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SYSTEMATIC REVIEW

Evaluation of the risk of heart failure with tumour necrosis factor inhibitors: A large-scale meta-analysis in immune-mediated inflammatory diseases

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Abstract

Background: Current therapeutic guidelines for immune-mediated inflammatory diseases (IMIDs) contraindicate the administration of tumour necrosis factor inhibitors (TNFis) in advanced heart failure (HF) and highlight the potential risk for new-onset HF. The current evidence has low certainty, and the results of studies in the past two decades have even challenged the recommendations regarding the impact of TNFis on the risk of HF.

Objectives: The objective was to systematically synthesize data on the risk of HF in TNFi-treated groups compared to non-treated controls in IMIDs.

Methods: A systematic search was conducted in August 2023. Randomized controlled trials (RCTs) and non-randomized observational studies of IMID patients comparing groups receiving TNFis to non-TNFi-exposed controls were included. The outcome was the incidence of worsening, de novo, and composite HF. Random-effects meta-analysis was conducted using risk ratios (RR) with 95% confidence intervals (CIs) to pool data.

Results: The systematic search identified 49 studies, with 45 included in the quantitative analysis. For the worsening of HF, the pooled results of non-randomized studies showed no statistically significant risk-increasing effect of TNFis (RR = 1.18, 95% CI: 0.69–2.00). Analyses from both RCTs and non-randomized data indicated no increased risk of de novo HF in the TNFi-group compared to controls (RR = 0.87, 95% CI: 0.60–1.25 and RR = 0.86, 95% CI: 0.64–1.14, respectively). Similarly, no increased risk was found for composite (worsening and de novo) HF in the TNFi-treated group versus controls, pooling non-randomized data.

Conclusions: Our findings indicate that TNFi-treated IMID patients do not have an increased risk for developing de novo HF, and no statistically significant risk enhancement could be observed in the risk of worsening HF with TNFis. Updating IMID guidelines should be considered regarding TNFis' non-risk increasing effect on de novo HF, whereas further validating data on the risk of worsening HF in TNFi-treated IMID patients is needed.

Péter Holló and András Bánvölgyi share the last authorship.

INTRODUCTION

Immune-mediated inflammatory diseases (IMID) refer to a heterogeneous group of patients in whom common immuno-inflammatory pathways are activated. Chronic inflammation leads to various clinical manifestations, affecting multiple organs, including the skin, joints and intestines.[1] Psoriasis (PsO), rheumatoid arthritis (RA) and inflammatory bowel diseases (IBD) are among the most frequent IMIDs, with global age-standardized prevalences of around 504, 224 and 59 per 100,000 persons, respectively.[2–4]

According to the signature cytokine-based concept, tumour necrosis factor-α (TNF-α) represents the hub of the shared immunological pathways of IMIDs, elevated levels of TNF-α contribute to tissue remodelling and organ damage. Through inhibiting this crucial role, TNF-α inhibitors (TNFis) have been proven to be highly effective, leading to breakthroughs in treating IMIDs.[1] Currently, five differently engineered TNF-α inhibitor agents (TNFi) are approved by the European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) for IMID treatment: infliximab (INF), adalimumab (ADA), golimumab (GOL), certolizumab-pegol (CZP) and etanercept (ETA).[5,6]

TNFis are generally well-tolerated biological treatments with mostly minor and self-limiting side effects. However, patients may occasionally also experience more serious adverse reactions.[7] The evidence for associating the worsening and new-onset of heart failure (HF) with TNFis was based on two pillars in the early 2000s.

The effect of TNFis in worsening HF was supported by studies testing the hypothesis of a potentially beneficial effect of TNFis on HF.[8] Randomized controlled trials (RCTs) on ETA and INF with New York Heart Association (NYHA) class II-IV HF found no benefits compared to placebo (PBO) examining the outcomes of the clinical status of HF, hospitalization due to HF or mortality risk.[9,10] In addition, in the INF-related (ATTACH) trial, although the hazard of reaching the end point of death or hospitalization due to HF did not improve with a medium dose (5 mg/ kg) of INF (HR = 0.80, 95% CI 0.22–2.99), it increased with a higher (10 mg/kg) dose compared to PBO (HR = 2.84, 95% CI 1.01–7.97).[10] These trials were stopped prematurely, and no further investigations on TNFi agents and doses in patients with HF were performed.

TNFi has been identified as a potential harm for the development of de novo HF in an FDA report that includes early post-marketing surveillance data in IMID patients. The report covers 38 new-onset and nine worsening cases of HF with ETA or INF registered in the FDA MedWatch system up to February 2002, by which time approximately 274,000 patients worldwide had received these therapies. A potential causal relationship was suggested by the fact that nine of the 10 patients under 50 achieved complete resolution or improvement after TNFi was withdrawn and HF treatment was initiated.[11]

To date, based on the evidence from these two pillars, the IMID therapeutic guidelines describe the absolute or relative contraindications for TNFi use in advanced HF cases and cautious use in milder HF cases and include the risk of de novo HF associated with the use of TNFis.[12–17] Despite this, TNFis have been widely used for over two decades among IMID patients, providing growing data on their safety and rising evidence of their beneficial effect on major adverse cardiovascular events.[18] The substantial amount of data available, which sometimes even challenges present guidelines, and the currently limited robustness of evidence necessitate a comprehensive synthesis of all existing data on the risk of new-onset and worsening HF in TNFi-treated versus non-exposed IMID populations.

Why was the study undertaken?

- The clinical question was whether tumour necrosis factor inhibitors (TNFis) increase the risk of worsening and de novo heart failure (HF) in immune-mediated inflammatory diseases (IMID).

