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THE EFFECTS OF TUMOUR NECROSIS FACTOR INHIBITORS ON CARDIOVASCULAR RISK IN IMMUNE-MEDIATED INFLAMMATORY DISEASES

Ph.D. Thesis

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"The secret to success in life is the same as the secret to success in science —perseverance."

Albert László Barabási

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1. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADA	adalimumab
AS	ankylosing spondylitis
CCVE	composite of cardiovascular events
CD	Crohn's disease
CE	cardiac event
CeVE	cerebrovascular event
CI	confidence interval
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSNB	conventional systemic non-biological
CV	cardiovascular
CZP	certolizumab pegol
EDF	European Dermatology Forum
EMA	European Medicines Agency
ETA	etanercept
EULAR	European Alliance of Associations for Rheumatology
FDA	Food and Drug Administration
GOL	golimumab
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HF	heart failure
HR	hazard ratio
IBD	inflammatory bowel disease
IgG1	immunoglobulin G1
IL	interleukin
IMID	immune-mediated inflammatory disease
INF	infliximab
IR	incidence rate

IRR	incidence rate ratio
MACE	major adverse cardiovascular events
MI	myocardial infarction
MTX	methotrexate
NSAID	non-steroidal anti-inflammatory drug
PBO	placebo
PICO	population-intervention-comparator-outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PsA	psoriatic arthritis
PsO	psoriasis
PY	person-year
RA	rheumatoid arthritis
RCT	randomised controlled trial
REML	restricted maximum likelihood
RoB 2	Revised tool for assessing risk of bias
ROBINS-I	Risk of Bias in Non-randomised Studies of Interventions
RR	risk ratio
SMC	smooth muscle cell
SpA	spondyloarthritis
TNF-α	tumour necrosis factor-α
TNFi	tumour necrosis factor inhibitor
UC	ulcerative colitis

2. STUDENT PROFILE

2.1. Vision and mission statement, specific goals

My vision is to reduce the burden caused by comorbidities, thus improving the quality of life and life expectancy of patients with immune-mediated inflammatory diseases (IMIDs).

My mission is to contribute to the optimisation of therapeutic sequences in IMIDs by investigating and taking into consideration their effects on comorbidities.

My specific goal focuses on investigating the effects of tumour necrosis factor inhibitors (TNFi) on the risk of the development of cardiovascular (CV) events in IMID patients.

2.2. Scientometrics

Number of all publications:	**6**
Cumulative IF:	36
Av IF/publication:	6
Ranking (Sci Mago):	D1: 3, Q1: 2, Q2: 1
Number of publications related to the subject of the thesis:	**2**
Cumulative IF:	16
Av IF/publication:	8
Ranking (Sci Mago):	D1: 2
Number of citations on Google Scholar:	51
Number of citations on MTMT (independent):	34
H-index:	3

2.3. Future plans

Looking ahead, my professional aspirations focus on gaining clinical experience and expertise in the field of management of IMID patients with a particular emphasis on dermatological conditions. I aim to integrate the latest scientific findings and evidence-based practices into everyday patient care through continuous learning and further active participation in research.

3. SUMMARY OF THE PH.D.

IMIDs are chronic systemic, inflammation-perpetuated conditions facing the burden of various comorbidities, including CV events. The excess CV risk may be attributable in part to tumour necrosis factor (TNF)-α-mediated inflammatory pathways, which represent a dominant common pathway involved in the pathomechanisms of both IMIDs and atherosclerosis. TNFis are effective anti-inflammatory agents; however, they are generally second-line systemic treatments for IMIDs. We aimed to comprehensively compare TNFis to first-line used conventional systemic non-biological (CSNB) treatments on the risk of atherosclerosis-derived CV events in IMIDs. Given the safety concerns regarding the potential risk of heart failure (HF) associated with TNFis, our objective was to conduct a distinct, comprehensive analysis, investigating the effect of TNFis on the risk of HF.

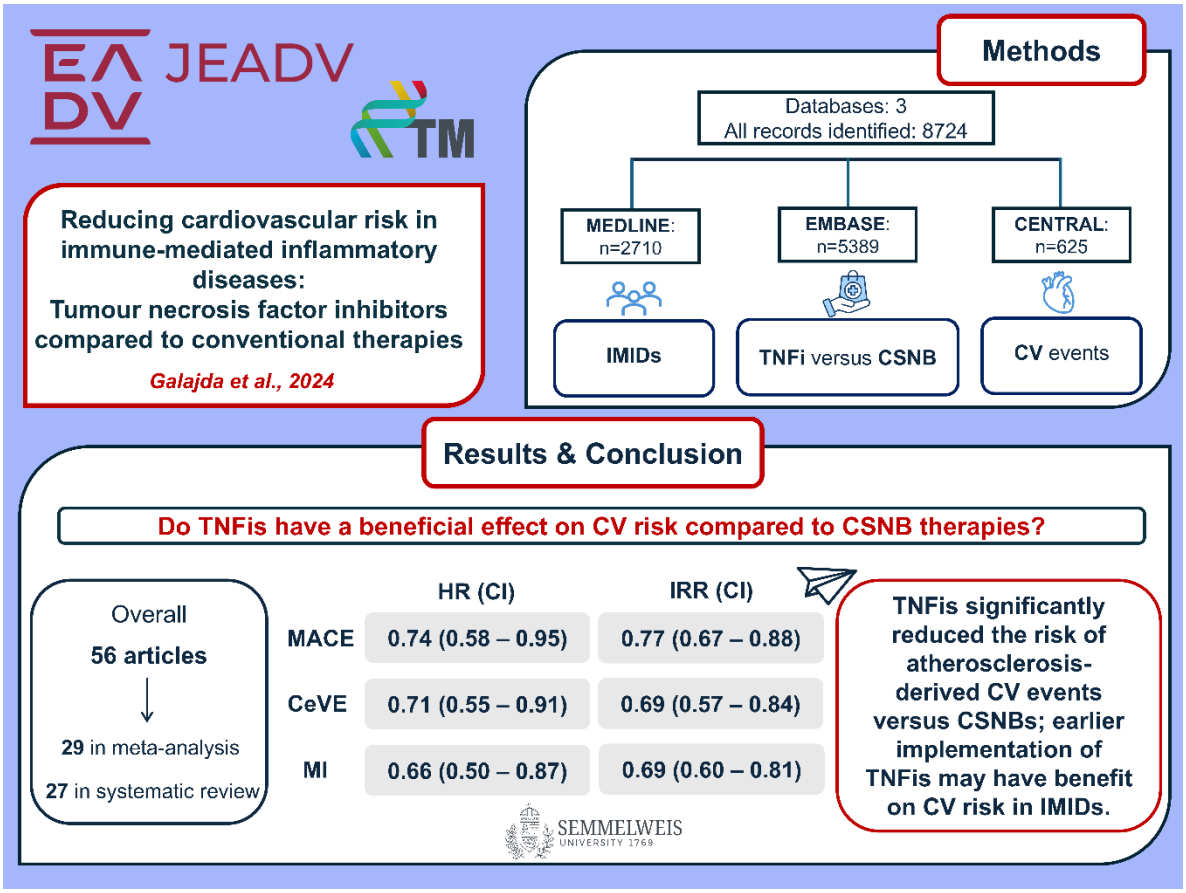
We conducted two meta-analyses. In the comparison of the TNFis and CSNBs, the incidences of major adverse cardiovascular events (MACE), myocardial infarction (MI) and cerebrovascular events (CeVE) were assessed as main outcomes. Regarding the effects of TNFis on the risk of HF, we compared TNFi-treated patients to non-treated groups, and we investigated the de novo and worsening cases of HF in separate analyses.

Our results demonstrated a significant CV risk reduction regarding MACE, MI and CeVE in TNFi-treated IMID patient groups compared to the CSNB controls. The beneficial effect of TNFis versus CSNBs remained in subgroups of rheumatoid arthritis (RA), psoriasis (PsO) and psoriatic arthritis (PsA) on the risk of MACE. Regarding the evaluation of the risk of HF, TNFis did not show a risk-increasing effect on de novo HF. No significant elevation in the risk of worsening of HF was observed with TNFis compared to controls.

Our results showed that early administration of TNFis in the therapeutic sequence of IMIDs may contribute to decreasing the incidence of major atherosclerosis-derived CV events. Regarding HF, an update on the therapeutic guidelines for IMIDs should be considered, implementing the non-increasing effect of TNFis on de novo HF, while further investigations are needed to rule out the effect of worsening HF associated with TNFis. The present results can contribute to optimising the management of CV comorbidities in IMID patients.

4. GRAPHICAL ABSTRACTS OF THE STUDIES

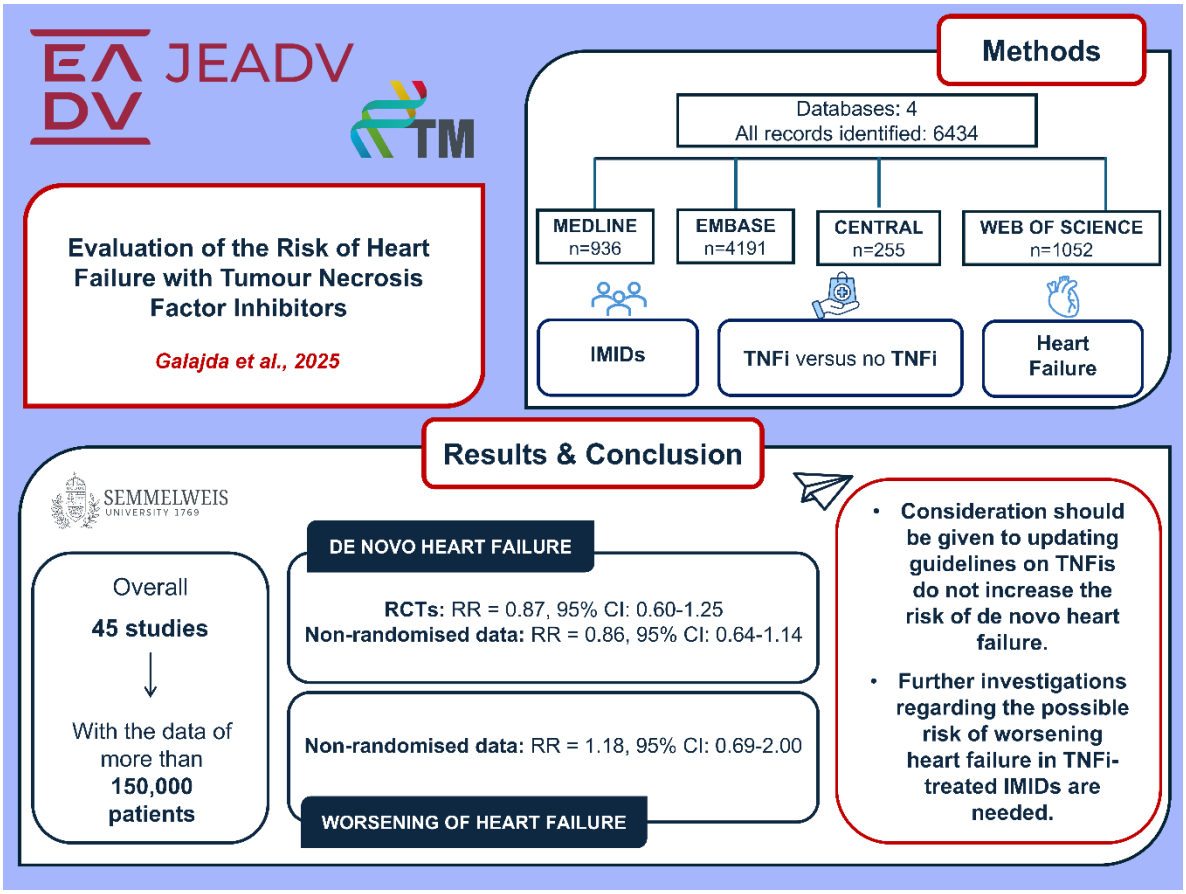
4.1. Study I.



