Anesthesiology 2010; 113:585–92

Variations in Pharmacology of β-Blockers May Contribute to Heterogeneous Results in Trials of Perioperative β-Blockade

Robert G. Badgett, M.D., F.A.C.P.,* Valerie A. Lawrence, M.D., F.A.C.P.,† Steven L. Cohn, M.D., F.A.C.P.‡

ABSTRACT

Background: Randomized controlled trials and meta-analyses provide conflicting guidance on the role of β-adrenergic receptor blockers (β-blockers) in reducing perioperative complications. We hypothesize that variability in trial results may be due in part to heterogeneous properties of β-blockers. First, we propose that the extent of β-blocker metabolism by cytochrome P-450 and the time available to titrate the dosage before surgery (titration time) may interact; dependence on P-450 may be most harmful when titration time is short. Second, β-blockers vary in their selectivity for the β-1 receptor and reduced selectivity may contribute to cerebral ischemia.

Methods: We used meta-analysis and meta-regression of existing trials to explore the role of these pharmacological properties.

Results: We found that both of these pharmacological factors are significantly associated with reduced efficacy of β-blockers.

Conclusions: Pharmacological properties of β-blockers may contribute to heterogeneous trial results. Many trials have used metoprolol, which is extensively metabolized by cytochrome P450 and is less selective for the β-1 receptor. For these two reasons, the efficacy of metoprolol to prevent perioperative cardiac complications should be compared with the efficacy of other β-blockers.

What We Already Know about This Topic

- The role of β-blockers in reducing overall mortality is unclear.

What This Article Tells Us That Is New

- The extent of β-blocker metabolism by CYP2D6, the time available to titrate β-blocker dosage preoperatively, and variations in β-blocker selectivity for the β-1 adrenergic receptor may contribute to the heterogeneous results of randomized controlled trials of perioperative β-blockade.
- Metoprolol should probably not be used for perioperative β-blockade when there is insufficient time to titrate its dose.

THE 2009 American College of Cardiology Foundation and American Heart Association practice guidelines recommend "careful titration" of β-adrenergic receptor blockers (β-blockers) in selected patients.[1] In the most comprehensive meta-analysis of perioperative β-blockers, Bangalore *et al.*[2] concluded that there was no reduction in total mortality and that heterogeneity in results regarding benefit was likely due to variable presence of bias in the trials. In that meta-analysis, trials reporting the greatest benefit from β-blockers were those deemed to be at most risk of bias. A more recent meta-analysis that included the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE) IV trial and selected trials from the meta-analysis by Bangalore *et al.*[2] provided an alternative interpretation.[3] Poldermans *et al.*[3] concluded that β-blockers are safe if adequate time exists to titrate the dose before surgery.[3] Although we agree with this claim, it does not address the use of β-blockers when the titration time is short.

We propose two additional hypotheses. First, the benefit of β-blockers is reduced for β-blockers metabolized by the CYP2D6 isoenzyme of cytochrome P-450. This reduction occurs because individual variations in CYP2D6 activity, as a result of inheritance and drug interactions, may cause both

* Professor, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas, and Audie L. Murphy Memorial Veterans Affairs Hospital, San Antonio, Texas. Current position: Professor, Department of Medicine, Kansas University School of Medicine-Wichita, Wichita, Kansas. † Professor, Department of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas, and Audie L. Murphy Memorial Veterans Affairs Hospital, San Antonio, Texas. ‡ Professor, Department of Medicine, State University of New York Downstate Medical Center, Brooklyn, New York.

Received from the Department of Medicine, University of Texas Health Science Center at San Antonio, and the Audie L. Murphy Division/South Texas Veterans Health Care System, San Antonio, Texas. Submitted for publication November 5, 2009. Accepted for publication April 15, 2010. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Badgett: Department of Medicine, Kansas University School of Medicine-Wichita, 1010 N. Kansas Street, Wichita, Kansas 67214-3199. rbadgett@kumc.edu.

insufficient and excessive β-blockade. Second, the reduced β-1 to β-2 adrenergic receptor selectivity may reduce the physiologic response to surgical anemia. If these hypotheses are correct, then use of β-blockers such as metoprolol, which are metabolized by CYP2D6 and have relatively low β-1 to β-2 selectivity, may not be appropriate choices for perioperative β-blockade, especially when little time for titration is available before surgery.

Review of Selected Pharmacological Aspects of β-Blockers

Genetic Polymorphisms. Potentially relevant polymorphisms identified to date affect β-blockade *via* β adrenergic receptors,[4,5] G-protein-coupled receptor kinases,‡ and metabolism by cytochrome P-450.§ Polymorphisms of β adrenergic receptors are the most extensively studied.[5] In the β Blocker in Spinal Anesthesia trial,[4] bisoprolol-related bradycardia and the c.16G>A polymorphism of ADRB2 were associated with hypotension. Among patients with acute coronary syndrome, c.46G>A and c.79C>G polymorphisms of ADRB2 may affect mortality among patients treated with β-blockers.[5] Although polymorphisms of the β adrenergic receptors are clinically important, they have not yet been shown to differentially affect specific β-blockers.

P-450 polymorphisms may be uniquely important, because we already know that β-blockers differ in their dependency on cytochrome P-450 for metabolism. Many (metoprolol, propranolol, carvedilol, labetalol, timolol) are metabolized by the P-450 CYP2D6 isoenzyme, and metoprolol is the most dependent, with 70–80% of its metabolism by CYP2D6.[6] The CYP2D6 isoenzyme may be the most problematic of the many cytochrome P-450 isoenzymes. CYP2D6 is estimated to metabolize 25% of prescribed drugs[7] and to underlie 38% of the most frequently cited adverse drug reactions.[8] Patients using β-blockers metabolized by CYP2D6 are more susceptible to bradycardia caused by lower functioning polymorphisms as well as drug interactions. Among European and American subjects, 5–10% have reduced function of CYP2D6.§ Other patients may be hyperfunctioning metabolizers.[9] Although these variations may not be important in managing chronic illness, where doses can be slowly titrated,[9] they may be very relevant in acute settings and have not been studied perioperatively.