What does this study add?

- The present meta-analysis provides evidence that the risk of de novo HF is not higher in TNFi-treated IMIDs than in controls not receiving TNFis, and no statistically significant risk increase was shown in worsening HF in TNFi-treated IMIDs.

What are the implications of this study for disease understanding and/or clinical care?

- TNFis do not increase the risk of de novo HF in IMID patients; updating therapeutic guidelines should be considered. Further validating data regarding the effect of TNFis on the worsening of HF is required.

METHODS

Systematic search and selection process

We conducted a systematic review and meta-analysis according to the instructions of the Cochrane Handbook.[19] The current study report aligns with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement.[20]

After submission of the protocol to the PROSPERO register system (ID CRD42023451099), a systematic search was performed in four databases (MEDLINE via Pubmed, Cochrane Library, EMBASE, Web of Science) without any search restrictions on 3 August 2023 (for the search key, see Section S1).

Journal articles were included if they reported results of RCTs or observational studies that met the following PICO (population-intervention-comparator-outcome)-determined

inclusion criteria: (1) adult IMID patients, (2) TNFi-treated cohorts, (3) non-TNFi-exposed control groups (application of PBO or conventional non-biologic treatments, but non-use of TNFis or other biological treatments) and (4) incidence of HF during comparative follow-up periods. The statement of the diagnosis of heart/cardiac/ventricular failure had to be present in the publications. Case reports, case series, abstracts, commentaries and notes were exclusion criteria. For the summary of the selection process, see Section S2.

Data extraction and quality assessment

The detailed procedure for data extraction, the types of data collected, the principles applied to identify de novo, worsening and composite HF events and the methods used to assess data quality are described in Sections S3 and S4.

Synthesis and analysis of data

A detailed description of principles for data synthesis is summarized in Section S5.

Methods for statistical analysis

In cases where more than one suitable reported effect measure was available in a study, primarily HR, secondly IRR and if neither of these was reported, then the crude incidences were included in the meta-analysis. Relative risks were calculated from the crude incidences. IRRs were calculated from IRs with 95% CIs and corresponding follow-up times. Either calculated by crude data or extracted directly from the study reports, IRRs and HRs were considered equivalent effects of measures and were generally referred to as risk ratios (RR). Random effects meta-analysis was applied to calculate the summary effects of RRs separately for RCTs and non-randomized studies.

For the analysis of both randomized and non-randomized data, we used the random effects model with the adjustment proposed by Hartung and Knapp (2001) to avoid false positive findings.[21] For the summary estimates of relative risks in RCTs, we used the Mantel–Haenszel method, as suggested by the Cochrane Handbook, for the analysis of rare events.[19] To assess statistical heterogeneity, the Q test and I^2 statistics were calculated. We also reported the 95% prediction interval (PI), following the recommendation of IntHout (2016).[22] We visualized our findings in forest plots, reporting the average RR, its 95% CI and the statistical test of no average effect as summary statistics. We used funnel plots to visually assess the signs of a possible small study effect. Statistical significance was considered if the p-value <0.05. All statistical analyses were performed with the R program (R Core Team 2020, V4.1.3) using the meta and metafor packages.[23]

RESULTS

Systematic selection

The systematic search and selection process yielded a total of 6434 records (see Table S1). After duplicate removal, selection by title and abstract, and subsequent screening of full texts, 34 hits met the inclusion criteria.[24–57] Backward and forward citation searching identified 19 additional full texts.[58–76] A total of 53 journal articles with the results of 49 individual studies were included in the systematic review and meta-analysis. The detailed selection process is summarized in Figure 1.

Characteristics of the studies and patients included

A total of 287,769 IMID patients were examined in the studies included in the systematic review. Of the 49 individual trials included, RA patients were solely involved in 21, IBD in 11 and PsO and/or PsA patients in 14 studies. One study analysed data from both patients with RA and IBD, and two trials incorporated data from patients with spondyloarthritis (SpA). The most frequently administered TNFi was ADA; its application was reported in 28 studies. Of the 49 studies, 28 provided results from randomized comparison groups, and 19 reported data from non-randomized patients. Data from both randomized and non-randomized cohorts could be retrieved from one trial. One additional study contained already pooled safety data from 19 RCTs that had already been analysed. The main characteristics of the 49 studies included in the systematic review are summarized in Table S2.

The meta-analysis was performed using data from 45 studies, 26 with randomized and 19 with non-randomized observational data, with a minimum of 152,829 patients. In all 26 randomized trials, the outcome was de novo HF. Of the 19 non-randomized trials, data on worsening HF were collected from 4, de novo HF from 10, whereas 13 studies included mixed populations of individuals with and without heart failure. Additional characteristics of these studies (i.e. follow-up periods) and patient demographics are shown in Table S3.

Worsening heart failure

Four observational studies with real-world data examined the worsening of HF in TNFi versus non-TNFi-treated groups. All four studies included only patients with RA. The overall analysis involving 1966 patients showed no statistically significant increase in the risk of worsening HF in the group receiving TNFi compared to the controls. The pooled effect size with RR was 1.18, with a 95% CI of 0.69–2.00 (Figure 2).

