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REVIEW ARTICLE

Vascular effects of biologic and targeted synthetic antirheumatic drugs approved for rheumatoid arthritis: a systematic review

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Abstract

Background Rheumatoid arthritis (RA) increases the risk of cardiovascular disease (CVD), with inflammation playing a key role. Biologic and targeted synthetic drugs used to treat RA can induce systemic immunomodulation and may have pleiotropic effects on vascular function, making it crucial to investigate their impact on CVD risk in RA patients.

Methods A systematic review of the literature was conducted to investigate the impact of biologic and targeted synthetic treatments approved for RA on various cardiovascular markers, including endothelial function, arterial stiffness, and subclinical atherosclerosis. Our analysis included a search of the MedLine (via PubMed) and Web of Science databases using a pre-determined search strategy. We conducted a narrative synthesis of the included studies due to heterogeneity in study design and outcome measures.

Results From an initial pool of 647 records, we excluded 327 studies based on their titles and abstracts, and we selected 182 studies for final examination. Ultimately, 58 articles met our inclusion criteria and were included in our systematic review. Our analysis of these studies revealed a positive effect of biologic and targeted synthetic therapies on vascular dysfunction associated with RA. However, the impact of these treatments on subclinical atherosclerosis was inconsistent.

Conclusion Overall, our systematic review provides important insights into the potential cardiovascular benefits of biologic and targeted synthetic treatments for RA by a still unknown mechanism. These findings can inform clinical practice and contribute to our understanding of their possible effects on early vascular pathology.

Key Points

- *Great heterogeneity of methods are used to evaluate the endothelial function and arterial stiffness in patients with RA on biologic and targeted synthetic antirheumatic drugs.*
- *Most studies have shown a considerable improvement in endothelial function and arterial stiffness with TNFi, despite some studies reporting only transient or no improvement.*
- *Anakinra and tocilizumab may have a beneficial effect on vascular function and endothelial injury, as indicated by increased FMD, coronary flow reserve, and reduced levels of biomarkers of endothelial function, while the overall impact of JAKi and rituximab remains inconclusive based on the reviewed studies.*
- *To fully comprehend the distinctions between biologic therapies, more long-term, well-designed clinical trials are necessary using a homogeneous methodology.*

Keywords Rheumatoid Arthritis · Cardiovascular Risk · Biological Therapy · Systematic Review · Antirheumatic Agents

Introduction

In recent years, extensive scientific research has been devoted to investigating cardiovascular risk, given its major contribution to global mortality [1]. One significant focus has been the link between inflammation and atherosclerosis which was first hypothesized by Virchow in the nineteenth century and later elaborated upon by Ross [2]. Nowadays, clear evidence supports the concept that immune responses are critical in the initiation, progression and destabilization of atherosclerosis [3–5]. Excess mortality from cardiovascular diseases is reported in inflammatory arthritides [6]. Rheumatoid arthritis (RA) is the most common autoimmune rheumatic disease, with a prevalence of approximately 1%

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of adults worldwide [7]. RA is characterized by an increase in cardiovascular disease risk, comparable to that conferred by type 2 diabetes [8].

RA is considered an independent risk factor for cardiovascular disease (CVD) according to guidelines set forth by the European Society of Cardiology. In recognition of this elevated risk, the European Alliance of Associations of Rheumatology (EULAR) recommends that traditional CVD risk scores, which were originally designed for the general population, be adjusted for RA patients. Specifically, these scores should be multiplied by 1.5 to account for the additional impact of non-traditional risk factors, such as the patient's inflammatory status. By adjusting traditional CVD risk scores to account for the impact of RA and related inflammatory factors, clinicians can more accurately predict an RA patient's likelihood of experiencing a cardiovascular event [9, 10].

Inflammatory arthropathies and autoimmune rheumatic disorders are associated with a significantly increased risk of cardiovascular morbidity and mortality, which is thought to be driven by a complex interplay between high-grade inflammation and traditional cardiovascular risk factors [11]. Proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin 1 (IL-1), and interleukin 6 (IL-6) are known to play a critical role in the development of atherosclerosis, contributing to endothelial dysfunction and the development of premature atherosclerosis [3, 5, 12]. In light of the common pathophysiology underlying both inflammation and atherosclerosis, the mainstay of managing increased cardiovascular risk in patients with inflammatory diseases is achieving sufficient control of disease activity while also adequately addressing traditional cardiovascular risk factors [9].

The endothelium, a thin layer of cells that lines the inner surface of blood vessels, plays a critical role in maintaining vascular homeostasis and regulating arterial tone, coagulation, and smooth muscle cell proliferation. Healthy endothelium is crucial for normal cardiovascular function. In contrast, endothelial dysfunction is characterized by increased expression of adhesion molecules, pro-inflammatory cytokines, pro-thrombotic factors, oxidative stress upregulation, and abnormal vascular tone modulation. Endothelial injury represents an early stage of vascular disorders, and if not addressed, can lead to arterial stiffening, subclinical atherosclerosis, and ultimately, the development of arterial disease. Importantly, endothelial dysfunction, a recognized CVD risk factor, can be measured and is predictive of cardiovascular events in the general population [13]. Therefore, preserving endothelial health is an important goal in the prevention and management of vascular disorders [14].

In the last two decades, the therapeutic options for RA have been expanded with the addition of biologic agents with different mechanisms of action (TNF-α inhibitors [TNFi], IL-1 inhibitors, anti-CD20 monoclonal antibodies, inhibitors of T-lymphocytic co-stimulation, IL-6 inhibitors) and more recently, targeted synthetic drugs (janus kinase inhibitors [JAKi]) [15]. There is a mounting body of evidence that targeted therapies are link to reduction of CVD risk in threated individuals [16–18].

We aimed to analyze the available evidence on the potential effects of biologic and targeted synthetic drugs for RA on vascular function. Therefore, a systematic review was conducted to investigate their impact on endothelial function, markers of endothelial injury, arterial stiffness, or subclinical atherosclerosis.

Methods

Search strategy

A comprehensive literature search was conducted up to November 2022 using the Medline (via PubMed) and Web of Science databases. The primary search strategy utilized in Medline consisted of a string of relevant MeSH keywords and subject headings: ("adalimumab" OR "etanercept" OR "infliximab" OR "certolizumab pegol" OR "golimumab" OR “abatacept” OR “anakinra” OR “rituximab” OR “tocilizumab” OR "tofacitinib" OR "baricitinib" OR "upadacitinib") AND (“atherosclerosis” OR “vascular stiffness” OR “Carotid Intima-Media Thickness” OR “cIMT” OR “flow mediated dilat*” OR “FMD” OR “pulse wave velocity” OR “PWV” OR “endothelial dysfunction” OR “endothelial function” OR “forearm blood flow” OR “FBF” OR “peripheral arterial tonometry” OR “cardio-ankle vascular index” OR ”CAVI”). Moreover, to enhance the sensitivity of the search strategy, various relevant keywords were utilized in different combinations for a manual search. Furthermore, the reference lists of the selected articles were reviewed to ensure that no relevant studies were overlooked.

Inclusion criteria and study selection

In order to be eligible for inclusion in the final review, studies were required to satisfy the following predetermined inclusion criteria:

1) Study design: randomized controlled trials (RCTs), quasi-randomized controlled trials (quasi-RCTs) which allocate treatments using methods such as alternation, alternate medical records, or date of birth, cross-sectional studies, prospective cohort studies that measured outcomes before and after an intervention, and meta-analyses.

2) Population: studies involving human subjects.
3) Intervention: treatment with TNF-α and IL-1 inhibitors, tocilizumab, rituximab, abatacept, and JAKi.
4) Outcome: evaluation of the effect of treatment on measures of endothelial function, vascular stiffness, or biochemical markers of endothelial damage and subclinical atherosclerosis.
5) Full-text articles.

