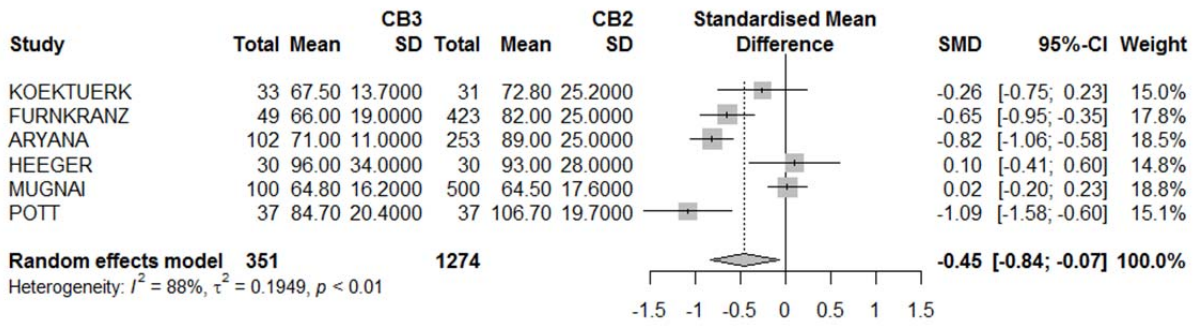

Figure 2: Procedure time

The analysis of fluoroscopy time favored the CB-2 group. The total fluoroscopy time was shorter in the CB-2 groups as compared to the CB-3 groups. The combined difference in mean of all the six studies was favorable for the CB-2 group for the total fluoroscopy time (SDM=0.19 [95% CI of -0.15; 0.53], p<0.01) with a significant heterogeneity (I^2=84%, τ^2=0.1448, p<0.01) as shown in Figure 3.

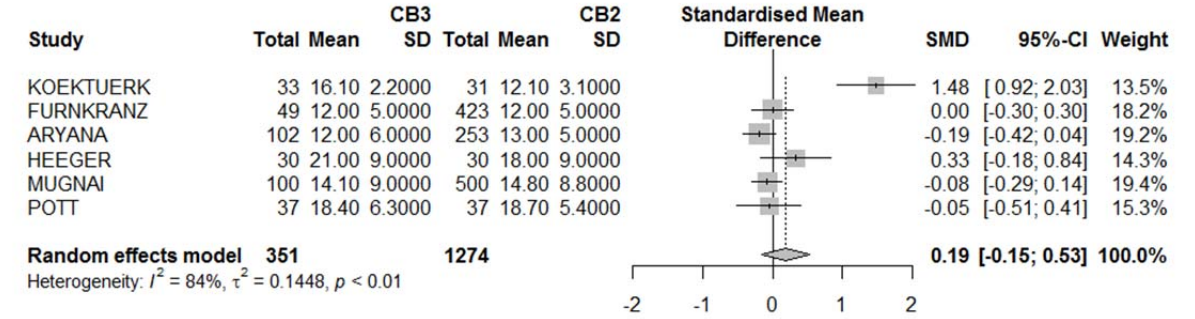

Figure 3: Fluoroscopy time

As for the nadir temperatures reached during the ablation, the results are as follows. In the LSPV, all the studies showed a higher temperature in the CB-3 groups, but the difference was statistically significant in only one trial [16]. The heterogeneity analysis was low (I^2=16%, τ^2=0.0052, p=0.31). The combined mean difference showed a lower temperature reached in the CB-2 groups (SDM=0.19[95% CI of 0.06; 0.31], p=0.31) (Figure 4). In the LIPV, RSPV and RIPV the trials had high heterogeneities of 80% (I^2=80%, τ^2=0.1108, p<0.01), 75% (I^2=75%, τ^2=0.0826, p<0.01) and 57% (I^2=57%, τ^2=0.0360, p=0.04) respectively. The combined standard mean difference also shows that the mean minimum temperature reached was higher for the CB-3 groups in LIPV (SDM=0.52[95% CI of 0.21; 0.83], p<0.01), RSPV (SDM=0.40[95% CI of 0.12; 0.67], p<0.01), and RIPV (SDM=0.26[95% CI of 0.05; 0.47], p=0.04) (Figures 5-7).