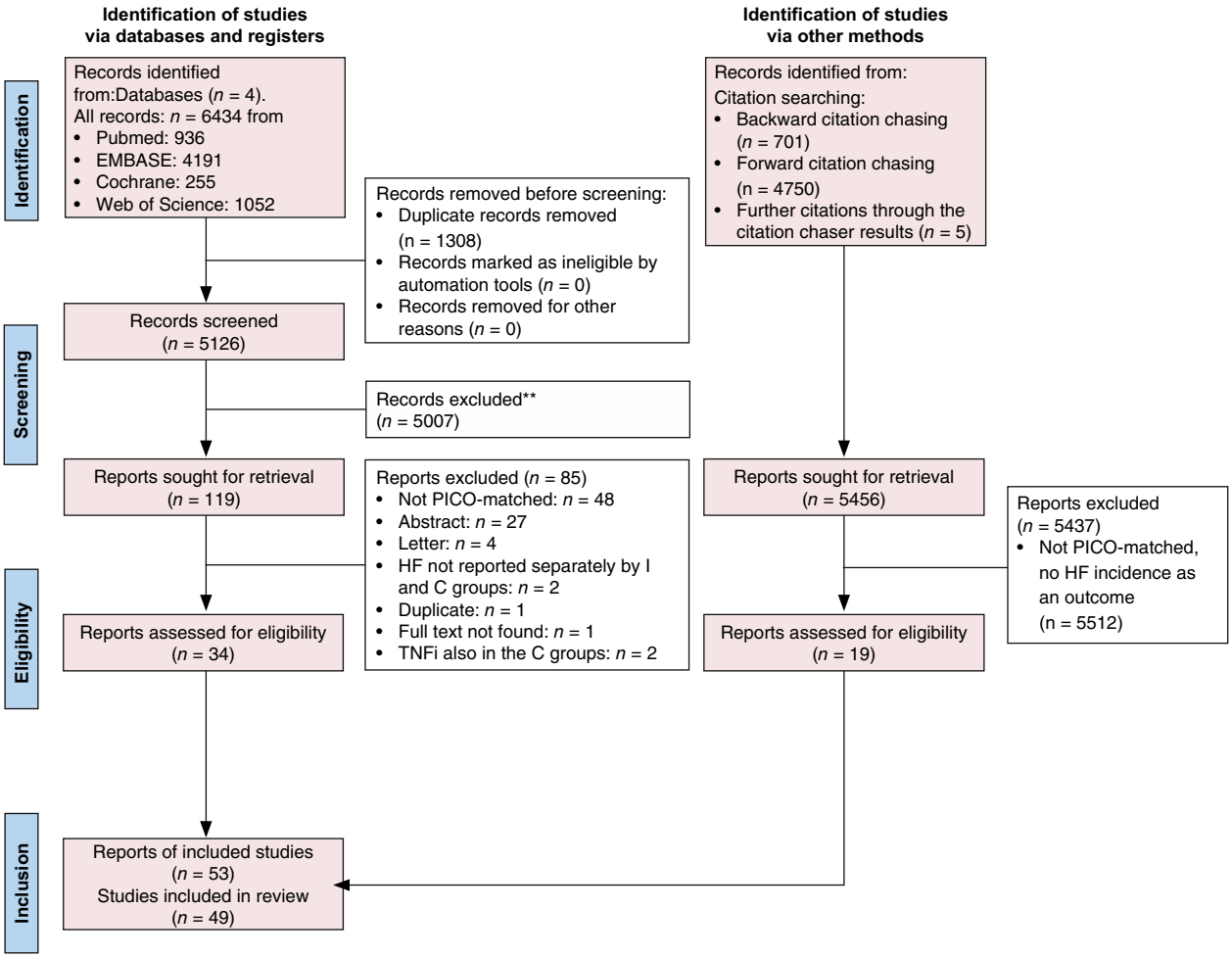

FIGURE 1 PRISMA flow diagram of the systematic selection process. HF, heart failure; PICO, Patients-intervention-comparator-outcome; TNFi, tumour necrosis factor inhibitor.

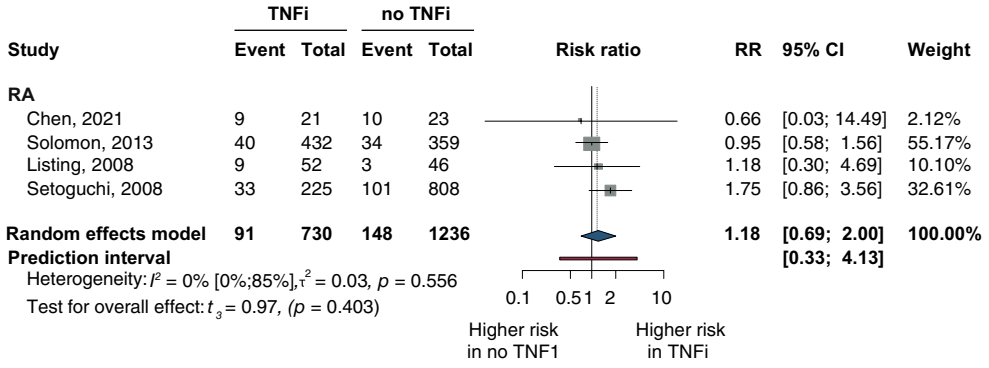

FIGURE 2 Forest plot on the results of pooled non-randomized data on the risk of worsening heart failure. CI, confidence interval; RA, Rheumatoid arthritis; RR, Risk ratio; TNFi, tumour necrosis factor inhibitor.

De novo heart failure—Randomized studies

Data from 26 randomized studies were pooled, including 10,981 IMID patients, comparing TNFi recipients with non-TNFi-treated groups for the risk of de novo HF. The pooled effect size showed no risk increase with TNFis for new-onset HF compared to controls (RR = 0.87, 95% CI 0.60–1.25). Similarly, pooled effects by subgroup analyses demonstrated that TNFis

did not increase the risk of de novo HF, whether different IMID subpopulations (IBD, PsO/PsA, RA) or TNFi agents (ADA, INF) were considered and compared. Heterogeneity measured by the I^2 test resulted in 0% for the overall and subgroup analyses, indicating high group homogeneity. Results presented in forest plots are shown in Figures 3 and 4.