Furthermore, we utilized the following exclusion criteria: a) studies published in a language other than English; b) studies that did not report p values for pre-post comparisons.

Data extraction and management

Two independent reviewers (GG and TG) evaluated the titles and abstracts of all the retrieved records to determine whether they met the inclusion criteria for the systematic review. After the initial screening phase, the same two reviewers independently assessed the remaining articles for eligibility based on the predetermined inclusion and exclusion criteria. Any discrepancies between the reviewers were resolved through discussion with two senior reviewers (MD and TS) until a consensus was reached. In instances where the necessary information was unclear, efforts were made to contact the authors of the original reports to obtain further details. The following information was extracted from each study: author names, publication year, study design, statistical method, risk factors (including hazard ratios or odds ratios and their corresponding 95% confidence intervals), as well as the number of cases and controls. Data relating to the impact of biologic and targeted synthetic treatment on endothelial function, vascular inflammation, vascular stiffness, and subclinical atherosclerosis were collected and recorded.

Reporting method

We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [http://www.prisma-statement.org/] and the recommendations for comprehensive searches through multiple databases of Gasparyan et al. [19] for preparing our manuscript.

Results

The search strategy yielded a total of 647 records, and no further relevant articles were identified through manual searching of bibliographies. After initial screening of titles and abstracts, 158 duplicate records were excluded, and 327 studies were considered ineligible based on predetermined inclusion and exclusion criteria. Thus, we retrieved the data from the remaining 162 studies. 32 studies examined endothelial function in patients with different inflammatory diseases (ankylosing spondylitis, systemic lupus, psoriasis) other than RA and thus were excluded. 28 studies were excluded because they studied the vascular effect of biologic drugs on non-inflammatory diseases – atherosclerosis, diabetes, heart failure, myocardial infarction, and others. We didn't also include 15 scientific abstracts and congress posters that fulfilled other inclusion criteria. Other 29 studies were excluded because of wrong outcomes, wrong study design, published not in English, wrong intervention, wrong route of administration, wrong setting, no p values given. Thus, 58 studies were included in the final review. A PRISMA flowchart demonstrating the process of identification, screening, inclusion and exclusion of the studies is presented in Fig 1.

Tumor necrosis factor-alpha inhibitors

The most commonly prescribed biologic disease-modifying antirheumatic drugs (DMARDs) for RA are TNF-α inhibitors, which encompass a class of five drugs authorized for the treatment of RA: infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol.

In our review, we included 40 studies examining the vascular effects of anti-TNF therapy. Vascular effects of TNFi were studied with different methods: endothelium-dependent (flow-mediated) dilatation of the brachial artery, endothelium-independent (nitro-glycerine induced) vasodilatation, laser-Doppler flowmetry, venous occlusion plethysmography, arterial stiffness assessed by pulse wave velocity, augmentation index and cardio-ankle vascular index (CAVI), common carotid artery intima thickness, dipyridamole Echocardiography and Coronary Flow Reserve, vascular inflammation by 18F-fluorodeoxyglucose positron emission tomography, aortic distensibility by cardiovascular MRI imaging. Studies also assessed biomarkers of endothelial injury including adiponectin, VEGF, ICAM-1, VCAM-1, E-selectin, endothelial progenitor cells (EPC), asymmetric dimethyl arginine (ADMA). An overview of the studies is presented in Table 1.

Out of the 40 studies that were included, 20 studies focused on analyzing the impact of TNF-α inhibitors on endothelial function. Sixteen studies used two primary methods for evaluating endothelial function, which were endothelium-dependent flow-mediated dilation (FMD) and endothelium-independent dilation following sublingual nitroglycerin of the brachial artery. Gonzales-Juanatey et al. [22], Irace et al. [23], and Bosselo et al. [32] found

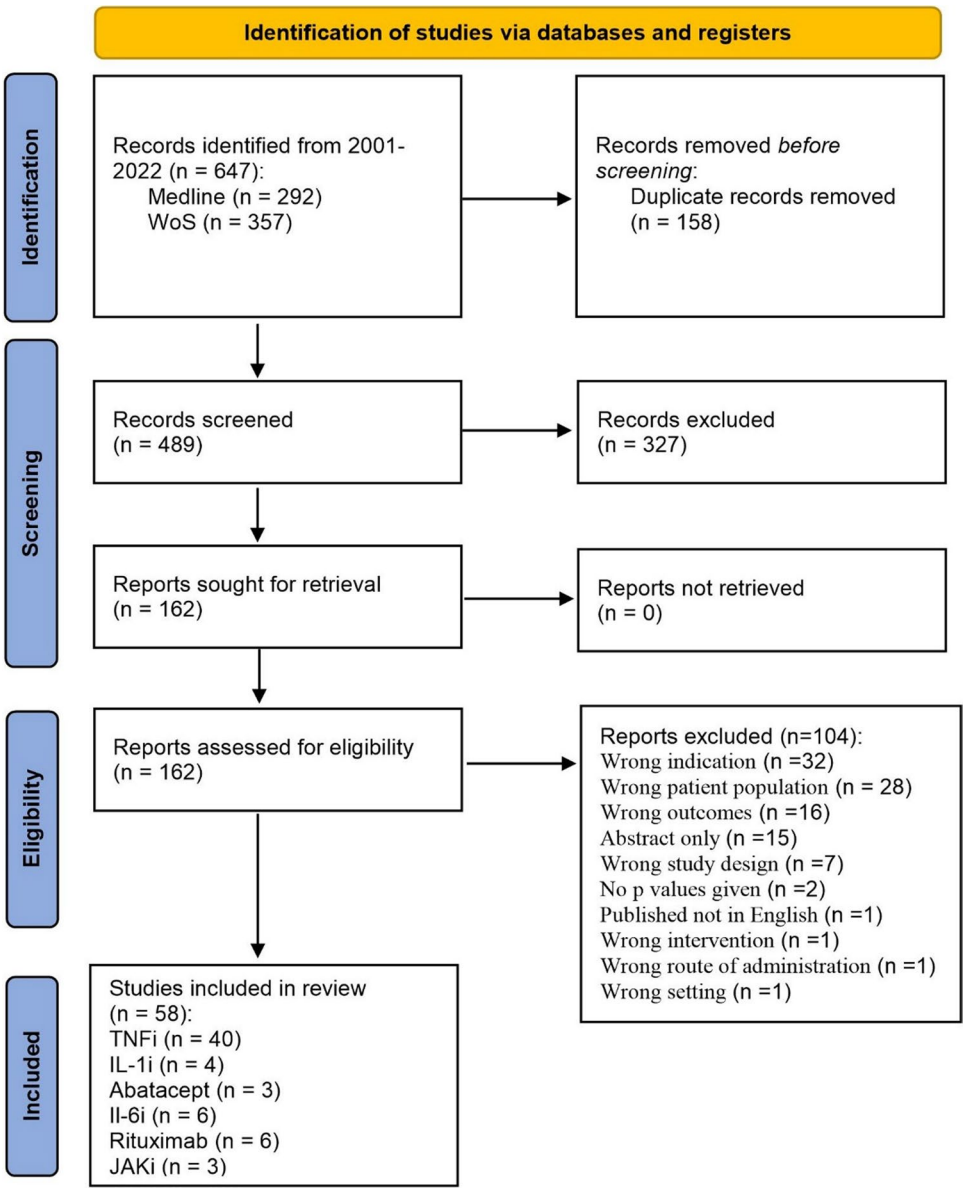

Fig. 1. A PRISMA flowchart presenting the process of systematic search and selection of studies on the vascular effects of novel treatments in rheumatoid arthritis. Abbreviations: n – number, JAKi – janus kinase inhibitors, IL-1i – interleukin 1 inhibitors, IL-6i – interleukin 6 receptor inhibitors, TNFi – Tumor necrosis factor alpha inhibitors, WoS – Web of Science.

