In response to Letter regarding "Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis"

We thank Dr Scholtens for his interest in our work and understand his concern for ostensible discrepancies in the reported data from published literature and our pooled analyses. When pooling data for our meta-analysis, we had to ensure that each study included in our final analysis is addressing the same clinical question, so that comparable data are being pooled. There was inconsistency in included studies regarding inclusion or exclusion of possible cases of endocarditis and this is one reason for discordance in their reported and our calculated sensitivity and specificity. For all practical purposes, cases of both definite and possible endocarditis are managed similarly in clinical practice and therefore were included in our pooled estimates. Also, the values used to calculate the pooled sensitivity and specificity in a meta-analysis need to be based on *n*, as in number of patients, rather than the sensitivity and specificity values calculated in individual studies based on the foci of infection observed on PET scan (a single patient may have multiple foci of infection identified on PET scanning). These are the two primary reasons for discrepancies in our reporting noted by the correspondent.

Below we have provided specific reasons and rationale for our decisions and addressed specific concerns raised by the correspondent.

JIMENEZ BALLVE 2016

Jimenez Ballve et al. reported their overall sensitivity and specificity in their abstract based on the 62 suspicious foci of infection found in 41 patients. The individual patient data were reported in Table 3 in ('PET/CT image interpretation') results of their article (page 2407). Based on these numbers, we assessed a true-positive number of 25, false positive of 13, false negative of 0, and true negative of 3. These are the values we used to calculate the specificity of 19% based on patient level data, rather than individual foci level data. We used this value in our pooled specificity calculation and meta-analysis and results are summarized in the forest plot in figure 1.

In clinical practice, the performance of a diagnostic test is determined by its utility to the patient rather than based on individual foci of infection (one patient may have multiple foci of infection). Therefore, we calculated sensitivity and specificity values based on the number of patients. Other studies included in our analysis reported their sensitivity and specificity based on the number of patients and not total number of suspicious foci of infection. Therefore, it would have been inappropriate to combine the reported sensitivity and specificity based on individual foci for this study alone.

Table 2 is a summary of the different visual and semi-quantitative interpretative methods used by the various studies. The value of 73% specificity is reported by Jimenez Ballve as related to the analysis of attenuation corrected (AC) and non-attenuation corrected (NAC) images. This value is reported in Jimenez Ballve 2016, results section, subsection entitled 'Visual analysis of both AC and NAC PET images' on page 2406. At our institution, we routinely compare AC and NAC images due to concern for misleading device or prosthesis-related artifact. Therefore, we felt this was the more appropriate number to highlight in this summary table of PET interpretive methods. There is considerable variation in the reported interpretive methods for PET scan for the evaluation of endocarditis, we hope further work in this area will assist in clarifying an optimal interpretive methodology for this promising diagnostic modality for endocarditis.

The specificity reported in table 1 is an error and should read 19% (4–46). We cannot find other instances where the individual specificity for Jimenez Ballve was mentioned in the text of our manuscript.

GRANADOS 2016

The numbers used for the pooled sensitivity and specificity calculation were obtained from table 3 ('Classification according to initial diagnosis criteria, 18F-FDG PET/CT results and final diagnosis criteria')

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in Granados 2016. Their reported values result in a true positive number of 24, false positive of 2, false negative of 7, and true negative of 47 for the 80 patients with possible endocarditis included in their study, with a resulting sensitivity of 77% and specificity of 95%. These are the values included in our pooled analysis, as well as the values reported in table 1 and figure 2 of our article. Granados et al. reported their sensitivity of 82% and specificity of 96% based on the subgroup of 31 patients with a final diagnosis of infection as reported in the text of their results section.