Ratio of β-1 to β-2 Adrenergic Receptor Selectivity. Even among β-blockers that are β-1 cardioselective, variations occur in the ratio of β-1 to β-2 receptor affinity. Among the β-blockers used perioperatively, the β-1/β-2 affinity ratios range from 13.5 for bisoprolol to 4.7 for atenolol and 2.3 for metoprolol.[10] The benefit of β-blockers is probably due to blunting tachycardia mediated by β-1 receptors.[11,12] The role of β-2 adrenergic receptors in perioperative care is uncertain. On one hand, β-2 blockade may prevent hypotension by blocking systemic vasodilation, whereas, on the other hand, β-2 blockade might cause cerebral ischemia by blocking cerebral vasodilation. An animal study has addressed the effects of metoprolol during acute anemia. Without metoprolol, brain oxygenation was preserved during acute anemia but kidney oxygenation fell.[13] However, during β-blockade with metoprolol, acute anemia led to loss of both cerebral and kidney oxygenation.[13] Although observational studies in humans have found that adverse effects from β-blockers are increased in patients with anemia,[14] it has not been established that the interaction between anemia and β-blockers is related to the ratio of β-1 to β-2 adrenergic receptor selectivity. In summary, β-blockade may be more harmful during acute anemia and the harm may be worse with increasing β-2 blockade.

β-Blocker Duration of Effect. Starting in the 1990s, it was recognized that some β-blockers, such as atenolol, should be dosed twice a day for hypertension.[15] We have no reason to think that dosing principles should be different in the perioperative setting. This may complicate interpretation of trials in which atenolol was used once daily.[16,17]

The benefits and risks of shorter- *versus* longer-acting β-blockers need consideration. We do not know whether longer-acting drugs may be more beneficial because they prevent rebound if doses are missed. Alternatively, shorter-acting β-blockers may be better perioperatively to avoid short-term toxicity and allow better titration, as has been shown in one study of angiotensin-converting enzyme inhibitors in heart failure.[18]

Materials and Methods

For our hypothesis-generating analysis, we included only studies of patients at increased risk of perioperative cardiac complications in accord with practice guidelines.[19,20] Thus, we included from the Bangalore meta-analysis studies of patients who had a Revised Cardiac Risk Index of 1 or greater without counting surgery type as one of the criteria. This led to excluding the trials by Brady *et al.*[21] and Yang *et al.*[22] Because perioperative ischemia occurs both during and after surgery,[23] we restricted our analysis to trials in which β-blocker administration was begun before induction of anesthesia and continued postoperatively. Therefore, seven trials met our inclusion criteria[4,16,17,24–27]: six from the meta-analysis by Bangalore *et al.*[2] and the more recent DECREASE IV trial.[25] Compared with the recent meta-analysis by Poldermans *et al.*,[3] we excluded the trials by Brady *et al.*[21] and Yang *et al.*[22] and included the DECREASE IV trial[25] and the trial by Neary *et al.*[17]

We restricted the outcomes to total mortality and stroke during hospitalization or at 30 days. In determining which trials had high risk of biased results, we used the judgments from the meta-analysis by Bangalore *et al.*[2] Bias was consid-

‡ Online Mendelian Inheritance in Man. G Protein-Coupled Receptor Kinase 5; GPRK5. Available at: http://www.ncbi.nlm.nih.gov/omim/600870. Accessed April 6, 2010.

§ Online Mendelian Inheritance in Man. Drug Metabolism, Poor, CYP2D6-Related. Available at: http://www.ncbi.nlm.nih.gov/omim/608902. Accessed April 6, 2010.