only transient improvement of FMD after treatment with infliximab, Spinelli et al. [50] did not find improvement, but other authors found significant improvement in their cohorts. In a cross-sectional analysis, Cypiene et al. [30], found greater effect of infliximab compared to synthetic DMARD, Tikiz et al. [39] compared etanercept to methotrexate (MTX) and found significant improvement of FMD after anti-TNF compared to MTX. In another study, Gonzales-Juanatey [27] examined patients that were non-responders to infliximab and switched from infliximab to adalimumab. In the observed cohort FMD increased to the same amount as in the control group. Two studies (Hansel [21] et al, Rongen et al. [52]) examined the effect of TNF-α inhibitors on venous occlusion plethysmography after receiving intrabrachial infusions of increasing doses of acetylcholine or a nitrate. Hansel et al examined patients on MTX with low disease activity starting etanercept and did not find improvement in endothelial function. In a substudy to the POEET trial, Roengen examined patients in clinical remission, randomized to stop or continue anti-TNF therapy. In patients who flared after stopping the biologic DMARD responses to acetylcholine and SNP were significantly reduced, but in patients who stopped and did not flare, vasodilator response did not differ between baseline and second visit. Dávida et al. [54] examined the effect of adalimumab on endothelial dysfunction by postocclusive reactive hyperemia (PORCH) tested by laser Doppler flow. They found favorable effects on endothelial function in the adalimumab group compared to the control group. Galaragga et al. [40] measured laser doppler

Table 1 An overview of the included studies on the vascular effects of tumor necrosis factor alpha inhibitors

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Hürlimann 2002 [20]	Observational	11	none	IFX	12 weeks	FMD	FMD improved after 12 weeks of therapy.	First study showing TNFi treatment improves endothelial function in RA.
Hansel 2003 [21]	Observational	8	8	ETN	2 weeks	VOP	Switching of DMARD from MTX to ETN did not result in an improvement of vascular response to acetylcholine.	Switching from MTX to ETN in stable RA patients has no beneficial effect on endothelial function.
Gonzales-Juanatey 2004 [22]	Observational	7	-	IFX	28 days	FMD	Increase of FMD 2 days after infusion. Values returned to baseline 4 weeks after infusion of the drug.	Infliximab induces active but transient effect on endothelial disfunction in patients with RA.
Irace 2004 [23]	Observational	10	10	IFX	6 weeks	FMD	Increase of FMD after 6 weeks of treatment.	Transient effect on FMD
Van Doornum 2005 [24]	Observational	14	-	ETN, ADA, IFX	6 weeks	AIx	AIx remained unchanged following 6 weeks of treatment	Arterial stiffness did not improved after 6 weeks of TNFi treatment
Gonzalez-Gay 2006 [25]	Observational	34	none	IFX	Before and 120 minutes after IFX	sICAM-1, sICAM-3, sVCAM-1, sE-selectin, and sP-selectin	Reduction of sICAM-3 and sP-selectin. The decrease of other markers did not reach statistical significance.	Rapid beneficial effect of infliximab infusion on expression of some adhesion molecules in RA
Bilsborough 2006 [26]	Observational	9	5 patients on conventional DMARDS	ETN IFX	36 weeks	FMD	FMD vs to those on conventional therapy improved	Addition of TNFi to conventional therapy improves endothelial function

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Gonzalez-Juanatey 2006 [27]	Observational	8 refractory to IFX	16	ADA	12 weeks	FMD	Decrease of FMD after 12 weeks. At week 12 FMD was not different to the control group.	Switching infliximab non-responders to adalimumab decreases FMD to values comparable to the control group
Mäki-Petäjä 2006 [28]	Observational	9	18	ETN	12 weeks	PWV AIx FMD	PWV was significantly reduced at w4 and w12 compared to baseline. AIx did not change FMD increased after ETN	Anti-TNF therapy reduced aortic stiffness to a level comparable to that of healthy individuals.
Komai 2007 [29]	Observational	15	-	IFX	6 weeks	VOP PWV adiponectin	Endothelium-dependent vasodilatation increased with INF. adiponectin increased at w2 and w6. PWV did not improve.	Endothelial disfunction, aortic stiffness and adiponectin improved after TNFi therapy
Cypiene 2007 [30]	Cross-sectional	68(15 patients on infliximab)	87	IFX	none	PWV	Infliximab affected values of PWV while there was no such tendency for AIx.	Arterial stiffness decreased in the TNFi group compared to other treatments.
Del Porto 2007 [31]	Observational	30 responders on therapy	10	IFX ETN	12 months	cIMT	Significant reduction of the right and left cIMT after 12 months of TNFi treatment.	TNFi was associated with cIMT reduction in RA patients, that are responders to therapy

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Bosello 2008 [32]	Observational	10	20	IFX	14 weeks	FMD VEGF ICAM-1 VCAM-1 E-selectin	FMD improved after each IFX infusion, but improvement was transitory, and FMD values returned to baseline values before each INF infusion No change was observed in ICAM-1, VCAM, VEGF and E-Selectin	Transitory improvement of endothelium function after loading with IFX was observed.
Wong 2009 [33]	Post hoc analysis of randomized, placebo controlled, double-blind study	17	9	IFX	56 weeks	PWV cIMT AIx CAP score	Reduction in PWV over 56 weeks CIMT, AIx and CAP did not change.	Arterial stiffness improves with infliximab treatment in RA.
Sidiropoulos 2009 [34]	Observational	12	6	IFX ADA	18 months	FMD cIMT	FMD did not improved at 3 months, but improved after 18 months of treatment CIMT did not change at month 3 and month 18	After 18 months of treatment with TNFi, endothelial function improved while cIMT remained stable.
Capria 2009 [35]	Observational	24	15	IFX ADA ETN	24 months	FMD	The TNFi treatment increased FMD at week 1, week 2, week 6, month 6, and month 24 compared to baseline	TNF inhibitors improves endothelial dysfunction after 2 years of treatment.
Galarraga 2009 [36]	Observational	26	21 on MTX	ETN	4 months	AIx	Treatment with ETN, but not with MTX reduced AIx at month 2 and 4	ETN but not MTX therapy reduces arterial stiffness in the observed cohort.

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Klimiuk 2009 [37]	Obseravtional	18	none	ETN	12 months	sICAM-1 sVCAM-1 sE-selectin VEGF	Significant reduction of sICAM-1, sVCAM-1, sE-selectin, and VEGF after 12 months of therapy	Reduction of markers of endothelial disfunction after ETN treatment
Turiel 2010 [38]	Observational	20(10 ADA, 10 MTX)	25	ADA	18 months	CFR cIMT ADMA	CFR improved in both treatment groups. cIMT and ADMA did not improve	CFR improves after MTX and ADA therapy, with no difference between the drugs.
Tıkız 2010 [39]	Observational	11	10 pt on MTX	ETN	12 weeks	FMD	In the ETN group, FMD improved after 12 weeks of treatment. No changes of FMD were observed in the MTX group.	Treatment with ETN for 12 weeks improved endothelial function in RA patients compared to those under methotrexate therapy
Galaragga 2010 [40]	Observational	30	21 pt on MTX	ADA, ETN	4 months	LDF	No improvement in endothelial dysfunction was observed in TNFi and MTX groups Improvement of endothelial dysfunction was observed only in DAS28 responders	Microvascular endothelial function improves in patients who respond to anti-rheumatic therapy
Ajeganova 2011 [41]	Observational	162	53 patients treated with RTX	ETN, INF, ADA	12 months	anti-PC IgM	In the anti-TNF group, anti-PC increased after therapy. In the rituximab group anti-PC decreased at month 12	Anti-TNF treatment demonstrated a favourable long-term effect on anti-PC levels.

