Early TAVR

Possible interpretations of the observed data Hazard ratio, 0.50 (95% CI, 0.40–0.63), P<0.001

1. TAVR is better
2. The design was biased and TAVR is not better

If one is going to criticize the study as being biased then one must provide some support for the counter hypothesis of TAVR not being better. Mere speculation about possible biases is not sufficient. Critics have previously noted no difference in objective measure of death or stroke and raised the possibility that the unblinded nature of the study could lead to an exaggeration of the main driver of increased cardiac hospitalizations.

1. There are 4 possible ways unbindedness could lead to reduced hospitalizations. Both the decision to seek medical care and the decision for hospitalization have subjective components. One could reasonably propose that since unblinded i) patients in the clinical surveillance group knew they had severe disease, and knew they were not "fixed." This could favor their conversion from asymptomatic to symptomatic patients—largely, because they knew they had severe disease and were unfixed. ii) medical staff also knew these patients were not "fixed" and thereby increasing their probability of attributing any symptoms, cardiac or not, to the underlying aortic stenosis iii) early surgery group knew they were "fixed" and would be less likely to consult for any symptoms cardiac or not iv) similarly medical staff of the early TAVR patients knowing they were "fixed" would be less likely to attribute any symptoms to heart disease.
2. Importantly all of these possibilities point in the same direction of a possible over-estimation of the benefit of TAVR to reduce hospitalization. Any of these hypotheses would lead to an exaggerated effect size.
3. If TAVR really decreased cardiac hospitalizations how would this likely occur. Scenario 1 where the decrease in the need for hospitalization occurs immediately following randomization, in the first year, with no longer term benefits or Scenario 2 whereby the benefit is present throughout the follow-up perhaps at a smaller initial rate but remains continuous, or perhaps even increases. over time.
4. Logic would dictate that Scenario 2 is more likely if TAVR is truly better.
5. The cumulative incidence curve in the original publication (shows the hospitalization curves separating immediately and continuimng to separate for approximately 1 year and then becoming parallel.

6. I have simulated the published data, and have reproduced the original Figure 1 (see below). Admittedly this is an approximation but the simulated data reveals a HR = 0.53, 95% CI 0.43, 0.66 which is reasonably close to the published data.
7. To test the two scenarios mentioned in point 3# above, a complete (Figure 2) and landmark (Figure 3) analysis at 1 year can be performed. The landmark analysis shows no benefit for TAVR 0.81 (95% CI 0.61, 1.07) p =0.14. This argues against Scenario 2 discussed in point #3 above.
8. The data thus seems best described by a model where the benefit occurs only early after randomization providing support for the hypothesis that the difference is not due to TAVR per se but rather due to bias from the unbinded trial design.