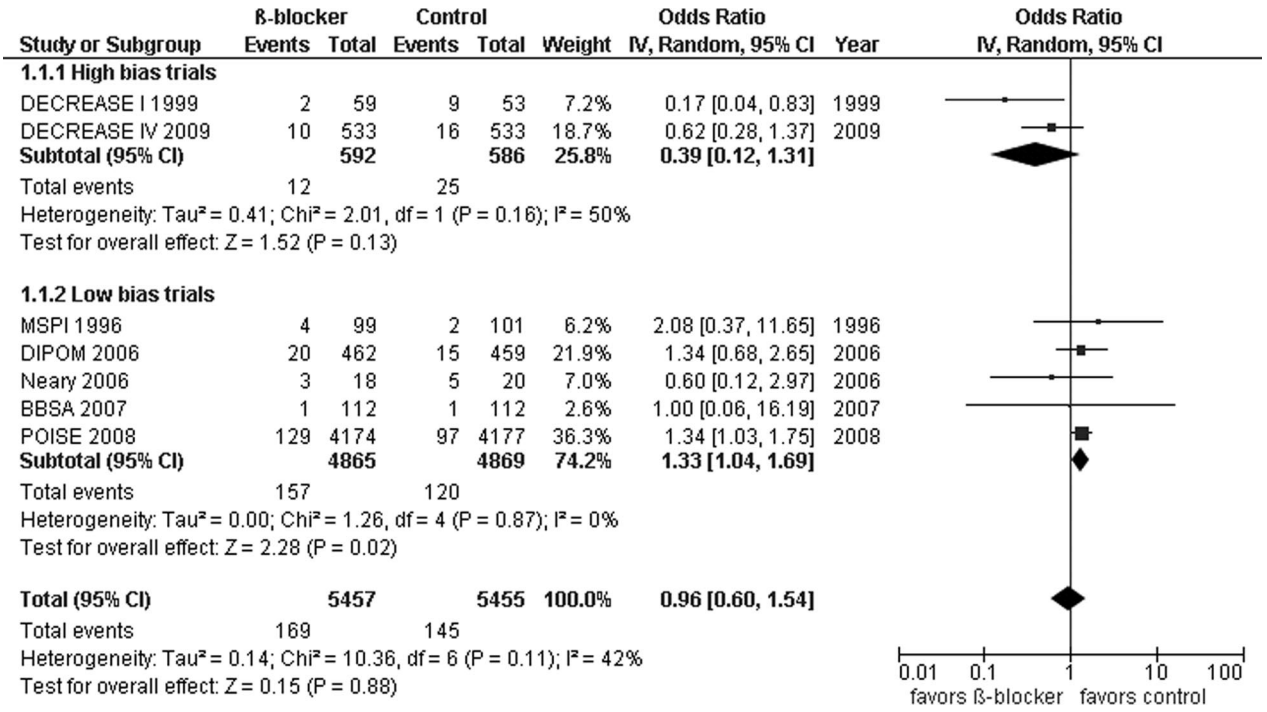

Fig. 1. Forest plot of odds ratio of mortality from β-adrenergic receptor blockers grouped by presence of bias and length of titration period. BBSA = β Blocker in Spinal Anesthesia[4]; DECREASE I = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[24]; DECREASE IV = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[25]; DIPOM = Diabetes postoperative mortality and morbidity[26]; MSPI = Multicenter Study of Perioperative Ischemia Research Group[16]; POISE = Perioperative Ischemic Evaluation.[27]

ered high if any of the first three items of the modified Cochrane Collaboration tool (randomization method, allocation concealment before and during enrollment, blinding) were not adequate.

Statistical Analysis

Meta-analysis was done with RevMan software (The Cochrane Collaboration, Copenhagen, Denmark). We used more conservative random effects models instead of fixed effects models to yield conservative results because of heterogeneity in some of the analyses. Studies were weighted by the Dersimonian and Laird variation of the inverse of the variance.

Heterogeneity of study results was measured using the I^2 statistic, as recommended by the Cochrane Collaboration.[28] The importance of heterogeneity in results as measured by the I^2 is described by the Cochrane as follows: 0–40%, might not be important; 30–60%, may represent moderate heterogeneity; 50–90%, may represent substantial heterogeneity; and 75–100%, may represent considerable heterogeneity.

To explore reasons for heterogeneous results and to test for interactions between subgroups of trials, we used meta-regression, also using Dersimonian and Laird weighting.‖ To analyze the interaction of length of titration period and metabolism by CYP2D6, we created an interaction variable whose value for studies was as follows: 0 if titration period was short and metoprolol was used; 1 if the titration period was short and a β-blocker without metabolism by CYP2D6 was used; and 2 if the titration period was long. Meta-regression was done with the R programming language (R: A Language and Environment for Statistical Computing. Version 2.10.1. Vienna, Austria) using the rmeta module.#

Results

An evidence table of the trials is tabulated and maintained online.** When the seven included trials are pooled, there is moderate heterogeneity (I^2 = 42%) in the mortality reported in the trials. We explored four possible sources for the heterogeneity.

The Role of Study Bias

Banglore *et al.*[2] proposed that a major source of heterogeneity was study quality. Trials with adequate description of methods of allocation and blinding based on the scale of the Cochrane Collaboration showed significant harm from β-blockers (pooled odds ratio, 1.34; 95% confidence interval [CI], 1.04–

‖ Comprehensive R Archive Network (CRAN): HSAUR2: A Handbook of Statistical Analyses Using R (2nd edition) Available at: http://cran.r-project.org/web/packages/HSAUR2/. Accessed April 6, 2010.

Comprehensive R Archive Network (CRAN): Rmeta package for R programming language. Available at: http://cran.r-project.org/web/packages/rmeta/. Accessed May 4, 2010.

** Citizendium. Beta-blocker evidence table. Available at: http://en.citizendium.org/wiki/Preoperative_care/Catalogs/Beta-blocker_evidence_table. Accessed May 5, 2010.

