then type `library(meta).` In future [R] session, simply type `library(meta)`.
12. This seemingly incoherent combination of manufacturer and software is recommended, because Macintosh computers are arguably the most reliable computers for the consumer, and the Windows versions of BUGS and [R] are discussed more extensively than any other approach in the recommended textbooks.[1, 8-11]

On a PC (Easier)[3]:

1. To perform statistical analyses using [R], get and run R-3.0.3-win.exe. Download the Windows version of the file from cran.r-project.org. You can get any of the previous versions by clicking on the "Old" button and scrolling, for example, to R-3.0.3.pkg 2014-03-06 16:47 66M.
2. To edit code in [R], run Tinn-R_3.0.3.6_setup.exe. Download the file from https://sourceforge.net/projects/tinn-r/files/Tinn-R setup/3.0.3.6/.
3. To get the [R] code in this Supplemental Appendix to work, you will need to copy it to Tinn-R or similar program, save it as a file on your computer and access it directly from [R]. Copying and pasting from the Supplemental Appendix into [R] will not work.
4. To run Markov chain Monte Carlo (MCMC) modeling, get and run OpenBUGS323setup.exe or latest version compatible with your OS. Download the file from www.openbugs.net/w/**Downloads.** In the Wine submenu on the menu bar, scroll down to **File Manager**. Double click on the folder **Program Files**, double click on the folder **OpenBUGS**, double click on the folder **OpenBUGS323**, double click on file **OpenBUGS.exe**, and watch OpenBUGS start.
5. In [R], scroll down from **File** to **Change dir…** to browse for a folder that you intend to use for data files, code files and figures.
6. To run OpenBUGS in the background with [R], you must install the package BRugs. To do this, open both [R] and OpenBUGS. In [R], scroll down from the **Packages** to **Install package(s)…** and select CRAN mirror **USA (CA 1)** or any other familiar source. Then, scroll down from **Packages** to **Load package…** and select **BRugs.** In [R], type

`install.packages("BRugs")` and then type `library(BRugs).` In future [R] sessions, simply type `library(BRugs).`

7. To run meta-analyses, type `install.packages("meta")` and then type `library(meta).` In future [R] session, simply type `library(meta).`

On a Mac using JAGS and [R] for Mac (An Emerging Approach)[12]:

1. Go to the Sourceforge.net site and follow instructions for downloading and installing JAGS that is compatible with your OS.
2. To perform statistical analyses using [R], get and run R for Mac from https://cran.r-project.org/bin/macosx/.
3. To run JAGS in [R], you must download and rjags_4-3 from Sourceforge.net and install.
4. This combination of hardware and software is gaining wider use,[13-15] but is not as widely cited as the Windows-based approaches.

Supplementary Appendix B—Example:
Mixed Treatment Comparisons for Left Main Coronary Artery Disease[16, 17]

A network meta-analysis allows practitioners to compare treatments indirectly when direct comparisons do not exist. For example, no trial has directly compared percutaneous coronary intervention (PCI) with medical therapy (MT) to improve survival in patients with unprotected left main CAD (ULMCAD), but the 2011 ACC/AHA revascularization guidelines contained a Class IIa recommendation to use PCI to improve survival in patients with ULMCAD.[7, 18] The recommendation was based on the reasoning that:

- CABG confers a survival advantage over MT for ULMCAD
- In selected patients PCI is equivalent to CABG for ULMCAD

∴ PCI confers a survival advantage over MT for ULMCAD

Evidence for the first premise came from subgroup analyses of 7 trials performed 30 years ago,[19-25] and evidence for the second came from 4 randomized trials[26-29] and 8 cohort studies,[30-37] all reported during the past 15 years.

In the absence of clinical trials directly comparing PCI with MT for this indication, a Bayesian network was constructed to perform the indirect comparison.[16, 17] In the Bayesian models, the treatment advantage of PCI over MT was represented as $\Delta_{PCI\text{-}MT}=\Delta_{PCI\text{-}CABG} - \Delta_{MT\text{-}CABG}$ and inferred from summary data. To compare PCI with MT for ULMCAD, we have individual studies that have compared CABG with MT and CABG with PCI. Suppose that the probability of dying after CABG, MT, and PCI is P_C, P_M, and P_P. The analysis of each of these trials can be assessed through *OR*s:

$$OR_{CM} = \frac{P_C/(1-P_C)}{P_M/(1-P_M)} \text{ and } OR_{CP} = \frac{P_C/(1-P_C)}{P_P/(1-P_P)}$$

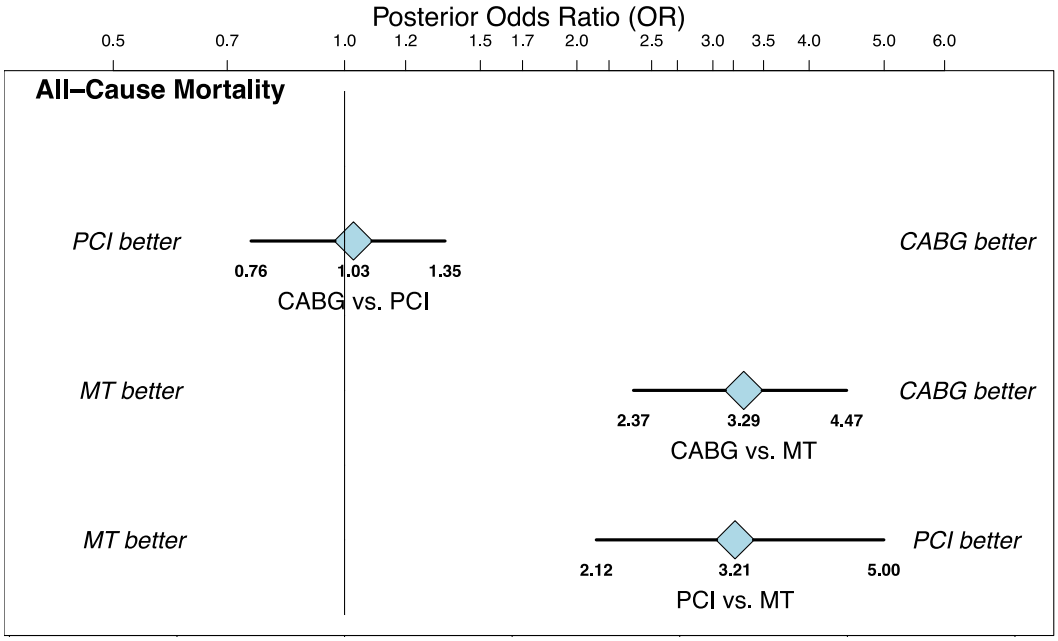
The summary *OR* of the indirect comparison of PCI vs. MT can be computed by the ratio of the *OR*s from the studies comparing CABG vs. MT and CABG vs. PCI:

$$\frac{OR_{CM}}{OR_{CP}} = OR_{PM}$$

To allow for parametric hypothesis testing (H_0: $OR_{PM} = 1$), a natural log transformation of the above equation yields:

$$log_e(OR_{PM}) = log_e(OR_{CM}) - log_e(OR_{CP}).$$

From the model presented in Table B1 below, we obtain the posterior distribution of $exp(PC)$ and $exp(MC)$, which are the summary odds ratios of PCI vs. CABG and MT vs. CABG, respectively. We also obtain $exp(PM)$, the indirect summary odds ratio of PCI vs. MT. As in prior reports,[16, 17] we can use MCMC modeling[8, 9] to draw a large simulated sample from the posterior distribution to identify accurate estimates for relative mortality rates after PCI, CABG and MT. As shown in the caterpillar plot below, the indirect comparison suggests a benefit of PCI over MT (*OR*, 3.21; 95% BCI, 2.12–5.00) and of CABG over MT (*OR*, 3.29; 95% BCI, 2.37–4.47) for 1-year mortality. There is no difference in mortality after PCI compared with CABG (*OR*, 1.03; 95% BCI, 0.76–1.35), as shown in the figure below:



Caterpillar Plot Showing Mortality Rates after Treatment of Left Main Coronary Artery Disease. A Bayesian network meta-analysis of 19 trials produced posterior median odds ratios and 95% credible intervals (data labels) for 1-year mortality after percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG) surgery, or medical therapy (MT). The distributions are plotted on the OR and θ ($\log_e$OR) scales. The indirect comparisons suggest that mortality rates were no different after CABG or PCI

but more than 3-fold higher after MT than after PCI, and more than 3-fold higher after MT than after CABG.

Because not all studies comparing PCI with CABG were randomized or matched, and many of the trials in the network analysis were published more than 30 years ago but arguably still relevant today,[38] the writing committee assigned a level of evidence (LOE) B to the recommendation.[7, 18] No classical statistical approach exists to directly quantify the probability of outcomes using indirect comparisons.

Although the details of methods can be found in original reports,[16, 17] practitioners interested in replicating the network meta-analysis can follow the methods outlined here by inputting the model, data and initial values directly into OpenBUGs or WinBUGS, using procedures in Appendix B Tables 2 and 3 below:

Supplementary Appendix B—Table 2:
How to Enter the Model, Data and Initial Values Directly into OpenBUGS or WinBUGS

1. In OpenBUGS or WinBUGS, under the File menu on the taskbar, click New 3 times to open 3 new files.
2. Copy and paste the model, data, and inits from Table D2 below into each of the 3 windows.
3. Under Model, click Specification, and a new window opens.
4. Place the cursor anywhere in open model window, and then click the check model box. At the bottom of the model window, you should see the message, model is syntactically correct.
5. Place the cursor anywhere in open data window, and then click the load data box. At the bottom of the model window, you should see the message, data loaded.
6. Click compile. You should see the message model compiled.
7. Place the cursor anywhere in open inits window, and then click the load inits box. At the bottom of the model window, you should see the message, initial values loaded…
8. Click the box gen inits.
9. Under Inferences, click Samples…
10. A new window opens. Enter the term lor into the node space. Click set.
11. Under Model, click Update… and change 1000 to 10000 in the updates tool. Click the update box.
12. Under Inferences, click Samples… if it is not open and review history. Enter an * into the node and click on stats to get your results, which present the $\log_e$(OR) for the comparisons of CABG (1), PCI (2), and MT (3).

