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Cost-effectiveness of the MitraClip device in secondary mitral regurgitation: comment upon the article by Estler et al.

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Keywords Cost-effectiveness · Percutaneous mitral repair · Mitral regurgitation · Germany

Although mature 3 year data from the COAPT RCT were first placed in the public domain in 2019 [1] and published in 2021 (J Am Coll Cardiol [2]), the recent 2022 cost-effectiveness analysis by Estler et al. [3] of the MitraClip device versus optimal medical therapy “in German heart failure patients” is a further analysis based on the 2 year results from the COAPT trial [4]. Estler et al. performed their search for relevant studies in April 2021. The authors either chose not to consider the 3 year data from COAPT published in 2021 [2] but already available in 2019 [1], or possibly missed its existence by not updating their search. As detailed below relative to 2 year follow-up, the 3 year all-cause mortality from COAPT reported by Mack et al. exhibits a distinct upturn in mortality rate in the intervention arm after year 2 (see Mack et al. [2] central illustration C).

A novel and interesting aspect of the Estler et al.’s study is that mortality modelling is handled in a different way to the studies of Cohen et al. [5], Baron et al. [6], and Shore et al. [7], who also derive survival data from the COAPT RCT 2 year follow-up [4] rather than 3 year [1, 2]. The use of the most mature data is generally considered desirable in CE analysis [8], and in this case seems particularly important, because the MitraClip arm in COAPT exhibits a distinct upturn in mortality during years 2–3, reflected in

the cumulative percentage mortality reported at years 1, 2 and 3 of 19%, 28.2% and 42.8%, respectively. These values translate to crude estimates of annual mortality rates of 19% over the 1 year, 9.2% over years 1 to 2, and 14.6% over years 2 to 3; an increase of 59% in rate for years 2–3 relative to years 1–2. In our opinion these considerations indicate that CE studies based on 2 year results from COAPT are likely to overestimate LYG in the MitraClip arm.

The Estler, Baron, Cohen, Shore and NICE-guideline-NG208 [9] CE analyses have differing perspective depending on jurisdiction (Germany, US, UK); however, one important element common to all is the estimation of the lifetime life-year-gain (LYG) from intervention (IN) and control (C) arms and the incremental difference (D) between arms. In each of these studies, lifetime LYG was discounted at annual rate of 3.5% (undiscounted LYG estimates were only reported by Cohen and by Baron), so that the resulting published estimates offer a means of comparison across different studies as listed below:

These estimates indicate a considerable discrepancy between this new study [3] and previous analyses in which the lifetime gain is at least 40% larger.

In the Estler study, modelled mortality depends on the evolution of different NYHA classes through time (Estler et al. Table 1), with only NYHA III and IV classes allocated a transition probability to death > than zero. Thus, the time-changing proportion of patients in these two NYHA classes governs mortality and these proportions in turn are determined by the transition probabilities (TP) applied for transitions between different NYHA classes (see model diagram Fig. 1 and TP listed in Table 1). The author’s request for these transition data from COAPT was unsuccessful, and so, an approximation was assumed. One-way sensitivity analyses (see Estler et al. Tornado diagram in Supplementary material) demonstrated that model output was highly sensitive to change in the TP from class II to III and from

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Table 1 Lifetime life years gained discounted 3.5%

Study	Clip arm	Control	Incremental LY	% vs. Estler
Estler et al. [3]	3.68	2.88	0.80	/
Cohen et al. [5]	Not reported	Not reported	1.57	196%
Baron et al. [6]	5.05	3.92	1.13	141%
Shore et al. [7]	4.56	3.01	1.55	194%
NICE ^a	Not reported	Not reported	1.44	148%

^aa further relevant study (NICE) used COAPT 3 year data from the optimal medical therapy arm and applied an HR to generate survival in the MitraClip arm; an unexpected methodology in view of post 2 year cross-over of some OMT to MitraClip, and the distinct upturn in mortality seen in the MitraClip arm after 2 years (see above)

III to IV (i.e., to those classes with a death TP > zero). We were unable to identify the magnitude of change to the TP between NYHA class used in this one-way sensitivity analysis, but assuming it was $\pm 10\%$ and then raising the TP II to III from 0.05 to 0.055 in the MitraClip arm increases the ICER by 40% from 60 K€/QALY to > 85 K€.

Estler et al. comment: “*at all times of the follow-up ... the model was consistent with the NYHA class distribution observed in the COAPT trial*”, and similarly “*.. the model could precisely predict all-cause mortality in both groups for the 2-year follow up period in comparison with trial data*”. This may be true; however, since in a lifetime model, nearly all the life-years-gain and QALYs accrue in the extrapolation beyond the observed 2-year period, it is the disposition of NYHA classes and consequently of mortality in extrapolation that mostly influences model outputs and is of prime interest; unfortunately, neither of these model outputs were reported by Estler et al. This is in contrast to other studies (e.g., see Figs. 1 in Baron and Cohen, supplementary Figure S1 in Shore, and Fig. 3 in NICE) that each provide graphs of lifetime survival generated from their models. When the modelled curves for the MitraClip arm in all these studies are compared with the observed 3 year observed survival in COAPT [1, 2], it is evident that survival in MitraClip arm has been overestimated survival from years 2 to 3 relative to observed 3 year follow-up (data available from correspondents on request), and since LYG in Estler is substantially lower than in these studies, it seems possible Estler mortality may more closely represent 3 year COAPT results than the other studies. Comparing 3 year MitraClip arm mortality from COAPT with that seen in real-world studies with

extended follow-up (Adamo et al. [10] and Levu et al. [11]) suggests that the upturn in mortality is not an anomaly seen only in the RCT (data available from authors of this comment on request).

Declarations

Conflict of interest The authors have read the journal's policy and declare the following competing interests: XA is a member of the steering committee of the Mitra-FR study. MC has nothing to disclose.

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