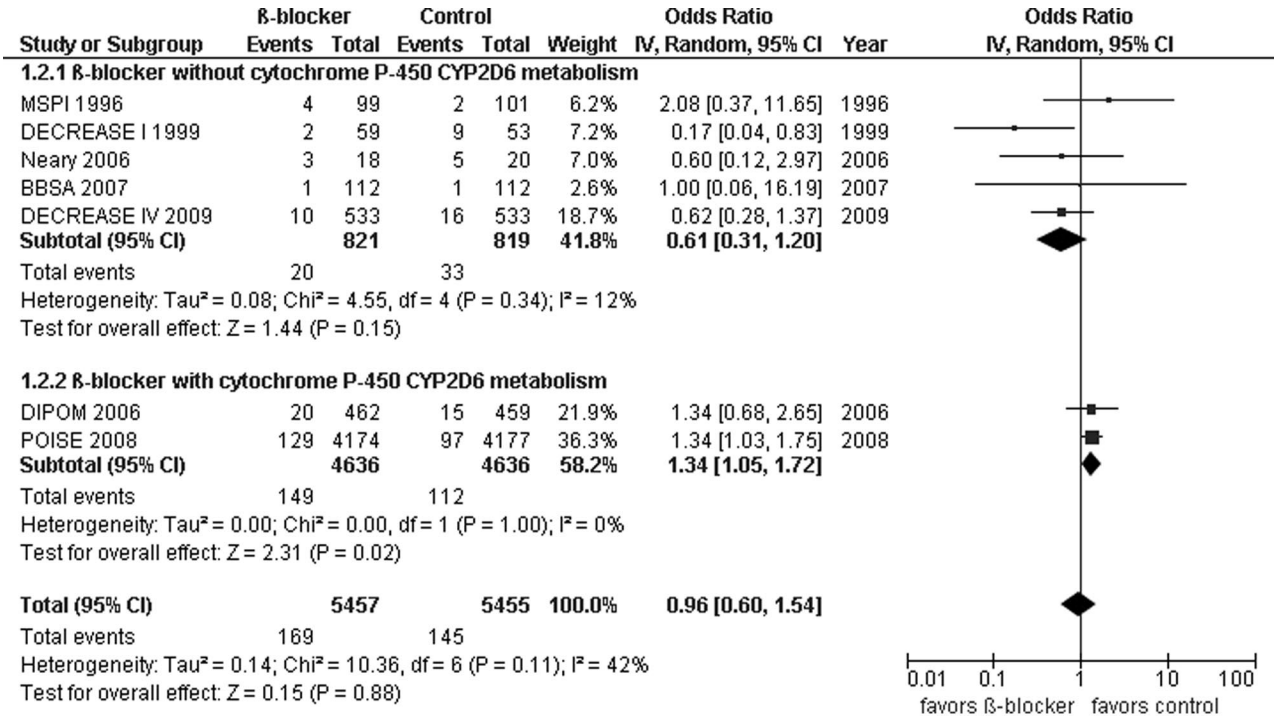

Fig. 2. Forest plot of odds ratio of mortality from β-adrenergic receptor blockers (β-blockers) grouped by β-blockers using cytochrome P-450 metabolism. BBSA = β Blocker in Spinal Anesthesia[4]; DECREASE I = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[24]; DECREASE IV = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[25]; DIPOM = Diabetes postoperative mortality and morbidity[26]; MSPI = Multicenter Study of Perioperative Ischemia Research Group[16]; POISE = Perioperative Ischemic Evaluation.[27]

1.69). In our analysis of the nine trials meeting our inclusion criteria (fig. 1), meta-regression showed that the presence of bias was a significant predictor of drug efficacy ($P = 0.038$).

The Role of Length of Titration Period

Poldermans *et al.*[3] meta-analyzed the rates of perioperative myocardial infarction and stroke on the basis of the amount of time to titrate the β-blocker.[3] When we replicated this analysis, using the studies meeting our inclusion criteria, the resulting two groups of studies contain the same trials as the analysis based on bias, because the two DECREASE studies are the only two studies with a long duration of titration and the only two studies deemed to have high bias by the Bangalore *et al.*[2] version of the Cochrane tool (fig. 2). Thus, among studies with a short titration period, the pooled odds ratio is again 1.34 (95% CI, 1.04–1.69), and by meta-regression, the *P* value is again significant at 0.038.

A New Analysis Based on the Metabolism of β-Blockers

We proposed that the degree of metabolism by the CYP2D6 isoenzyme of cytochrome P-450 is another plausible explanation for heterogeneity (fig. 2). In figure 3, the studies are further grouped by both metabolism and duration of titration. This analysis suggests that increased mortality from perioperative β-blockers is confined to trials that combined a short titration period with CYP2D6 metabolism (pooled odds ratio, 1.34; 95% CI, 1.05–1.72). Meta-regression of the interaction between these two factors yields a statistically significant correlation ($P = 0.044$), with the highest mortality in the short titration-CYP2D6 trials, intermediate mortality in the short titration-no CYP2D6 trials, and the lowest mortality in the long titration trials (fig. 4).

We found no interaction between the route of metabolism and the odds ratio of stroke from β-blockers. Data were sparse because two trials that did not use a β-blocker metabolized by CYP2D6 did not report the incidence of perioperative stroke.[16,17]

A New Analysis Based on Ratio of β-1/β-2 Selectivity

We proposed that the ratio of β-1/β-2 selectivity is another possible cause of heterogeneity. Figure 5 is a meta-regression of the β-1/β-2 affinity ratios. This analysis suggests that benefit from β-blockers correlates with cardioselectivity ($P = 0.046$).

We found no interaction between the ratio of β-1 to β-2 selectivity and the odds ratio of stroke from β-blockers. Again, data for stroke are not reported in all trials.

Discussion

β-Blockers vary in their pharmacology, and, in our analysis, both the metabolic pathway and the degree of β-1 selectivity of the β-blocker showed a statistically significant interaction with benefit on total mortality. These observations provide alternative or additional explanations for the source of heterogeneous trial results. These findings contrast with the conclusion by Bangalore *et al.*[2] that there is "potentially in-