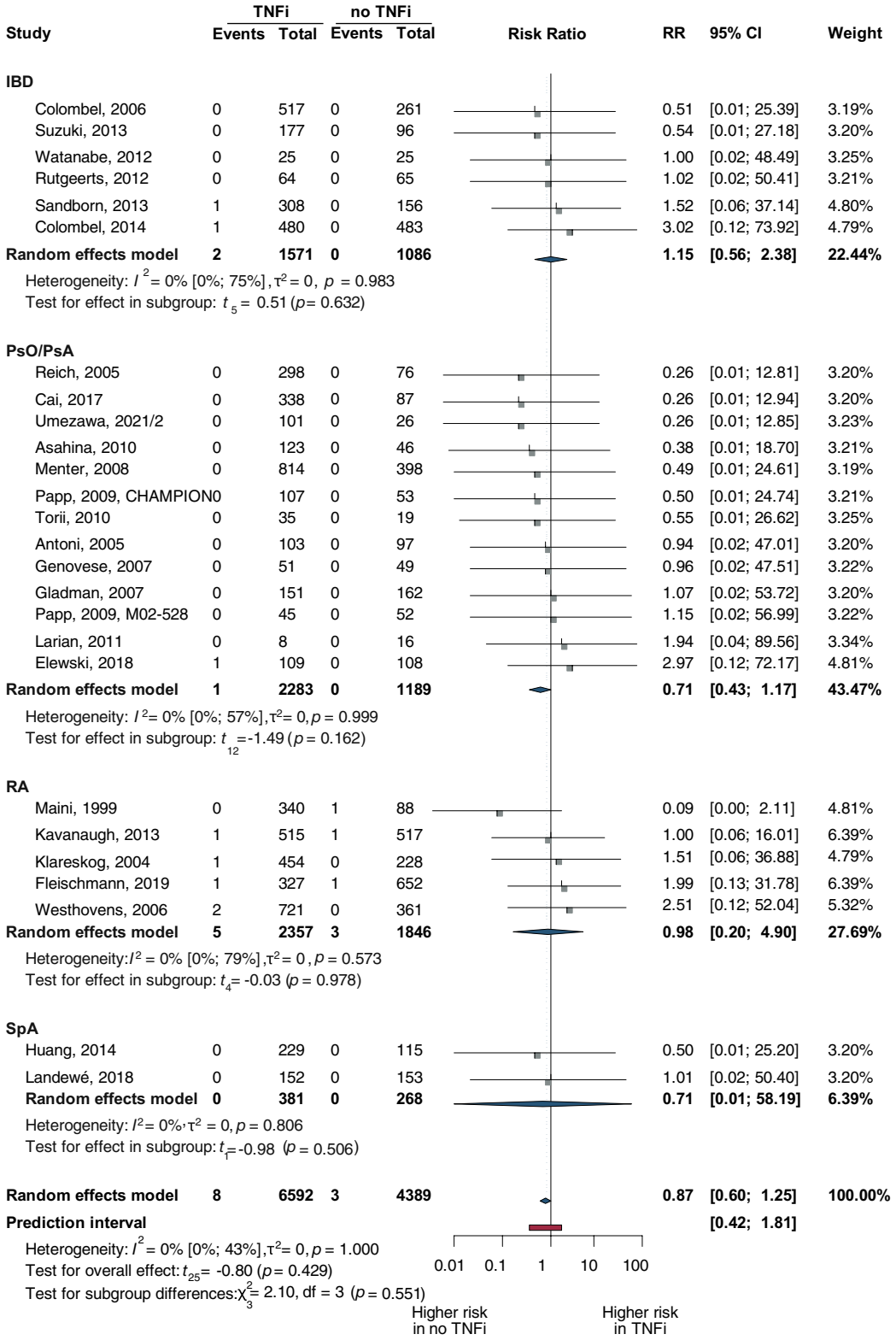

FIGURE 3 Forest plot on the results of pooled randomized data on the risk of de novo heart failure with subgroups of immune-mediated inflammatory diseases. CI, confidence interval; IBD, inflammatory bowel diseases; PsA, psoriatic arthritis; PsO, psoriasis; RA, rheumatoid arthritis; SpA, spondyloarthritis; TNFi, tumour necrosis factor inhibitor.