Supplementary Appendix B—Table 3:
Direct-Entry Commands for WinBUGS or OpenBUGS

```
#model
model
{ # i counts the two arms of all 19 studies
for (i in 1:38)
{
r[i] ~ dbin(p[i], n[i]);
logit(p[i]) <- mu[s[i]]+delta[i]*(1-equals(t[i],b[i]));
delta[i] ~ dnorm(md[i], prec);
md[i] <- d[t[i]]-d[b[i]];
}
# j represents the CABG arm
for (j in 1:19)
{
mu[j] ~ dnorm(0, .001);
}
prec ~ dgamma(0.001, 0.001);
d[1] <- 0;
# K represents the relative treatment comparator: k=2 is PCI, k=3 is MT
for (k in 2:3)
{
d[k] ~ dnorm(0, .001)
}
for (c in 1:2)
{
for (k in (c+1):3)
{
lor[c,k] <- d[k]-d[c];
log(or[c,k]) <- lor[c,k];
}
}
}
```

```
#data (from table
list(s=c(1,1,2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,12,12,13,13,14,14,15,15,16,16,17,17,18,18,19,19),t=c(1,2,1,2,1,
2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,2,1,3,1,3,1,3,1,3,1,3,1,3,1,3),r=c(15,15,4,1,5,2,20,26,7,9,12,3,18,20,25,2,19,21,20,5,
8,22,12,7,3,10,59,46,16,6,5,4,16,12,2,2,61,93),n=c(348,357,53,52,101,100,300,300,67,67,142,107,542,542,238,49,15
4,157,245,96,135,135,190,97,48,43,1183,309,141,24,40,17,89,32,28,31,899,440),b=c(1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,
1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1,1))
```

```
#inits
list(d=c(NA,0,0), prec=1, mu=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0,0))
```

Supplementary Appendix B—Table 4:
Data Source and Format for Indirect Inference "LMNetworkData.csv"

	s[]	t[]	r[]	nn[]	b[]
SYNTAX[26]	1	1	15	348	1
	1	2	15	357	1
LEMANS[27]	2	1	4	53	1
	2	2	1	52	1
Boudriot[28]	3	1	5	101	1
	3	2	2	100	1
PRECOMBAT[29]	4	1	20	300	1
	4	2	26	300	1
Cedars-Sinai[30]	5	1	7	67	1
	5	2	9	67	1
Chieffo[34]	6	1	12	142	1
	6	2	3	107	1
MAIN-COMPARE[39]	7	1	18	542	1
	7	2	20	542	1
Mäkikallio[35]	8	1	25	238	1
	8	2	2	49	1
Palmerini[36]	9	1	19	154	1
	9	2	21	157	1
Sanmartín[37]	10	1	20	245	1
	10	2	5	96	1
Wu[32]	11	1	8	135	1
	11	2	22	135	1
Brener[33]	12	1	12	190	1
	12	2	7	97	1
Takaro[19, 40]	13	1	3	48	1
	13	3	10	43	1
Chaitman[20]	14	1	59	1183	1
	14	3	46	309	1
Oberman[21]	15	1	16	141	1
	15	3	6	24	1
Cohen[22]	16	1	5	40	1
	16	3	4	17	1
Talano[23]	17	1	16	89	1
	17	3	12	32	1
European[24]	18	1	2	28	1
	18	3	2	31	1
Dzavik[41]	19	1	61	899	1
	19	3	93	440	1

Supplementary Appendix C: Conjugate Normal Analysis of Revascularization Choices in Diabetic Patients with Multivessel Coronary Artery Disease[42]

"Modern statisticians have … deprived themselves of any way of saying precisely what they mean when they decide between hypotheses."

—Sir Harold Jeffreys, in *A Theory of Probability*[43]

Table C1: Pop Quiz

Q—What answer (A) describes the correct interpretation of a *P* value of <0.05 for a mortality advantage of bypass surgery over percutaneous coronary intervention from the FREEDOM[44] Trial?

A1—At most, only 5% of diabetic patients with multivessel CAD would have a survival advantage with CABG as compared with PCI.
A2—If we were to repeat the FREEDOM trial many times (eg, FREEDOM-1, FREEDOM-2, FREEDOM-3, and so on), using new data each time, and if the null hypothesis (H_0) were really true, then on only 5% of those occasions would we (falsely) reject H_0.
A3—There is less than a 5% chance that the null hypothesis is true.

Inspired by O'Hagan & Luce.[45] Abbreviations: CABG, coronary artery bypass graft; CAD, coronary artery disease; FREEDOM, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease [44]; PCI, percutaneous coronary intervention.

(Correct answer *A2*)

Bayesian Inference: In the analysis of trial evidence, the Bayesian approach introduces the symbol θ to denote the hypothesis governing an underlying treatment effect, the prior probability $p(\theta)$ to denote our existing belief in θ based on external sources like older RCTs, and the variable y to signify new trial evidence or data, which for convenience is often analyzed on the natural log scale.[1-3, 10, 45] In frequentist statistics the parameter θ is a fixed but unknown value best supported by the data, but in Bayesian analysis θ is a random variable. In both statistical approaches, the probability of occurrence of y depends on θ, but in Bayesian framework the dependence is formalized as the likelihood $p(y|\theta)$ to describe the conditional probability of y,† usually in the form of $\log_e(OR)$, for each possible value of θ in a mathematical relation that is commonly represented by a normal distribution (N):

$$\log_e(OR) \quad \sim \quad \mathrm{N}[\theta, V],^{\ddagger}$$

where θ is the unknown parameter governing the underlying hypothesis governing the difference between 2 treatments, and V is the variance.[1]

The evidence relevant to the parameter θ, after m observations, can be summarized by:

† | denotes "given" or "conditional on," as in "the data *y*, *given* the underlying hypothesis θ."
‡ ~ denotes "distributed from or sampled from," as in the normal distribution $\mathrm{N}[\theta, V]$; that is, gaussian distribution with mean θ and variance V.

$$\mathrm{y} = \log_e(OR) \sim \quad \mathrm{N}\left[\theta, \frac{\sigma^2}{m}\right],$$

where θ is the parameter or treatment effect of interest, *m* is the effective number of events, and σ^2 is the variance (standard deviation σ) obtained using standard approaches.[1]

What we want to know, however, is how the probability of θ is altered by the new trial evidence *y*, which is denoted by $p(\theta|y)$. This is the "posterior probability" of θ based on the new trial data *y*, which is calculated from Bayes theorem:

$$p(\theta|y) = \frac{p(y|\theta) \cdot p(\theta)}{p(y)}.$$

In other words, Bayes' theorem expresses how the new evidence *y* from FREEDOM changes the probability of θ. For a series of clinical trials h=1, 2, …, n, we have the general form of Bayes' equation:

$$p(\theta|y) = \frac{p(y|\theta) \cdot p(\theta)}{p(y)},$$
$$= \frac{p(y|\theta) \cdot p(\theta)}{\sum_{h=1}^{n} p(y_h|\theta) \cdot p(\theta)},$$
$$= \frac{p(y|\theta) \cdot p(\theta)}{\int_{h=1}^{n} p(y_h|\theta) \cdot p(\theta)}$$

Basic definitions. As a convention, if observations in the *h*th trial are cross classified by treatment after CABG or PCI in a 2 x 2 table, and the odds of, say, 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 the numerator and denominator, and the trial result OR_h on the $\log_e$ scale becomes y_h, to represent the treatment effect of the *h*th trial,[1]

$$y_h = \log\left[\frac{(\mathrm{a} + \frac{1}{2})(\mathrm{d} + \frac{1}{2})}{(\mathrm{b} + \frac{1}{2})(\mathrm{c} + \frac{1}{2})}\right].$$

The estimator has an approximate variance

$$\mathrm{V}(y_h) = \frac{1}{\mathrm{a} + \frac{1}{2}} + \frac{1}{\mathrm{b} + \frac{1}{2}} + \frac{1}{\mathrm{c} + \frac{1}{2}} + \frac{1}{\mathrm{d} + \frac{1}{2}}.$$

Conjugate Normal Model: If we let $p(\theta)$ denote the prior probability distribution of θ, which for the purposes of this analysis is not subjective opinion but rather is derived empirically from 8 existing trials,[46-53] each of which has an outcome described by the summary statistic $y_{old,}$ and we now observe some new trial evidence from FREEDOM, $y_{FREEDOM}$, then the probability of occurrence of $y_{FREEDOM}$ is conditional on θ and is denoted by $p(y_{FREEDOM}|\theta)$. The conditional

probability of $y_{FREEDOM}$ for each possible value of θ is called the "likelihood." What we are looking for, however, is the probability distribution of θ, which takes into account the trial evidence $y_{FREEDOM}$ and is denoted by $p(\theta|y_{FREEDOM})$. This is the posterior probability of θ, which is conditional on the trial data $y_{FREEDOM}$, and is calculated from Bayes theorem above. In words, the posterior probability for the hypothesis θ given the evidence $y_{FREEDOM}$ is proportional to the likelihood times the prior probability for the hypothesis θ independent of the evidence.54 In summary, Bayes theorem expresses how the new evidence $y_{FREEDOM}$ changes the probability of θ, and incorporates it with what is already known based on y_{old}.

In older studies,[46-53] we have data $y_1, \ldots, y_8$, each of which is assumed to have a normal distribution, governed by an underlying treatment parameter θ_h and its variance σ_h^2 for $h = 1,2, \ldots, 8$ trials. 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,[1] which is obtained from setting the variance of the $\log_e(OR)$ to σ^2/m and a normal likelihood with $V(\mu) = s^2$. Accordingly, the evidence relevant to the parameter θ, after m observations, can be summarized by:

$$y \quad \sim \quad N\left[\theta, \frac{\sigma^2}{m}\right],$$

where $y = \log_e(OR)$, θ is the parameter of interest or treatment effect, m is the effective number of events, and σ^2 is the variance (standard deviation σ) obtained using standard approaches.[1] 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 events a ≈ b are very small compared with the number of enrolled patients c ≈ d in each treatment group, so that:

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

where m = a + b is the number of events, allowing $\sigma = 2$ to be an appropriate choice.[1]

After calculating m_h for each trial, we can obtain the "pooled" results by summing the ms for the $h = 1, 2, \ldots, 8$ trials. The summed ms 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 $\log_e(OR_{old})$ for the prior distribution by weighting the individual $\log_e(OR_h)$s by their respective ms divided by the sum m_0.[55]

Likelihood. In the context of clinical trials, it is reasonable to assume that the data from a new trial like FREEDOM can likewise be summarized by a statistic, $y = log_e(OR_{FREEDOM})$, and will assume a normal distribution containing θ as the underlying treatment effect that governs the trial observation with its variance σ_i^2. The study-specific trial result y_i can estimate the true underlying treatment effect with standard error $\sigma/\sqrt{n}$.[1] Similar to the prior discussion, we need to set $y_{FREEDOM} = log_e(OR_{FREEDOM})$, and $\sigma^2/n = V(y_{FREEDOM})$.[1] The summed ns can be relabeled n_0 to represent the overall "effective number of events" in the likelihood.

Given that the normal prior $\theta \sim \mathrm{N}[\mu_m, \sigma_m^2/m_0]$ and the normal likelihood $y \sim N[\mu_n, \sigma_n^2/n_0]$ belong to the same family of mathematical functions,[§] we have thus defined a "conjugate normal model."[1] The data table below can be entered into [R] using the code that follows to complete a conjugate-normal analysis.

Supplementary Appendix C: Data table "DMDeathCABGvPCI.csv":

study	n.cabg[]	n.pci[]	r.cabg[]	r.pci[]
BARI[46]	180	173	16	47
ARTS[47]	96	112	8	15
ERACI II[48]	39	39	4	4
MASS II[49]	59	56	9	9
SoS[50]	74	68	1	7
CARDia[51]	248	254	32	37
SYNTAX[52]	202	226	26	44
VA CARDS[53]	97	101	5	21
FREEDOM[44]	761	699	83	114

where: n.cabg = number of patients undergoing CABG, n.pci = number of patients undergoing PCI, r.cabg = number of deaths in the CABG group, and r.pci = number of deaths in the PCI group.