Graphical abstract of Study I, showing the summary of the investigation of the effect of TNFis compared to CSNBs on the risk of atherosclerosis-derived CV events in IMIDs.

CeVE: cerebrovascular events, CI: confidence interval, CSNB: conventional systemic non-biological, CV: cardiovascular, HR: hazard ratio, IMID: immune-mediated inflammatory disease, IRR: incidence rate ratio, MACE: major adverse cardiovascular events, MI: myocardial infarction, TNFi: tumour necrosis factor inhibitor

4.2. Study II.



Graphical abstract of Study II, showing the summary of the investigation of the risk of de novo and worsening of heart failure in TNFi versus non-TNFi-treated IMID patients.
CI: confidence interval, IMID: immune-mediated inflammatory disease, RCT: randomised-controlled trial, RR: risk ratio, TNFi: tumour necrosis factor inhibitor

5. INTRODUCTION

5.1. Overview of the topic

5.1.1. What is the topic?

In our work, we investigated the effects of TNFis on the risk of CV events in IMIDs.

5.1.2. What is the problem to solve?

Optimisation of the sequence of effective anti-inflammatory therapies for patients with IMIDs is crucial to prevent the development of CV events in IMID patients with high CV burden.

5.1.3. What is the importance of the topic?

Patients with IMIDs have an up to 50% higher risk of developing CV diseases compared to the non-affected general population. The presence of CV diseases and, through their progression, the occurrence of severe CV events impair the quality of life and shorten the life expectancy of IMID patients. Moreover, CV comorbidities impose a distinct economic burden on healthcare systems worldwide through their long-term and complex management.

5.1.4. What would be the impact of our research results?

The results of our two studies contribute to extending the knowledge on the effects of TNFis on CV risk and thus help formulate international and regional recommendations for treating IMID patients with high CV burden. Our findings, therefore, may potentially support the CV-risk reduction of IMID patients, the prevention of the development of severe CV events, the improvement of their quality of life and the enhancement of their life expectancy.

5.2. IMIDs and cardiovascular comorbidities

IMIDs are a broad group of chronic, excessive inflammation-sustained disorders affecting multiple organ systems, characterised by common overlapping pathogenic mechanisms. The skin, gut and joints–serving as external and internal barriers– are especially susceptible to IMIDs (1). PsO, rheumatologic disorders like RA and inflammatory bowel diseases (IBD) are among the most prevalent IMIDs, with an estimated prevalence exceeding 700 cases per 100,000 people worldwide (2-4). A substantial proportion of patients with IMIDs have an elevated, in some cases exceeding 50% excessive mortality risk compared to the unaffected general population (5-8). CV diseases–particularly in RA, spondyloarthritis (SpA), and severe PsO– are significant determinants of excess risk among the leading causes of death (5, 7, 9). Based on the existing data, the prevalence of CV diseases ranges approximately between 3% and 16% in IMIDs (10-14). The presence of CV disease in general is associated with traditional CV risk factors (e.g. hypertension, diabetes), severity of IMID, male gender, and age (10-14), except for IBD, where younger age showed a significantly stronger association with atherosclerotic CV disease (14).

In varying degrees, the incidence of atherosclerotic CV events is higher among IMID populations compared to controls according to European epidemiologic data (15-18). The data of a large-scale observational cohort study showed an enhanced incidence of MACE in PsO patients compared to controls (4.13 versus 3.87 per 1000 person-years, PY); furthermore, separately in severe PsO cases, notably higher rates could be observed (5.90 per 1000 PY) (15). According to the literature, similar incidence rates can be observed among inflammatory arthritides (RA, PsA, and ankylosing spondylitis—AS) and IBD populations. In these extensive prospective and retrospective cohort studies, the risk of atherosclerosis-derived CV events was increased in IMIDs after adjusting for age and sex, as well as for traditional CV factors (16-18). In the PsO population, after the traditional CV risk factor-extended adjustment, the risk attenuated in the full population; however, in the severe group, a non-significant enhancement remained (15). Data from recent meta-analyses strengthened the enhanced risk of atherosclerotic CV events in IMIDs; approximately 20-50%

significantly higher CV risks were estimated in PsO, PsA, AS and IBD populations compared to unexposed controls (19-22).

Most traditional CV risk factors—hypertension, diabetes, dyslipidaemia, smoking, and obesity—have an increased prevalence in IMID populations (23). However, the enhanced CV risk cannot be entirely explained by the higher burden caused by the major CV risk factors.

Among the IMID populations, RA has been studied most extensively, with the earliest evidence showing that the RA itself increases the risk of CV diseases independently of traditional CV risk factors (24). The results of a nationwide cohort study indicated that the CV risk associated with RA is the same as in patients with diabetes (25). Furthermore, the findings of another observational study showed that the number of RA flare-ups and the cumulative disease severity burden enhance the risk of the development of CV diseases (26). Growing evidence suggests that severe PsO patients face a higher CV burden than mild patients and the non-affected general population (19). Moreover, a recent prospective registry study demonstrated a clear association between even a one-point increase in psoriasis area severity index and an increased risk of future CV events (27). In recent years, emerging data suggest that IBD and SpA are also independent CV risk factors (14, 28). These strong correlations can be explained by the intertwining of the pathomechanisms of atherosclerosis and IMIDs at several points.

5.3. The role of TNF-α in the pathomechanism of IMIDs and atherosclerosis

Each of the IMID populations has unique cytokine profiles, with key contributors among others, including interleukin (IL)-23 in PsO, PsA and IBD, IL-17 in PsO, PsA and SpA, or IL-6 in RA (1, 29). Beyond the characteristic, distinct immunological hubs, the TNF-α cytokine acts as a common downstream effector in the inflammatory pathways of IMIDs. TNF-α is primarily produced by macrophages and plays a key role in inflammation by activating them, sustaining a self-perpetuating cycle (30). Through the activation of dendritic cells, TNF-α stimulates the effector immune cells, leading to the activation of fibroblasts and keratinocytes that drive tissue remodelling and organ damage. TNF-α is also produced by neutrophils and activated T-cells, which are abundant in inflamed skin, synovial membranes, and entheseal structures (1, 29, 31, 32).

A substantial body of literature explores the role of TNF-α in atherosclerosis, spanning its involvement from the initiation, through plaque progression, to plaque rupture. At the phase of endothelial activation, TNF-α induces endothelial dysfunction by upregulating adhesion molecules and chemokines, promoting monocyte and T-cell infiltration. In further steps, TNF-α is secreted by macrophages and smooth muscle cells (SMC) in the intima, sustaining local inflammation (33). It contributes to monocyte recruitment and an increased oxidised low-density lipoprotein uptake by macrophages through different mechanisms, leading to the formation of foam cells and fatty streak formation (33, 34). Furthermore, by enhancing the proliferation and migration of SMCs, that produce extracellular matrix, TNF-α promotes plaque progression, thus facilitating the formation of fibrotic caps (33). Through the induction of matrix metalloproteinases, it intensifies the extracellular matrix turnover, leading to cap destabilisation. Moreover, TNF-α contributes to further thinning of the fibrotic cap and the formation of necrotic cores by inducing neointimal apoptosis and necrosis, thereby increasing the chance of atherosclerotic plaque rupture (35).

Clinical research data strengthen the role of TNF-α in atherosclerosis; elevated serum concentration of TNF-α is associated with the amount of coronary calcium, thus the severity of subclinical atherosclerosis, independent of CV risk factors (36). Furthermore, indirectly,

data on the endothelial function-improving effect of TNFis also points to the role of this cytokine in atherosclerosis. Treatments inhibiting TNF-α have been found to reduce the intima-media thickness and improve the plaque stability in IMID patients (37-39).

5.4. Introduction of the TNF-inhibitors

Biological therapies inhibiting TNF-α are widely applied and highly effective anti-inflammatory treatments in IMIDs.

Since the introduction of the first TNFi in the late 1990s, to the present day, five distinct TNFi agents have been approved by the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA) for clinical use (40, 41).

Etanercept (ETA) was the first active substance registered by the FDA for the indication of RA. ETA was engineered as a fusion protein consisting of two identical TNF receptor 2 extracellular domains linked to a human immunoglobulin G1 (IgG1) Fc portion (42, 43). It binds to both soluble and transmembrane TNF-α and blocks their interactions with the receptors, modulating proinflammatory gene expression, resulting in decreased production of TNF-α; furthermore, it inhibits the TNF-related positive feedback mechanisms by inducing the early apoptosis of dendritic cells (44).

Infliximab (INF), initially approved for the treatment of patients with Crohn's disease (CD), was launched on the market at around the same time as ETA (45). Regarding its structure, INF is a monoclonal chimera consisting of a murine variable and a human constant IgG1 region. INF inhibits the binding of TNF-α to both soluble and transmembrane TNF receptors. Among others, it exerts its anti-inflammatory effect through the promotion of the lysis of TNF-α-expressing cells and antibody-dependent cytotoxicity (46). INF can now be indicated in patients with RA, plaque PsO, or PsA, among others (42, 45).

Adalimumab (ADA), the most widely used TNFi, was introduced in the early 2000s (47, 48). ADA is a fully human monoclonal IgG1 antibody that can specifically bind TNF-α to its receptors, as it possesses the same structural and functional characteristics as endogenous human IgG1. The structural design of ADA contributes to an extended half-life, improved

tolerability and reduced immunogenicity compared to the previous active substances. Following the initial approval of ADA for RA, its use has been expanded to include CD and plaque PsO among others (45).