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Kerekes 2011 [42]	Observational	8	none	ADA	3 months	FMD cIMT PWV	Increase of FMD after 12 weeks 11.9% decrease of cIMT Non-significant improvement of PWV was observed	Treatment with adalimumab decreased FMD and cIMT in the examined group.
Kume 2011 [43]	Randomized controlled trial	60 patients randomized 1:1:1 on TCZ(22),ETN(21),ADA(21)	-	TCZ ETN ADA	24 weeks	CAVI AIx75 cIMT	CAVI was attenuated significantly by TCZ and ADA Changes did not significantly differ between groups. AIx was attenuated significantly by TCZ, ETN and ADA. The AIx change was not significantly different between groups. No change of cIMT was observed	The 3 types of monotherapy limited arterial stiffness in patients with RA to a similar extent.
Tam 2012 [44]	Prospective randomized study	20 MTX+ INF	20 MTX	MTX INF	12 months	cIMT AIx PWV	MTX plus IFX showed superior efficacy to MTX alone regarding the change in PWV after 6 months. No significant changes in cIMT and AIx were observed in the 2 groups.	MTX plus IFX causes a more significant reduction af arterial stiffness than MTX alone in patients with early RA after 6-month treatment.
Gonzalez-Juanatey 2012 [45]	Observational	34	none	ADA	12 months	FMD cIMT	FMD increased at 14 day and at 12 months compared to baseline. No change of cIMT was observed.	ADA improved arterial stiffness in the observed cohort.

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Hjeltnes 2012 [46]	Observational	64	none	MTX or MTX+INF/ ADA/ETN	6 months	Lip A E-selectin, VCAM-1, ICAM-1	Reduction of Lip A and E -selectin after 6 weeks and 6 months of treatment compared to baseline values in the MTX group and MTX+TNFi Significant reduction of ICAM-1 at 6 weeks for both groups, but no reduction on month 6.	MTX and MTX+TNFi decrease serum levels of lipoprotein a and E-selectin.
Daïen 2012 [47]	Observational	28	20 on DMARDS	ETN	6 months	PWV AIx LVMI	No changes of PWV or AIx were observed. LVMI was significantly decreased at 3 and 6 months with ETN but not in the synthetic DMARDS group.	Etanercept induced a significant decrease in LVMI with medium-term treatment with no change in PWV or AIx.
Mäki-Petäjä K 2012 [48]	Observational	17	34	ADA ETN	8 weeks	18FDG-PET PWV FMD	Following TNFi therapy, there was a significant reduction in aortic 18FDG uptake. FMD and PWV improved after TNFi treatment.	RA patients have increased aortic 18FDG- uptake, PWV and FMD in compared to patients with stable cardiovascular disease. TNFi therapy reduces aortic inflammation, aortic stiffens and endothelial disfunction.

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Spinelli 2013 [49]	Observational	17	12	ETN ADA	12 weeks	EPC ADMA FMD	At 3 months follow-up, the number of EPCs was significantly higher compared to basal values. ADMA decreased after treatment. No change of FMD was observed after therapy	Short-term treatment with anti-TNF was able to increase circulating EPCs and decrease ADMA.
Spinelli 2014 [50]	Observational	33	none	ETN ADA	12 weeks	ADMA	After 3 months of TNFi treatment ADMA levels decreased	TNF inhibitors decrease ADMA levels in patients with rheumatoid arthritis.
Vassilopoulos 2014 [51]	Observational	18	18 patients on MTX	ADA	12 weeks	PWV AIx	ADA treatment led to a reduction of PWV after 12 weeks with no significant change in AIx. MTX treatment did not change PWV or AIx. Reduction of PWV did not correlate with response to therapy.	Treatment with ADA reduced arterial stiffness in RA patients regardless of their response to therapy.
Rongen 2017 [52]	Bolt-on study to a randomized control trial	27 patients stopping TNFi therapy	8 on stable treatment	ADA ETN	6 months	VOP	Patients who flared after stopping ADA or ETN had a worsening vasodilatory response. In patients who stopped but did not flare, vasodilator response did not differ between visit 1 and 2.	Endothelial function worsens after interruption of ADA or ETN but only when rheumatoid arthritis reactivates.

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Vlachopoulos 2017 [53]	Meta-analysis	320 patients from 14 studies		ADA ETN INF	6-56 weeks	Meta-analyse including studies evaluating PWV and AIx.	TNFi therapy decreased PWV and AIx	The balance of evidence suggests that TNFi may have a beneficial effect on aortic stiffness and, therefore, on cardiovascular risk.
Dávida 2019 [54]	Observational	8	46	ADA	12 weeks	LDF PORCH	ADA improved TH1 time and TH2 time at week twelve	ADA exerted favourable effects on endothelial dysfunction measured by PORCH
Plein 2019 [55]	Bolt-on study to a phase IV randomised control trial	82	30	Randomised to MTX+ETN OR MTX	2 years	AD by MRI	AD improved by 20% from baseline to year 1 in both treatment groups Improvement of AD by 10% from baseline at year 2	MTX monotherapy and combination therapy of MTX and ETN improve AD in RA patients.
Blanken 2021 [56]	Observational	23 patients with established RA	26 patients with early RA	Patients with established RA starting ADA Patients with early RA starting csDMARD	6 months	18FDG- PET	Arterial wall 18FDG uptake was reduced in most arterial segments after 6 months of treatment with reductions in the carotid and femoral arteries reaching statistical significance. Combining all arterial segments showed that overall arterial wall inflammation was reduced by 4%	Arterial wall inflammation in RA patients is reduced by anti-inflammatory treatment and this reduction correlates with reductions of serological inflammatory markers.

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Anghel 2022 [57]	Observational	115	none	INF, ADA, ETN	12 months	cIMT homocystein	Decrease of cIMT after 1 year of treatment in the INF, ADA and ETN group. After 12 months a decrease of homocysteine was noted in all treatment groups Decrease of homocysteine corelated with the decrease of cIMT	TNFi therapy reduces cIMT and homocysteinemia in patient with RA
Blanken 2022 [58]	Observational	61 patients (30 on csDdMARD and 31 on ADA)	29 patients with OA	ADA	48 months	PWV AIx cIMT	After 6 months, decrease of AIx and insignificant decrease of PWV were observed in the whole group. At 48 months, AI75 remained lower than before therapy, PWV was comparable to that at baseline. cIMT slightly increase at 6 months, but was comparable to baseline at 48 months. In the ADA group cIMT and PWV decreased after 48 months of treatment compared to the csDMARDS group.	Modest beneficial changes in some surrogate markers of subclinical vascular disease after anti-inflammatory therapy

Table 1 (continued)

First author, year	Design	n° patients	Control group	Medication	Follow-up	Measured outcome	Results	Main findings
Szeremeta 2022 [59]	Observational	45	20	ADA ETN CZM	15 months	CS/DS ratio HS/H ratio sVCAM-1 MCP-1 MMP-9 ADMA	CS/DS did not significantly decrease after 15 months of TNFi therapy. HS/H decreased after 15 months of therapy. sVCAM-1, MCP-1, MMP-9, ADMA significantly decreased after treatment.	Anti-TNF treatment decreases HS/H and the tested markers of endothelial dysfunction after 15 months of treatment.

Abbreviations: MTX methotrexate, INF infliximab, ADA adalimumab, ETN etanercept, TCZ tocilizumab, CZM certolizumab pegol, RTX rituximab, csDMARDS conventional synthetic disease modifying drugs, FMD flow mediated dilatation, VOP venous occlusion plethysmography, AIx augmentation index, VEGF vascular endothelial growth factor, LDF laser doppler flow, Ant-PC IgM IgM antibodies against phosphorylcholine, CAVI cardio-ankle vascular index, Lip A lipoprotein A, 18FDG PET 18F-fluorodeoxyglucose positron emission tomography, EPC Circulating Endothelial Progenitor Cell, ADMA asymmetric dimethyl arginine, LVMI left ventricular mass index, PORH postocclusive reactive hyperemia, TH1 time to half before hyperemia, TH2 time to half after hyperemia, AD aortic distensibility, MRI magnetic resonance imaging, CS/DS chondroitin/dermatan sulphate, HS/H heparan sulphate/heparin (HS/H)

flow after iontophoresis with acetylcholine and sodium nitroprusside on 31 patients treated with a TNF-α inhibitor and 20 patients treated with MTX. The authors found improvement of endothelial function only in patients that had responded to therapy, irrespective of treatment.