[R] code for Figure 1: Conjugate Normal Analysis.

```
#Export data from Excel in comma-separated format containing a csv suffix, which is the best way to
input data into [R}. Remember that "Z:" is a common designation of the hard disk on a Mac running
Windows, but "C:" is used on a PC. Remember also to replace "johnbittl" with your user name on your
computer, "Dropbox" and "BayesReview" with your folder names, and "DMDeathCABGvPCI.csv" with your file
name:
dmdat<-read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/DMDeathCABGvPCI.csv",as.is=TRUE, header=T)
str(dmdat);
study<-c(dmdat$study);
r.cabg<-c(dmdat$r.cabg);
n.cabg<-c(dmdat$n.cabg);
r.pci<-c(dmdat$r.pci);
n.pci<-c(dmdat$n.pci);
#Calculate ORs, log(OR)s, variance, and effective number of events, m:
for (k in 1:9)
{
or <- ((r.cabg+0.5)/(n.cabg-r.cabg+0.5))/((r.pci+0.5)/(n.pci-r.pci+0.5))
logor <- log(or);
varlogor <- (1/(r.cabg+0.5))+(1/(n.cabg-r.cabg+0.5))+(1/(r.pci+0.5))+(1/(n.pci-r.pci+0.5));
m.theta<-4/varlogor;
}
#Convert to data frame with all variables listed as col heads
mdmdat<-data.frame(study,m.theta,logor);
mdmdat;
#Split dataframe "mdmdat" into subsets, FREEDOM ("new" = likelihood) vs. non-FREEDOM ("old" = prior),
separated by size of report
old<-subset(mdmdat,n.cabg<=500);
new<-subset(mdmdat,n.cabg>=500);
```

```
#calculate total number of events m.0 for prior distribution
m.0<-sum(c(old$m.theta));
#sum log odds weighted by m/m.0
for (k in 1:8)
{
# calculate weighted log odds ratios;
PriorLogOdds <- ((old$m.theta)/m.0)*(old$logor);
}
#sum log odds
PriorPooledLogOR<-sum(c(PriorLogOdds));
PriorPooledLogSD <- 2/(sqrt(m.0));
PriorPooledLogCI <- 1.96*4/(sqrt(m.0));
#calculate 95% CIs for the prior distribution
PriorLower <- PriorPooledLogOR-(PriorPooledLogCI/2);
PriorUpper <- PriorPooledLogOR+(PriorPooledLogCI/2);
#exponentiate to get Prior ORs and 95% CIs
PriorPooledOR <- exp(PriorPooledLogOR);
LowerCI <- exp(PriorLower);
UpperCI <- exp(PriorUpper);
#To get the SD of the backtransformed data in a normal distribution
#-------------------------------------------------------------------------------
#calculate effective number of events n.0 for likelihood from FREEDOM
n.0 <- sum(c(new$m.theta));
likeLogSD<-2/(sqrt(n.0));
for (k in 1:1)
{
# calculate "weighted" log odds ratios;
LikeLogOdds <- ((new$m.theta)/n.0)*(new$logor);
}
likeLogOR<-  sum(c(LikeLogOdds));
likeLogCI <- 1.96*4/(sqrt(n.0));
likeSD<- exp(likeLogSD);
likeOR<-exp(likeLogOR);
#calculate the 95%CIs for the likelihood
likeLogLower <- likeLogOR-(likeLogCI/2);
likeLogUpper <- likeLogOR+(likeLogCI/2);
#exponentiate
likeLowerCI <- exp(likeLogLower);
likeUpperCI <- exp(likeLogUpper);
#-------------------------------------------------------------------------------
#calculate posterior
PostLogOR<-(((m.0*PriorPooledLogOR)+(n.0*(likeLogOR)))/((m.0+n.0)));
PostLogSD<-2/(sqrt(m.0+n.0));
PostCI <- 1.96*4/(sqrt(m.0+n.0));
PostLower<-PostLogOR-(PostCI/2);
PostUpper<-PostLogOR+(PostCI/2);
#exponentiate
PostOR<-exp(PostLogOR);
PostLowerCI<-exp(PostLower);
round(PostLowerCI,2);
PostUpperCI<-exp(PostUpper);
#To get the SD of the backtransformed data in a normal distribution
#-------------------------------------------------------------------------
#print all
PriorLogVariable <-
c("PriorPooledLogOR","PriorPooledLogCI","PriorLower","PriorUpper","PriorPooledLogSD");
PriorLogResult <- c(PriorPooledLogOR,PriorPooledLogCI,PriorLower,PriorUpper,PriorPooledLogSD);
PriorLog <- data.frame(PriorLogVariable, PriorLogResult);
PriorVariable <- c("PriorPooledOR","LowerCI","UpperCI");
PriorResult <- c(PriorPooledOR,LowerCI,UpperCI);
Prior <- data.frame(PriorVariable, PriorResult);
print (PriorLog);
print (Prior);
likeVariable <- c("likeLogSD","likeLogOR","likeSD","likeOR","likeLowerCI","likeUpperCI");
likeResult <- c(likeLogSD,likeLogOR,likeSD,likeOR,likeLowerCI,likeUpperCI);
likeData <- data.frame(likeVariable,likeResult);
```

```
like <- data.frame (likeData);
print (like);
PostLogVariable <- c("PostLogOR", "PostLower", "PostUpper", "PostLogSD");
PostLogResult <- c(PostLogOR, PostLower, PostUpper, PostLogSD);
PostLog <- data.frame(PostLogVariable, PostLogResult);
PostVariable <- c("PostOR", "PostLowerCI", "PostUpperCI");
round(PostLowerCI,2);
PostResult <- c(PostOR, PostLowerCI, PostUpperCI);
Post <- data.frame(PostVariable, PostResult);
print (PostLog);
print (Post);
#------------------------------------------------------------------------
#triplot
x<-seq(from=-1,to=0.3,by=0.01);
#Prior
y1=dnorm(x,mean<-PriorPooledLogOR,sd<-PriorPooledLogSD);
#Likelihood
y2=dnorm(x,mean<-likeLogOR,sd<-likeLogSD);
#Posterior
y3=dnorm(x,mean<-PostLogOR, sd<-PostLogSD);
maxY = max( c(y1,y2,y3) );
plot(x,y1,type="l", ylim = c(0,maxY), cex.axis=1.0, xlab=bquote(theta), cex.lab=1.6, ylab="Probability
Density", axes=TRUE, lwd=3,col="blue");
axis (4, pos=0.0, tck = 0, labels=FALSE, col="black");
text (-0.8,3,"Prior (8 trials)",col="blue", cex= 1.4, font=3);
text (-0.8,2.7,"(Refs. 23-30)",col="blue", cex= 1.4, font=3);
text (-0.12,2.5,"Likelihood (FREEDOM) (19)",col="red",cex = 1.4, font =3);
text (-0.35, 3.5, "Posterior", cex = 1.4, font=3);
text (-0.90, 3.8,"A. All-cause",cex = 1.6);
text (-0.90, 3.5,"mortality",cex = 1.6);
text(-0.9,1.5,"CABG better",cex=1.2, font=3);
text(0.2,1.5,"PCI better",cex=1.2, font=3);
text (PostLogOR, 0.55, round(PostOR,2))    ;
text (PostLower-0.05, 0.55, round(PostLowerCI,2)) ;
text (PostUpper+0.05, 0.55, round(PostUpperCI,2)) ;
text (PriorPooledLogOR, max(y1)/7, col="blue",round(PriorPooledOR,2));
text (PriorLower-0.04, max(y1)/7, col="blue",round(LowerCI,2));
text (PriorUpper+0.04, max(y1)/7, col="blue",round(UpperCI,2)) ;
text (likeLogOR, max(y2)/7.5, col="red", round(likeOR,2)) ;
text (likeLogLower-0.04, max(y2)/7.5, col="red", round(likeLowerCI,2)) ;
text (likeLogUpper+0.04, max(y2)/7.5, col="red", round(likeUpperCI,2))  ;
segments(PostLower, max(y3)/7, PostLogOR-0.04, max(y3)/7, lty=1, col="black", lwd=2) ;
segments(PostUpper, max(y3)/7, PostLogOR+0.04, max(y3)/7, lty=1, col="black", lwd=2) ;
segments(PriorLower, max(y1)/7, PriorPooledLogOR-0.04, max(y1)/7, lty=1, col="blue", lwd=2) ;
segments(PriorUpper, max(y1)/7, PriorPooledLogOR+0.04, max(y1)/7, lty=1, col="blue", lwd=2) ;
segments(likeLogLower, max(y2)/7.5, likeLogOR-0.04, max(y2)/7.5, lty=1, col="red", lwd=2) ;
segments(likeLogUpper+0.005, max(y2)/7.5, likeLogOR+0.04, max(y2)/7.5, lty=1, col="red", lwd=2)  ;
mtext ("Odds Ratio",3, line =2, cex = 1.6);
axis (3, at=c(-0.91,-0.69, -0.51, -0.35, -0.22, -0.105, 0.0, 0.095, 0.262), labels=c(0.4,0.5, 0.6, 0.7,
0.8, 0.9, "1.0", 1.1, 1.3));
lines(x,y2,type="l",lwd=3,col="red");
lines(x,y3,type="l", lwd=3,col="black");
#To create good margins
mar.default <- c(5,4,4,2) + 0.1;
par(mar = mar.default + c(0, 4, 0, 0));
#To copy in eps and pdf formats to your original folder. (Change the date each time or you will
overwrite.)
dev.copy2eps(file="DMDeathJun10.eps");
dev.copy2pdf(file="DMDeathjun10.pdf");
```

Bayes factors. The use of Bayes factors (BFs) is a potentially superior approach to quantifying evidence than is the potentially conflicting mix of approaches based on *P* values and

hypothesis testing.[1, 56] The BF is defined as a likelihood ratio (LR) or relative likelihood of two different hypotheses and can range from 0 to ∞, with small values close to 0 simultaneously providing strong evidence against the null hypothesis and for the alternative hypothesis.[1, 43, 56]

Bayes factors can be derived from the relation:

$$Prior\ Odds\ of\ Null\ Hypothesis\ \times\ Bayes\ factor\ =\ Posterior\ Odds\ of\ Null\ Hypothesis,$$

where the Bayes factor =

$$\frac{Prob(Data, given\ the\ null\ hypothesis)}{Prob(Data, given\ the\ alternative\ hypothesis)}$$

Using data from Figure 1 in the main report, we obtain:

Comparison	Bayes Factor	Prior Probability (%)	Prior Probability	Prior Odds	Posterior Odds	Posterior Probability	Posterior Probability (%)
FREEDOM	1.19E-02	2.70E-04	2.70E-06	2.70E-06	3.22E-08	3.22E-08	3.22E-06

Calculations as follows[56]: Odds = Prob/(1-Prob). Posterior odds = Bayes factor × prior odds. Minimum Bayes factors (BF) can also be calculated from[56]:

$$Minimum\ Bayes\ Factor\ =\ e^{-Z^2/2},$$

using 2-tailed outputs for Z from [R] functions "pnorm" and "qnorm," which in this case produced a value of 1.09E-02, in good agreement with the previous calculation.

Hierachical meta-analysis using a noninformative prior. We created a hierarchical Bayesian model to compare PCI with CABG in diabetic patients with multivessel CAD:

$$\begin{aligned} Log_e(OR_i)|\theta_i, s_i^2 &\overset{independent}{\sim} N(\theta_i, s_i^2), \\ \theta_i|\theta, \tau^2 &\overset{independent}{\sim} N(\theta, \tau^2), \\ (\theta, \tau^2) &\sim p(\theta, \tau^2), \end{aligned} \qquad (1)$$

where OR_i denotes the odds ratio for mortality after CABG compared with PCI in the i-th (i =1,... 9) study, θ_i the unknown study-level treatment effect (a quantity that is not directly observable but is a parameter that governs the hypothetical processes leading to the observed treatment effect[11]) s_i^2 the (asymptotic) variance of $\log_e(OR_i)$, θ the population-average treatment effect, and τ^2 the between-study variance of study-level effects.[**]

[**] In Bayesian meta-analysis, we have a separate parameter for mean treatment effect in each trial, θ_i, but we can formulate a structural prior to state that these treatment effects should not be too different from each other in a hierarchical model, where a common underlying mean efficacy is postulated and each trial effect is independently distributed around this mean.