Another licensed human monoclonal IgG1 antibody is golimumab (GOL). It selectively binds to TNF-α, exhibiting stronger affinity to neutralise both soluble and membrane-bound TNF-α than INF or ADA (49). Like the other monoclonal antibodies, GOL has a wide range of indications among IMIDs (45).

The fifth approved TNFi, certolizumab pegol (CZP), is a humanised monoclonal antibody with a polyethylene glycol Fab fragment (50). Due to the structure of CZP, it can penetrate deeper into the inflamed tissues, and the half-life of the active substance is extended. Initially, CZP was registered by the authorities for CD, ulcerative colitis (UC) and RA, which was later expanded in 2018 to plaque PsO (45, 51).

Since the initial authorisation of each TNFi agent, not only has the range of indications been extended, but several biosimilars with minor changes in the molecular structure of clinically inactive constituents have been approved by regulatory authorities.

5.5. Current place of TNF inhibitors in the therapeutic management of IMIDs

TNFis are among the early biological therapeutic options in IMIDs; however, according to the current guidelines, they generally represent a second-line systemic treatment after CSNBs.

According to the European dermatology treatment guidelines, use of TNFis is recommended for moderate-to-severe PsO, after an inadequate response to at least one CSNB (referred to as "conventional synthetic disease-modifying antirheumatic drug—csDMARD" in the recommendations)—like methotrexate (MTX), ciclosporin, acitretin, or fumarates (52-54). Compared to the European Dermatology Forum (EDF) EuroGuiDerm guidelines, the recommendations of the American Academy of Dermatology—National Psoriasis Foundation express a more permissive stance regarding the early use of TNFis in moderate-to-severe PsO (55). As per the current EULAR (European Alliance of Associations for Rheumatology) recommendations, for the treatment of PsA, TNFis are recommended as first-line biological therapies for patients who do not reach the treatment goals with non-steroidal anti-inflammatory drugs (NSAIDs) and/or csDMARDs. However, in PsA patients with predominantly axial disease, TNFis may be administered earlier (56). In contrast with the EULAR recommendations, the GRAPPA (Group for Research and Assessment of Psoriasis and Psoriatic Arthritis) does not adopt the step-up strategy, but rather recommends a domain-based, individualised approach, thus supporting the use of TNFis even as a first-line therapy in certain clinical conditions, such as active peripheral or axial disease, concomitant skin or nail involvement (57).

In the EULAR therapeutic recommendations for RA, TNFis are firmly established as first-line biological therapies in cases where MTX or alternate CSNB strategies have failed; this approach is also reflected in relevant ACR (American College of Rheumatology) guidelines (58, 59). In line with these, for patients with AS, TNFis are recommended after the treatment failure of NSAIDs administered first, according to both the European and American guidelines (60, 61).

The recommendations of the international treatment guidelines for IBD diverge partly from the general guidance for IMIDs summarised above. While in CD, TNFis are strongly recommended to be administered for inducing remission, in UC, they are advised in moderate-to-severe disease after the failure of CSNBs (62-65).

Besides reducing the burden caused by the traditional CV risk factors, considerable evidence highlights that the effective control of chronic systemic inflammation in IMIDs represents a pivotal part in contributing to reducing the CV risk (23). In recent years, there has been growing research interest in investigating the effects of CSNBs and biologicals on the CV burden, mostly atherosclerosis-derived CV diseases. While CSNBs, like MTX, have shown protective impacts on these outcomes (66), evolving data from RA and PsO populations suggest that TNFis may confer an even greater reduction in CV risk compared to CSNBs (67-70), that may be explained by the more potent and targeted anti-inflammatory action of TNFis. The current IMID therapeutic guidelines provide limited guidance on the preferred treatment strategies for managing CV comorbidities beyond highlighting the potentially harmful agents in terms of CV risk enhancement (e.g. NSAIDs or systemic glucocorticoids) (71). An exception is the recommendation of the EDF EuroGuiDerm for the treatment monitoring and specific clinical and comorbid situations for PsO, in which MTX is suggested as preferred first-line systemic therapy for PsO patients with ischaemic heart disease (52). The growing body of data on the potentially superior efficacy of TNFis on CV risk—alongside their general categorisation as second-line systemic agents in IMIDs—served as a foundational reason for formulating the hypothesis and initiating our Study I.

5.6. TNF inhibitors and heart failure

Throughout more than 20 years of clinical use, TNFis have proven to be reliable, high-safety systemic anti-inflammatory therapies. The frequent side effects tend to be mild and self-limiting, like injection-site reactions. However, in a subset of IMID patients, more severe side effects may also occur (72). Evidence linking TNFis to the de novo and worsening of pre-existing HF as serious adverse effects was grounded on two sets of scientific findings.

The HF-worsening effect of TNFis has been highlighted by research findings initially investigating the favourable actions of TNFis on HF (73). ETA and INF were investigated in randomised controlled trials (RCTs) involving New York Heart Association class II-IV non-IMID patients, and they showed no benefits on the clinical status of HF, hospitalisation for HF or the risk of mortality in comparison with placebo (PBO) (74, 75). Furthermore, in the study focusing on INF (ATTACH), while with a medium dosage of the agent (5 mg/kg) no decrease in the risk of death or hospitalisation due to HF could be observed, the higher dose of INF (10 mg/kg) was associated with an elevated risk (HR=2.84, 95% CI 1.01-7.97) for these outcomes when compared with PBO (75). These studies were discontinued early, and no subsequent research has been conducted on TNFi active substances in HF patients.

TNFis have been labelled as a potential risk for the occurrence of new-onset HF in the report of the FDA on early post-marketing surveillance data with IMIDs. The report includes 38 de novo and nine worsening cases of HF with the use of ETA or INF, which were reported in the MedWatch System of the FDA, through February 2002. By that time, an estimated 274,000 patients had been treated with these biologics globally. The possible causative link was supported by the observation that nine out of 10 patients under the age of 50 showed complete or partial recovery after the discontinuation of TNFis and starting the therapy of HF (76).

As of yet, shaped by the evidence from these two cornerstones, the recommendations for the treatment of IMIDs outline the absolute or relative contraindications for the administration of TNFis in advanced and cautious utilisation in milder HF, and list the development of de novo HF as a potential adverse event with TNFis. Nevertheless, TNFis have been applied

extensively in IMIDs for more than 20 years with evolving safety data. Given the substantial body of data, some of which even calls into question the current guidelines, and the limitations of the present evidence, we were prompted to conduct Study II.

6. OBJECTIVES

6.1. Study I. – Investigating the effect of TNF inhibitors compared to conventional therapies on atherosclerotic CV events in IMIDs

Numerous studies have investigated the effects of both CSNBs, like methotrexate (MTX) and biological therapies, on the CV comorbidities, theorising that mitigating the systemic inflammation could reduce the CV risk in IMIDs (66). However, there is emerging evidential supporting findings suggesting TNFis may be more effective than CSNBs in decreasing the risk of CV events (67-69). Our aim was therefore to comprehensively investigate TNFis compared to CSNBs in IMIDs, focusing on their effects on the incidence of atherosclerosis-derived CV events.

6.2. Study II. – Investigating the effect of TNF inhibitors on the risk of heart failure in IMIDs

Current therapeutic guidelines for IMIDs and prescribing information for TNFis contain the contraindication of the use of TNFis in advanced HF, the cautious administration in milder cases, while they warn about the potential risk of de novo HF as a side effect (52-55, 57, 59, 61, 77, 78). However, since the data underlying the recommendations were established, TNFis have been widely used, and accumulating data questions the existing guidelines. Therefore, our objective was to comprehensively collect and analyse the data on worsening and development of de novo HF in IMID patients treated with TNFis compared to non-TNFi-receiving controls.

7. METHODS

In both studies, systematic literature reviews and meta-analyses were conducted following the latest updated recommendations of the Cochrane Handbook for Systematic Reviews and Interventions, version 6.3. and 6.4. (79, 80). The study protocols were registered on PROSPERO with the identification numbers of CRD42022375491 (Study I.) and CRD42023451099 (Study II.). The study reports adhere to the 2020 Statement of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (81)

7.1. Literature search and eligibility criteria

The systematic literature search was conducted using three electronic databases in Study I.: MEDLINE via PubMed, Cochrane Library (CENTRAL), and Embase, while in Study II., we added to these three search engines another interface (Web of Science). Details regarding the dates of searches and query terms can be found in the *original articles* (82, 83).

Original journal articles were eligible that examined IMID populations, comparing TNFi-treated patients with those receiving CSNBs, with the outcome of the incidence of CV events for Study I. In Study II., journal articles involving IMID populations were included that compared TNFi-treated versus non-TNFi-exposed groups, specifically investigating the incidence of HF as an outcome. In both projects, RCTs and non-randomised observational studies were eligible, while case reports, case series, abstracts, notes and commentaries were excluded.

7.2. Study selection and data collection

The hits identified from the databases were organised into reference libraries, and duplicates were removed using EndNote 20 (84, 85). Then, abstract and full text selections were conducted by two independent authors via Rayyan Systems (86), followed by conflict resolution of a third author. In Study II., the program Citationchaser was employed to find additional eligible publications after the primary selection process (87).

From the eligible articles, the following data were collected into predefined sheets: name of the first author, year of publication, study design, original source of data, types of IMID

populations, data on intervention and comparator groups, follow-up times or durations of data collection periods, the definitions of the outcomes and data for analyses, general demographic and comorbidity data of the included populations. In instances where the required data was solely available in figures, WebPlotDigitizer was used for data extraction (88).

7.3. Quality assessment

Quality assessments were performed by using the revised tool for assessing the risk of bias (RoB 2) for the data of RCTs (89), and the ROBINS-I (Risk of Bias in Non-randomised Studies of Interventions) for the non-randomised data included (90), in both studies. The instructions of the "Grades of Recommendation, Assessment, Development, and Evaluation (GRADE)" workgroup were followed to evaluate the quality of the evidence (91). GRADEPro Guideline Development Tool was used to visualise the quality of evidence. (92)

7.4. Data synthesis and analysis

7.4.1. Common synthesis and statistical analysis principles — Study I. and II.

In both Study I. and II., general principles were pre-specified to avoid overlapping populations and to improve the quality of the analyses.