We included 13 studies examining the effect of anti-TNF therapy on arterial stiffness and one meta-analysis. The used methods for measurement were pulse wave velocity (PWV) in 11 studies, Augmentation index (AIx) in 10 studies, and CAVI in 1 study. Three studies did not find improvement in PWV after anti-TNF therapy (Komai et al. [29], Kerekes et al. [42], Daïen et al. [47]) and other studies found significant improvement. Interestingly Tam et al. [44] found a reduction in PWV regardless of clinical efficacy in patients treated with MTX+ Infliximab and a superior reduction of PWV compared to MTX monotherapy. Also, Vassilopoulos et al. [51] found statistically significant reduction in PWV both in responders and non-responders to adalimumab.

AIx is a composite measure of arterial stiffness. We included 10 studies that used AIx as an outcome. From them, 3 studies found a statistically significant reduction after treatment with TNFi. In the other studies, there was no change or the reduction was insignificant.

We included one meta-analysis in our review. Vlachopoulos et al. [53] analyzed 14 studies, examining the effect of TNFi on PWV and AIx on 320 patients. Some of the studies incorporate data from patients with different types of inflammatory arthritides and thus, were excluded from our review. Nonetheless, after a sensitivity analysis excluding studies recruiting both RA and seronegative spondylarthritis patients, the authors found a significant decrease in both PWV and AIx.

We included 10 studies on the effect of anti-TNF in carotid intima thickness (cIMT). In 4 studies (Del Porto et al. [31], Kerekes et al. [42], Anghel et al. [57], and Blanken et [58]) anti-TNF therapy led to a decrease in cIMT, but the other studies did not find any change. We should note that one of the studies [31] that found improvement, included only responders to anti-TNF therapy, while another [58] did not report a p-value for that outcome.

From the included studies, 8 studied different serological markers of endothelial dysfunction and early atherosclerosis. Gonzalez-Gay et al. [25], found a rapid decrease of ICAM-3 and P-selectin, 120 minutes after infusion of infliximab and no improvement of ICAM-1, VCAM-1, or E-selectin. Bosello et al. [32] did not find an effect of anti-TNF-α therapy on ICAM-1, VCAM, VEGF, and E-Selectin levels; however, Klimiuk et al. [37] found a reduction of them in 18 patients treated with etanercept. Furthermore, Komai et al. [29] reported that infliximab increased levels of adiponectin in RA patients. Hjeltnes et al. [46] found a reduction of E-selectin and lipoprotein A but no effect on VCAM-1 and ICAM-1. Four studies used ADMA to measure endothelial

dysfunction while 3 of them found a decrease after TNFi therapy [49, 50, 59] and one did not [38]. Ajeganova et al. [41] found that TNFi treatment increases atheroprotective IgM antibodies against phosphorylcholine, In contrast, a decrease of the antibodies were observed with rituximab treatment. One study [59] showed a reduction of homocysteine after treatment, that correlated with cIMT reduction. One study examined serum levels of sulphated glycosaminoglycans and in RA patients treated with TNFi as a novel biomarker of atherosclerosis. They found reduction of heparan sulphate/heparin after treatment associated with reduction of VCAM-1, MCP-1, MMP-9 and ADMA.

Two studies examined the effect of TNF-α inhibition on vascular inflammation measured by 18F-fluorodeoxyglucose-positron emission tomography. Blanken et al. [56] included patients with early RA starting conventional synthetic DMARD therapy and RA patients with established RA starting adalimumab. They reported a reduction of glucose uptake after treatment, regardless of treatment and DAS28 response, but the effect correlated with markers of systemic inflammation (ESR and CRP). The other study from Mäki-Petäjä K et al. [48] examined 17 patients with RA and a control group of patients with stable cardiovascular disease. After 8 weeks of TNFi treatment reduction of 18F-fluorodeoxyglucose uptake was found that correlated with reduction of PWV.

A bolt-on study [55] to a randomised control trial examined aortic distensibility measured by cardiovascular MRI on RA patients randomized to MTX plus etanercept or MTX-only treatment. Anti-inflammatory therapy improved aortic distensibility regardless of the treatment and DAS28 response.

Abatacept

Abatacept is a recombinant fusion protein that modulates the CD80/96-CD28 co-stimulatory signal required for T-cell activation. In our literature review, we identified three studies investigating the vascular effect of abatacept.

Mathieu et al. [60] investigated the effect of abatacept on aortic stiffness measured by PWV on a cohort of 21 RA patients fulfilling the 1987 ACR criteria, which did not respond to at least 2 TNFi or had contraindications for TNFi treatment. Following 6 months of treatment with abatacept, there was a significant rise in PWV levels (9.8±2.9 versus 8.5±3.9 m/second; P=0.02). The alterations in PWV demonstrated a correlation with changes in the Disease Activity Score on 28 joints based on erythrocyte sedimentation rate (r=0.46; P=0.035). The authors inferred that the insufficient reduction in systemic inflammation might have led to the progression of aortic stiffness in their study population. Of the 21 patients, only 6 reached remission during treatment and have no changes of PWV. The other 15 had persisting disease activity and their PWV increased.

In a longitudinal observational study conducted by Provan et al. [61], PWV was evaluated in RA patients before treatment and at 3, 6, and 12 months after receiving abatacept, rituximab, or tocilizumab. A total of 36 patients were recruited for the study, and administered different medications, including abatacept, rituximab, and tocilizumab to 5, 24, and 7 patients, respectively. No statistically significant change of PWV was observed in the 5 patients treated with abatacept. In the tocilizumab group, a statistically significant change of PWV (-0.9 p=0.03) was observed compared to other treatment groups.

Benucci et al. [62] retrospectively observed a group of 45 RA patients treated with abatacept with no known CVD or CV risk factors. They evaluated common carotid intima thickness (ccIMT) and flow-mediated dilatation (FMD) of the brachial artery at baseline and at the 12th month after treatment. During abatacept treatment, ccIMT remained stable and a low statistically insignificant increase of FMD was observed between baseline and at the 12th month. At baseline ccIMT inversely correlated with baseline TNF-α values (p=0.0245). At the end of the 12-month follow-up, a statistically significant correlation was observed between the number of CD3/CD8+ lymphocytes and ccIMT (p=0.0351), while CRP levels showed a significant correlation with FMD (p=0.0075). Furthermore, regression analysis demonstrated that baseline ccIMT and FMD had weak predictive ability for TNF-α (p=0.011) and CRP (p=0.049) at the 12th month.

Interleukin-1 receptor antagonist

Three articles were retrieved from the same author team in our systematic literature review related to anakinra, which is a recombinant human IL-1 receptor antagonist.