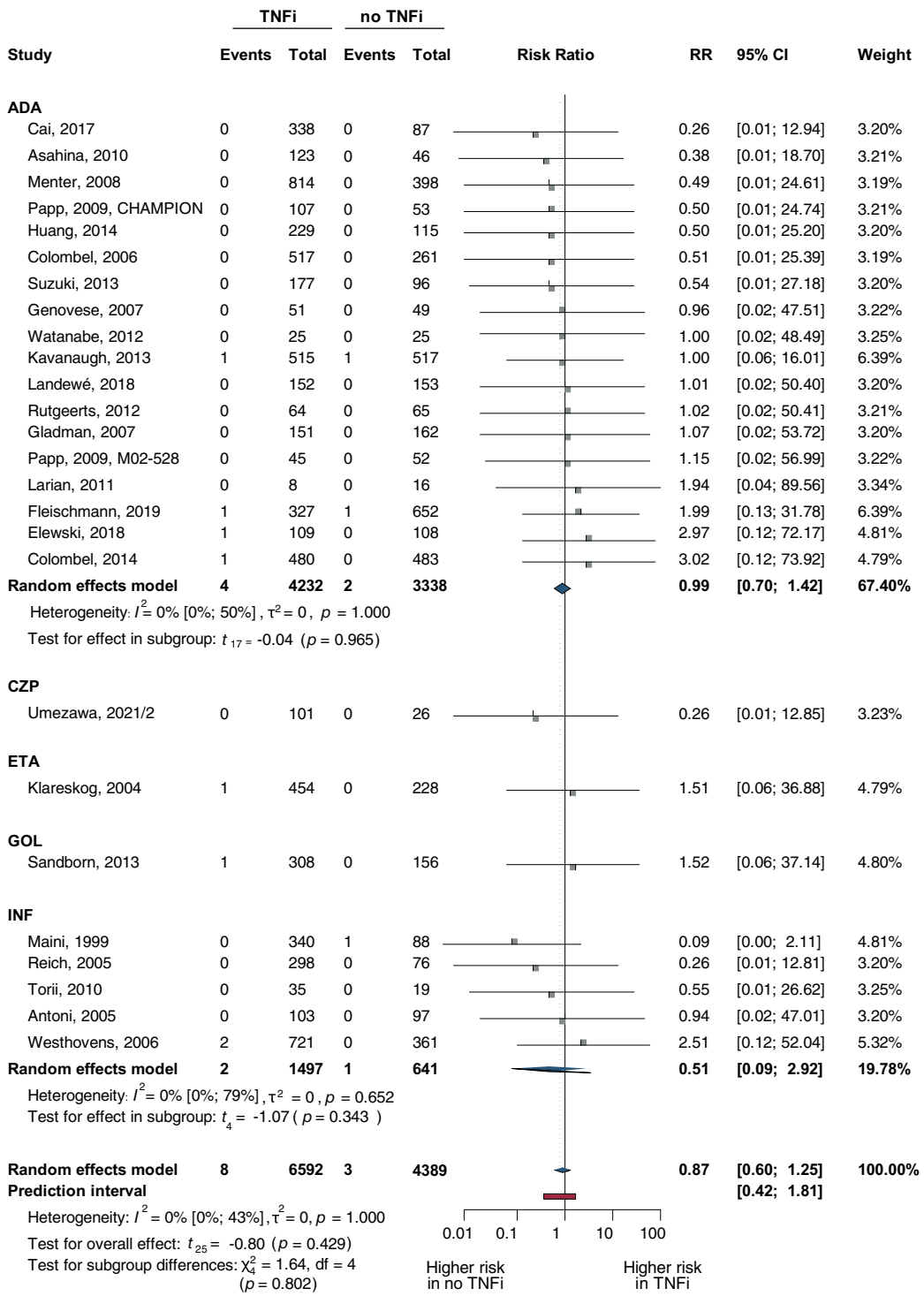

FIGURE 4 Forest plot on the results of pooled randomized data on the risk of de novo heart failure with subgroups of tumour necrosis factor inhibitor agents. ADA, adalimumab; CI, confidence interval; CZP, certolizumab-pegol; ETA, etanercept; GOL, golimumab; INF, infliximab; TNFi, tumour necrosis factor inhibitor; RR, risk ratio.

De novo heart failure—Comparison of INF dosages in randomized studies

As one of the main reasons for the potentially increased risk of HF associated with TNFi treatment was the increased risk observed in patients with advanced HF who received higher doses of INF (10 mg/kg),[10] we aimed to compare the effects of different INF doses to non-treated control groups.

Although subgroup analysis of higher doses (10 mg/kg) published in articles included could not be performed, the lower dose of INF (5 mg/kg), commonly used in clinical

practice, did not show an associated risk compared to control (RR = 0.51, 95% CI: 0.10–2.58, Figure 5).

De novo heart failure—Non-randomized studies

The risk of de novo HF risk was also analysed using non-randomized, observational, real-world data from 11 studies. The overall effect of this analysis of patients with mainly RA, similar to the results of pooled randomized data, indicated no risk increase with TNFi compared to patients not treated with TNFi (RR = 0.86, 95% CI: 0.64–1.14, see Figure 6).

Composite (de novo and worsening) of heart failure—Non-randomized studies

Data from 13 non-randomized studies of more than 100,000 patients examined the risk of composite HF outcome (de novo and worsening cases) by comparing TNFi-treated and non-TNFi-exposed groups. The overall effect showed no increase in risk in the TNFi- compared to the control group, tending rather towards a beneficial effect of TNFis (RR = 0.71, 95% CI: 0.48–1.04) among patients with RA, PsO and IBD. The heterogeneity between the studies was high ($I^2 = 72\%$) due to the observational nature of patient data. The findings for the composite outcome presented in the forest plot can be seen in Figure 7.

Studies not involved in the quantitative analyses

Four studies could not be included and statistically synthesized in the meta-analysis; their findings on the risk of HF are qualitatively summarized.