In instances when the studies included multiple PICO (population-intervention-comparator-outcome)-matched and overlapping populations, we sought to homogenise the intervention and reference groups by selecting the most similar active substance-containing cohorts in the distinct analyses. Furthermore, we preferentially used data from multivariable analyses with the most adjustments applied, data from the longest follow-up times, involvement of propensity-matched cohorts or application of propensity score, "as-treated" or "current use" analyses over "first exposure carried forward" analyses in non-randomised studies, and "intention-to-treat" analyses in RCTs.

In both studies, random-effect meta-analyses were conducted. The Hartung-Knapp adjustment was implemented for the analyses to reduce the risk of type I error (93). The summary results were graphically represented by building forest plots. 95% prediction

intervals were reported according to the methodology proposed by IntHout et al (94). To quantify statistical heterogeneity among the included studies, we applied the Q test and I^2 statistics. Potential small-study effects were visually evaluated through funnel plots. Statistical significance was determined using a threshold value of $p<0.05$. All analyses were conducted using the R program (R Core Team 2020, version 4.1.0 in Study I., and version 4.1.3. in Study II.) (95).

7.4.2. Specific methods of synthesis and analysis — Study I.

We endeavoured to ensure the consistency and standardisation of the CV event definitions. Outcomes identified as atherosclerosis-derived events were classified into five different categories according to their event composition: MI, CeVE, MACE (including MI and CeVE), cardiac events (CE, extended definitions used for MI), composite of cardiovascular events (CCVE, extended definition of MACE), and CV death. Further detailed descriptions of the classes can be found in the *Supplementary Material* of the *original publication* (82).

For the statistical analyses, univariate and multivariate hazard ratios (HR) and incidence rate ratios (IRRs) along with 95% confidence intervals (CIs) were employed. The τ^2 and the variance of the random effects were calculated by applying the REML (restricted maximum likelihood) estimator.

Before the statistical pooling of multivariate HRs, covariates previously applied in the models were evaluated. The multivariate HRs in each analysis were only involved if they were adjusted for the following four domains: a.) general data, demographics, b.) baseline comorbidities, including pre-existing CV diseases, c.) baseline use of non-IMID related medications and d.) IMID-related factors (e.g. severity) and medications.

For IRRs, with the availability of incidence rates (IR) and corresponding CIs in the study arms, the number of events and follow-up times could be estimated. These arm-specific data served as input in the analyses and were utilised to construct the corresponding forest plots. Given the raw data, Mantel-Haenszel weighting was applied in the analyses of IRRs.

7.4.3. Specific methods of synthesis and analysis — Study II.

Outcome categories were preliminarily defined based on the presence or absence of a prior or baseline diagnosis of HF. Accordingly, events were classified as worsening and de novo HF. The reported outcomes were also categorised as de novo when HF was listed among the exclusion criteria for the initially included populations. Outcomes encompassing the worsening and de novo events were labelled composite HF. The composite HF category was also applied when patient characteristics indicated a history of CV diseases, but did not specifically identify HF. In instances where the definition of HF was not reported, initially, the outcome was marked as "no information". During the data synthesis, these outcomes were treated as de novo HF events for RCTs, since most RCTs were phase II/III trials, which assumably excluded patients with pre-existing HF. For non-randomised studies, "no information" outcomes were synthesised with composite events, as observational designs are more likely to include patients with pre-existing CV diseases, including HF.

Data from RCTs and non-randomised studies were handled separately, both during the phases of synthesis and statistical analysis. When multiple applicable effect measures were reported in a study, primarily HRs, then IRRs, in the absence of both, crude incidence data were included in the analysis. From the raw incidences, relative risks were derived. IRRs were computed from IRs along with 95% CIs and corresponding follow-up durations. Whether sourced from raw data or directly from study reports, the ratios were treated as equivalent measures of effects and were collectively referred to as risk ratios (RR) with 95% CIs throughout the analyses.

8. RESULTS

8.1. Search and selection, characteristics of the included studies

8.1.1. Study I.

A total of 8,724 hits could be identified during the systematic search using three databases. Following the steps of duplicate removal, the screening process by title and abstract, full texts, and searching citations, 56 articles met the inclusion criteria. (10, 28, 96-147) Corrections (148, 149) are associated with two articles and cited in the results alongside the original publications (100, 108). The summary of the selection process is presented in ***Figure 1.***

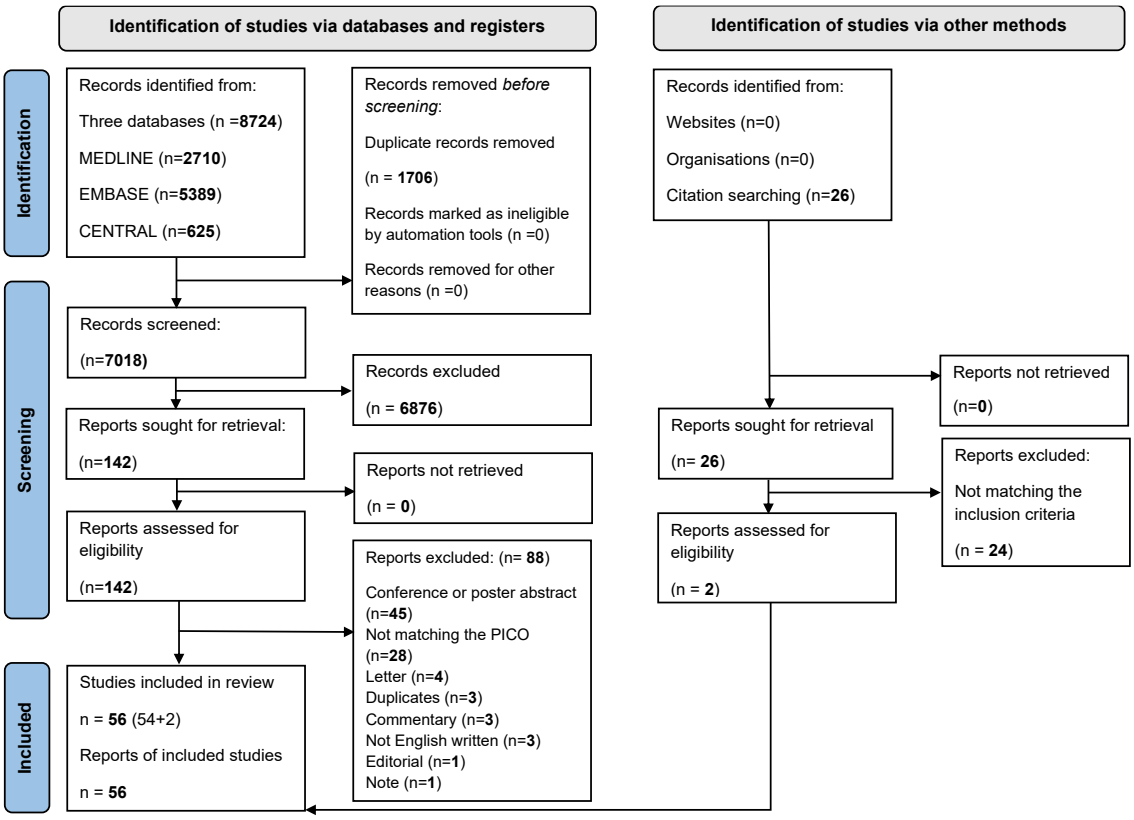


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram of the selection process of Study I. (82)

The detailed characteristics of the included studies are summarised in ***Table 1***, whereas the characteristics of the involved IMID patients can be overviewed in ***Table S2***, *Supplementary Material* of the *original publication*. (82)

8.1.2. Study II.

Throughout the systematic search and selection process, 6,434 records were initially identified. After eliminating duplicates, reviewing the hits by title and abstract, and full text, 34 articles were (98, 150-182) eligible. A further 19 articles (183-201) were identified through backward and forward reference searches. Altogether, 53 original journal articles (98, 150-166, 168-202) were included, reporting the findings of 49 individual studies. The results of the systematic search and the process of selection are detailed in ***Figure 2***.

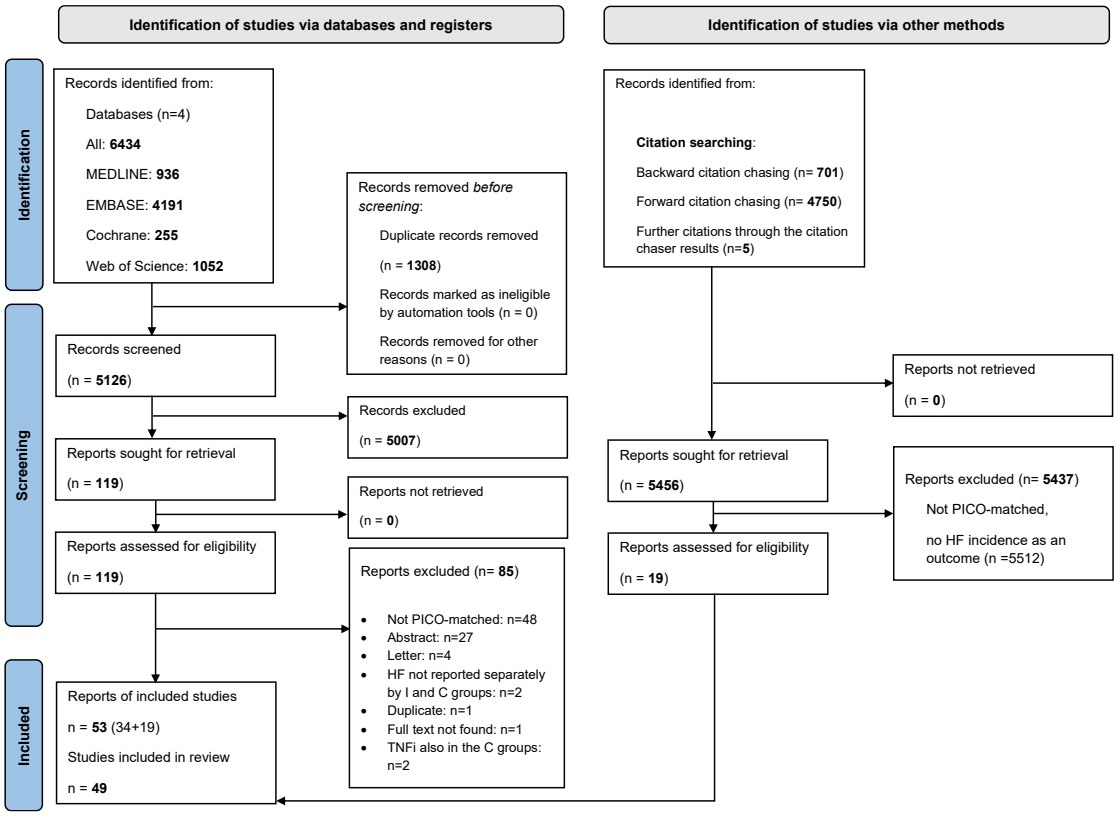


Figure 2 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Diagram of the selection process of Study II. (83)

A detailed summary of the studies included in the systematic review and meta-analysis can be found in ***Table S2,*** and general data on the populations included in the meta-analysis are summarised in ***Table S3***, *Supplementary Material* of the *original article* (83).

