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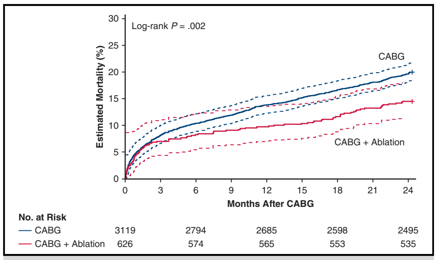
Commentary: Questionable statistical routines

J. Scott Rankin, MD



Piecewise Cox model of 2013 Medicare beneficiaries having CABG with/without AF ablation.[1]

CENTRAL MESSAGE

Hazard ratio for mortality was no different in the first 90 days after CABG (HR, 1.03 [0.74-1.43]), but after 90 days, ablation patients experienced lower risk-adjusted mortality (HR, 0.71 [0.52-0.97]).

> *There are no routine statistical questions, only questionable statistical routines*
>
> —Sir David R. Cox

In this issue of the *Journal*, Malaisrie and colleagues[2] analyzed Medicare outcome data in 34,600 patients with atrial fibrillation undergoing coronary artery bypass grafting from 2006 to 2013. In total, 10,541 (30.5%) had surgical ablation (SA) and 23,059 (69.5%) did not. On average, patients with atrial fibrillation and no SA had greater risk profiles. Using propensity matching techniques, the authors compared 9771 matched pairs of SA versus no SA. Thus, 15,058 (or 44%) of overall patients were omitted from the analysis, and importantly, the prognostic effects of the majority of the greater-risk no-SA group (13,288 or 58%) were removed from consideration. The mathematical effect would be to underestimate the detrimental effects of no-SA in the analysis. An extreme example of this problem is a bariatric surgery propensity study, which has been criticized for omitting 90% of the population and overlooking a significant treatment effect.[3]

No perfect clinical research technique exists. All observational methods have advantages and disadvantages. Propensity matching is a useful approach that can control for imbalances in baseline patient characteristics.[4] First, the probability of treatment assignment is modeled by regression analysis of observed covariates, and the model is used to balance the treatment groups for risk factors. However, the data reduction can hide outcome heterogeneity, and failure to compensate by also adjusting for baseline covariates can result in a bias in the treatment effect toward a hazard ratio of 1.0. Choice of the matching algorithm also is arbitrary,[4] usually depending on the order of observations and creating a type of nonreproducibility. Nonmatched observations are discarded, reducing precision and power. Matching not only rejects hard-to-match observations, but

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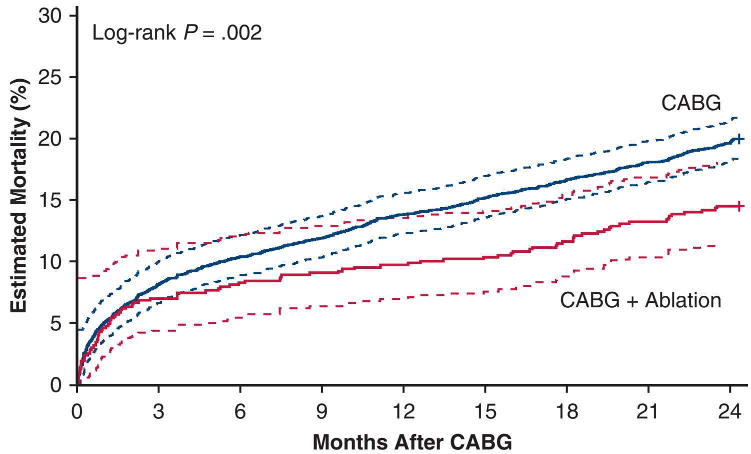

No. at Risk					
CABG	3119	2794	2685	2598	2495
CABG + Ablation	626	574	565	553	535

FIGURE 1. Estimated mortality for Medicare beneficiaries with previous AF undergoing CABG with (n = 626) or without (n = 3119) concomitant surgical atrial ablation.[1] Kaplan–Meier-estimated mortality at 24 months was significantly lower with surgical ablation (14.5%) than without (20.0%) (log-rank test $P = .0019$). *Dashed lines* are Hall–Wellner 95% confidence bands. The study cohort was derived from the 2013 Medicare 100% Standard Analytic File. General mortalities in this study were greater than those in Figure 2, because these were older Medicare patients. *CABG*, Coronary artery bypass grafting.

also discards many "good" matches in the overlap region with ineffective interior interpolation. Covariate adjustment for strong prognostic factors still should be employed to derive treatment effects, due to non-collapsibility of odds and hazards ratios. Finally, matching hides interactions with treatment and covariates.