Figure 1 Simulated Cumulative incidence curve

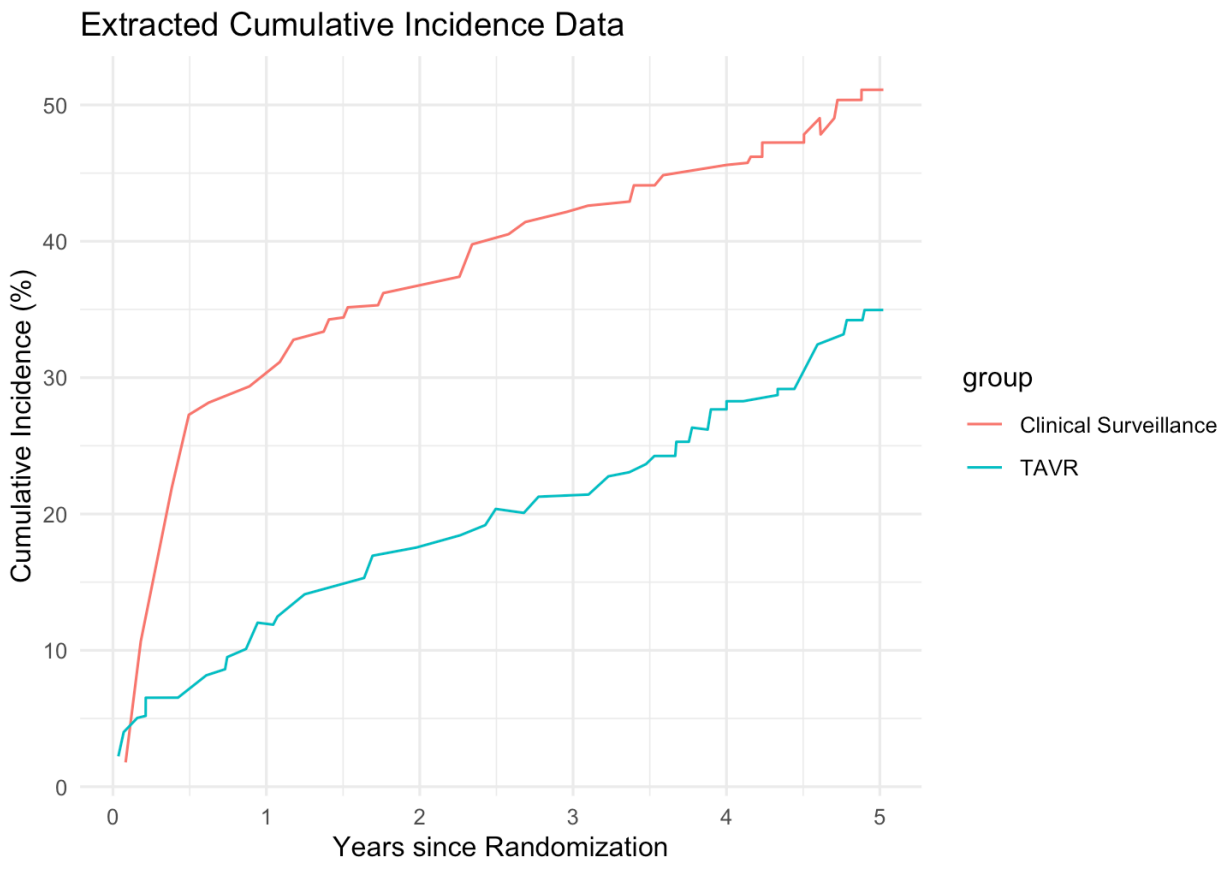

Figure 2 Transposed Kaplan Meier plot of the simulated data set

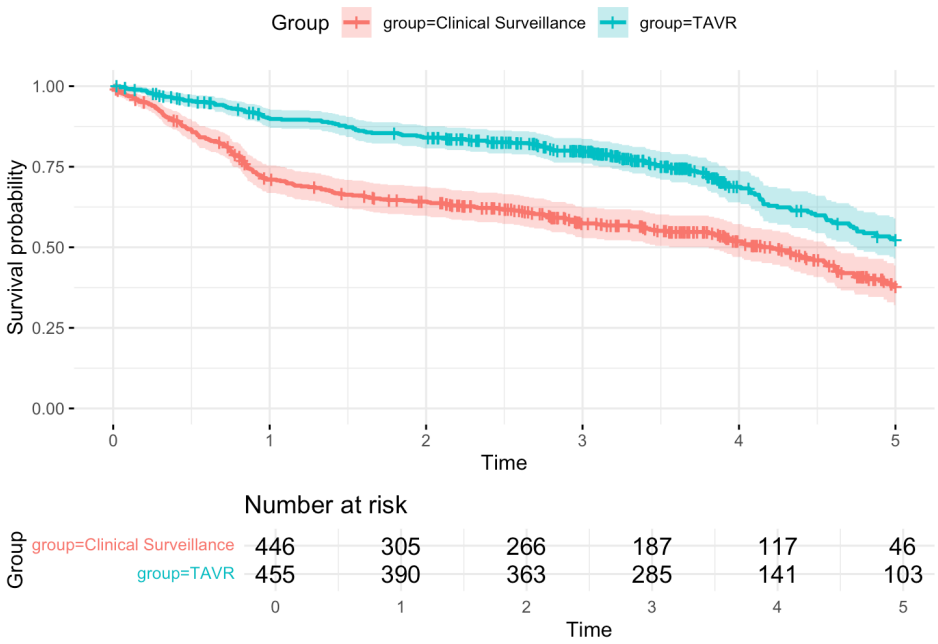

Figure 3 Landmark analysis at 1 year and KM curves