8.2. Results of the quantitative analysis

8.2.1. Study I.

The quantitative analysis of Study I was conducted by using data from 29 studies (96, 97, 99, 103, 104, 106, 108-113, 116, 119, 120, 122, 124, 126, 127, 129, 130, 132, 134, 135, 141, 142, 145, 147, 149, 203).

Main analyses

8.2.1.1. MACE

Analysis with multivariate HRs. Data from seven studies were involved, examining the risk of MACE with multivariate HRs, including a total of 84,320 PsO, PsA and RA patients (109, 110, 126, 134, 135, 141, 147). The overall effect size indicated a significantly reduced risk of MACE compared to those receiving CSNBs (HR=0.74, CI: 0.58-0.95, I^2= 76%). Subgroup analysis of RA patients also demonstrated a comparable and statistically significant risk-reduction with TNFis versus CSNBs (HR=0.78, CI 0.67-0.91, I^2= 7%). The forest plot of the analysis can be seen in ***Figure 3/1***.

Analysis with IRRs. Data retrieved from 14 studies could be included in the MACE analysis using the effect measure of IRR (97, 103, 104, 108-110, 116, 126, 129, 130, 135, 142, 147, 149, 203). A total of 192,677 PsO, PsA, RA and IBD patients were included in the overall analysis, and parallel subgroup analyses were conducted with PsO, PsA and RA patients. A more than 20% statistically significant lower risk was observed in the TNFi-treated IMID patients compared to the CSNB-treated ones (IRR=0.77, CI 0.67-0.88, I^2= 46.32%). The risk-reducing effect demonstrated in TNFis was maintained for the subgroup analyses in comparison with the CSNB patient groups; a 32% lower risk in RA, and a 21% decreased risk in PsO, PsA subgroup analyses could be observed in the TNFi-treated IMID cohorts (IRR=0.68, CI 0.46-1.00 and IRR=0.79, CI 0.64-0.98 respectively, see ***Figure 3/2***)

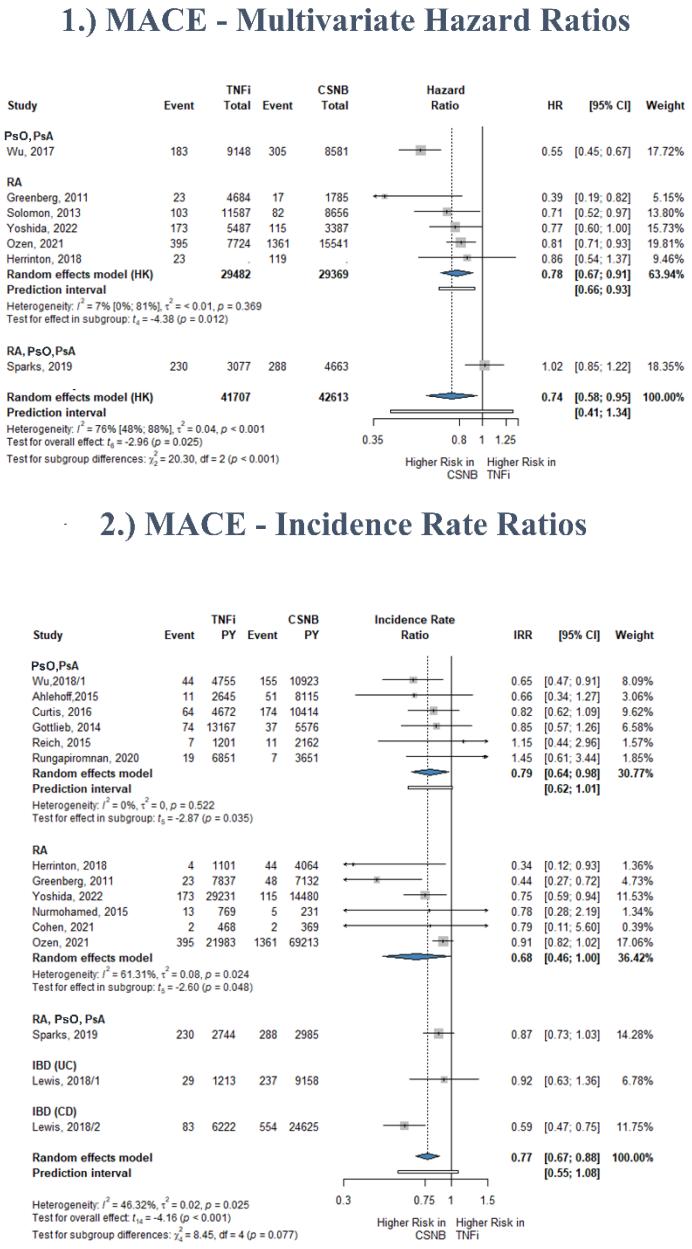


Figure 3 Forest plots of the analyses of the risk of MACE comparing TNFis and CSNBs using 1.) multivariate HRs, and 2.) IRRs (82)

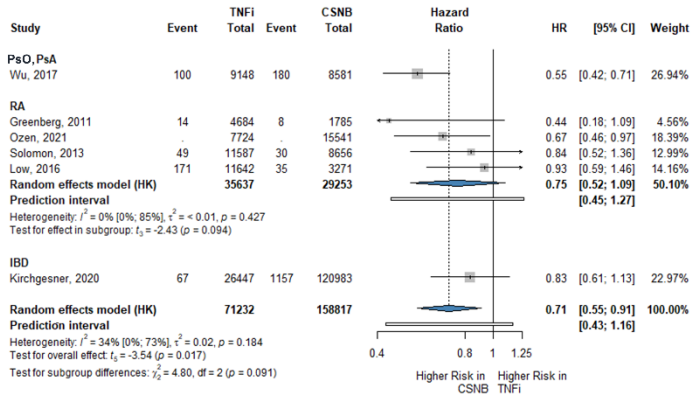
CD: Crohn's disease, *CI:* confidence interval, *CSNB*: conventional systemic non-biological, *HR:* hazard ratio, *IBD*: inflammatory bowel disease, *IRR:* incidence rate ratio, *MACE:* major adverse cardiovascular events, *PsA*: psoriatic arthritis, *PsO*: psoriasis, *PY*: person-year, *RA*: rheumatoid arthritis, *TNFi:* tumour necrosis factor inhibitor, *UC*: ulcerative colitis

8.2.1.2. CeVE

Analysis with multivariate HRs. Data from six studies could be included in the analysis of CeVE with multivariate HRs, involving 230,049 IMID patients with PsO, PsA, RA and IBD diagnoses (109, 112, 119, 126, 134, 141). The overall effect size was HR=0.71 (CI 0.55-0.91, I^2= 34%), showing a statistically significantly lower risk for CeVE in the TNFi IMID groups compared to the CSNB controls. Subgroup analysis with RA patients showed a similar, though statistically nonsignificant, risk reduction in the TNFi group compared to the controls, accompanied by a decrease in the heterogeneity (HR=0.75, CI 0.52-1.09, I^2=0%, see ***Figure 4/1***)

Analysis with IRRs. Eight studies were included for the analysis of the risk of CeVE pooling IRRs, with 242,425 (PsO, PsA, RA, IBD) patients. The pooled overall effect presented a statistically significant risk reduction in the TNFi group compared to the CSNB (IRR=0.69, CI 0.57-0.84, I^2=18,42%). In the subgroup analyses of PsO, PsA and RA patients, statistically non-significant 20% and 21% risk-lowering effects were indicated towards the TNFis. (See ***Figure 4/2***)

1.) CeVE - Multivariate Hazard Ratios



2.) CeVE - Incidence Rate Ratios

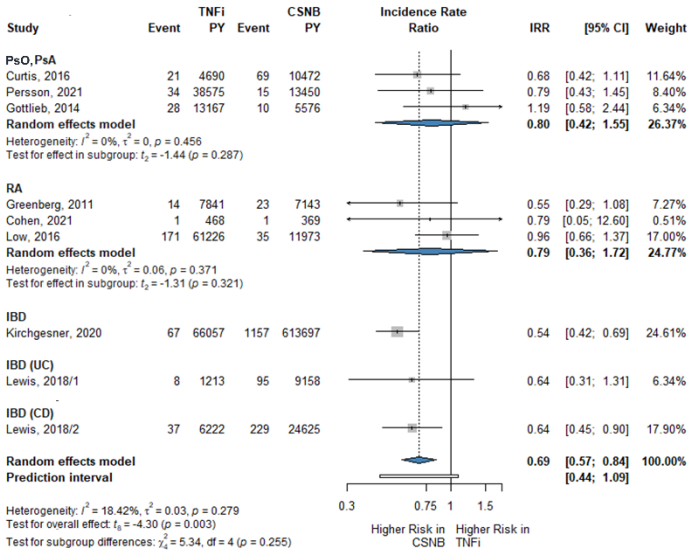


Figure 4 Forest plots of the analyses of the risk of CeVE comparing TNFis and CSNBs using 1.) multivariate HRs, and 2.) IRRs (82)

CD: Crohn's disease, *CeVE*: cerebrovascular event, *CI:* confidence interval, *CSNB*: conventional systemic non-biological, *HR:* hazard ratio, *IBD*: inflammatory bowel disease, *IRR:* incidence rate ratio, *PsA*: psoriatic arthritis, *PsO*: psoriasis, *PY*: person-year, *RA*: rheumatoid arthritis, *TNFi:* tumour necrosis factor inhibitor, *UC*: ulcerative colitis

8.2.1.3. MI

Analysis with multivariate HRs. The risk of MI in TNFi-treated versus CSNB-treated IMID patients was analysed using multivariate HRs, including data from six studies (109, 112, 120, 126, 134, 141). With a total of 229,394 IMID patients, in the overall analysis, a 34% reduced risk was observed in the TNFi group compared to the controls (HR=0.66, CI 0.50-0.87, I2=40%). Through the involvement of four studies, a subgroup analysis of RA patients was performed, indicating the maintained risk-lowering effect of the TNFis (HR=0.70, CI: 0.49-1.00, I2=24%). For the results, see ***Figure 5/1***.