Edwards (2019) reported the results of 19 ETA-interventional, phase I–IV PBO-controlled RCTs that have already been pooled and analysed. Data analysed were from elderly (≥65 years) and non-elderly (<65 years) RA patients. In the analysis of elderly patients, data from 821 patients treated with ETA and 196 patients treated with PBO were included, whereas, in the non-elderly group, 4325 patients treated with ETA and 634 patients treated with PBO were involved. There was no difference in the magnitude of the mean percentage occurrence between the ETA and PBO cohorts in the elderly (1.22 vs. 1.22) and non-elderly (0.18 vs. 0.16) populations (Edwards, 2019, Table S6).[33]

Of the PBO-controlled induction and maintenance RCTs reported in Watanabe (2012), the maintenance study was selected for inclusion in the meta-analysis to avoid overlapping data based on a more extended follow-up period than the induction trial (52 vs. 4 weeks). At 4 weeks of the induction period, none of the 67 CD patients treated with ADA experienced de novo HF-related adverse events (Watanabe, 2012, table 3).[55]

One RCT was excluded from the meta-analysis due to its population consisting of RA patients infected with the hepatitis C virus and having a higher risk of cardiovascular adverse events[77] than the populations in the other RCTs

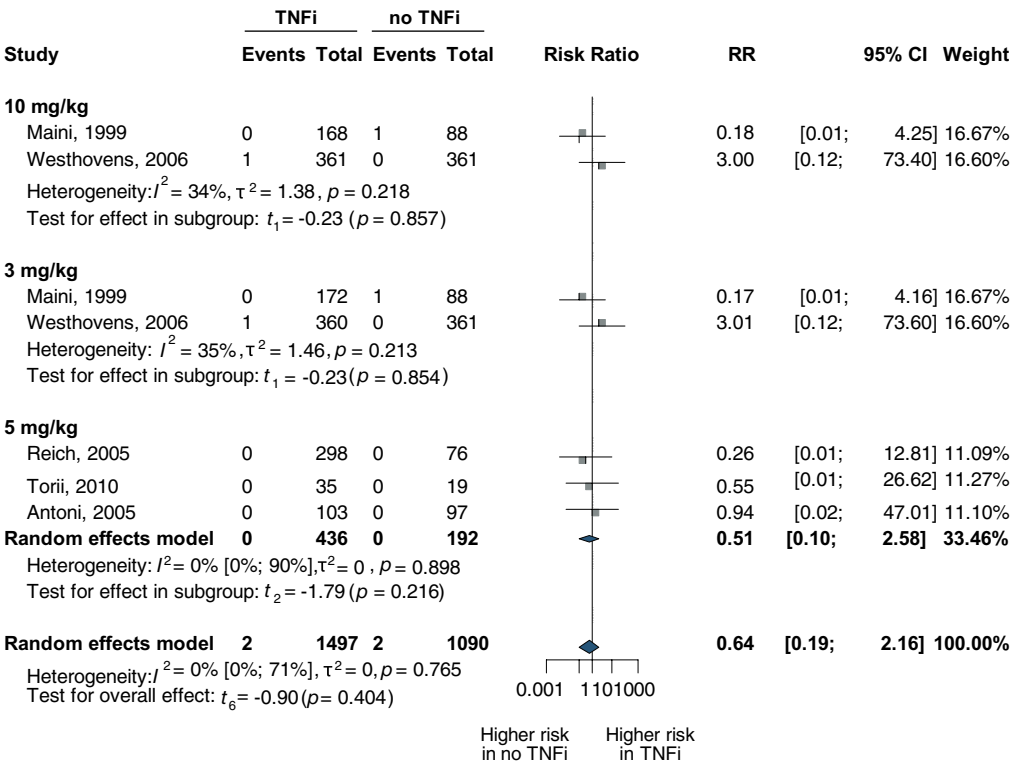

FIGURE 5 Comparison of infliximab dosages compared to non-treated controls in randomized studies on de novo heart failure. CI, confidence interval; RR, risk ratio; TNFi, tumour necrosis factor inhibitor.

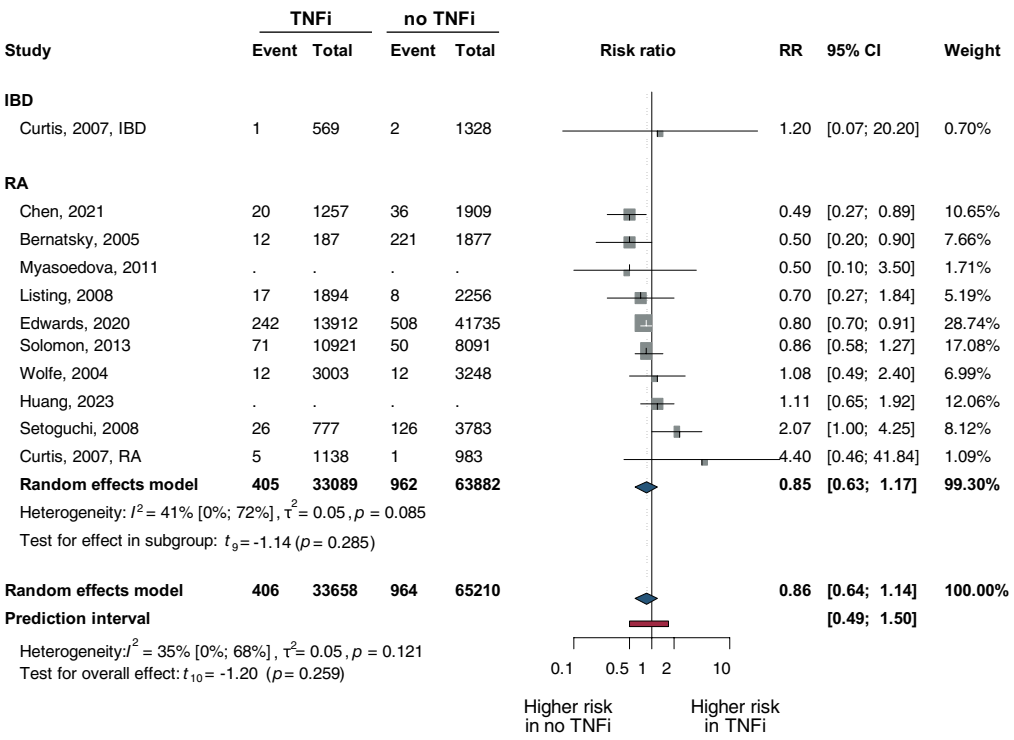

FIGURE 6 Forest plot on the results of pooled non-randomized data on the risk of de novo heart failure with subgroups of immune-mediated inflammatory diseases. CI, confidence interval; IBD, inflammatory bowel disease; RR, risk ratio; TNFi, tumour necrosis factor inhibitor.