Compared with the fixed-effects approach to meta-analysis (i.e., assuming $\theta_1 = \theta_2 = \cdots = \theta$), the random-effects meta-analysis model acknowledges the existence of between-study variation and incorporates it explicitly into the estimation process.[57] Moreover, the prior belief about the summary effect size θ and between-study heterogeneity is incorporated into the prior distribution $p(\theta, \tau^2)$.[58]

[R] Code for Figure 2: Hierarchical Meta-Analysis

```
#Export data from Excel in comma-separated format containing a csv suffix, which is the best way to
input data into [R}. Remember that "Z:" is a common designation of the hard disk on a Mac running
Windows, but "C:" is used on a PC. Remember also to replace "johnbittl" with your user name on your
computer, "Dropbox" and "BayesReview" with your folder names, and "DMCABGvPCI.csv" with your file name:
Ddat<-read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/DMDeathCABGvPCI.csv",as.is=TRUE, header=T);
str(Ddat);
study_name<-c(Ddat$study_name);
r.cabg<-c(Ddat$r.cabg);
n.cabg<-c(Ddat$n.cabg);
r.pci<-c(Ddat$r.pci);
n.pci<-c(Ddat$n.pci);
#Specify the model in BUGS language, but save it as a string in [R]
modelString="
model
{
# K1 is the number of trials;
for (k in 1:9)
{
# calculate odds ratios;
or[k] <- ((r.cabg[k]+0.5)/(n.cabg[k]-r.cabg[k]+0.5))/((r.pci[k]+0.5)/(n.pci[k]-r.pci[k]+0.5));
logor[k] <- log(or[k]);
varlogor[k] <- (1/(r.cabg[k]+0.5))+(1/(n.cabg[k]-r.cabg[k]+0.5))+(1/(r.pci[k]+0.5))+(1/(n.pci[k]-
r.pci[k]+0.5));
invlogor[k] <- 1/varlogor[k];  #variance;
logor[k] ~ dnorm(theta[k], invlogor[k]);
or.est[k] <- exp(theta[k]);
theta[k] ~ dnorm(mu.theta, prec.theta); # random effects distribution;
}
mu.theta ~ dnorm(0, 0.001); # uninformative prior distribution
prec.theta ~ dgamma(0.001, 0.001);  # uninformative prior distribution;
or.theta <- exp(mu.theta);
# probability of mean effect greater than zero;
pmu0 <- equals(min(mu.theta,0),0);
theta.new ~ dnorm(mu.theta, prec.theta);  # predicted theta for a new study;
or.new <- exp(theta.new);  # calculate the new OR;
# BUGS model specification ends
}
  "
# Write the modelString to a file
writeLines (modelString,con="model.txt");
# Use BRugs to check model
modelCheck ("model.txt");
#load data
dataList = list(n.cabg=c(n.cabg),
     n.pci=c(n.pci),
     r.cabg=c(r.cabg),
     r.pci=c(r.pci)
);

#Use BRugs commands to put the data into a file and ship the file to BUGS
modelData(bugsData(dataList));
#Initialize the chains
nChain=1;
```

```
modelCompile(numChains = nChain); #Compile the model
initsList = list(mu.theta=0, prec.theta=1);
modelInits(bugsData(initsList));
modelGenInits()
#R defines a new variable to specify an arbitrary chain length
chainLength1 = 5000;
#BRugs tells BUGS to generate a MCMC chain
modelUpdate (chainLength1);
#BRugs keeps a record of parameters
samplesSet(c("mu.theta","or.new","prec.theta","or.theta","theta.new"));
#BRugs asks BUGS for summary statistics
chainLength2 = 10000;
thinStep = 2;
modelUpdate (chainLength2);
thetaSummary = samplesStats (c("mu.theta","or.new","prec.theta","or.theta","theta.new")); thetaSummary;
print(thetaSummary);
```

[R] Code for Figure 2: Standard Meta-Analysis

Traditional forest plots can be created with the open-source statistical program [R] 3.0.3[59] and library package “meta” 3.8-0[60] using the following [R] code:

```
#Export data from Excel in comma-separated format containing a csv suffix, which is the best way to
input data into [R}. Remember that "Z:" is a common designation of the hard disk on a Mac running
Windows, but "C:" is used on a PC. Remember also to replace "johnbittl" with your user name on your
computer, "Dropbox" and "BayesReview" with your folder names, and "DMDeath.csv" with your file name:
deathdat<-read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/DMDeathCABGvPCI.csv",as.is=TRUE, header=T);
str(deathdat);
study<-c(deathdat$study);
r.cabg<-c(deathdat$r.cabg);
n.cabg<-c(deathdat$n.cabg);
r.pci<-c(deathdat$r.pci);
n.pci<-c(deathdat$n.pci);
mdeathdat<-data.frame(study,n.cabg,n.pci,r.cabg,r.pci);
mdeathdat;
mdeath1 = metabin(r.cabg, n.cabg, r.pci, n.pci, sm = "OR", data = mdeathdat, studlab = study);
str(mdeath1);
class(mdeath1);
mdeath1;
summary(mdeath1);
X11(width=10,height=7);
forest(mdeath1,col.square="blue",col.diamond="blue",rightcols=c("effect",
"ci"),lab.e="CABG",lab.c="PCI",xlim=c(0.1,10),xlab="CABG better      PCI better");
dev.copy2eps(file="metaDMDeathJun10.eps");
dev.copy2pdf(file="metaDMDeathJun10.pdf");
```

Supplemental Appendix D: Network Meta-Analysis of Outcomes after Various Durations of Dual Antiplatelet Therapy (DAPT) after Drug-Eluting Stent (DES) Implantation

We developed Bayesian meta-analysis models to perform indirect comparisons after short (S), medium (M) or long (L) durations of DAPT because direct comparisons do not exist, using a technique also called mixed treatment comparisons or network meta-analysis.[61] For each of the RCTs, we assume that the number of deaths after each duration of DAPT has a binomial distribution, and the logit of the mortality rate has a non-informative prior distribution. For the 7 studies that have both 3-6 month and 12 month arms,[62-68] we model the number of death events after short DAPT as a binomial distribution, and assume that the difference of log odds between a short (S) duration of DAPT and a 12 month duration (M) of DAPT from each study $\delta_{i,SM}$ follows a normal random effects distribution with mean d_{SM} and variance τ^2_{SM}, where d_{SM} characterizes the comparative effectiveness between a short duration of DAPT and 12 months of therapy. Similarly, for the 4 studies that have arms treated with 12 months (M) of DAPT and long (L) durations of DAPT, we model the number of deaths after prolonged DAPT as a binomial distribution, and assume that the difference of log odds from each study δ_{LM} follows a normal random effects distribution with mean d_{LM} and variance τ^2_{LM}, where d_{LM} characterizes the comparative effectiveness between prolonged DAPT and 12 months of therapy.

The difference between d_{SM} and d_{LM}, which can be denoted by $d_{SL} = d_{SM} - d_{LM}$, parameterizes the comparative effectiveness between short and long durations of DAPT under the model. Finally, we complete the model specification by imposing prior distributions to the parameters. The complete model is as follows:

$$
\begin{aligned}
12\ mos\ arm\ for\ studies: r_{iM} &\overset{independent}{\sim} Binomial(p_{iM}, N_{iM}),\\
Log(p_{iM}/(1-p_{iM})) &= \mu_{iM},\\
\mu_{iM} &\overset{independent}{\sim} N(0, 10^3), i = 1, \dots, 11,\\
Short\ arm\ for\ relevant\ studies: r_{iS} &\overset{independent}{\sim} Binomial(p_{iS}, N_{iS}),\\
Short\ vs.\ 12\ mos: Log(p_{iS}/(1-p_{is})) = \mu_{iS} &= \mu_{iS} + \delta_{i,SM},\\
\delta_{i,SM} &\overset{independent}{\sim} N(d_{SM}, \tau^2_{SM}), i = 1, \dots, 7,\\
Long\ DAPT\ arm\ for\ relevant\ studies: r_{iL} &\overset{independent}{\sim} Binomial(p_{iL}, N_{iML}),\\
Long\ vs.\ 12\ mos: Log(p_{iL}/(1-p_{iL})) = \mu_{iL} &= \mu_{iM} + \delta_{i,LM},\\
\delta_{i,LM} &\overset{independent}{\sim} N(\delta_{LM}, \tau^2_{LM}), i = 8, \dots, 11,\\
Priors: d_{SM} &\sim N(0, 10^3),\\
d_{LM} &\sim N(0, 10^3),\\
\tau^2_{SM} &\sim IG(10^{-3}, 10^{-3}),\\
\tau^2_{LM} &\sim IG(10^{-3}, 10^{-3}),
\end{aligned}
$$

where r_{iM}, p_{iM}, and N_{iM} are the number of deaths, associated mortality, and number of subjects from the 12-month arm of 11 studies, respectively, r_{iS}, p_{iS}, and N_{iS} are the number of deaths, associated mortality, and number of subjects from short DAPT arm of 9 studies, and r_{iL}, p_{iL}, and N_{iL} are the number of deaths, associated mortality, and number of subjects from the prolonged DAPT arm of 5 studies.

Data Table for Mortality in the DAPT Network Meta-Analysis: "NetworkDAPTDeath"

	s[]	t[]	r[]	nn[]	b[]
DES-LATE (36 vs. 12 mo)	1	2	32	2514	1
DES-LATE (36 vs. 12 mo)	1	3	46	2531	1
PRODIGY (24 vs. 6 mo)	2	1	45	751	1
PRODIGY (24 vs. 6 mo)	2	3	49	750	1
EXCELLENT (12 vs. 6 mo)	3	1	4	722	1
EXCELLENT (12 vs. 6 mo)	3	2	7	721	1
RESET (12 vs. 3 mo)	4	1	5	1059	1
RESET (12 vs. 3 mo)	4	2	8	1058	1
OPTIMIZE (12 vs. 3 mo)	5	1	43	1563	1
OPTIMIZE (12 vs. 3 mo)	5	2	45	1556	1
ARCTIC (18 vs. 12 mo)	6	2	9	624	1
ARCTIC (18 vs. 12 mo)	6	3	7	635	1
SECURITY (12 vs. 6 mo)	7	1	8	682	1
SECURITY (12 vs. 6 mo)	7	2	8	717	1
DAPT (30 vs. 12 mo)	8	2	74	4941	1
DAPT (30 vs. 12 mo)	8	3	98	5020	1
ITALIC (24 vs. 6 mo)	9	1	8	912	1
ITALIC (24 vs. 6 mo)	9	3	7	910	1
ISAR-SAFE (12 vs. 6 mo)	10	1	8	1997	1
ISAR-SAFE (12 vs. 6 mo)	10	2	12	2003	1
OPTIDUAL (48 vs. 12 mo)	11	2	24	690	1
OPTIDUAL (48 vs. 12 mo)	11	3	16	695	1
I-LOVE-IT 2 (12 vs. 6 mo)	12	1	11	909	1
I-LOVE-IT 2 (12 vs. 6 mo)	12	2	14	920	1
IVUS-XPL (12 vs. 6 mo)	13	1	5	699	1
IVUS-XPL (12 vs. 6 mo)	13	2	10	701	1
NIPPON (18 vs. 6 mo)	14	1	16	1654	1
NIPPON (18 vs. 6 mo)	14	3	7	1653	1

Abbreviations: ARCTIC[69] is Assessment by a double Randomisation of a Conventional antiplatelet strategy versus a monitoring-guided strategy for drug-eluting stent implantation and of Treatment Interruption versus Continuation 1 year after stenting; CI, confidence interval; DAPT,[70] Dual Antiplatelet Therapy; DES-LATE,[71] Optimal Duration of Clopidogrel Therapy With Drug Eluting Stents to Reduce Late Coronary Arterial Thrombotic Events; EXCELLENT,[64] Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting; ISAR-SAFE,[66] Intracoronary Stenting and Antithrombotic Regimen: Safety And EFficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting; I-LOVE-IT 2,[67] Evaluate Safety and Effectiveness of the Tivoli DES and the Firebird DES for Treatment of Coronary Revascularization 2; ITALIC,[72] Is There A LIfe for DES After Discontinuation of Clopidogrel; IVUS-XPL, Impact of Intravascular Ultrasound Guidance on Outcomes of Xience Prime stents in Long lesions; NIPPON,[73] Nobori Dual Antiplatelet Therapy as Appropriate Duration; OPTIDUAL,[74] OPTImal DUAL Antiplatelet Therapy; OPTIMIZE, Optimized Duration of Clopidogrel Therapy Following Treatment With the Zotarolimus-Eluting Stent in Real-World Clinical Practice; OR, odds ratio; PRODIGY,[75] Prolonging Dual Antiplatelet Treatment After Grading Stent-Induced Intimal Hyperplasia; RESET,[62] REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation; SECURITY,[65] Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy.