Analysis with IRRs. IRRs for the risk of MI were pooled from studies involving PsO, PsA, RA and IBD patients. (96, 103, 104, 106, 108, 109, 112, 116, 120, 124, 127, 132, 145, 149) Involving a total of 284,505 patients, the overall effect showed a statistically significant risk-reduction in the TNFi versus the CSNB groups (IRR=0.69, CI 0.60-0.81, I^2=26.29%). The subgroup analysis of RA patients also yielded a significantly lower risk in the TNFi group (IRR=0.62, CI 0.46-0.84, I^2=13.55%), while in the subgroup analysis of PsO and PsA patients, a non-significant beneficial risk-decreasing tendency could be observed in the TNFi-treated patients (IRR=0.78, CI 0.59-1.04, I^2=32.91%). See ***Figure 5/2***.

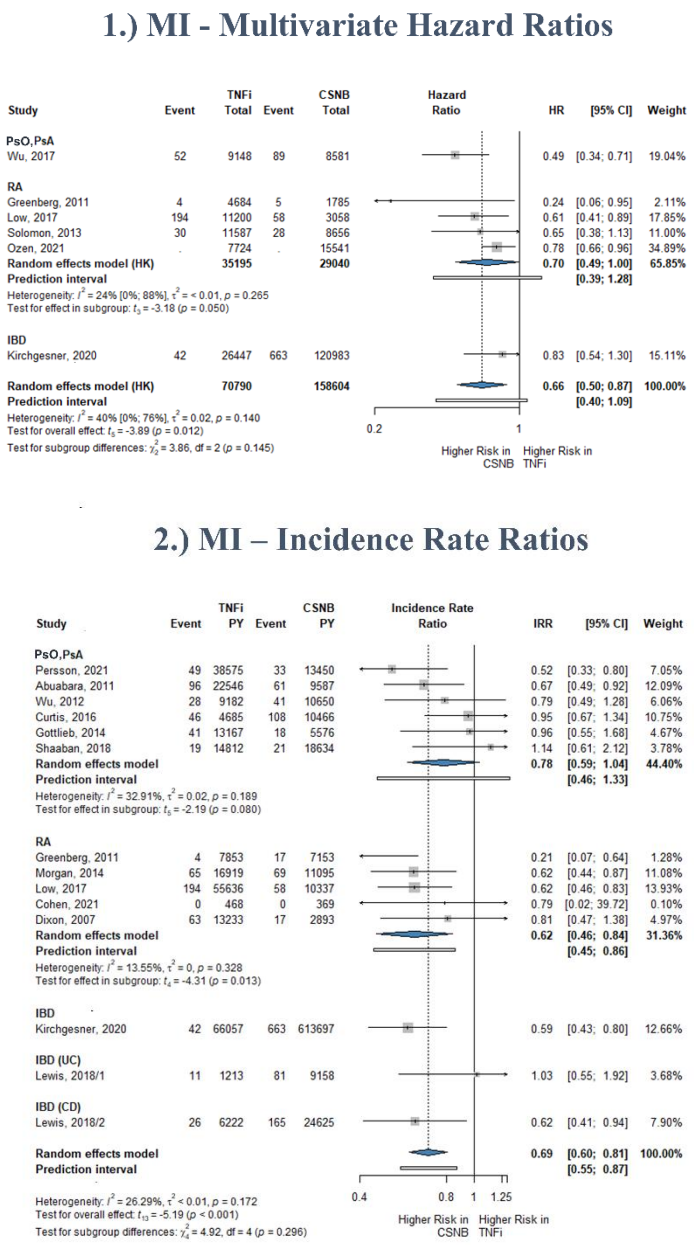


Figure 5 Forest plots of the analyses of the risk of MI comparing TNFis and CSNBs using 1.) multivariate HRs, and 2.) IRRs (82)

CD: Crohn's disease, *CI:* confidence interval, *CSNB*: conventional systemic non-biological, *HR:* hazard ratio, *IBD*: inflammatory bowel disease, *IRR:* incidence rate ratio, *MI*: myocardial infarction, *PsA*: psoriatic arthritis, *PsO*: psoriasis, *PY*: person-year, *RA*: rheumatoid arthritis, *TNFi:* tumour necrosis factor inhibitor, *UC*: ulcerative colitis

8.2.1.4. Further analyses

Further analyses were conducted, comparing TNFi-treated and CSNB-treated IMID patients, with the outcomes of MACE, CeVE, CE, CCVE, and CV death, with the effect measures of univariate HRs and IRRs. Consistent with previously presented findings, the results of these analyses corroborate the beneficial impact of the use of TNFis in comparison with CSNBs in IMIDs. The analyses can be found in *the original publication* (*Supplementary Material*) (82).

8.2.2. Study II.

Data from 45 studies were incorporated in the meta-analysis investigating the risk of de novo, worsening and composite (de novo and worsening) HF in IMIDs treated with TNFis compared to untreated controls (98, 150-157, 159-161, 163-165, 168-196, 198-202).

8.2.2.1. De novo HF – synthesis of randomised data

Data obtained from 26 randomised studies (150, 152, 153, 155, 159, 160, 163, 165, 166, 171-174, 176, 179-181, 183, 186, 188-195, 199-202, 204) could be included in the analysis of the risk of de novo HF in TNFi-treated patients compared to non-treated controls. Including 10,981 IMID patients, the overall effect size demonstrated no risk enhancement in TNFi cohorts compared to the non-recipient controls in terms of the risk of new-onset HF. (RR=0.87, CI 0.60-1.25, I^2=0%). Subgroup analyses were conducted according to different IMID populations and TNFi agents. Based on the pooled effects of the subgroups, TNFis did not increase the risk of de novo HF, regardless of the IMID population (IBD, PsO/PsA, RA) or the TNFi active substance (ADA, INF). See ***Figures 6/1*** and ***6/2***.

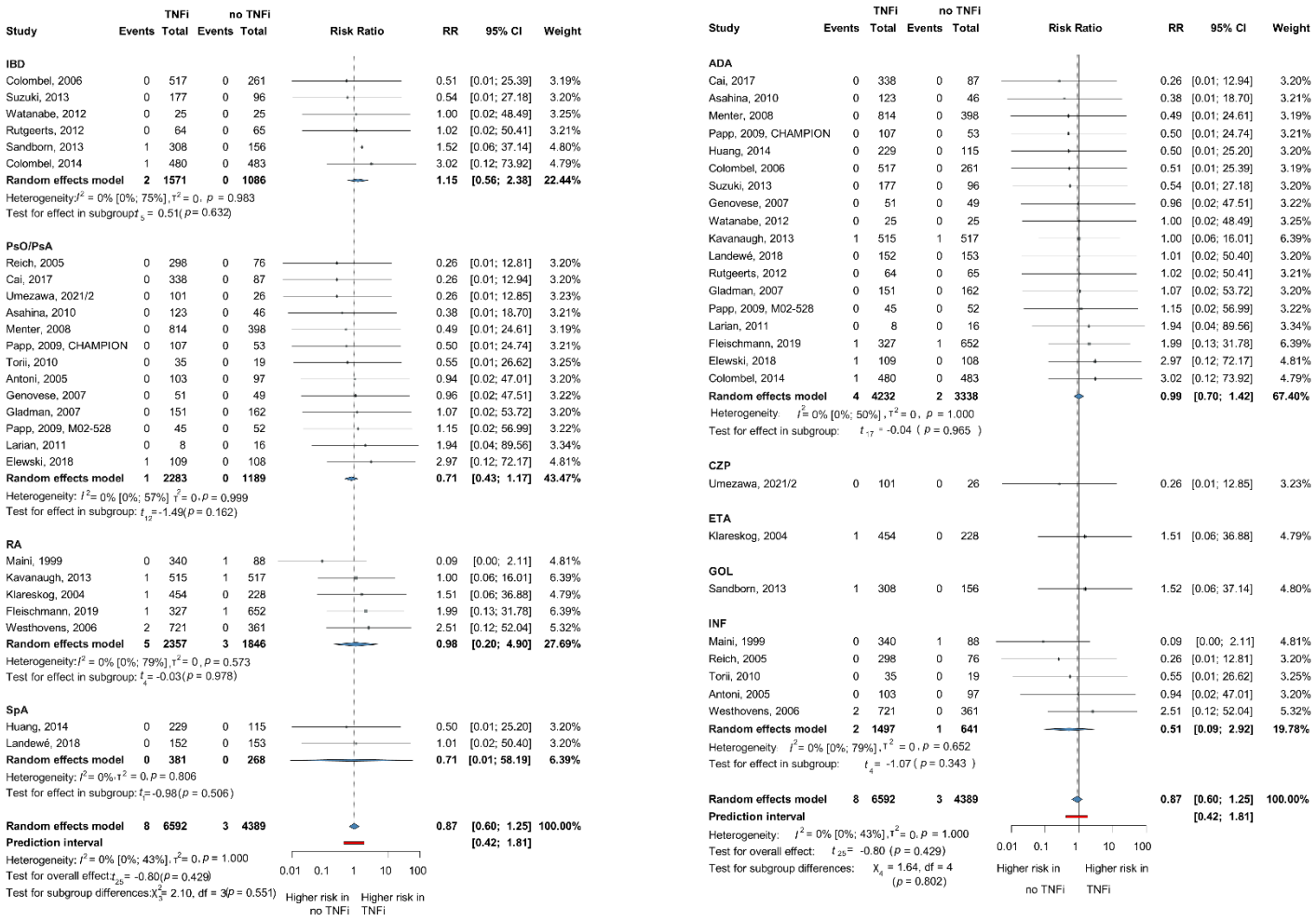


Figure 6 Forest plots on the results of synthesised randomised data on the risk of de novo heart failure with subgroups of 1.) (left) IMIDs and 2.) (right) TNFi agents (83)

ADA: adalimumab, *CI:* confidence interval, *CZP*: certolizumab pegol, *ETA*: etanercept, *GOL*: golimumab, *IBD*: inflammatory bowel disease, *INF*: infliximab, *PsA*: psoriatic arthritis, *PsO*: psoriasis, *RA*: rheumatoid arthritis, *RR*: risk ratio, *SpA*: spondyloarthritis, *TNFi:* tumour necrosis factor inhibitor

One of the main concerns regarding the elevated risk for HF with TNFis stems from the report of higher risk in patients with advanced HF receiving high-dose INF (10 mg/kg) (75). Therefore, we sought to compare the different INF doses to untreated control groups, which was only possible by incorporating randomised data from IMID patients without a prior history of advanced HF (173, 181, 183, 191, 195, 200). Although a subgroup analysis for the 10 mg/kg, higher dose of INF could not be conducted, the lower 5 mg/kg dose—more commonly administered in clinical care—was not associated with an elevated risk compared to untreated controls (RR=0.51, CI 0.10-2.58, I^2=0%). Due to the limited data, no comparison between dosage subgroups (3, 5, and 10 mg/kg) was feasible. For results, see ***Figure 7.***