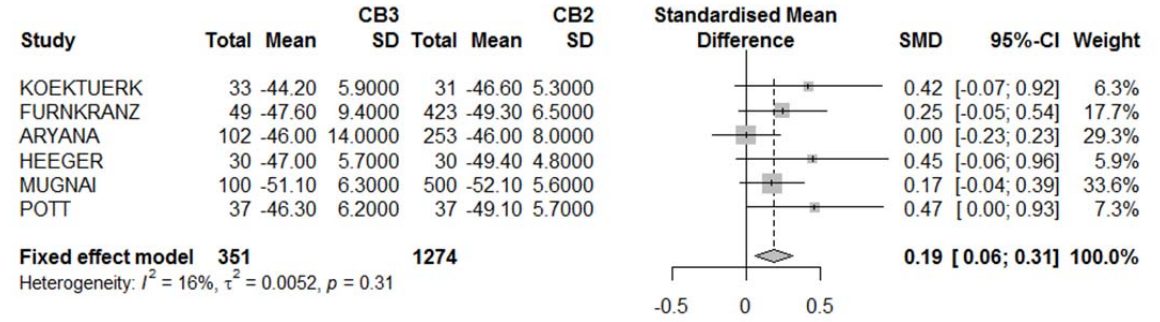

Figure 4: Minimum temperature in LSPV

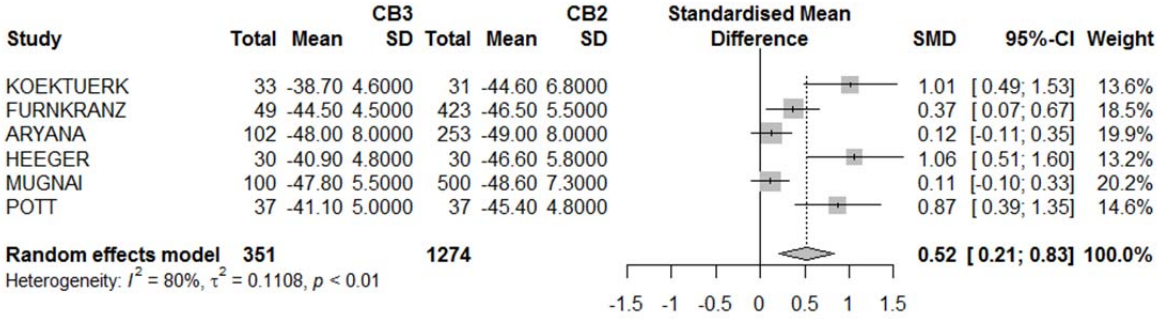

Figure 5: Minimum temperature in LIPV

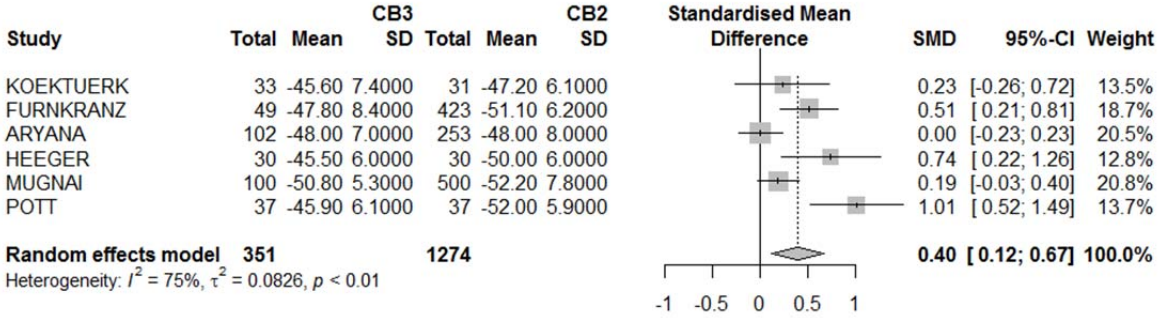

Figure 6: Minimum temperature in RSPV

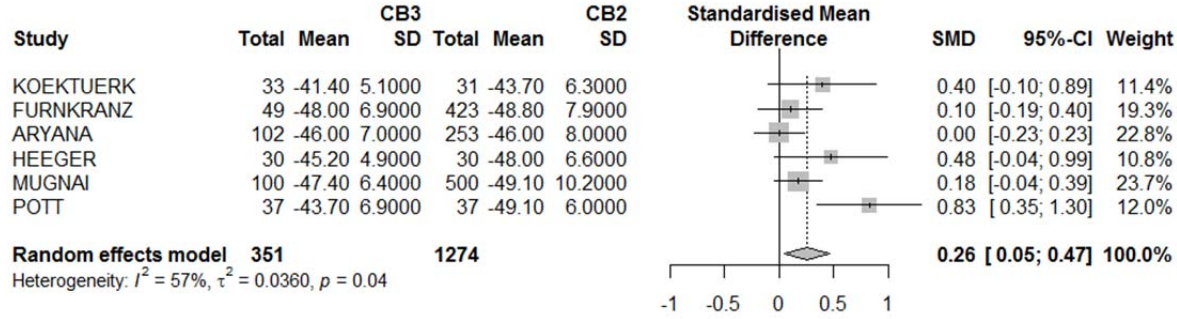

Figure 7: Minimum temperature in RIPV

Analysis of real time recording data showed that there was a higher isolation recording achieved with the CB-3 compared to that in CB-2 but the difference was not statistically significant [OR=3.53(95% CI 2.47,5.05), p=0.44]. The heterogeneity between the studies was not significant (I^2=0%, τ^2=0, p=0.44) (Figure 8).

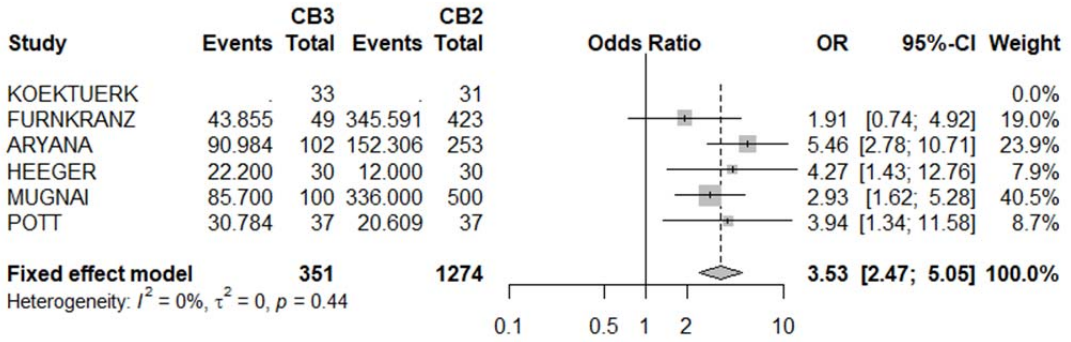

Figure 8: Real time recording

4. Complications

Transient ischemic attack, ischemic stroke, pulmonary vein stenosis, atrio-esophageal fistula, pericardial effusion and phrenic nerve palsy (PNP) have all been mentioned in several literatures as frequent complications that occur during cryoablation procedures. Except for one paper [16] which did not assess complications rates during the procedure, all the studies included in our paper also recorded those transient and persistent PNP, access site complications (hematoma, AV fistula, pseudoaneurysm), pericardial effusion and TIA. But, in all the papers, the difference was not statistically significant between the third generation and second generation cryoballoon ablation groups.

5. Discussion

The main difference between the third generation cryoballoon and the second generation cryoballoon is the 40% shorter tip of the third generation counterpart. In terms of other aspects, the two types of balloons have a rather similar design. This difference, in theory should provide a better visualization of pulmonary vein isolation allowing for quicker assessment of pulmonary isolation and thereby provide the operator with more information that can be used for an individualized treatment for each patient [15, 16].

The main findings of this meta-analysis are as follows. Firstly, the third generation cryoballoons are associated with a shorter total duration of the procedure. The fluoroscopy time with the third generation cryoballoon was significantly longer than that of the second generation. The minimum freeze temperature was significantly higher in the LIPV, the RSPV and the RIPV with the third generation cryoballoon. However, although the real time monitoring was more likely to be achieved in a greater proportion of patients with the CB-3, that difference showed to be not statistically significant.