included in the meta-analysis. Altogether, nine patients were treated with methotrexate, 13 with ETA, and 7 with combination methotrexate-ETA, and they were followed for 54 weeks. One patient developed de novo HF in the combined methotrexate-ETA group.[37]

In the fourth study (Nurmohamed, 2015), retrospective data were analysed for composite HF events. In the analysis of 113,677 patients with RA, TNFi exposure was associated with a reduced HF risk (HR = 0.80).[72] Without a CI or range of estimates, this outcome could not be included in the quantitative analysis. However, the large-scale real-world data analysed contribute significantly to the assessment of the effect of TNFis on HF, refuting current evidence of an increased risk of HF with TNFis.

Risk of bias assessment, publication bias and certainty of evidence

For most studies, the risk of bias assessment resulted in a high overall risk. In RCTs, the main reasons for downgrading were deviations from intended interventions (D2) and bias due to measurement of the outcome (D4) domains. During the evaluation of non-randomized observational trials, downgrading was caused by bias due to confounding (D1 domain). The results of the risk of bias for each outcome are shown in the Figures S1–S8. Figures S9–S13 present the funnel plots for evaluation of publication bias; the results show that no publication bias can be detected among the included studies. According to GRADEpro's assessment, the certainty of evidence was rated very low for all outcomes. However, the rigorous as possible methodology and the comprehensive data set analysed in the present study provide a higher level of evidence compared to previous ones in the literature. See the detailed certainty of evidence in the Table S4.

DISCUSSION

Our results from the meta-analyses with more than 150,000 IMID patients demonstrated no risk-increasing effect of TNFis on new-onset and worsening of HF.

Presumably, because of concerns raised by the initial RCTs among non-IMID, advanced HF-diagnosed patients, no RCTs were performed in IMID patients to investigate the risk of worsening HF. Consequently, only non-randomized, real-world observational data could be used to analyse worsening HF in IMID patients treated with TNFi. The results of our analysis on the risk of worsening HF showed no statistically significant risk-increasing effect in the TNFi-treated group compared to the control. However, it only includes data from patients with RA with a low number of individuals with mixed TNFi groups, leading to high uncertainty in the evaluation of the results.

De novo HF as an endpoint was assessed by analysing both RCTs and non-randomized observational data. In addition, the overall effects did not indicate an increased risk; there was a tendency to suggest a beneficial effect of TNFis on the new onset of HF in both analyses.

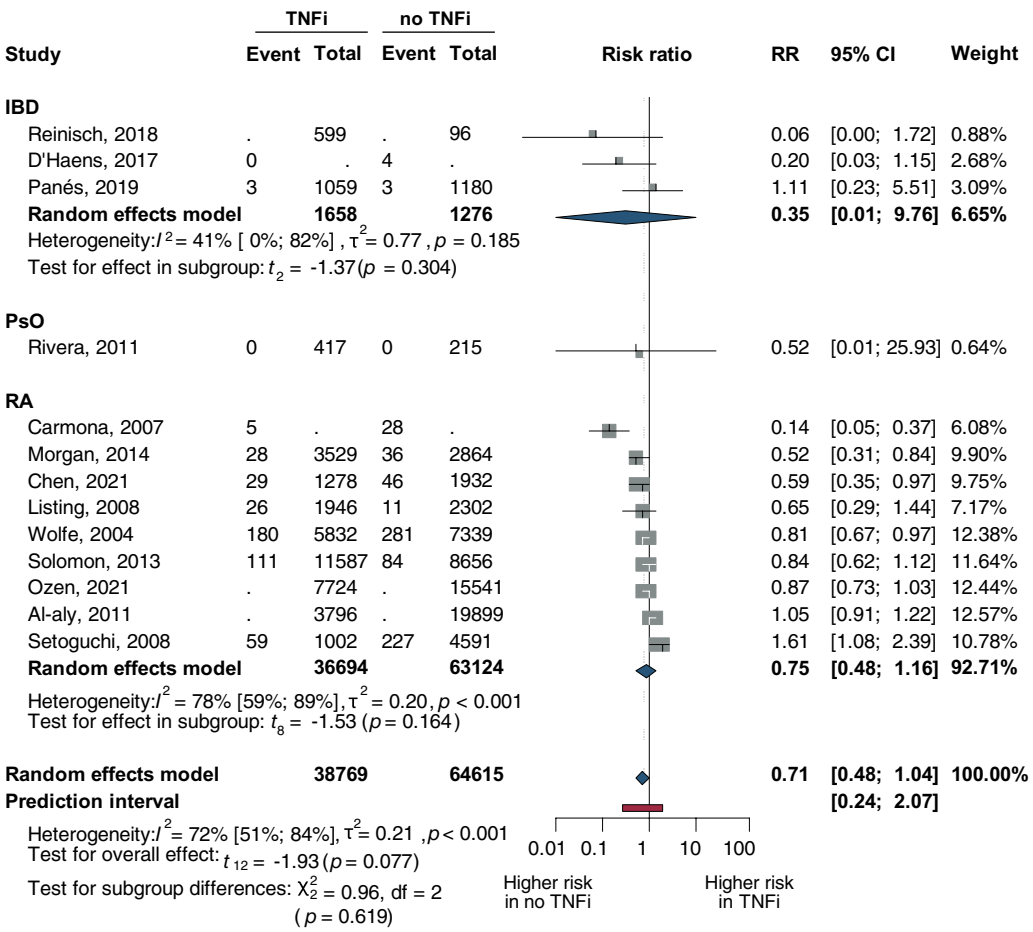

FIGURE 7 Forest plot on the results of pooled non-randomized data on the risk of composite (de novo and worsening) heart failure with subgroups of immune-mediated inflammatory diseases. CI, confidence interval; IBD, inflammatory bowel diseases; PsO, psoriasis; RA, rheumatoid arthritis; RR, risk ratio.