FAGMAN 2015

The reported sensitivity and specificity in Fagman et al. included 19 control patients, in addition to the 11 patients with suspected endocarditis. As our meta-analysis evaluated the utility of PET in diagnosis of possible endocarditis, only the 11 patients with suspected endocarditis were included in our pooled analysis. This resulted in a true-positive number of 6 patients, false positive of 0, false negative of 3, and true negative of 2 as gathered from the reported data in Fagman et al., results section, table 1 ('18F-FDG PET/CT Findings'). These values result in a sensitivity of 67% and specificity of 100%; these are the values reported in table 1 and figure 2 of our article, as well as the values that were included in our pooled analysis.

GRAZIOSI 2014

Graziosi et al. report a true-positive number of 8, false positive of 2, false negative of 4, and true negative of 13 resulting in a calculated sensitivity of 67% and specificity of 87%. These are the values used to calculate the sensitivity and specificity in our pooled analysis, and the values reported in table 1 and figure 2 of our article. Graziosi et al. did not include the positive PET scan that was clinically classified as possible IE in their sensitivity/specificity. However, in order to reflect the real-life use of this test in clinical practice and to be consistent in our analysis, we included these possible IE cases in our sensitivity/specificity calculations as a true-positive scan.

PIZZI 2015

The values included in our pooled sensitivity and specificity analysis are for the 64 patients with prosthetic valve endocarditis, obtained from table 6 in Pizzi et al., results section, page 1123. This gives a true-positive number of 34, false positive of 2, false negative of 5, and true negative of 23 with resulting sensitivity of 89% and specificity of 84%. We excluded the 28 patients with device-related infection from our pooled analysis as it was unclear from the methodology reported by Pizzi et al. whether they were referring to CIED lead infection or CIED-related valvular endocarditis.

RICCIARDI 2014

The values we used to calculate sensitivity and specificity were obtained from table 1, page 222, in Ricciardi et al. They report a true-positive number of 16, false positive of 0, false negative of 9, and true negative of 2 for the 27 patients in their study who underwent PET/CT to evaluate for possible endocarditis. This results in a calculated sensitivity of 64% and specificity of 100%; these are the values reported in table 1 and figure 2 of our article. The value of 55% sensitivity reported by Ricciardi et al. and noted by the correspondent refers to the sensitivity of PET/CT for only the 20 patients within their cohort who had an eventual diagnosis of definite endocarditis; this is detailed by Ricciardi et al. on page 221 in the results section of their article.

ROUZET 2014

In the text of their article, specifically in the results section, subsection 'Performance of 18 F-FDG PET imaging,' page 1982, the Rouzet et al. report a true-positive number of 15, false positive of 6, false negative of 3, and true negative of 15, resulting in a sensitivity of 83% and a specificity of 71%. These are the values used to calculate our pooled sensitivity and specificity, and the values were reported in table 1 and figure 2 of our article.

In their reported sensitivity and specificity values, Rouzet et al. did not include the 4 patients with an eventual clinical diagnosis of possible endocarditis, which results in their reported sensitivity of 93% (TP 13, FP 6, FN 1, TN 15). We chose to include these patients in our analysis for consistency (other studies included in our pooled analysis included both possible and definite endocarditis cases) and that this is more reflective of the clinical use of PET/CT in diagnosis of endocarditis.

SABY 2013

Saby et al. report in the text of their article and in table 3 in the results section on page 2377, a true-positive number of 32, false positive of 4, false negative of 20, and true negative of 16. This results in a calculated sensitivity of 62% and a specificity of 80%. These are the values used to calculate our pooled sensitivity and specificity, and the values were reported in table 1 and figure 2 of our article.

The sensitivity and specificity values reported by Saby et al. in their article excluded the 22 patients with possible infective endocarditis, resulting in their reported sensitivity of 73% (TP 22, FP 4, TN 16, FN 8). As noted above, for the sake of consistency and to reflect the clinical use of PET/CT as a diagnostic test, we included both definite and possible endocarditis cases in our analysis as clinically these patients are managed similarly.

Disclosure *The author declares that there is no conflict of interest to disclose.*

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