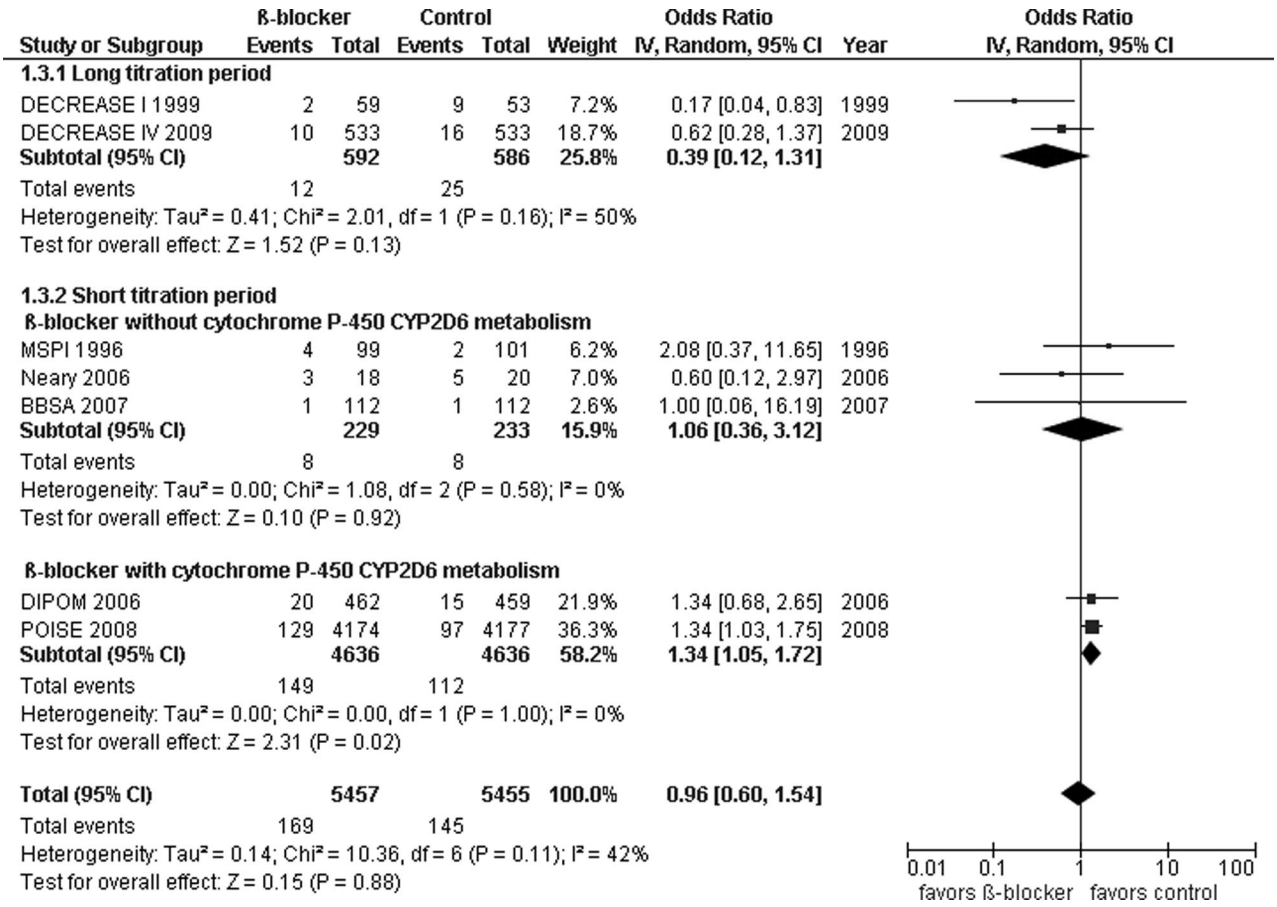

Fig. 3. Forest plot of odds ratio of mortality from β-adrenergic receptor blockers (β-blockers) grouped by length of titration period and β-blockers using cytochrome P-450 metabolism. BBSA = β Blocker in Spinal Anesthesia[4]; DECREASE I = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[24]; DECREASE IV = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[25]; DIPOM = Diabetes postoperative mortality and morbidity[26]; MSPI = Multicenter Study of Perioperative Ischemia Research Group[16]; POISE = Perioperative Ischemic Evaluation.[27]

creased mortality" from using any β-blocker. In the analysis of mortality by Bangalore *et al.*,[2] after grouping trials by bias, substantial heterogeneity remained in the subgroup of trials with high bias (I^2 = 62%), whereas low heterogeneity remained in the subgroup of trials with low bias (I^2 = 28%)[29]; however, sources for this heterogeneity were not explored.

Our finding that metabolic pathway is associated with efficacy of β-blockers is consistent with a prior meta-analysis of trials through 2003.[11] Beattie *et al.*[11] concluded that controlling heart rate correlated with fewer perioperative myocardial infarctions and that heart rate was less consistently controlled with metoprolol. Our finding that the degree of β-1 selectivity is associated with efficacy of β-blockers is consistent with the two major trials of early β-blocker use for acute coronary syndrome. In acute coronary syndrome, quick titration of β-blockade is needed. The Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT)[30] found no benefit from metoprolol, whereas the First International Study of Infarct Survival (ISIS-1)[31] found benefit from atenolol. Both trials reported a 5% rate of hypotension from β-blockade; however, atenolol reduced vascular mortality whereas metoprolol did not.

Both findings, reduced efficacy associated with both CYP2D6 metabolism and low ratio of β-1 of β-2 selectivity, are consistent with a large retrospective cohort study.[32] Redelmeier *et al.*[32] found that atenolol was associated with greater reduction in mortality compared with metoprolol in a cohort of 37,151 patients. Whether this might be due to more sympathetic rebound with the shorter half-life of metoprolol, as proposed by Redelmeier *et al.*,[32] inconsistent sympatholysis by metoprolol in patients with abnormal cytochrome P-450 CYP2D6 activity, or reduced cerebral protection from low β-1 selectivity is not known.

Our stroke results are consistent with the meta-analysis by Poldermans *et al.*[3] and show that the risk of stroke does not vary by method of β-blockade. However, two of the seven studies, both using drugs not metabolized by CYP2D6, reported no strokes, and so our results may exaggerate the rate of stroke in this group as a result of selective outcome reporting bias.[33] The impact of method of β-blockade on stroke needs more investigation.