R Code for Fig. 5: Network Meta-Analysis for DAPT Mortality and Caterpillar Plot

```
#Export data from Excel in comma-separated format containing a csv suffix, which is the best way to
input data into [R}. Remember that "Z:" is a common designation of the hard disk on a Mac running
Windows, but "C:" is used on a PC. Remember also to replace "johnbittl" with your user name on your
computer, "Dropbox" and "BayesReview" with your folder names, and "NetworkDAPTDeath.csv" with your file
name:
DDdat<-read.csv("Z:/Users/johnbittl/Dropbox/BayesReview/NetworkDAPTDeath.csv",as.is=TRUE, header=T)
str(DDdat)
s<-c(DDdat$s)
t<-c(DDdat$t)
r<-c(DDdat$r)
nn<-c(DDdat$nn)
b<-c(DDdat$b)
#Specify the model in BUGS language, but save it as a string in [R]
modelString="
model
{ # i counts the two arms of all 14 studies
for (i in 1:28)
{
r[i] ~ dbin(p[i], nn[i]);
logit(p[i]) <- mu[s[i]]+delta[i]*(1-equals(t[i],b[i]));
delta[i] ~ dnorm(md[i], prec);
md[i] <- d[t[i]]-d[b[i]];
}
# j represents the CABG arm
for (j in 1:14)
{
mu[j] ~ dnorm(0, .001);
}
prec ~ dgamma(0.001, 0.001);
d[1] <- 0;
```

```
# K represents the relative treatment comparator: k1 = Short, k=2 is 12 mo, k=3 is Long
for (k in 2:3)
{
d[k] ~ dnorm(0, .001)
}
for (c in 1:2)
{
for (k in (c+1):3)
{
lor[c,k] <- d[k]-d[c];
log(or[c,k]) <- lor[c,k];
}
}
}
  "
# Write the modelString to a file
writeLines (modelString,con="model.txt")
# Use BRugs to check model
modelCheck ("model.txt")
#load data
dataList = list(s=c(s),
     t=c(t),
     r=c(r),
     nn=c(nn),
     b=c(b)
)

#Use BRugs commands to put the data into a file and ship the file to BUGS
modelData(bugsData(dataList))
#Initialize the chains
nChain=1
modelCompile(numChains = nChain) #Compile the model
initsList = list(d=c(NA,0,0), prec=1, mu=c(0,0,0,0,0,0,0,0,0,0,0,0,0,0))
modelInits(bugsData(initsList))
modelGenInits()
#R defines a new variable to specify an arbitrary chain length
chainLength1 = 5000
#BRugs tells BUGS to generate a MCMC chain
modelUpdate (chainLength1)
#BRugs keeps a record of parameters
samplesSet(c("lor"))
#BRugs asks BUGS for summary statistics
chainLength2 = 10000
thinStep = 2
modelUpdate (chainLength2)
thetaSummaryObs = samplesStats (c("lor")); thetaSummaryObs
thetaSummaryObs<-thetaSummaryObs[order(thetaSummaryObs$mean),]
expTheta<-exp(thetaSummaryObs)
print(thetaSummaryObs)
print(expTheta)
#forest plot
x<-seq(from=-0.8,to=0.6,by=0.01)
#Short vs. 12 mo
x<-thetaSummaryObs$mean
y<-c(1,2,3)
plot(x,y,xlim=c(-0.7,0.6),ylim=c(3.5,0),pch=23,cex=4,ylab="",yaxt="n",col="black",bg="lightblue",
cex.axis=1.0, xlab="log(e)OR", cex.lab=1.6)
axis (4, pos=0.0, tck = 0, labels=FALSE, col="black")
text (-0.555,1,"3-6 mos vs. 12 mos", cex= 1.4)
text (-0.53,3,"3-6 mos vs. 18-48 mos",cex = 1.4)
text (-0.54,2, "12 mos vs. 18-48 mos", cex = 1.4)
text (0, 0,"All-Cause Mortality",cex = 1.6,font =2)
text (0.4, 0.6, "Short DAPT Better",cex=1.6,font=3)
text (-0.4, 0.6, "Long DAPT Better",cex=1.6,font=3)
text (thetaSummaryObs$mean[3], 3.2, font=2, round(expTheta$mean[3],2))
text (thetaSummaryObs$val2.5pc[3], 3.2, font=2,round(expTheta$val2.5pc[3],2))
```

```
#text (thetaSummaryObs$val97.5pc[3], 3.2, font=2,round(expTheta$val97.5pc[3],2))
text (thetaSummaryObs$val97.5pc[3], 3.2, font=2,"1.60")
text (thetaSummaryObs$mean[1],1.2,font=2,round(expTheta$mean[1],2))
#text (thetaSummaryObs$val2.5pc[1], 1.2, font=2,round(expTheta$val2.5pc[1],2))
text (thetaSummaryObs$val2.5pc[1], 1.2, font=2,"0.70")
text (thetaSummaryObs$val97.5pc[1], 1.2, font=2,round(expTheta$val97.5[1],2))
text (thetaSummaryObs$mean[2], 2.2,  font=2,round(expTheta$mean[2],2))
text (thetaSummaryObs$val2.5pc[2], 2.2,  font=2,round(expTheta$val2.5pc[2],2))
text (thetaSummaryObs$val97.5pc[2], 2.2,  font=2,round(expTheta$val97.5pc[2],2))
segments(thetaSummaryObs$val2.5pc[3], 3, thetaSummaryObs$mean[3]-0.025, 3, lty=1, col="black", lwd=3)
segments(thetaSummaryObs$val97.5pc[3], 3, thetaSummaryObs$mean[3]+0.025, 3, lty=1, col="black", lwd=3)
segments(thetaSummaryObs$val2.5pc[1], 1, thetaSummaryObs$mean[1]-0.025, 1, lty=1, lwd=3)
segments(thetaSummaryObs$val97.5pc[1], 1, thetaSummaryObs$mean[1]+0.025, 1, lty=1,  lwd=3)
segments(thetaSummaryObs$val2.5pc[2], 2, thetaSummaryObs$mean[2]-0.025, 2, lty=1,  lwd=3)
segments(thetaSummaryObs$val97.5pc[2], 2, thetaSummaryObs$mean[2]+0.025, 2, lty=1,  lwd=3)
mtext ("Posterior Odds Ratio (OR)",3, line =2, cex = 1.6)
axis (3, at=c(-0.91,-0.69, -0.51,-0.35, -0.22, -0.105,0.0, 0.095,0.182, 0.262,0.336,
0.405,0.47,0.531,0.588,0.693, 0.833, 0.956, 1.10,1.19, 1.281,1.386,1.46,1.53,1.61,1.67,1.72,1.79),
labels=c(0.4,0.5,0.6, 0.7, 0.8,0.9, "1.0", 1.1,1.2, 1.3,1.4,1.5, 1.6,1.7, 1.8, "2.0", 2.3, 2.6, "3.0",
3.3,3.6,"4.0",4.3,4.6,"5.0",5.3,5.6,"6.0"))
#To create good margins
mar.default <- c(5,4,4,2) + 0.0
par(mar = mar.default + c(0, 2, 0, 0))
#To copy in eps and pdf formats to your original folder. (Change the date each time or you will
overwrite.)
dev.copy2eps(file="NetworkDAPTDeathJun10Caterpillar.eps")
dev.copy2pdf(file="NetworkDAPTDeathJun10Caterpillar.pdf")
```

Supplemental Appendix E: Hierarchical Model for Cross-Design Meta-Analysis

Justification: In this setting a hierarchical model is appropriate, because when we have uncertainty about a parameter such as θ, which reflects the overall treatment difference between the 2 PCI strategies, we make inferences about it. When other parameters such as $OR_{i(k)}$, reflecting treatment differences from studies i = 1,…n of study type k = 1,…n, are also uncertain but dependent on an uncertain parameter such as θ, we have a chain of uncertainty, formalized in a hierarchical model.[3]

Selection of priors: Following the guidance of published reports,[77, 78] we choose vague prior distributions for the parameters θ, σ^2 and τ_k^2.[1, 17] Specifically, for θ, the overall population effect, a relatively vague prior distribution is specified on the basis that that the global summary OR is unlikely to exceed 500 in favor of either culprit vessel-only or multivessel PCI, and therefore a prior distribution has the standard deviation $\log_e(500)/1.96 = 3.17$, or $\theta \sim N[0, 10]$.[1]

A prior distribution for each τ_k^2 is based on the assumption that were 95% sure that the true underlying risk ratio for a particular type will be within a range from 4x to ¼ the overall risk of that type, which means that the upper 95% point of the prior for each τ_k is $\log_e(16)/(2 \cdot 1.96) = 0.71$. A half-normal distribution $\tau_k \sim HN[0.36^2]$ has this property.[1]

Likewise, a prior for the between-type variance σ^2 can be derived from assuming 95% belief that the underlying risk ratio for a particular study type will less than 2x or more than ½ the overall population effect. On this basis, a half-normal prior distribution $\sigma \sim HN[0.18^2]$ is used.[1]

Despite the subjectiveness of the priors, they represent reasonable guesses for the magnitudes and ranges of the parameters. On the other hand, because only 3 study designs are included, both the mean and variance estimates for θ would have been imprecise if they are inferred from noninformative priors.

Data for Cross-Design Meta-Analysis

Study	Year of Report	Follow-Up (days)	Number Enrolled		Number with Events		Study Type
			Multivessel	*Culprit*	*Multivessel*	*Culprit*	
Randomized controlled trials							
Di Mario et al[79]	2004	365	52	17	1	0	1
Politi et al[80]	2010	900	65	84	6	13	1
Wald et al[81]	2013	700	234	231	12	16	1
Gershlick et al[82]	2015	365	150	146	4	10	1
Total			**501**	**478**	**23**	**39**	

Matched cohort studies							
Roe et al[83]	2001	180	79	79	19	13	2
Hannan et al[84]	2010	1260	503	503	59	54	2
Iqbal et al[85]	2014	365	403	2418	41	164	2
Total			**985**	**3000**	**119**	**231**	
Other observational studies							
Corpus et al[86]	2004	365	26	354	5	42	3
Qarawani et al[87]	2008	365	95	25	9	2	3
Varani et al[88]	2008	In-hospital	147	156	12	8	3
Cavender et al[89]	2009	In-hospital	3134	25802	246	1321	3
Dziewerz et al[90]	2010	365	70	707	11	57	3
Toma et al[91]	2010	90	217	1984	27	111	3
Bauer et al[92]	2013	In-hospital	419	2118	6	72	3
Jaguszewski et al[93]	2013	In-hospital	1108	3833	81	168	3
Jeger et al[94]	2014	365	442	1467	12	40	3
Santos et al[95]	2014	in-hospital	77	180	2	14	3
Manari et al[96]	2014	730	367	706	26	127	3
Total observational studies			**6102**	**37322**	**437**	**1962**	
TOTAL			**7588**	**40810**	**579**	**2232**	

Study types, 1 = randomized controlled trial, 2 = matched cohort study, 3 = other type of observational study.

