Meta-analyses with rare events should use adequate methods

To the Editor:

With great interest we read the meta-analysis of randomized clinical trials of Takagi and associates¹ on postoperative stroke risk in off-pump and on-pump coronary artery bypass grafting. Their work is a welcome update of the most recent meta-analysis on this topic by Sedrakyan and colleagues.²

Contrary to Sedrakyan and associates, however, Tagaki and colleagues do not find a significant difference between off- and on-pump surgery (relative risk [95% confidence interval]: 0.60 [0.34–1.06]; $P = .08$), whereas Sedrakyan's group found 0.50 [0.27,0.93; $P = .03$] for the relative risk. As an explanation, Tagaki's group points to the methodical difficulties of dealing with studies reporting no events in both treatment groups. Whereas Sedrakyan and associates removed these studies from analysis, Tagaki and colleagues obviously used a "0.5-correction" rule, where 0.5 is added to the number of events as well as to the number of nonevents in both groups (at least, this is how we were able to reproduce their results).

However, we object to both ideas of dealing with studies with zero events. Inasmuch as those studies point to equal risk for both treatments (as Tagaki's group noted correctly), deleting them, as Sedrakyan's group did, would probably overestimate the treatment effect. On the contrary, using the "0.5-correction" rule, as Tagaki and colleagues did, adds 13 pseudoevents in the off-pump group and another 13 in the on-pump group. Thus, the analysis is performed with 59 pseudo-observed, instead of 33 actually observed, events, rendering the analysis also somewhat dubious.

We would rather recommend methods that adequately account for studies with zero observations. These methods have been proposed,³ are straightforward extensions of the familiar Mantel-Haenszel method,⁴ and standard software (eg, SAS PROC FREQ, CMH option, code is available from the authors on request) is available for computation. We reanalyzed the Tagaki data* and found an estimated relative risk of 0.376 [0.175, 0.807; $P = .0091$]. Note that this value compares very closely with the relative risk from the simple and most intuitive analysis performed by collapsing the

data from the 32 studies into a simple 4-fold table: 0.377 [0.176, 0.810; $P = .0092$].

We therefore conclude that there is still significant evidence that the off-pump method is superior to the on-pump method in reducing postoperative stroke risk after coronary bypass grafting.

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*Note a printing error in Table 1 of the study by Tagaki and associates.¹ The number of randomized patients in the off-pump group from the Lonn study should be "15," not "60." We performed all analyses with the corrected data set.

References

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Factors predicting poor survival after resection of stage IA non-small cell lung cancer

To the Editor:

We have read with interest the paper by Chang and associates.¹ Interestingly, we observe that the factors considered to predict poor survival after resection of stage IA non-small cell lung cancer (NSCLC) still remain tumor size, gender, age, and extent of resection.

It is true, in fact, that lung cancer staging currently rests on histopathologic and clinical criteria that have only limited power to predict relapse and survival. A major effort to improve the control of NSCLC entails the use of molecular profiling to characterize tumors and provide accurate predictions of the outcome after standard or novel treatments. Moreover, molecular profiling, as we² already discussed in 2003, could really provide an entirely new classification system.

Recently, one study has demonstrated the potential clinical applications of gene expression profiling in a cohort of 89 patients with early-stage NSCLC in predicting the risk of disease recurrence.³ The authors evaluated the predictor in two independent groups of 25 patients from the American College of Surgeons Oncology Group Z0030 study and 84 patients from the Cancer and Leukemia Group B 9761 study. The overall predictive accuracy was 72% and 79%, respectively. The predictor also identified a subgroup of patients with stage IA disease who were at high risk for recurrence and who might be best treated by adjuvant chemotherapy. Additionally, an 11-gene expression signature associated with "stem cellness" was found to divide patients with different cancers, including NSCLC, into good- and poor-prognosis groups; however, this stem cell-associated signature has not been validated or further studied in NSCLC.⁴ On a pragmatic basis, a rigorous prospective approach, using training and testing cohorts, to study molecular prognostic markers could improve chances of identifying true molecular prognostic markers that may be reliably applied to clinical practice. Potential research goals may include the following (1): identify molecular tissue, blood, and plasma markers (ie, gene expression profile, genetic polymorphism, genetic/epigenetic alterations, plasma proteomic) predictive of survival, recurrence, and metastasis development in patients with NSCLC; (2) establish characteristics of precursor lesions and the field of cancerization phenomenon in NSCLC pathogenesis by smoking status, gender, and ethnic background; (3) establish molecular markers to discover occult micrometastasis in lymph nodes (sentinel lymph node); (4) evaluate the presence of "stem-cancer cells"; (5) identify molecular tissue and blood markers to predict response to adjuvant chemotherapy; (6) identify molecular markers predictive of response to chemotherapeutic