Bangalore *et al.*[2] concluded that the heterogeneity across trials was due to biases, including lack of blinding. Although we recognize the importance of blinding in general, it may be

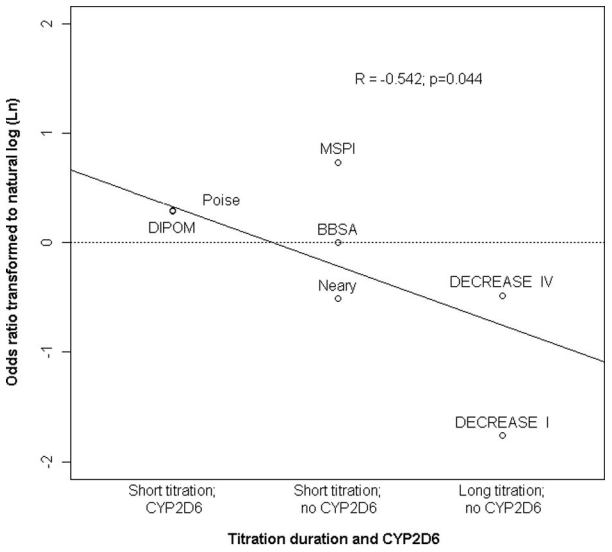

Fig. 4. Meta-regression of odds ratio of mortality from β-adrenergic receptor blockers (β-blockers) by interaction of length of titration period and β-blockers using cytochrome P-450 metabolism. Ln(odds ratio) of 0 indicates odds ratio = 1. Values of Ln(odds ratio) less than 0 indicate benefit from β-blockers. BBSA = β Blocker in Spinal Anesthesia[4]; DECREASE I = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[24]; DECREASE IV = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[25]; DIPOM = Diabetes postoperative mortality and morbidity[26]; MSPI = Multicenter Study of Perioperative Ischemia Research Group[16]; POISE = Perioperative Ischemic Evaluation.[27]

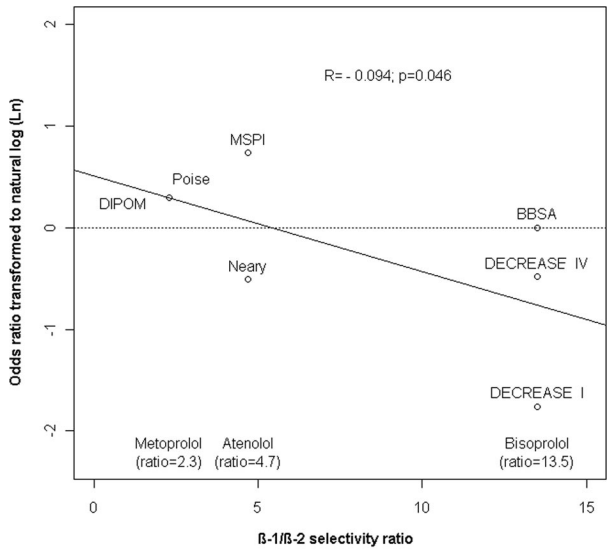

Fig. 5. Meta-regression of odds ratio of mortality from β-adrenergic receptor blockers (β-blockers) by β-1 relative selectivity of the β-blockers used in the trials. Ln (odds ratio) of 0 indicates odds ratio = 1. Values of Ln (odds ratio) less than 0 indicate benefit from β-blockers. BBSA = β Blocker in Spinal Anesthesia[4]; DECREASE I = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[24]; DECREASE IV = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography I[25]; DIPOM = Diabetes postoperative mortality and morbidity[26]; MSPI = Multicenter Study of Perioperative Ischemia Research Group[16]; POISE = Perioperative Ischemic Evaluation.[27]

less important for the clinical question of perioperative β-blockers for two reasons. First, trials of β-blockers are difficult to blind if the values for heart rates are not masked.[34] In addition, blinding may actually interfere with achieving goal heart rates.[11] Thus, we are not certain that the studies with stated blinding are better than those without stated blinding. Moreover, if efficacy is measured by an objective outcome such as total mortality, then the role of blinding is less important.[35]

Other important markers of study quality should be added to blinding. The DECREASE I trial was stopped early. We doubt that the lack of blinding in the DECREASE I trial would change the direction of the results in our analysis of total mortality. However, we agree that the early termination exaggerates the benefit of treatment.[36] This may contribute to the moderate heterogeneity found when pooling the two DECREASE trials in group 1.31 of figure 3.

All four explanations (study bias, duration of titration period, presence of metabolism by CYP2D6, and β-1 selectivity) show statistically significant ability to explain heterogeneity in total mortality. With the studies to date, we believe that none of these explanations can be rejected and all may interact. For example, when patients are not anemic and sufficient time exists to titrate a β-blocker (such as 5 weeks, as in the DECREASE studies), the choice of β-blocker may not matter. Studies of metoprolol in outpatients have found increased adverse effects[37] and dose adjustments[38] among patients who are genetically slow metabolizers of metoprolol; however, when sufficient time permits dose adjustment, small studies do not report an increase adverse events among slow metabolizers.[9,39] However, our analysis suggests that when little time is available, metoprolol may be hazardous because of drug interactions and genetic variability in metabolism.

We note the contrasting results in the two trials that used atenolol, the Multicenter Study of Perioperative Ischemia Research Group trial and the trial of Neary *et al.*,[17] in the middle group of figure 3. Neither trial found a statistically significant impact on mortality, and the different results could be due to small study size and random error. However, we note that Neary *et al.*,[2] who used a lower dose of atenolol, found a trend toward benefit, whereas the Multicenter Study of Perioperative Ischemia Research Group trial used a higher dose and found a trend toward increased mortality. Both studies dosed atenolol once per day, although twice a day may be more effective.[40,41]

A randomized controlled trial comparing outcomes after starting β-blockers with and without favorable pharmacological properties, with patients stratified by length of the titration period, could test this hypothesis. If atenolol is used in the study, we believe it should be dosed twice a day. The trial could be limited to patients with known abnormal alleles. However, an observational study may be easier. For

example, a case control study of patients using metoprolol could compare the prevalence of abnormal P-450 alleles and other medications metabolized by CYP2D6 among patients with and without perioperative complications. The study design could be more efficient by only including patients at high cardiac risk or taking other medications metabolized by CYP2D6 who recently started taking metoprolol. Likewise, a cohort design could be used, as was done in investigating cardiovascular events due to patients taking clopidogrel combined with proton pump inhibitors[42] or the presence of hypofunctioning CYP2C19 alleles.[43]