Direct covariate adjustment may be preferable if the number of potential confounders is not large in comparison to the effective sample size.[4] For example, if the outcome is binary with more than 5 events per covariate, full covariate adjustment may be superior. Because of greater early mortality, a piecewise Cox proportional hazards model can be required, breaking at 90 days[5] (Figure 1). This regression approach has the advantage of including all the data in the analysis.[4] Considering the paper by Malaisrie and colleagues,[2] the data set might have been addressed in multiple different ways, including an overall Cox model, but the authors rejected this suggestion. Especially since the Malaisrie data are at variance with so many other studies showing a consistent treatment effect (Figure 2),[1,6-8] Cox regression analysis of the primary overall data might have been useful. Finally, the average patient in this study was operated more than a decade ago, and one half were earlier than that. Ablation has changed significantly over that time, with more effective procedures recently. Thus, more current positive results may have been diluted by analyzing older patients, and the findings may not be relevant for contemporary practice.

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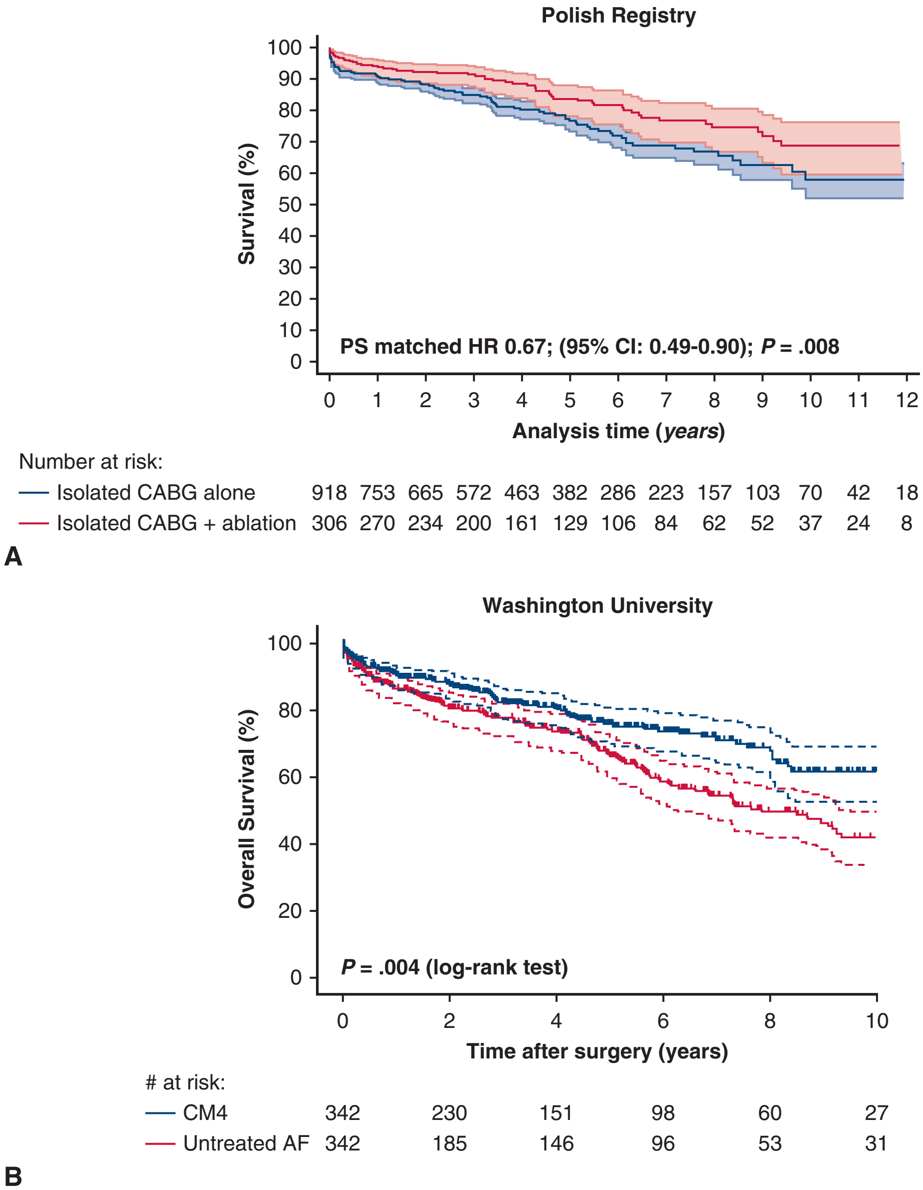

FIGURE 2. A, Recent data from the Polish registry.[7] Propensity-matched Kaplan–Meier survival curves between isolated CABG + ablation versus isolated CABG alone. B, Recent data from Washington University.[8] Kaplan–Meier curves showing survival of the matched CM4 and Untreated AF groups. In total, 33% of these patients had CABG procedures. *PS*, Propensity score; *HR*, hazard ratio; *CI*, confidence interval; *CABG*, Coronary artery bypass grafting; *CM4*, Cox maze IV procedure; *AF*, atrial fibrillation.