[R] code for Fig. 7: Bayesian cross-design meta-analysis using imbedded data

```
#Specify the model in BUGS language, but save it as a string in [R]
modelString="
model
{
# K1 is the number of trials;
for (k in 1:18)
{
# calculate odds ratios;
or[k] <- ((r.multi[k]+0.5)/(n.multi[k]-
r.multi[k]+0.5))/((r.culprit[k]+0.5)/(n.culprit[k]-r.culprit[k]+0.5))
logor[k] <- log(or[k]);
varlogor[k] <- (1/(r.multi[k]+0.5))+(1/(n.multi[k]-
```

```
r.multi[k]+0.5))+(1/(r.culprit[k]+0.5))+(1/(n.culprit[k]-r.culprit[k]+0.5));
invlogor[k] <- 1/varlogor[k];
logor[k] ~ dnorm(theta[k], invlogor[k]);
or.est[k] <- exp(theta[k]);
# study-type level random-effects distributions
theta[k] ~ dnorm(mu.theta.study[study[k]], prec.theta.study[study[k]]);
}
# K2 is the number of study types
for (l in 1:3)
{
mu.theta.study[l] ~ dnorm(mu.theta, prec.theta);
or.theta.study[l] <- exp(mu.theta.study[l]);
prec.theta.study[l] <- 1/(tau.theta.study[l]*tau.theta.study[l]);
# prior distribution for tau.theta.study based on HN[0.36^2], giving precision 7.72
tau.theta.study[l] ~ dnorm(0, 7.72)I(0,);
}
# prior distribution for mu.theta based on log(500)/1.96 = 3.17 for N[0,10], giving
precision 0.1
mu.theta ~ dnorm(0, 0.1);
# prior distribution for tau.theta based on HN[0.18^2], giving precision 30.86
tau.theta ~ dnorm(0, 30.86)I(0,);
prec.theta <- 1/(tau.theta*tau.theta);
# global summary odds ratio;
or.theta <- exp(mu.theta);
# K1 is the number of trials;
# DATA list(K1=21, K2=3);
# INITIAL VALUES list(mu.theta=0, tau.theta = 1);
# BUGS model specification ends
} .

  "
# Write the modelString to a file
writeLines (modelString,con="model.txt")
# Use BRugs to check model
modelCheck ("model.txt")
#load data
dataList = list(n.multi=c(52, 65, 234, 150, 79, 503, 403, 26, 95, 147, 3134, 70, 217,
419, 1108, 442, 77, 367),
     n.culprit=c(17, 84, 231, 146, 79, 503, 2418, 354, 25, 156, 25802, 707, 1984,
2118, 3833, 1467, 180, 706),
     r.multi=c(1, 6, 12, 4, 19, 59, 41, 5, 9, 12, 246, 11, 27, 6, 81, 12, 2, 26),
     r.culprit=c(0, 13, 16, 10, 13, 54, 164, 42, 2, 8, 1321, 57, 111, 72, 168, 40, 14,
127),
     study=c(1, 1, 1, 1, 2, 2, 2, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3)
)

#Use BRugs commands to put the data into a file and ship the file to BUGS
modelData(bugsData(dataList))
#Initialize the chains
nChain=1
modelCompile(numChains = nChain) #Compile the model
initsList = list(mu.theta=0, tau.theta=1)
modelInits(bugsData(initsList))
modelGenInits()
#R defines a new variable to specify an arbitrary chain length
```

```
chainLength1 = 5000
#BRugs tells BUGS to generate a MCMC chain
modelUpdate (chainLength1)
#BRugs keeps a record of parameters
samplesSet(c("mu.theta","prec.theta","or.theta","tau.theta"))
#BRugs asks BUGS for summary statistics
chainLength2 = 10000
thinStep = 2
modelUpdate (chainLength2)
thetaSummary = samplesStats (c("mu.theta","prec.theta","or.theta","tau.theta"));
print(thetaSummary)
```

---

output

```
> source("Z:\\Users\\jabittl\\Dropbox\\BayesCulpritCCI\\BRugs18StudiesCrossDesign.R")
model is syntactically correct
data loaded
model compiled
Initializing chain 1:
initial values generated, model initialized
5000 updates took 0 s
monitor set for variable 'mu.theta'
monitor set for variable 'prec.theta'
monitor set for variable 'or.theta'
monitor set for variable 'tau.theta'
10000 updates took 0 s
            mean       sd            MC_error  val2.5pc   median    val97.5pc  start   sample
mu.theta   8.358e-02 1.803e-01 6.970e-03 -0.301500  0.09143 4.089e-01  5001  10000
prec.theta 1.080e+05 2.844e+06 8.695e+04  6.367000 47.98000 2.273e+04  5001  10000
or.theta   1.105e+00 1.959e-01 7.564e-03  0.739700  1.09600 1.505e+00  5001  10000
tau.theta  1.579e-01 1.063e-01 3.704e-03  0.006652  0.14440 3.964e-01  5001  10000
```

References

1. Spiegelhalter DJ, Abrams KR, Myles JP. *Bayesian Approaches to Clinical Trials and Health Care Evaluations*. Chichester, England: Wiley; 2004.
2. Bertsekas DP, Tsitsiklas JN. *Introduction to Probability*. Belmont, Massachusetts: Athena Scientific; 2008.
3. Kruschke JK. *Doing Bayesian Data Analysis: A Tutorial with R and BUGS*. Oxford, England: Elsevier; 2011.
4. Browner WS. Bayesian reasoning and diagnostic testing. In: Wachter RM, Goldman L, Hollander H, eds. *Hospital Medicine*. Philadelphia: Lippincott Williams & Wilkins; 2005:37-42.
5. Diamond GA, Forrester JS. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. *N Engl J Med*. 1979;300:1350-1358
6. Morice JC, Serruys PW, Sousa JE, Fajadet J, Hayashi EB, Perin M, Colombo A, Schuler G, Barragan P, Guagliumi G, Molnar F, Falotico R. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revacularization. *N Engl J Med*. 2002;346:1773-1780
7. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, Chambers CE, Ellis SG, Guyton RA, Hollenberg SM, Khot UN, Mauri L, Mehran R, Moussa ID, Mukherjee D, Nallamothu BK, Ting HH. 2011 ACCF/AHA/SCAI guidelines for percutaneous coronary intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574-e651
8. Lunn D, Jackson C, Best N, Thomas A, Spiegelhalter D. *The BUGS Book: A Practical Introduction to Bayesian Analysis*. Boca Raton, FL: CRC Press; 2013.
9. Carlin JB, Louis TA. *Bayesian Methods for Data Analysis*. Boca Raton, FL: Chapman & Hall/CRC; 2009.
10. Welton N, Sutton AJ, Cooper NJ, Abrams KR, Ades AE. *Evidence Synthesis for Decision Making in Healthcare*. Chichester, West Sussex, United Kingdom: Wiley; 2012.
11. Gelman A, Carlin JB, Stern HS, Rubin DB. *Bayesian Data Analysis*. Boca Raton, FL: Chapman and Hall/CRC; 2013.
12. Kruschke JK. *Doing Bayesian Data Analysis: A Tutorial with R, JAGS, and Stan*. Oxford, England: Academic Press/Elsevier; 2015.
13. Biondi-Zoccai G. Network Meta-Analysis: Evidence Synthesis with Mixed Treatment Comparison. 2014
14. Palmerini T, Benedetto U, Bacchi-Reggiani L, Della Riva D, Biondi-Zoccai G, Feres F, Abizaid A, Hong M-K, Kim B-K, Jang Y, Kim H-S, Park KW, Genereux P, Bhatt DL, Orlandi C, De Servi S, Rapezzi C, Stone GW. Mortality in patients treated with extended duration dual antiplatelet therapy after drug-eluting stent implantation: a pairwise and Bayesian network meta-analysis of randomised trials. *Lancet*. 2015;385:2371-2382
15. Palmerini T, Biondi-Zoccai G, Della Riva D, Mariani A, Sabate M, Smits PC, Kaiser C, D'Ascenzo F, Frati G, Mancone M, Genereux P, Stone GW. Clinical outcomes with bioabsorbable polymer-based versus durable polymer-based drug-eluting stents and bare

metal stents: evidence from a comprehensive network meta-analysis. *J Am Coll Cardiol*. 2014;63:299-307

16. Bittl JA, He Y, Jacobs AK, Yancy CW, Normand S-LT. Bayesian methods affirm the use of percutaneous coronary intervention to improve survival in patients with unprotected left main coronary artery disease. *Circulation*. 2013;127:2177-2185
17. He Y, Bittl JA, Wouhib A, Normand S-LT. Case study in cardiovascular medicine: unprotected left main coronary artery disease. In: Biondi-Zoccai G, ed. *Network Meta-Analysis: Evidence Synthesis with Mixed Treatment Comparison*. New York: Nova Science Publishers, Inc.; 2014:285-386.
18. Hillis LD, Smith PK, Anderson JL, Bittl JA, Byrne JG, DiSesa VJ, Hiratzka LF, Hutter AM Jr, Jessen ME, Keeley E, Lahey S, Lange RA, London M, Mack MJ, Patel M, Puskas JD, Selnes O, Shahian DM, Trost JC, Winniford MD. 2011 ACCF/AHA Guidelines for Coronary Bypass Graft Surgery: Executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124:2610-2642
19. Takaro T, Peduzzi P, Detre KM, Hultgren HN, Murphy ML, van der Bel-Kahn J, Thomsen J, Meadows WR. Survival in subgroups of patients with left main coronary artery disease: Veterans Administration Cooperative Study of Surgery for Coronary Arterial Occlusive Disease. *Circulation*. 1982;66:14-22
20. Chaitman BR, Fisher LD, Bourassa MG, Davis K, Rogers WJ, Maynard C, Tyras DH, Berger RL, Judkins MP, Ringqvist I, Mock MB, Killip T. Effect of coronary bypass surgery on survival patterns in subsets of patients with left main coronary artery disease. Report of the Collaborative Study in Coronary Artery Surgery (CASS). *Am J Cardiol*. 1981;48:765-777
21. Oberman A, Kouchoukos NT, Harrell RR, Holt JH Jr, Russell RO Jr, Rackley CE. Surgical versus medical treatment in disease of left main coronary artery. *Lancet*. 1976;2:591-594
22. Cohen MV, Gorlin R. Main left coronary artery disease: clinical experience from 1964-1974. *Circulation*. 1975;52:275-285
23. Talano JV, Scanlon PJ, Meadows WR, Kahn M, Pifarre R, Gunnar RM. Influence of surgery on survival in 145 patients with left main coronary artery disease. *Circulation*. 1975;51(suppl I):I-105–I-111
24. European Coronary Surgery Study Group. Long term results of prospective randomised study of coronary artery bypass surgery in stable angina pectoris. *Lancet*. 1982;2:1173-1180
25. Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, Davis K, Killip T, Passamani E, Norris R. Effect of coronary artery bypass surgery on survival: overview of 10-year results from randomised trials by Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet*. 1994;344:563-570
26. Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, Mack MJ, Holmes DR, Torracca L, van Es GA, Leadley K, Dawkins KD, Mohr F. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010;121:2645-2653