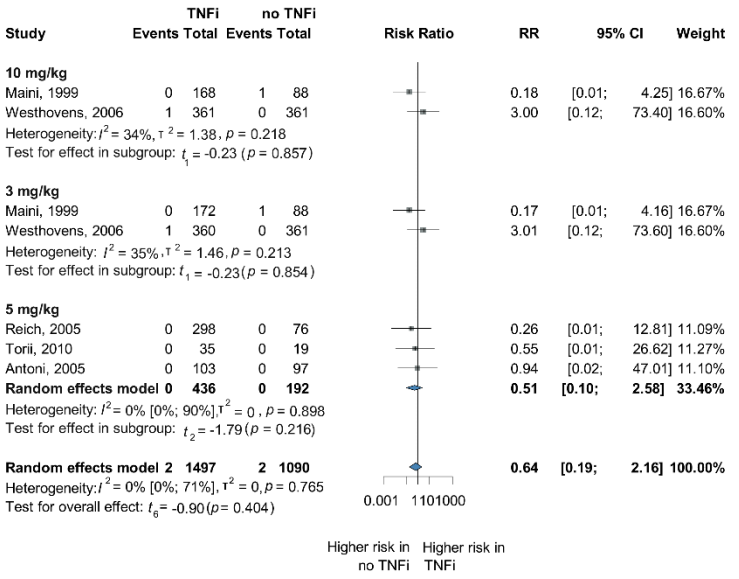


Figure 7 Comparison of infliximab dosages compared to untreated controls with data from randomised studies on the risk of de novo heart failure (83)

CI: confidence interval, *RR*: risk ratio, *TNFi:* tumour necrosis factor inhibitor

8.2.2.2. De novo HF – synthesis of non-randomised data

The risk of de novo HF was also evaluated by pooling non-randomised, observational, real-world data from more than 98,000 IMID patients (151, 154, 156, 157, 161, 164, 177, 178, 182, 196). Consistent with the findings of the analysis of randomised data on the risk of de novo HF, the overall effect derived from the synthesis of 11 studies did not demonstrate any significant risk-elevation in the TNFi-treated cohorts compared to the controls (RR=0.86, 95% CI 0.64-1.14, I^2=35%, see ***Figure 8)***.

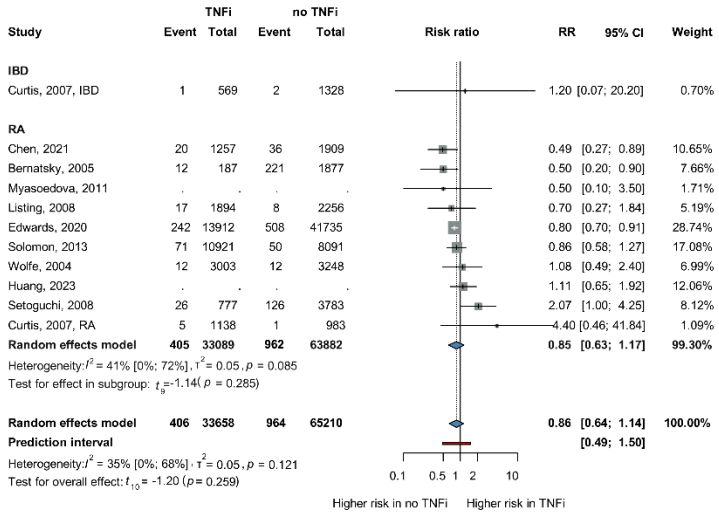


Figure 8. Forest plots on the results of synthesised non-randomised data on the risk of de novo heart failure (83)

CI: confidence interval, *IBD*: inflammatory bowel disease, *RA*: rheumatoid arthritis, *RR*: risk ratio, *TNFi:* tumour necrosis factor inhibitor

8.2.2.3. Worsening of HF

Four non-randomised observational studies, including 1,966 RA patients, were involved in the analysis of the risk of worsening HF in TNFi-treated patients compared to non-TNFi-treated ones (134, 154, 164, 177). The overall effect indicated no statistically significant

increase in worsening HF in the TNFi group compared to the controls (RR=1.18, CI 0.69-2.00, I^2=0%). ***Figure 9*** shows the forest plot of the analysis.

We performed a live-one-out sensitivity analysis by excluding the study of *Setoguchi, 2008,* as the mean age of the comparison cohorts in this study was significantly higher than in the other three studies included (see ***Table S3***, *Supplementary Material* of the *original publication (83)* for specific data). The overall effect of the sensitivity analysis was lower (RR=0.97, 95% CI: 0.74-1.27, result not shown in forest plot), indicating no risk-increasing effect of TNFis on worsening of HF.

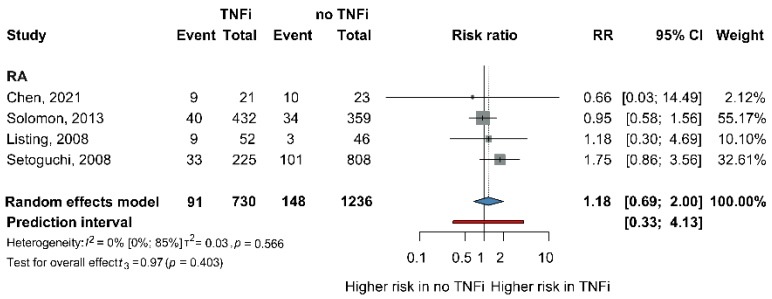


Figure 9 Forest plot of the results of synthesised non-randomised data on the risk of worsening heart failure (83)

CI: confidence interval, *RA*: rheumatoid arthritis, *RR*: risk ratio, *TNFi:* tumour necrosis factor inhibitor

8.2.2.4. Composite (de novo and worsening) HF

The composite HF outcome could be investigated by incorporating data from more than 100,000 patients from non-randomised studies in TNFi-treated IMID patients compared to controls (98, 154, 164, 168-170, 175, 177, 178, 182, 185, 187, 198). The pooled effect size did not indicate any risk-enhancement associated with TNFis, rather suggesting a potential protective effect of TNFis compared to the unexposed control group (RR=0.71, CI 0.48-1.04, I^2=72%, see ***Figure 10***).

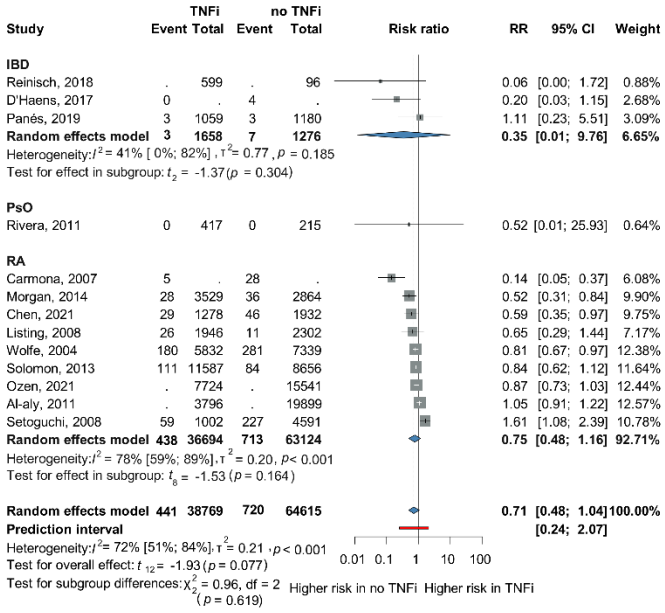


Figure 10. Forest plots on the results of synthesised non-randomised data on the risk of composite (de novo and worsening) heart failure (83)

CI: confidence interval, *IBD*: inflammatory bowel disease, *PsO*: psoriasis, *RA*: rheumatoid arthritis, *RR*: risk ratio, *TNFi:* tumour necrosis factor inhibitor

8.3. Qualitative analysis

The summaries of the findings of studies that could not be involved in the quantitative analyses of Study I and Study II can be found in the *original publications* (82, 83).

8.4. Quality assessment

8.4.1. Study I.

Upon evaluating the risk of bias, the majority of the included studies were classified as having a moderate or high risk, primarily due to their observational design. No significant publication bias was observed in our main analyses. The certainty of evidence across the analyses was dominantly very low to low, and three analyses were rated as moderate quality of evidence. The results of the quality assessments of Study I can be seen in the *Supplementary Material* of the *original article* (82).

8.4.2. Study II.

Most of the included studies were determined to have a high overall risk of bias. In RCTs, the primary factors for enhancing the risk of bias were deviations from intended interventions and bias related to outcome measurements. For non-randomised studies, downgrading was mainly due to confounding bias. Through the evaluation of the funnel plots, no publication bias could be observed among the articles involved. The certainty of evidence was rated as very low for all outcomes. The findings for each quality assessment are available in the *Supplementary Material* of the *original publication* of Study II (83).

9. DISCUSSION

9.1. Summary of findings, international comparisons

Therapies that specifically inhibit the immunological pathways in IMIDs have become cornerstone treatments, as they not only effectively control the specific IMID-related symptoms but also provide potential benefits in the management of the associated comorbidities. The growing body of evidence enables the integration of TNFis into the IMID treatment algorithms in a way that optimises timely and effective treatment for the most appropriate IMID patient groups, considering their effects on CV diseases.

In IMIDs, the enhanced CV risk, driven by accelerated atherosclerosis, highlights the importance of considering the CV effects of anti-inflammatory therapies when selecting treatment options. Our objective in performing a systematic review and meta-analysis was to investigate the effect of TNFis, generally second-line systemic treatment, compared to first-line used CSNBs on the risk of mainly atherosclerosis-derived CV events, widely in IMIDs. Our Study I, through the findings of comprehensive analyses, contributes to better therapeutic decision-making for IMID patients with high CV burden.

The comparative analyses of Study I showed the superiority of TNFis in reducing CV risk compared to conventional therapies. The beneficial effect was observed not only in the overall IMID populations, but also separately in RA, PsO and PsA subgroups. To our knowledge, our analyses are the first to statistically significantly demonstrate the more beneficial effect of TNFis versus conventional treatments in patients with PsO and PsA on CV risk. While the meta-analysis of *Roubille et al.* could not yet perform a subgroup analysis with PsO and PsA patients (66), in a subsequent work by *Yang et al.*, a non-significant tendency toward the beneficial effect of TNFis over conventional therapies was observed on CV events (68). Our analysis supports the beneficial effect of TNFis compared with CSNBs in these subgroups, specifically for the outcome of MACE.