Clinical Implications

We believe that future studies and meta-analyses of β-blockers for preventing perioperative morbidity should consider pharmacological properties of β-blockers. How should clinicians manage perioperative β-blockade pending further research to clarify the predictors of benefit from β-blockers? The only trials with significant results used bisoprolol. Our analysis supports two physiologic reasons why bisoprolol and atenolol may be safer than metoprolol. Thus both empirical and theoretical evidence favor medications other than metoprolol. Using the Diamond and Kaul[44] schema of assessing evidence, we propose that there is "reasonable suspicion" of harm from metoprolol and that clinicians should consider not starting metoprolol preoperatively unless a long period of titration is available or a patient needs hepatic metabolism as a result of reduced renal function.

The authors acknowledge the role of the anonymous reviewer who suggested that the ratio of β-1/β-2 selectivity may be a cause of heterogeneity and who referred us to an important study regarding this hypothesis.

References

1. American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine, Society for Vascular Surgery, Fleischmann KE, Beckman JA, Buller CE, Calkins H, Fleisher LA, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Robb JF, Valentine RJ: 2009 ACCF/AHA focused update on perioperative beta blockade. J Am Coll Cardiol 2009; 54:2102–28
2. Bangalore S, Wetterslev J, Pranesh S, Sawhney S, Gluud C, Messerli FH: Perioperative beta blockers in patients having non-cardiac surgery: A meta-analysis. Lancet 2008; 372: 1962–76
3. Poldermans D, Schouten O, van Lier F, Hoeks SE, van de Ven L, Stolker RJ, Fleisher LA: Perioperative strokes and β-blockade. ANESTHESIOLOGY 2009; 111:940–5
4. Zaugg M, Bestmann L, Wacker J, Lucchinetti E, Boltres A, Schulz C, Hersberger M, Kälin G, Furrer L, Hofer C, Blumenthal S, Müller A, Zollinger A, Spahn DR, Borgeat A: Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: The Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: A double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. ANESTHESIOLOGY 2007; 107:33–44
5. Lanfear DE, Spertus JA, McLeod HL: Beta2-adrenergic receptor genotype predicts survival: Implications and future directions. J Cardiovasc Nurs 2006; 21:474–7
6. Shin J, Johnson JA: Pharmacogenetics of beta-blockers. Pharmacotherapy 2007; 27:874–87
7. Wolf CR, Smith G: Pharmacogenetics. Br Med Bull 1999; 55:366–86
8. Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W: Potential role of pharmacogenomics in reducing adverse drug reactions: A systematic review. JAMA 2001; 286:2270–9
9. Fux R, Mörike K, Pröhmer AM, Delabar U, Schwab M, Schaeffeler E, Lorenz G, Gleiter CH, Eichelbaum M, Kivistö KT: Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: A prospective clinical study. Clin Pharmacol Ther 2005; 78:378–87
10. Baker JG: The selectivity of beta-adrenoceptor antagonists at the human beta1, beta2 and beta3 adrenoceptors. Br J Pharmacol 2005; 144:317–22
11. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G: Does tight heart rate control improve beta-blocker efficacy? An updated analysis of the noncardiac surgical randomized trials. Anesth Analg 2008; 106:1039–48
12. Mangano DT, Wong MG, London MJ, Tubau JF, Rapp JA: Perioperative myocardial ischemia in patients undergoing noncardiac surgery–II: Incidence and severity during the 1st week after surgery. The Study of Perioperative Ischemia (SPI) Research Group. J Am Coll Cardiol 1991; 17: 851–7
13. Ragoonanan TE, Beattie WS, Mazer CD, Tsui AK, Leong-Poi H, Wilson DF, Tait G, Yu J, Liu E, Noronha M, Dattani ND, Mitsakakis N, Hare GM: Metoprolol reduces cerebral tissue oxygen tension after acute hemodilution in rats. ANESTHESIOLOGY 2009; 111:988–1000
14. Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G, Mitsakakis N, Hare GM: Acute surgical anemia influences the cardioprotective effects of β-blockade: A single-center, propensity-matched cohort study. ANESTHESIOLOGY 2010; 112:25–33
15. Kaplan NM, Lieberman E: Treatment of hypertension: Drug therapy, Clinical Hypertension, 6th edition. Edited by Kaplan NM. Baltimore, Williams & Wilkins, 1994, pp 191–280
16. Mangano DT, Layug EL, Wallace A, Tateo I: Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study of Perioperative Ischemia Research Group. N Engl J Med 1996; 335:1713–20
17. Neary WD, McCrirrick A, Foy C, Heather BP, Earnshaw JJ: Lessons learned from a randomised controlled study of perioperative beta blockade in high risk patients undergoing emergency surgery. Surgeon 2006; 4:139–43
18. Packer M, Lee WH, Yushak M, Medina N: Comparison of captopril and enalapril in patients with severe chronic heart failure. N Engl J Med 1986; 315:847–53
19. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, Freeman WK, Froehlich JB, Kasper EK, Kersten JR, Riegel B, Robb JF, ACC/AHA TASK FORCE MEMBERS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Buller CE, Creager MA, Ettinger SM, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Lytle BW, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW: ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery): Developed in Collaboration With the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular

Medicine and Biology, and Society for Vascular Surgery. Circulation 2007; 116:1971–96

20. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, Van den Berghe G, Vermassen F, Hoeks SE, Vanhorebeek I, Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery, European Society of Cardiology, European Society of Anaesthesiology: Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). Eur Heart J 2009; 2769–812
21. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR, POBBLE trial investigators: Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: Results of a randomized double-blind controlled trial. J Vasc Surg 2005; 41:602–9
22. Yang H, Raymer K, Butler R, Parlow J, Roberts R: The effects of perioperative beta-blockade: Results of the Metoprolol after Vascular Surgery (MaVS) study, a randomized controlled trial. Am Heart J 2006; 152:983–90
23. Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM: Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990; 323: 1781–8
24. Poldermans D, Boersma E, Bax JJ, Thomson IR, van de Ven LL, Blankensteijn JD, Baars HF, Yo TI, Trocino G, Vigna C, Roelandt JR, van Urk H: The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. N Engl J Med 1999; 341:1789–94
25. Dunkelgrun M, Boersma E, Schouten O, Koopman-van Gemert AW, van Poorten F, Bax JJ, Thomson IR, Poldermans D, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group: Bisoprolol and fluvastatin for the reduction of perioperative cardiac mortality and myocardial infarction in intermediate-risk patients undergoing noncardiovascular surgery: A randomized controlled trial (DECREASE-IV). Ann Surg 2009; 249:921–6
26. Juul AB, Wetterslev J, Gluud C, Kofoed-Enevoldsen A, Jensen G, Callesen T, Nørgaard P, Fruergaard K, Bestle M, Vedelsdal R, Miran A, Jacobsen J, Roed J, Mortensen MB, Jørgensen L, Jørgensen J, Rovsing ML, Petersen PL, Pott F, Haas M, Albret R, Nielsen LL, Johansson G, Stjernholm P, Mølgaard Y, Foss NB, Elkjaer J, Dehlie B, Boysen K, Zaric D, Munksgaard A, Madsen JB, Øberg B, Khanykin B, Blemmer T, Yndgaard S, Perko G, Wang LP, Winkel P, Hilden J, Jensen P, Salas N, DIPOM Trial Group: Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: Randomised placebo controlled, blinded multicentre trial. BMJ 2006; 332:1482
27. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing noncardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
28. Deeks JJ, Higgins JPT, Altman DG, Cochrane Statistical Methods Group: 9.5.2 Identifying and measuring heterogeneity, Cochrane Handbook for Systematic Reviews of Interventions, 5.0.2 (updated September 2009) edition. Edited by Higgins JPT and Green S. Copenhagen, Denmark, The Cochrane Collaboration, 2009
29. Higgins JPT, Green S: Cochrane Handbook for Systematic Reviews of Interventions, 5.0.2 (updated September 2009) edition. Copenhagen, Denmark, The Cochrane Collaboration, 2009
30. Chen ZM, Pan HC, Chen YP, Peto R, Collins R, Jiang LX, Xie JX, Liu LS, COMMIT (ClOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group: Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: Randomised placebo-controlled trial. Lancet 2005; 366:1622–32
31. Anonymous: Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. First International Study of Infarct Survival Collaborative Group. Lancet 1986; 2:57–66
32. Redelmeier D, Scales D, Kopp A: Beta blockers for elective surgery in elderly patients: Population based, retrospective cohort study. BMJ 2005; 331:932
33. Chan AW, Altman DG: Identifying outcome reporting bias in randomised trials on PubMed: Review of publications and survey of authors. BMJ 2005; 330:753
34. Byington RP, Curb JD, Mattson ME: Assessment of double-blindness at the conclusion of the beta-Blocker Heart Attack Trial. JAMA 1985; 253:1733–6
35. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, Gluud C, Martin RM, Wood AJ, Sterne JA: Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: Meta-epidemiological study. BMJ 2008; 336:601–5
36. Goodman SN: Stopping at nothing? Some dilemmas of data monitoring in clinical trials. Ann Intern Med 2007; 146: 882–7
37. Wuttke H, Rau T, Heide R, Bergmann K, Böhm M, Weil J, Werner D, Eschenhagen T: Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects. Clin Pharmacol Ther 2002; 72:429–37
38. Terra SG, Pauly DF, Lee CR, Patterson JH, Adams KF, Schofield RS, Belgado BS, Hamilton KK, Aranda JM, Hill JA, Yarandi HN, Walker JR, Phillips MS, Gelfand CA, Johnson JA: Beta-adrenergic receptor polymorphisms and responses during titration of metoprolol controlled release/extended release in heart failure. Clin Pharmacol Ther 2005; 77:127–37
39. Zineh I, Beitelshees AL, Gaedigk A, Walker JR, Pauly DF, Eberst K, Leeder JS, Phillips MS, Gelfand CA, Johnson JA: Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension. Clin Pharmacol Ther 2004; 76:536–44
40. Neutel JM, Schnaper H, Cheung DG, Graettinger WF, Weber MA: Antihypertensive effects of beta-blockers administered once daily: 24-hour measurements. Am Heart J 1990; 120:166–71
41. Sarafidis P, Bogojevic Z, Basta E, Kirstner E, Bakris GL: Comparative efficacy of two different beta-blockers on 24-hour blood pressure control. J Clin Hypertens (Greenwich) 2008; 10:112–8
42. Ho PM, Maddox TM, Wang L, Fihn SD, Jesse RL, Peterson ED, Rumsfeld JS: Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. JAMA 2009; 301: 937–44
43. Simon T, Verstuyft C, Mary-Krause M, Quteineh L, Drouet E, Méneveau N, Steg PG, Ferrières J, Danchin N, Becquemont L, French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) Investigators: Genetic determinants of response to clopidogrel and cardiovascular events. N Engl J Med 2009; 360:363–75
44. Diamond GA, Kaul S: Bayesian classification of clinical practice guidelines. Arch Intern Med 2009; 169:1431–5