First, Ikonomidis et al. [63] studied the effects of anakinra administration on vascular function assessed in 23 RA patients by using FMD, coronary flow reserve, aortic distensibility, systolic, and diastolic (Em) velocity of the mitral annulus, and E to Em ratio (E/Em) using echocardiography, and markers of endothelial injury (malondialdehyde, nitrotyrosine, endothelin-1). The study evaluated the effects in "acute" and "chronic" conditions. A double-blind trial was conducted to study the impact of anakinra in the acute arm, in which a group of patients were randomly assigned to receive either a single subcutaneous injection of anakinra (n=12) or a placebo (n=11), and after 48 hours, they were administered the alternative treatment. In a non-randomized trial conducted on patients with chronic conditions, 23 of them received anakinra while 19 were treated with prednisolone for 30 days, and thereafter, all indicators were evaluated again. In the acute setting, the results of the study showed that anakinra caused an increase in FMD, while placebo resulted in a decrease (P=0.001), whereas nitrate-induced vasodilation remained unchanged (P=0.2). Resting and hyperaemic CF-Vmax,

CF-VTI, and CF-VTId increased compared to placebo (P=0.001 for all comparisons). Coronary flow reserve (CFR) and aortic distensibility and strain were greater in anakinra than in placebo (P=0.001). From the biomarkers of endothelial function: a reduction of malondialdehyde, nitrotyrosine, and ET-1 was observed in the treatment group compared to placebo (P=0.001). In the chronic arm analysis, the authors observed a greater percentage increase in FMD and CFR after the use of anakinra compared to prednisolone (P=0.001). Additionally, there was a higher relative increase in all coronary flow indices after anakinra use (P=0.05). Nitrate-induced vasodilation remained unchanged between the two treatment groups. The study also found that aortic distensibility and strain showed a 3-fold increase after anakinra, which was significantly higher than the 7±3% and 11±3% increase observed after prednisolone (P=0.001 for all comparisons). Furthermore, anakinra treatment resulted in a greater percent reduction in malondialdehyde, nitrotyrosine, and endothelin-1 (ET-1) compared to prednisolone (malondialdehyde 33±2% versus 3±2%, P=0.006; nitrotyrosine 50±8% versus 0.5±1%, P=0.006; and ET-1 40±7% versus 22±4%, P=0.04).

A second paper [64] from the same authors observed a cohort of 46 RA patients compared to 23 healthy individuals. Half of the patients received anakinra and the other half did a 5-mg increase in prednisolone dose for 30 days. Study outcomes were myocardial deformation by speckle tracking echocardiography, CFR, FMD nitrotyrosine and malondialdehyde blood levels. In the anakinra group, there was an improvement of myocardial deformation, FMD, CFR, nitrotyrosine and malondialdehyde compared to baseline (p<0.05 for all comparisons). No effect in the prednisolone group was observed on myocardial deformation and worsening of FMD and CFR (p<0.001 for both).

A third paper [65] from the same authors examined the effects of anakinra on RA patients with known coronary atherosclerosis. In a double-blinded crossover trial, 60 patients with CAD and RA and 20 with RA only were randomized to receive a single injection of anakinra or placebo and then the alternative treatment after 48 hours. Compared to individuals without CAD, those with CAD exhibited lower levels of FMD, CFR, and impaired left ventricular function markers, along with significantly elevated levels of IL-1, oxidative stress, and soluble apoptotic markers. Anakinra treatment led to improvements in FMD, CFR-VTId, CFR-VTItotal, and systemic arterial compliance compared to baseline and placebo (all P<0.05). CAD patients had greater relative improvements in CFR, FMD, systemic arterial compliance, and resistance compared to non-CAD patients. Anakinra also improved tissue Doppler and speckle tracking markers of myocardial deformation and twisting. Levels of oxidative stress markers were markedly decreased after anakinra compared to placebo, and the relative decrease of the markers was greater in CAD than in non-CAD patients.

Rituximab

Rituximab is a chimeric monoclonal antibody that depletes CD20 positive B-lymphocytes and their precursors. We included 6 studies of rituximab effect on vascular dysfunction in RA patients. An overview of the studies can be found in Table 2.

Of the 6 described studies, none had a comparable control group and all studies included small numbers of patients. Flow-mediated dilatation of the brachial artery was used in 4 studies and all of them found an increase in FMD after treatment. cIMT was measured in two studies with no effect of therapy. Aortic stiffness measured by PWV and augmentation index were used in two studies. Provan et al found a decrease in PWV after 12 months while Mathieu et al did not find any change. Aix did not change after treatment in both studies.

Tocilizumab

Tocilizumab is a humanized IL-6 receptor-binding protein that binds to soluble and membrane-bound IL-6 receptors. We included 6 studies in our review found in Table 3.

Of the included studies, two were randomized control trials with different treatment arms, while the other 4 were observational cohorts. Three studies measured endothelial dysfunction by brachial FMD and found improvement of FMD after treatment. Arterial stiffness was assessed by 5 studies, 4 of them used PWV and one used cardio-ankle vascular index (CAVI). All studies found a decrease in arterial stiffness after treatment. cIMT was measured by Kume et al on 22 patients on tocilizumab and did not find a significant change after 24 weeks of therapy. Ikonomidis et al measured CFR in two studies and found a decrease after IL-6 treatment. In the two studies, markers of oxidative stress were measured- malondialdehyde (MDA) and protein carbonyls (PCs), which decreased by treatment. The second study by Ikonomidis et al. measured perfused boundary region (PBR) of the sublingual arterial microvessels – an indirect test for endothelial glycocalyx thickness. The authors found a decrease of PBR after treatment, which indicates improvement of endothelial glycocalyx thickness.

Janus kinase inhibitors

JAKi are novel targeted synthetic drugs inhibiting the JAK/STAT intercellular signaling. Three drugs are approved for the treatment of rheumatoid arthritis – tofacitinib, baricitinib, upadacitinib. We included 2 studies of the vascular effect of tofacitinib.

In the first study, Kume at al. (2017) [74] observed a cohort of 48 patients with RA on a stable dose of

methotrexate who started treatment with tofacitinib (10mg/daily) due to disease activity (DAS28>3.2). The primary endpoint of the study was the change of cIMT; secondary endpoints were the change of cIMT in patients with atherosclerosis at baseline (cIMT>1.10mm), change of CAVI and AiX@75, change of carotid artery plaque (CAP) score, change of disease activity and lipid profile. After 54 weeks of treatment, no significant change of cIMT was observed (1.09 ± 0.69 and 1.08 ± 0.78 mm, $p = 0.82$). In contrast, there was a small but statistically significant decrease of cIMT (0.05± 0.026 mm; $p < 0.05$) in patients with atherosclerosis (n=12) at baseline. CAVI and AIX@75 decreased in the treatment groups ($p < 0.01$ and $p< 0.01$ respectively). CAP score did not change at follow-up; serum total cholesterol increased from baseline. The authors discussed that tofacitinib seemed to improve cIMT, CAVI and AIx@75 despite increasing serum lipid levels. Importantly, reducing cIMT in patients with RA who already have high levels of cIMT may help to diminish the extent of atherosclerosis.