27. Buszman PE, Kiesz SR, Bochenek A, Peszek-Przybyla E, Szkrobka I, Debinski M, Bialkowska B, Dudek D, Gruszka A, Zurakowski A, Milewski K, Wilczynski M, Rzeszutko L, Buszman P, Szymszal J, Martin JL, Tendera M. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. *J Am Coll Cardiol*. 2008;51:538-545
28. Boudriot E, Thiele H, Walther T, Liebetrau C, Boeckstegers P, Pohl T, Reichart B, Mudra H, Beier F, Gansera B, Neumann FJ, Gick M, Zietak T, Desch S, Schuler G, Mohr FW. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. *J Am Coll Cardiol*. 2011;57:538-545
29. Park S-J, Kim Y-H, Park D-W, Yun S-C, Ahn J-M, Song HG, Lee J-Y, Kim W-J, Kang S-J, Lee S-W, Lee CW, Park S-W, Chung D-H, Lee J-W, Lim D-S, Rha S-W, Sang-Gon L, Gwon H-C, Kim H-S, Chae I-H, Jang Y, Jeon M-H, Tahk S-J, Seung KB. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med*. 2011;364:1718-1727
30. White AJ, Kedia G, Mirocha JM, Lee MS, Forrester JS, Morales WC, Dohad S, Kar S, Czer LS, Fontana GP, Trento A, Shah PK, Makkar RR. Comparison of coronary artery bypass surgery and percutaneous drug-eluting stent implantation for treatment of left main coronary artery stenosis. *JACC Cardiovasc Interv*. 2008;1:236-245
31. Park D-W, Seung KB, Kim Y-H, Lee J-Y, Kim W-J, Kang S-J, Lee S-W, Lee CW, Park S-W, Yun S-C, Gwon H-C, Jeong M-H, Jang Y-S, Kim H-S, Kim PJ, Seong I-W, Park HS, Ahn T, Chae I-H, Tahk S-J, Chung W-S, Park S-J. Long-term safety and efficacy of stenting versus coronary artery bypass grafting for unprotected left main coronary artery disease: 5-year results from the MAIN-COMPARE (Revascularization for Unprotected Left Main Coronary Artery Stenosis: Comparison of Percutaneous Coronary Angioplasty Versus Surgical Revascularization) Registry. *J Am Coll Cardiol*. 2010;56:117-124
32. Wu C, Hannan EL, Walford G, Faxon DP. Utilization and outcomes of unprotected left main coronary artery stenting and coronary artery bypass graft surgery. *Ann Thorac Surg*. 2008;86:1153-1159
33. Brener SJ, Galla JM, Bryant R 3rd, Sabik JF 3rd, Ellis SG. Comparison of percutaneous versus surgical revascularization of severe unprotected left main coronary stenosis in matched patients. *Am J Cardiol*. 2008;101:169-172
34. Chieffo A, Morici N, Maisano F, Bonizzoni E, Cosgrave J, Montorfano M, Airoldi F, Carlino M, Michev I, Melzi G, Sangiorgi G, Alfieri O, Colombo A. Percutaneous treatment with drug-eluting stent implantation versus bypass surgery for unprotected left main stenosis: a single-center experience. *Circulation*. 2006;113:2542-2547
35. Mäkikallio TH, Niemelä M, Kervinen K, Jokinen V, Laukkanen J, Ylitalo I, Tulppo MP, Juvonen J, Huikuri HV. Coronary angioplasty in drug eluting stent era for the treatment of unprotected left main stenosis compared to coronary artery bypass grafting. *Ann Med*. 2008;40:437-443
36. Palmerini T, Marzocchi A, Marrozzini C, Ortolani P, Saia F, Savini C, Bacchi-Reggiani L, Gianstefani S, Virzi S, Manara F, Kiros Weldeab M, Marinelli G, Di Bartolomeo R, Branzi A. Comparison between coronary angioplasty and coronary artery bypass surgery for the treatment of unprotected left main coronary artery stenosis (the Bologna Registry). *Am J Cardiol*. 2006;98:54-59

37. Sanmartín M, Baz JA, Claro R, Asorey V, Duran D, Pradas G, Iniguez A. Comparison of drug-eluting stents versus surgery for unprotected left main coronary artery disease. *Am J Cardiol*. 2007;100:970-973
38. Goodman SN. Bayesian methods for evidence evaluation: are we there yet? *Circulation*. 2013;127:2367-2369
39. Seung KB, Park D-W, Kim Y-H, Lee S-W, Lee CW, Hong M-K, Park S-W, Yun S-C, Gwon H-C, Jeong M-H, Jang Y, Kim H-S, Kim PJ, Seong I-W, Park HS, Ahn T, Chae I-H, Tahk S-J, Chung WS, Park S-J. Stents versus coronary-artery bypass grafting for left main coronary artery disease. *N Engl J Med*. 2008;358:1781-1792
40. Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation*. 1976;54(Suppl III):III-107–III-117
41. Dzavik V, Ghali WA, Norris C, Mitchell LB, Koshal A, Saunders LD, Galbraith PD, Hui W, Faris P, Knudtson ML. Long-term survival in 11,661 patients with multivessel coronary artery disease in the era of stenting: a report from the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) Investigators. *Am Heart J*. 2001;142:119-126
42. Lang CD, He Y, Bittl JA. Bayesian inference supports the use of bypass surgery over percutaneous coronary intervention to reduce mortality in diabetic patients with multivessel coronary disease. *Int J Stat Med Res*. 2015;4:26-34
43. Jeffreys H. *Theory of Probability*. Oxford: Clarendon Press; 1961.
44. Farkouh ME, Domanski M, Sleeper LA, Dangas G, Mack M, Yang M, Cohen DJ, Rosenberg Y, Solomon SD, Desai AS, Gersh BJ, Magnuson EA, Lanksy A, Boineau R, Weinberger J, Ramanathan K, Sousa JE, Rankin J, Bhargava B, Buse J, Hueb W, Smith CR, Muratov V, Bansilal S, King S III, Bertrand M, Fuster V, for the FREEDOM Trial Investigators. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med*. 2012;367:2375-2384
45. O'Hagan A, Luce BR. *A Primer on Bayesian Statistics in Health Economics and Outcomes Research (with preface by Fryback DG)*. Bethesda, MD: MEDTAP International; 2003.
46. The BARI Investigators. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation*. 1997;96:1761-1769
47. Abizaid A, Costa MA, Centemero M, Abizaid AS, Legrand VM, Limet RV, Schuler G, Mohr FW, Lindeboom W, Sousa AG, Sousa JE, Van Hout B, Hugenholtz PG, Unger F, Serruys PW. Clinical and economic impact of diabetes mellitus on percutaneous and surgical treatment of multivessel coronary disease patients: insights from the Arterial Revascularization Therapy Study (ARTS) trial. *Circulation*. 2001;104:533-538
48. Rodriguez AE, Baldi J, Fernandez Pereira C, Navia J, Rodriguez Alemparte M, Delacasa A, Vigo F, Vogel D, O'Neill W, Palacios IF. Five-year follow-up of the Argentine randomized trial of coronary angioplasty with stenting versus coronary bypass surgery in patients with multiple vessel disease (ERACI II). *J Am Coll Cardiol*. 2005;46:582-588
49. Hueb W, Gersh BJ, Costa F, Lopes N, Soares PR, Dutra P, Jatene F, Pereira AC, Gois AF, Oliveira SA, Ramires JA. Impact of diabetes on five-year outcomes of patients with multivessel coronary artery disease. *Ann Thorac Surg*. 2007;83:93-99

50. The SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. *Lancet*. 2002;360:965-970
51. Kapur A, Hall RJ, Malik IS, Qureshi AC, Butts J, De Belder M, Baumbach A, Angelini G, de Belder A, Oldroyd KG, Flather M, Roughton M, Nihoyannopoulos P, Bagger JP, Morgan K, Beatt KJ. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. *J Am Coll Cardiol*. 2010;55:432-440
52. Kappetein AP, Head SJ, Morice M-C, Banning AP, Serruys PW, Dawkins KD, Mack MJ, on behalf of the SYNTAX Investigators. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. *Eur J Cardiothorac Surg*. 2013;43:1006-1013
53. Kamelesh M, Sharp TG, Tang XC, Shunk K, Ward HB, Walsh J, King SB III, Colling C, Mortiz T, Stroupe KT, Reda D, VA CARDS Investigators. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. *J Am Coll Cardiol*. 2013;61:808-816
54. Diamond GA, Kaul S. Prior convictions: Bayesian approaches to the analysis and interpretation of clinical megatrials. *J Am Coll Cardiol*. 2004;43:1929-1939
55. Albert J. *Bayesian Computation with R*. New York, NY: Springer Science+Business Media, LLC; 2007.
56. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes factor. *Ann Int Med*. 1999;130:1005-1013
57. Normand S-LT. Tutorial in biostatistics: Meta-analysis: Formulating, evaluating, combining and reporting. *Stat in Med*. 1999;18:321-359
58. Gelman AE, Carlin JB, Stern HS, Rubin DB. *Bayesian Data Analysis*. London: Chapman and Hall; 2004.
59. R Core Team. *R: A language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing; 2013.
60. Schwarzer G. *Package 'meta'*. Freiburg, Germany: version 3.8-0; 2012.
61. Lumley T. Network meta-analysis for indirect treatment comparisons. *Stat in Med*. 2002;21:2313-2324
62. Kim B-K, Hong J-K, Shin D-H, Nam C-M, Kim J-S, Ko Y-G, Choi D, Kang T-S, Park B-E, Kang W-C, Lee S-H, Yoon J-H, Hong B-K, Kwon H-M, Jang Y, for the RESET Investigators. A new strategy for discontinuation of dual antiplatelet therapy: the RESET Trial (REal Safety and Efficacy of 3-month dual antiplatelet Therapy following Endeavor zotarolimus-eluting stent implantation). *J Am Coll Cardiol*. 2012;60:1340-1348
63. Feres F, Costa RA, Abizaid A, Leon MB, Marin-Neto A, Botelho RV, King S III, Negoita M, Liu M, de Paula JET, Mangione JA, Meireles GX, Castello HJ Jr, Nicolela EL Jr, Perin MA, Devito FS, Labrunie A, Salvadori D Jr, Gusmão M, Staico R, Costa JR Jr, de Castro JP, Abizaid AS, Bhatt DL, for the OPTIMIZE trial investigators. Three vs twelve months of dual antiplatelet therapy after zotarolimus-eluting stents: the OPTIMIZE randomized trial. *JAMA*. 2013;310:2510-2522
64. Gwon H-C, Hahn J-Y, Park KW, Song YB, Chae I-H, Lim D-S, Han K-R, Choi J-H, Choi S-H, Kang H-J, Koo B-K, Ahn T, Yoon J-H, Jeong M-H, Hong T-J, Chung W-Y,

Choi Y-J, Hur S-H, Kwon H-M, Jeon D-W, Kim B-O, Park S-H, Lee N-H, Jeon H-K, Jang Y, Kim H-S. Six-month versus 12-month dual antiplatelet therapy after implantation of drug-eluting stents: the Efficacy of Xience/Promus Versus Cypher to Reduce Late Loss After Stenting (EXCELLENT) Randomized, Multicenter Study. *Circulation*. 2012;125:505-513

65. Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N. Second-generation drug-eluting stent implantation followed by 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol*. 2014;64:2086-2097
66. Schulz-Schüpke S, Byrne RA, ten Berg JM, Neumann F-J, Han Y, Adriaenssens T, Tölg R, Seyfarth M, Maeng M, Zrenner B, Jacobshagen C, Mudra H, von Hodenberg E, Wöhrle J, Angiolillo DJ, von Merzljak B, Rifatov N, Kufner S, Morath T, Feuchtenberger A, Ibrahim T, Janssen PWA, Valina C, Li Y, Desmet W, Abdel-Wahab M, Tiroch K, Hengstenberg C, Bernlochner I, Fischer M, Schunkert H, Laugwitz K-L, Schömig A, Mehilli J, Kastrati A, on behalf of the ISAR-SAFE trial investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 versus 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36:1252-1263
67. Han Y, Xu B, Xu K, Guan C, Jing Q, Zheng Q, Li X, Zhao X, Wang H, Zhao X, Li X, Yu P, Zang H, Wang Z, Cao X, Zhang J, Pang W, Li J, Yang Y, Dangas GD. Six versus 12 months of dual antiplatelet therapy after implantation of biodegradable polymer sirolimus-eluting stent: randomized substudy of the I-LOVE-IT 2 Trial. *Circ Cardiovasc Interv*. 2016;9:3003145. doi: 3003110.3001161/CIRCINTERVENTIONS.3003115.3003145
68. Hong S-K, Shin D-H, Kim J-S, Kim B-K, Ko Y-G, Choi D, Her A-Y, Kim YH, Jang Y, Hong M-K, for the IVUS-XPL Investigators. 6-month versus 12-month dual-antiplatelet therapy following long everolimus-eluting stent implantation: the IVUS-XPL randomized clinical trial. *J Am Coll Cardiol Intv*. 2016;9:1438-1446
69. Collet J-P, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, Cuisset T, Elhadad S, Schiele F, Lhoest N, Ohlmann P, Carrié D, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Beygui F, Vicaut E, Montalescot G, for the ARCTIC Investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet*. 2014;384:1577-1585
70. Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, Normand S-LT, Braunwald E, Wiviott SD, Cohen DJ, Holmes DR, Jr., Krucoff MW, Hermiller J, Dauerman HL, Simon DI, Kandzari DE, Garratt KN, Lee DP, Pow TK, Ver Lee P, Rinaldi MJ, Massaro JM, for the DAPT Study Investigators. Twelve or 30 months of dual-antiplatelet therapy after drug-eluting stents. *N Engl J Med*. 2014;371:2155-2166
71. Lee CW, Ahn J-M, Park D-W, Kang S-J, Lee S-W, Kim Y-H, Park S-W, Han S, Lee S-G, Seong I-W, Rha S-W, Jeong MH, Lim D-S, Yoon J-H, Hur S-H, Choi Y-S, Yang J-Y, Lee N-H, Kim H-W, Lee B-K, Kim K-S, Lee S-U, Chae J-K, Cheong S-S, Suh Iw, Park H-S, Nah D-Y, Jeon D-S, Seung K-B, Lee K, Jang J-S, Park S-J. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation. *Circulation*. 2014;129:304-312
72. Gilard M, Barragan P, Noryani AAL, Noor HA, Majwal T, Hovasse T, Castellant P, Schneeberger M, Maillard L, Bressolette E, Wojcik J, Delarche N, Blanchard D, Jouve B,

Ormezzano O, Paganelli F, Levy G, Sainsous J, Carrie D, Furber A, Berland J, Darremont O, Le Breton H, Lyuycx-Bore A, Gommeaux A, Cassat C, Kermarrec A, Cazaux P, Druelles P, Dauphin R, Armengaud J, Dupouy O, Champagnac D, Ohlmann P, Endresen K, Benamer H, Kiss RG, Ungi I, Boschat J, Morice M-C. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stent in patients nonresistant to aspirin: the randomized, multicenter ITALIC Trial. *J Am Coll Cardiol*. 2015;65:777-786

73. Nakamura M, Iijima R, Ako J, Shinke T, Okada H, Ito Y, Ando K, Anzai H, Tanaka H, Ueda Y, Takiuchi S, Nishida Y, Ohira H, Kawahuchi K, Kadotani M, Niinuma H, Omiya K, Morita T, Zen K, Yasaka Y, Inoue K, Ishiwata S, Ochiai M, Hamasaki T, Yokoi H, on behalf of the Nippon investigators. Dual antiplatelet therapy for 6 versus 18 months after biodegradable polymer drug eluting stent implantation. *J Am Coll Cardiol Intv*. 2017;10:1189-1198
74. Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, Furber A, Leclercq F, Eltchaninoff H, Falquier J-F, Henry P, Cattan S, Sebagh L, Michel P-L, Tuambilangana A, Hammoudi N, Boccara F, Cayla G, Douard H, Diallo A, Berman E, Komajda M, Metzger J-P, Vicaut E, on behalf of the OPTImal DUAL Antiplatelet Therapy trial investigators. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial. *Eur Heart J*. 2016;37:365-374
75. Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, Castriota F, Colombo F, Tebaldi M, Fucà G, Kubbajeh M, Cangiano E, Minarelli M, Scalone A, Cavazza C, Frangione A, Borghesi M, Marchesini J, Parrinello G, Ferrari R, for the PRODIGY investigators. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. *Circulation*. 2012;125:2015-2026
76. Cates CJ. Simpson's paradox and calculation of number needed to treat from meta-analysis. *BMC Med Res Methodol*. 2002;2:1-4
77. Peters JL, Rushton L, Sutton AJ, Jones DR, Abrams KR, Mugglestone MA. Bayesian methods for the cross-design synthesis of epidemiological and toxocological evidence. *Appl Stat*. 2005;54:159-172
78. Prevost TC, Abrams KR, Jones DR. Hierarchical models in generalized synthesis of evidence: an example based on studies of breast cancer screening. *Stat in Med*. 2000;19:3359-3376
79. Di Mario C, Mara S, Flavio A, Imad S, Antonio M, Anna P, Emanuela P, Stefano DS, Angelo R, Stefania C, Anna F, Carmelo C, Antonio C, Monzini N, Bonardi MA. Single vs multivessel treatment during primary angioplasty: results of the multicentre randomised HEpacoat for cuLPrit or multivessel stenting for Acute Myocardial Infarction (HELP AMI) Study. *Int J Cardiovasc Intervent*. 2004;6:128-133
80. Politi L, Sgura F, Rossi R, Monopoli D, Guerri E, Luezzi C, Bursi F, Sangiorgi GM, Modena MG. A randomised trial of target-vessel versus multi-vessel revascularisation in ST-elevation myocardial infarction: major adverse cardiac events during long-term follow-up. *Heart*. 2010;96:662-667
81. Wald DS, Morris JK, Wald NJ, Chase AJ, Edwards RJ, Hughes LO, Berry C, Oldroyd KG, for the PRAMI Investigators. Randomized trial of preventive angioplasty in myocardial infarction. *N Engl J Med*. 2013;369:1115-1123
82. Gershlick A, Khan JN, Kelly DJ, Greenwood JP, Sasikaran T, Curzen N, Blackman DJ, Dalby M, Fairbrother KL, Banya W, Wang D, Flather M, Hetherington SL, Kelion AD, Talwar S, Gunning M, Hall R, Swanton H, McGann GP. Randomized trial of complete

versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: The CvLPRIT Trial. *J Am Coll Cardiol*. 2015;65:963-972

83. Roe MT, Cura FA, Joski PS, Garcia E, Guetta V, Kereiakes DJ, Zijlstra F, Brodie BR, Grines CL, Ellis SG. Initial experience with multivessel percutaneous coronary intervention during mechanical reperfusion for acute myocardial infarction. *Am J Cardiol*. 2001;88:170-173
84. Hannan EL, Samadashvili Z, Walford G, Holmes DR, Jr.,, Jacobs AK, Stamato NJ, Venditti FJ, Sharma S, King SB, III,. Culprit vessel percutaneous coronary intervention versus multivessel and staged coronary intervention for ST-segment elevation myocardial infarction patients with multivessel disease. *J Am Coll Cardiol Intv*. 2010;3:22-31
85. Iqbal B, Ilsely C, Kabir T, Smith R, Lane R, Mason M, Archbold A, Clarke T, Firoozi S, Kalra S, Knight C, Lim P, Mathur A, Malik IS, Meier P, Rakhit R, Redwood S, Whitbread M, Rathod K, Bromage D, Wragg A, MacCarthy P, Dalby M. Culprit vessel versus multivessel intervention at the time of primary percutaneous coronary intervention in patients with ST-segment–elevation myocardial infarction and multivessel disease: real-world analysis of 3984 patients in London. *Circ Cardiovasc Qual Outcomes*. 2014;7:936-943
86. Corpus RA, House JA, Marso SP, Grantham JA, Huber KC Jr, Laster SB, Johnson WL, Daniels WC, Barth CW, Giorgi LV, Rutherford BD. Multivessel percutaneous coronary intervention in patients with multivessel disease and acute myocardial infarction. *Am Heart J*. 2004;148:494-500
87. Qarawani D, Nahir M, Abboud M, Hazanov Y, Hasin Y. Culprit only versus complete coronary revascularization during primary PCI. *Int J Cardiol*. 2008;123:288-292
88. Varani E, Balducelli M, Aquilina M, Vecchi G, Hussien MN, Frassineti V, Maresta A. Single or multivessel percutaneous coronary intervention in ST-elevation myocardial infarction patients. *Catheter Cardiovasc Interv*. 2008;72:927-933
89. Cavender MA, Milford-Beland S, Roe MT, Peterson ED, Weintraub WS, Rao SV. Prevalence, predictors, and in-hospital outcomes of non-infarct artery intervention during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (from the National Cardiovascular Data Registry). *Am J Cardiol*. 2009;104:507-513
90. Dziewierz A, Siudak Z, Rakowski T, Zasad W, Dubiel JS, Dudek D. Impact of multivessel coronary artery disease and noninfarct-related artery revascularization on outcome of patients with ST-elevation myocardial infarction transferred for primary percutaneous coronary intervention (from the EUROTRANSFER Registry). *Am J Cardiol*. 2010;106:342-347
91. Toma M, Buller CE, Westerhout CM, Fu Y, O'Neill WW, Holmes DR Jr, Hamm CW, Granger CB, Armstrong PW, APEX-AMI Investigators. Non-culprit coronary artery percutaneous coronary intervention during acute ST-segment elevation myocardial infarction: insights from the APEX-AMI trial. *Eur Heart J*. 2010;31:1701-1707
92. Bauer T, Zeymer U, Hochadel M, Möllmann H, Weidinger F, Zahn R, Nef HM, Hamm CW, Marco J, Gitt AK. Prima-vista multi-vessel percutaneous coronary intervention in haemodynamically stable patients with acute coronary syndromes: a analysis of over 4.400 patients in the EHS-PCI registry. *Int J Cardiol*. 2013;166:596-600

93. Jaguszewski M, Radavanovic D, Nallamothu BK, Lüscher TF, Urban P, Eberli FR, Bertel O, Pedrazzini GB, Windecker S, Jeger R, Erne P, Investigators ftAP. Multivessel versus culprit vessel percutaneous coronary intervention in ST-elevation myocardial infarction: is more worse? *Eurointervention*. 2013;9:909-915
94. Jeger R, Jaguszewski M, Nallamothu BK, Lüscher TF, Urban P, Pedrazzini GB, Erne P, Radavanovic D, AMIS Plus Investigators. Acute multivessel revascularization improves 1-year outcome in ST-elevation myocardial infarction: a nationwide study cohort from the AMIS Plus registry. *Int J Cardiol*. 2014;172:76-81
95. Santos AR, Piçarra BC, Celeiro M, Bento Â, Aguiar J, investigadores do Registo Nacional de Síndromes Coronárias Agudas. Multivessel approach in ST-elevation myocardial infarction: impact on in-hospital morbidity and mortality. *Rev Port Cardiol*. 2014;33:67-73
96. Manari A, Varani E, Guastaroba P, Menozzi A, Valgimigli M, Menozzi A, Magnavacchi P, Franco N, Marzocchi A, Casella G. Long-term outcome in patients with ST segment elevation myocardial infarction and multivessel disease treated with culprit-only, immediate, or staged multivessel percutaneous revascularization strategies: insights from the REAL Registry. *Catheter Cardiovasc Interv*. 2014;84:912-922