In the pooled synthesis of RCTs, subgroup analyses of the active agents (ADA, INF) were performed, supplemented by a dosage comparison analysis of INF. The currently widely used dose of INF (5 mg/kg) did not show any risk-increasing effect on developing HF. The 10 mg dose of infliximab, previously in the literature linked to the enhanced risk of HF,[10] could not be investigated in the present study. Although this higher dose is rarely applied in clinical practice, it should be noted that a dose-dependent threshold effect with infliximab still cannot be ruled out. A subgroup analysis of PsO and PsA patients in the randomized data synthesis also showed no increase in risk in the group receiving TNFi compared to controls. These findings were consistent with the results of a meta-analysis published by Champs et al. (2019), conducted in patients with PsO and PsA, where there was no HF-risk difference between TNFi and PBO groups (risk difference = 0.00, 95% CI −0.01 to 0.01).[78] Compared with this prior work, our current analysis provides a more comprehensive assessment of the safety of TNFis, as it also includes data from patients with RA, IBD and SpA.

The analysis of data from non-randomized studies on the risk of de novo HF with almost exclusively RA patients showed a non-significantly lower risk in the TNFi-treated group. Consistent with our results, a previous meta-analysis from Roubille et al. on supposedly mainly new onset of HF outcomes with fewer RA patients demonstrated a non-significant risk-reducing effect in TNFi-treated versus non-TNFi-treated groups.[79]

Strengths and limitations

The major strength of our work is that it is the first meta-analysis of TNFi-treated IMID patients to distinguish between worsening, de novo events of HF in separate comparative analyses. An additional strength is that it synthesizes data from a large number of patients from both randomized trials and non-randomized observational studies, presumably representing the highest level of evidence in the study on the effect of TNFis on HF to date. However, a limitation is that definitions of HF cases in individual studies are different and insufficient. Although the assessment of real-world data is a strength of the present meta-analysis, these observational studies have a high degree of heterogeneity; due to the lack of randomisation, selection bias can cause a difference in the baseline risk of the outcome investigated between the comparison groups, potentially increasing the

inconsistency of the analyses. As for the analyses of randomized trials, the reliability of the results may be reduced by the very low event rate in the individual studies.

Implications for research and practice

Given that current guidelines contraindicate the use of TNFis in advanced HF, it is crucial to further investigate the outcome of worsening HF and strengthen the findings of the present analysis with new data. Findings from recent basic research suggest that the complex dual pro-inflammatory and late anti-inflammatory cardiac effects of TNF-α signalling might play a role in the exacerbation of HF with TNFis.[80] However, the mechanism still needs to be clarified. Further studies using animal models are inevitable to exclude the association between TNFis and the worsening of HF.

Both on worsening and de novo HF outcomes, detailed subgroup analyses using individual patient data are also warranted, particularly for different stages, NYHA classes and aetiologies of HF. Further separate analyses with all the active substances of TNFis are also needed. As initial RCTs with ETA and INF suggested that the application of increased doses may carry a potential risk for worsening HF, investigating the effect of different dose regimens of TNFi agents on the risk of HF would also be essential to refine recommendations for the use of TNFis in IMIDs. The guidelines should be continuously revised as additional data become available and synthesized with the present findings.

The early translation of the findings of synthesized data derived from both basic and clinical research into everyday practice is undeniably required to ensure that IMID patients receive the most appropriate anti-inflammatory treatment, also tailored to their comorbidities.[81,82]

CONCLUSION

The present findings indicate that TNFis have no risk-increasing effect on the development of de novo HF in IMID patients; additionally, no statistically significant risk enhancement could be detected on worsening of HF with TNFis. An update of IMID guidelines should be considered to specify that TNFis do not increase the risk of new-onset HF, and further data are needed on the worsening of HF with TNFis in IMIDs.

AUTHOR CONTRIBUTIONS

N.Á.G. was responsible for conceptualization, project administration, data curation, visualization, and writing—original draft. F.A.M. was responsible for conceptualization, data curation, validation, and writing—review and editing. P.M. was responsible for methodology, formal analysis, validation and visualization. A.F. was responsible for formal analysis, validation, and visualization; A.S.L. was responsible for conceptualization and data curation. M.V.K. was responsible for data curation, validation and visualization. L.V.K. was responsible for conceptualization and methodology. D.C. and P.He. were responsible for conceptualization, methodology and supervision. P.Ho. and A.B. were responsible for conceptualization, methodology, supervision and writing—original draft.

FUNDING INFORMATION

None.

CONFLICT OF INTEREST STATEMENT

None declared.

DATA AVAILABILITY STATEMENT

The data sets used for the present study can be accessed in the full texts of the articles included in the systematic review and meta-analysis. The data underlying this article will be shared upon reasonable request to the corresponding author.

ETHICAL APPROVAL

None.

ETHICS STATEMENT

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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