Regarding RA patients, a significant risk reduction in the analyses with outcomes of MACE and MI was found in the TNFi-treated patients compared to the CSNB-treated controls. Formerly, meta-analyses have examined the comparison of TNFis and conventional therapies

regarding CV risk in this patient group. Consistent with our findings, one of the earliest meta-analyses evaluating TNFis versus traditional treatments reported a reduced risk for all CV events and MI with about 50% and 20% respectively, in TNFi-treated RA patients (67). The findings of a subsequently conducted meta-analysis also presented a favourable effect of TNFis compared to csDMARDs on the risk of MACE (69). A further recent systematic review and meta-analysis investigated the safety of biologics in RA, comparing TNFis and conventional systemic DMARDs, mainly MTX, in subgroup analysis on the risk of CV events. This work by *de Queiroz et al.* found no difference between the comparison groups (205). One possible explanation for the inconsistency is the inclusion of different study groups using varying definitions of CV events, which generally limits the comparability of the results across the meta-analyses.

Unlike IMID subgroups of PsO, PsA and RA, data on patients with AS and IBD remain limited regarding the comparison of TNFis and CSNBs on CV safety. Owing to the small number of studies, subgroup analyses could not be performed for these subpopulations; thus, further comprehensive analyses are needed.

Although accumulating evidence indicates that TNFis reduce the CV burden, mainly the risk of atherosclerosis-derived events, concerns remained about their association with worsening of pre-existing and even de novo HF. Accordingly, our objective of Study II was to specifically investigate the effect of TNFis on the risk of HF in the same IMID populations, with a particular focus on the separate evaluation of de novo and pre-existing events.

The risk of de novo HF events comparing TNFi-treated patients and non-TNFi controls was assessed by analysing both randomised and non-randomised data. Our results did not present any increased risk; instead, the overall effects of both analyses suggested a trend towards the protective effect of TNFis. Besides performing subgroup analyses by agents of ADA and INF, we sought to compare the different dosages of INF, as concerns about the higher dose of this active substance shaped the current recommendations. With the dose of 5 mg/kg INF more frequently administered in everyday practice, no significant risk increase of de novo HF was observed. However, the higher (10 mg/kg) dosage, associated with the risk of HF based on prior non-IMID data (75), could not be analysed separately statistically. Although the higher

INF dosage is rarely applied in clinical practice, a potential dose-dependent threshold risk enhancement could not be ruled out. In the de novo HF event analysis comparing TNFi versus non-TNFi cohorts based on randomised data, subgroup analyses stratified by IMIDs, specifically with RA, PsO and PsA patients, were also performed. A previous meta-analysis by *Champs et al.* assessed the risk of HF among PsO and PsA patients, reporting no statistically significant difference between the TNFi and PBO groups (206)—a finding consistent with our subgroup analysis.

The result of the analysis of evaluating the de novo HF risk involving non-randomised data indicated a non-significant beneficial risk-reducing trend towards the use of TNFis compared to non-TNFi-treated, dominantly involving RA patients. Similarly, a prior meta-analysis by *Roubille et al.* among a smaller RA population with observational data assessing presumably mainly de novo events also reported a non-significant trend toward lower risk in TNFi-treated cohorts compared to those not receiving TNFis (66).

Apparently, because of risks observed in early RCTs involving non-IMID, advanced-HF patients, no further randomised studies were performed evaluating the risk of worsening of pre-existing HF status. For this reason, the assessment of the risk of worsening HF with TNFis was solely based on non-randomised, observational data. Our analysis of this outcome showed no statistically significant risk enhancement with TNFis compared to non-treated controls. Nonetheless, the result should be interpreted with caution, given that data from only a limited number of, solely RA-patient-included studies could be derived for the analysis; therefore, further investigations are needed based on these data. However, it is worth highlighting that no prior meta-analysis focused on evaluating the worsening events separately, associated with TNFis in IMIDs.

9.2. Strength

9.2.1. Study I

Study I, investigating the effect of TNFis compared to CSNBs on the risk of CV events in IMIDs, has several strengths. First, our meta-analysis provides a comprehensive summary including large-scale studies across various IMID populations. Furthermore, we implemented

a rigorous methodology to establish both the outcomes investigated and the composition of groups compared in the analyses involved. In our main analyses, we integrated fully adjusted multivariate HRs, which enable the control of confounding factors and enhance the accuracy and validity of the outcomes assessed in the present work.

9.2.2. Study II

In Study II—investigating the effect of TNFis on the risk of HF in IMIDs, a remarkable strength is that the work represents the first meta-analysis to distinguish between worsening and new-onset cases of HF as outcomes. Using real-world data, it synthesises data from wide IMID populations from RCTs and non-randomised observational studies. The findings of this systematic review and meta-analysis potentially offer the highest level of evidence on the impact of TNFis on the risk of HF.

9.3. Limitations

9.3.1. Study I

The main limitation of Study I lies in the methodological heterogeneity of the individual studies included, especially the inconsistent definitions of outcomes and differences in characteristics of the comparison cohorts. Another limitation is that patients in some of the comparator groups received systemic corticosteroids and NSAIDs. Since these treatments are known to increase CV risk (66), their involvement may cause selection bias and amplify the apparent CV benefit of TNFis.

9.3.2. Study II

Similarly, to Study I, the inconsistent and often scantily detailed definitions of the outcome assessed reveal one of the limitations of Study II. While the involvement of observational real-world data enhances the clinical relevance of the present meta-analysis, through the lack of randomisation, selection bias might lead to disparities in the baseline risk of the outcome being assessed, potentially resulting in the inaccuracy of the analyses. In the analysis of RCTs, the low, frequently zero incidence of the outcome within the individual studies may limit the robustness of the findings.

10. CONCLUSION

TNFis substantially reduce the risk of CV events compared to conventional systemic agents in IMID populations. Early implementation of TNFis in the therapeutic sequence of IMIDs might decrease the occurrence of major atherosclerosis-derived CV events, potentially alleviating the burden caused by CV comorbidities, thus improving the quality of life and life expectancy of these patient populations.

Based on present findings, TNFis have no risk-enhancing effect on de novo HF, and no significant increase in the risk of worsening of HF was observed associated with TNFis. Revision of therapeutic guidelines for IMIDs is warranted to reflect current evidence showing that TNFis do not increase the risk of de novo HF, while further investigations are needed for the worsening of pre-existing HF.

11. IMPLEMENTATION FOR PRACTICE

The early integration of novel findings of the research field into clinical practice is of paramount importance (207, 208).

Although TNFis are currently widely applied therapies, they are mainly available for moderate-to-severe disease as second-line systemic treatments. For IMID patients with major CV risk factors and elevated based on risk assessments or clinical signs, the early use of TNFis in the therapeutic sequence is expected to prevent serious CV events.

Current findings indicate that TNFis do not increase the risk of de novo HF; therefore, the revision of safety concerns of TNFi agents should be considered. However, their administration in mild HF cases still requires caution and consultation with cardiologist specialists. Importantly, consistent with the existing recommendations, yet they remain contraindicated in IMID patients with advanced HF.

Continuous update of international and regional guidelines is crucial to incorporate novel evidence on the efficacy and safety of anti-inflammatory treatments of IMIDs, including their impact on comorbidities.

12. IMPLEMENTATION FOR RESEARCH

Performing further RCTs with longer follow-up times and well-designed single- and multicenter registries enabling the systematic collection of comprehensive efficacy and safety data on TNFis and other systemic anti-inflammatory therapies would play a crucial role in building the highest possible quality evidence.

In future research, the adoption of standardised definitions for CV events is essential to enhance the reliability and comparability of synthesising meta-analyses. In evaluating the CV risk with TNFis compared to CSNBs, the homogenization of the comparison groups and agent-to-agent comparisons would be needed.

Regarding the investigation of the effect of TNFis on HF, further expanding research is warranted on the outcome of worsening of HF with the use of TNFis for strengthening the validity of the present findings. Results from experimental research, that indicate the dual role of TNF-α signalling—proinflammatory and late anti-inflammatory—may contribute to the complex pathophysiology of TNFi-associated HF development (209). The underlying mechanisms are not yet thoroughly understood; therefore, preclinical research using animal models is primed to be imperative to establish the potential causal relation between TNFis and worsening of pre-existing HF. For both worsening and new-onset HF outcomes, detailed subgroup analyses, particularly across different stages and etiologies of HF, are warranted. Separate evaluations of TNFi agents to examine substance-specific risks are also needed. Given that the early RCTs raised dose-dependent adverse effects of INF and ETA (74, 75), further investigations of varying dosing regimens on the risk of HF would be essential for the complete establishment of evidence on the use of TNFis in IMID populations.

A desirable further requirement for future research in this field is to ensure reliable and unbiased estimates in survival analyses; using harmonised statistical methodologies capable of adequately addressing confounding is crucial.

13. IMPLEMENTATION FOR POLICYMAKERS

Due to their chronic nature, IMIDs impose a significant burden on individuals and healthcare systems as well. Therefore, it is indispensable for policymakers to emphasise the necessity of the complex and effective management of these diseases.

Despite the unceasing development of targeted anti-inflammatory therapies in these conditions, many patients still face fragmented care and suboptimal treatment, particularly regarding the management of the comorbidities. Professional societies and medical boards have a pivotal role in patient education, raising awareness about the multisystemic nature of IMIDs. Moreover, policymakers have a role in facilitating integrated care models that address IMIDs and their associated comorbidities holistically and provide ground for effective multidisciplinary collaborations. Furthermore, restrictive reimbursement policies may delay access to biological therapies, despite evidence supporting their role in IMID progression and treating comorbidities. Optimal reimbursement models created by policymakers should consider long-term healthcare savings from early and effective treatments, like reduced hospitalisations, or costs related to managing comorbidities in IMID patients.

14. FUTURE PERSPECTIVES

Developments in the field of dermatology, rheumatology and gastroenterology forecast remarkable health breakthroughs for IMID patients in the future. Integrating emerging knowledge and evidence on targeted therapies into the management of IMID populations is expected to enhance long-term outcomes and improve quality of life and life expectancy.

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16. BIBLIOGRAPHY

16.1. Publications related to the thesis

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16.2. Publications not related to the thesis

Bokor, L. A., Martyin, K., Krebs, M., **Galajda, N. Á.**, Meznerics, F. A., Szabó, B., Hegyi, P., Lőrincz, K., Kiss, N., Bánvölgyi, A., & Hidvégi, B. (2025). Deucravacitinib shows superior efficacy and safety in cutaneous lupus erythematosus compared to various biologics and small molecules - A systematic review and meta-analysis. *Autoimmunity reviews*, *24*(3), 103723.

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