The mean procedure time for the third generation cryoballoon group was 75min and that for the second generation was 84.7min. There are several reasons that may have lead to this shorter procedural time. As mentioned earlier, the

shorter tip of the CB-3 placed the electrode closer to the ablation site. This proximity to the ablation site provides a better measurement of the signals inside the pulmonary veins and helps the operator to assess the achievement of pulmonary vein isolation earlier than in the second generation cryoballoon[7]. This increases the efficiency of the procedure and shortens the procedure time. The pulmonary vein characteristics of each patient are different which means the amount of freezing required by each individual patient is also different. Provided with more information, operators can therefore design a tailored plan for every patient. This eliminate the standardized protocols and allows for a targeted and patient specific approach when using the CB-3. Fewer freeze cycles were administered in the CB-3 group and this did not affect the procedure outcome. An additional freeze means more time spent therefore making the procedure with the CB-2 longer. Pott et al. [16] also mentioned that the shorter tip helped when using this catheter in patients with short main trunk of the pulmonary veins. In this situation, compared to the longer tip counterpart, which may be problematic and require more maneuvers for positioning the catheter, the shorter tip eased the occlusion of the pulmonary vein making the whole procedure easier and faster. A shorter time to isolation means a more durable PVI while longer time to isolation has been associated with early recurrence [17-20].

Analysis of fluoroscopy time showed that more fluoroscopy was required for the CB-3 group than that of the CB-2 group. This may be attributed to the shorter tip of the CB-3 catheter. Furnkranz et al[12] describe a decrease in maneuverability and stability due to this shorter tip making it difficult to position the catheter and also, decreasing the stability of the catheter inside the pulmonary vein. The need for repeated positioning may account for the increased use of fluoroscopy with the third generation cryoballoons.

Pott. et al. [16] mentioned that the higher temperature recordings inside the pulmonary veins can be explained by the shorter duration of the freeze and quicker visualization of pulmonary vein isolation thereby allowing the freeze to be of shorter durations which did not allow the temperature in the pulmonary vein to drop as much as in patients treated with the second generation cryoballoons. This faster detection of isolation of the pulmonary veins helps to reduce the amount of freezing required to attain isolation. Another author, namely Heeger et al. [14] hypothesized that a modified freeze cycle duration may be the reason leading to these higher temperature recordings noted when using the third generation cryoballoons. Another plausible explanation for this finding can be explained by Furknanz et al. [12], Pott. et al. [16] and Aryana et al. [13] who mentioned that this higher nadir temperature maybe be due to the more proximal positioning of the catheter. Mugnai et al. [15] suggested that the difference in temperature maybe due to a longer distance between the thermocouple and the coil dispersing the refrigerant. Another explanation for this higher minimum temperature may be due to the decreased occlusion of the PV ostium when using the third generation cryoballoon [11].

All the papers included in our study showed a statistically significant real time recording of pulmonary vein isolation except one. Due to a lack of information, this paper was not included in our analysis of the real time recording. The insignificant difference between real time monitoring may be attributed to the artifact formation which is more prone to happen when using the short tip cryoballoon as compared to the second generation cryoballoon. In the CB-3, the short tip places the mapping catheter to the PV ostium. But this can also be achieved in most cases by prolapsing the circular mapping catheter of the CB-2. Only a few cases with anatomical varieties renders this

maneuver difficult. Koektuerk et al. also mentioned that the short tip caused more signal artifacts than the CB-2 [11].

6. Study limitations

Several limitations exist in this present meta-analysis. All the studies included in our paper were not randomized controlled trials. Any cofounding factors that may have lead to a difference between the two treatment arms cannot be excluded. Most of the studies had a short follow-up period or did not mention any follow-up. Longer follow-up studies to assess the long term outcomes are needed. Arrhythmia recurrence was not recorded in all the studies therefore only the procedural outcomes could be compared. The third generation cryoballoon arm in most studies had a small number of patients. Any conclusions should therefore be confirmed by larger randomized controlled trials. This paper also bears the limitations of a meta-analysis.

7. Conclusion

Pulmonary vein isolation using the third generation cryoballoon allows for a shorter procedure time, offers an enhanced ability to assess time to pulmonary vein isolation, facilitates the individual freeze strategy dosing scheme and enables a time dependent freeze protocol with equivalent procedural safety and efficacy.

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None

Conflict of interests

Authors declare that there is no conflict of interest

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