Two studies from the same institution [75, 76] observed the same cohort of 30 patients with rheumatoid arthritis starting tofacitinib (randomly assigned to 5mg bid [n=15] and 10mg bid [n=15]) for 12 months. They were assessed at baseline, at 6 and 12 months. Assessment included brachial FMD, common cIMT and aortic PWV, as well as serological markers of early vascular disfunction, oxidative stress and cardiovascular risk: L-arginine, L-citrulline, L-ornithine, inducible nitric oxide synthase (iNOS), asymmetric ADMA and symmetric dimethylarginine (SDMA), L-N-monomethyl-arginine (L-NMMA), cysteine, homocysteine in the first study and lipid analyses (including TC, LDL-C, HDL-C, TG, lipoprotein(a), APOA and APOB), adipokines (adiponectin, chemerin, leptin, adipsin and resistin), myeloperoxidase, thrombospondin-1, paraoxonase 1 for the second study . From the observed cohort 4 patients dropped out, thus 26 patients completed the study. After 6 and 12 months of treatment FMD and PWV did not change, while cIMT slightly increased after 6 months (0.56 ± 0.12 mm; $p = 0.05$) and 12 months (0.59 ± 0.14 mm; $p = 0.002$). The first study found an increase of cysteine, homocysteine and methionine after 12 months of treatment in the 10mg bid group ($p = 0.028$, $p = 0.049$ and $p < 0.001$ respectively), but in the 5mg bid only change was seen in methionine ($p = 0.002$), but no change in homocysteine and cysteine. Authors also found increase of levels of L-arginine ($p = 0.004$ and $p = 0.043$), L-ornithine ($p = 0.025$ and $p = 0.119$) at 6 and 12 month compared to baseline. L-citrulline increase after 6 months ($p = 0.006$), but decreased at month 12th ($p = 0.023$) compared to the 6th month. iNOS levels after 12 months of treatment were significantly higher than those at baseline ($p = 0.045$) and 6 months ($p = 0.020$) in all patients. ADMA and SDMA did not alter significantly during JAKi treatment, whereas L-NMMA showed a transient increase at 6 months and a decrease after that. The study found a significant increase in TC, HDL, LDL, APOA, and APOB after treatment ($p = 0.007$, $p = 0.004$, $p = 0.003$, $p = 0.001$, $p = 0.006$ respectively). Leptin increased significantly at 12 months ($p = 0.003$), while chemerin showed a significant decrease after 12 months ($p = 0.040$). PON1 and MPO showed a numerical decrease after 6 and 12 months respectively, but PON1 significantly decreased after 12 months ($p = 0.040$) and MPO significantly decreased after 6 months ($p = 0.028$). TSP-1 significantly increased after 6 months ($p = 0.009$). Adiponectin, adipsin, and resistin only showed numerical changes. The authors concluded that tofacitinib has a balanced effect on metabolic markers of vascular dysfunction and does not affect endothelial dysfunction and aortic stiffness.

Discussion

The pathophysiology underlying the heightened risk of CVD in RA remains incompletely understood [77], although vascular dysfunction has emerged as a putative mechanism. The development of atherosclerosis is believed to involve endothelial dysfunction as a crucial factor that can be observed both on macrovasculature [78] and microvasculature [79] levels, leading to arterial stiffening and impaired vasodilation, respectively. Endothelial dysfunction is an early functional abnormality and if treated is potentially reversible, making it an interesting treatment target in RA patients [80]. Our systematic literature review reveals that biologic and targeted synthetic antirheumatic drugs have the potential to enhance vascular function among patients with RA. Our systematic review of 40 studies over the past two decades reveals that TNF inhibitors (infliximab, etanercept, and adalimumab) can improve endothelial function, which is often assessed by FMD. FMD measures the response of the endothelium to hypoxia by inducing reactive hyperemia through cuff inflation, which triggers vasodilation by releasing NO. Of the 20 studies that assessed FMD after treatment with TNF inhibitors, 16 reported improvement. Although four studies did not find improvement, three of them showed a transient increase after infliximab infusion, which may be due to the timing of drug administration. Other biologic treatments such as tocilizumab, anakinra, and rituximab also demonstrated improvement in FMD, while abatacept did not. A study on the JAK inhibitor tocilizumab did not show improvement in FMD.

Another method used for endothelial dysfunction measurement is forearm blood flow (FBF) occlusion plethysmography [81]. This is an invasive method in which acetylcholine is injected into the brachial artery and FBF is measured by a strain gauge plethysmograph. It was used in 2 studies for TNFi, but we did not find studies on other

Table 2 An overview of the included studies on the vascular effects of rituximab

First author, year	Design	n° patients	Control group	Follow-up	Measured outcome	Results	Main findings
Gonzales-Juanatey, 2008 [66]	Observational	6 patients refractory to TNFi	none	6 months	FMD	Increase of FMD two weeks after rituximab infusions. After 6 months of treatment FMD was still increased compared to baseline.	First study demonstrating improvement of endothelial function after rituximab treatment in RA patients refractory to TNF inhibitors.
Kerekes, 2009 [67]	Observational	5	none	4 months	FMD, cIMT	Improvement of FMD after 16 weeks of therapy Numerical improvement of cIMT,	Rituximab improved endothelial disfunction in the examined patients.
Mathieu, 2012 [60]	Observational	33	none	52 weeks	AIx, PWV	After rituximab treatment, no change was observed in PWV and AIx after 6 and 12 months of therapy.	Arterial stiffness did not improve after 6 and 12 months of rituximab therapy.
Benucci, 2013 [62]	Observational	38 patients refractory to TNFi	none	24 months	FMD, cIMT	After 24 months of therapy a significant improvement of FMD was found. After 24 month, numerical improvement of cIMT was found, that did not reach statistical significance.	Improvement of endothelial disfunction after 24 months of rituximab therapy
Hsue, 2014 [68]	Observational	20	none	24 weeks	FMD	After 12 weeks marked improvement of FMD was observed, but after 24 weeks a decline towards basline [2] cIMT did not improved after 24 weeks of therapy.	Depletion of B-cells with rituximab transiently improved endothelial function.
Provan, 2015 [61]	Observational	24pts on rituximab 5 on abatacept 7 on tocilizumab	none	12 months	PWV, AIx	No significant change of PWV an AIx after 3 months of treatment with rituximab. After 12 months there was significant decrease of PWV, and no change of AIx	Reduction of PWV after 12 months of treatment with rituximab

Abbreviations: FMD flow mediated dilatation, cIMT carotid intima-media thickness, AIx augmentation index, PWV pulse wave velocity, TNFi tumor necrosis factor inhibitor

Table 3 An overview of the included studies on the vascular effects of interleukin-6 receptor inhibitor tocilizumab

First author, year	Design	n° patients	Control group	Follow-up	Measured outcome	Results	Main findings
Kume 2011 [43]	Randomized controlled trial	22 patients on TCZ	22 patients on ADA 22 patients on ETN	24 weeks	CAVI AIx75 cIMT	CAVI was attenuated significantly by TCZ, ETN, and ADA. Changes did not significantly differ between groups. AIx@75 was attenuated significantly by TCZ , ETN, and ADA. The Δ AIx was not significantly different between groups. No change of cIMT was observed	Tocilizumab, etanercept and adalimumab decreased endothelial dysfunction
Protogerou 2011 [69]	Observational	16	16	6 months	FMD PWV	FMD increased at follow-up at 3rd and 6th month of treatment PWV decreased after 3 and 6 months of tocilizumab treatment	Tocilizumab decreased endothelial disfunction and aortic stiffness of the observed cohort.
McInnes 2015 [70]	Randomised control trial	69(MTX+TCZ)	63(MTX+placebo)	6 months	PWV	PWV decreased in placebo group in week 12, but non-significant decrease was observed at week 24 compared to TCZ group	Arterial stiffness decreased in placebo group, but did not decrease with tocilizumab
Bacchiega 2017 [71]	Observational	18	24 on csDMARDs 18 on TNFi(ADA/ETN)	16 weeks	FMD	After 16 weeks, FMD increased in the tocilizumab and TNFi group compared to baseline. In the csDMARD group FMD there was not significant change.	Tocilizumab improved endothelial disfunction.

Table 3 (continued)

First author, year	Design	n° patients	Control group	Follow-up	Measured outcome	Results	Main findings
Ikonomidis 2018 [72]	Observational	40 on TCZ	40 on anakinra 50 on prednislolone	3 months	CFR GLS FMD PWV malondialdehyde PCs	Tocilizumab treatment improved GLS, FMD , CFR, PWV, malondialdehyde , PCs after 3 months. Greater improvement of PWV was observed in the tocilizumab group compared to anakinra and placebo. GLS and CFR improved more in the anakinra group compared to tocilizumab.	Tocilizumab improves left ventricular strain, coronary flow reserves, endothelial disfunction, arterial stiffness and markers of oxidative stress. Compared to anakinra tocilizumab leads greater improvement of PWV, but worse improvement to GLS and CFR.
Ikonomidis 2020 [73]	Observational	40 on tocilizumab 40 on MTX+prednisolone	40		Endothelial glycocalyx thickness by PBR PWV AIx GLS MDA PCs	Treatment with tocilizumab decreased PBR, PWV and AIx compared to baseline. Treatment with tocilizumab induced greater improvement of PBR, PWV and AIx compared to MTX+prednisolone. Compared with MTX+prednisolone, tocilizumab achieved a greater increase of GLS, and reduction of MDA and PC	Tocilizumab improves endothelial glycocalyx, aortic stiffness, left ventricular function and markers of oxidative stress.

Abbreviations: TCZ tocilizumab, ADA adalimumab, ETN etanercept, CAVI cardio-ankle vascular index, FMD flow mediated dilatation, cIMT carotid intima-media thickness, PWV pulse wave velocity, PCs protein carbonyls, GLS global longitudinal strain, CFR coronary flow reserve, PBR perfused boundary region, MDA malondialdehyde

drugs using this method. Two other non-invasive measuring methods assessing endothelial dysfunction were also used: laser Doppler flow (LDF) imaging with iontophoresis [82] and endothelial glycocalyx thickness. The latter was evaluated by measuring the perfused boundary region (PBR) by Sidestream Darkfield (SDF) imaging [83]. LDF was used in two studies on TNFi, while PBR was assessed in a single study on IL-6 inhibitor. Positive effects were observed for both drug classes.

Arterial stiffness is a measurement of the elastic properties of the large bore arteries. Abnormal stiffening of the arterial wall evaluated by means of PWV represents a well-established independent predictor of CVD in the general population. The most common measurement method used is pulse wave velocity. This method measures the speed at which a pulse wave travels through the arteries. A faster pulse wave velocity indicates increased arterial stiffness. PWV is measured non-invasively using a device that measures blood pressure at two points on the body. Different points can be used, making three different PWV methods: carotid-femoral PWV (cfPWV) [84], heart-femoral (hfPWV) [85], and brachial-ankle (baPWV) [86]. Another method for arterial stiffness measurement is the CAVI [87]. The principle is based on stiffness parameter β, which is an index obtained from changes in arterial diameter and measured with the pulse in one section by a two-dimensional imaging technique. The β factor is used to calculate CAVI from the PWV and is adjusted for body size making it independent of height and body weight. In our review, we found 9 studies showing improvement of PWV after anti-TNF therapy. IL-6 inhibitors improved PWV in 5 studies. In one small non-controlled study, the JAK inhibitor tofacitinib improved CAVI after 54 weeks of treatment. One study found improvement of PWV in rituximab patients but another study did not find any effect. We found no studies on the effect of anakinra on arterial stiffness and one study on the effect of abatacept, where PWV increased.

Aortic distensibility is a measure of the ability of the aorta to expand and contract in response to changes in blood pressure. Aortic distensibility can be measured using magnetic resonance imaging by assessing changes in the diameter of the aorta in response to changes in blood pressure [88]. A higher value of aortic distensibility indicates that the aorta is more compliant and able to expand and contract in response to changes in blood pressure, while a lower value indicates that the aorta is less compliant and less able to accommodate changes in blood pressure. Aortic distensibility is a surrogate marker for aortic stiffness and its decrease is associated with an increased risk of cardiovascular disease and mortality [89, 90]. We found one bolt-on study to the VEDERA (Very Early vs. Delayed Etanercept in Rheumatoid Arthritis) randomized controlled trial which demonstrated improvement of aortic distensibility after 1 year of treatment with etanercept in patients with early rheumatoid arthritis.

cIMT measurement is an ultrasound technique used to assess the thickness of the inner lining of the carotid artery [91]. The usefulness of cIMT in CVD risk assessment has been consistently confirmed in RA patients [92]. The cIMT is measured as the distance between the lumen-intima and media-adventitia interfaces, typically at the far wall of the carotid artery. cIMT is considered a fixed structural alteration of the arterial wall, in which both inflammatory and non-inflammatory mechanisms play an important role. Results of the effects on cIMT are inconsistent. We included 10 studies on TNF-alpha inhibitors and 4 of them showed a decrease of cIMT after treatment, but the other showed no improvement (and apparently no worsening). The analyzed studies did not find an effect on cIMT with IL-6 inhibitor and rituximab treatment. We did not found data for the other therapies of interest.

Our findings suggest that inflammation in the major arteries may contribute to the vascular complications seen in RA. Increased uptake of radioisotopic glucose measured by PET-CT is predictive of cardiovascular risk in the general population [93] and in patients with inflammatory joint diseases [94, 95]. Two studies were identified that investigated the effects of TNF-alpha inhibition on vascular inflammation using 18F-fluorodeoxyglucose-positron emission tomography. In one of the studies, no significant differences were found between responders and non-responders to anti-inflammatory treatment, and no correlation was observed between changes in RA disease activity markers and vascular inflammation. The study also suggested that synovitis and vascular inflammation may be distinct processes, as treatment responses did not coincide in the joints and the vasculature. In the other study, there was a correlation between decreased fluorodeoxyglucose uptake and a reduction in pulse wave velocity after TNF inhibitor treatment, indicating that vascular inflammation may play a role in the development of arterial stiffness.

Our systematic review included studies that looked at various serological markers for early vascular damage, and the results were inconsistent. One such marker is ADMA, which is a marker of endothelial dysfunction that works by inhibiting the nitric oxide synthases (NOSs) that play a role in the development of endothelial dysfunction. High levels of ADMA can result in reduced production of nitric oxide (NO), which can contribute to the development of cardiovascular disease [96]. Three studies on TNFi demonstrated a decrease in ADMA after treatment and one study on tofacitinib did not show any effect.

sVCAMs are a group of molecules that are shed from the surface of endothelial cells into the bloodstream [97]. They play an important role in the regulation of leukocyte (white blood cell) recruitment to sites of inflammation. sVCAMs are involved in the adhesion and migration of immune cells to the walls of blood vessels, which is a crucial step

in the initiation and progression of inflammatory diseases, including atherosclerosis and rheumatoid arthritis [98–100]. Although several studies have investigated the impact of TNFi on adhesion molecules, the findings have been inconclusive, and no studies have yet assessed the effects of the other medications of interest.

Strengths and limitations

Although we conducted a thorough and inclusive review of the existing literature, our study has significant limitations, and the results should be interpreted with caution. The primary constraint of our systematic literature review is the inadequate methodological quality of the majority of the studies included. Out of the 58 studies we included in our analysis, only 9 were randomized controlled trials and just 4 studies compared the effects of different biologic therapies on vascular function. In addition, our search strategy did not consider sarilumab, which is an inhibitor of IL-6, because there is insufficient information about its vascular effects to draw meaningful conclusions. The limited number of studies examining off-target effects on vascular repair mechanisms and endothelial damage highlights the need for improved understanding to ensure optimal treatment and personalized care based on individual cardiovascular risk profiles. Although there is a rationale for adverse cardiovascular effects of novel treatments for RA [101], they were outside the scope of this review. To fully comprehend the distinctions between biologic therapies, more long-term, well-designed clinical trials are necessary.

Conclusion

Overall, our systematic review provides important insights into the potential cardiovascular benefits of biologic and targeted synthetic treatments for RA, as those drugs may improve vascular function by a still unknown mechanism. Considering the persistent and chronic nature of RA, the management plan should consider all potential advantages and drawback of immunosuppressive treatments on cardiovascular outcomes. As the most extensively studied, TNF inhibitors have demonstrated efficacy in enhancing endothelial function, reducing arterial stiffness, improving aortic distensibility, and decreasing cIMT, all of which are essential indicators of cardiovascular health in individuals diagnosed with RA. These findings can inform clinical practice, contribute to our understanding of the medications impact on early vascular pathology, and help guide treatment decisions in RA patients with CVR factors. Future studies are warranted to observe potential differences in their effects on CVR.

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