ESC European Society of Cardiology

Cardiovascular Research (2021) **117**, 2589–2609
doi:10.1093/cvr/cvab330

INVITED SPOTLIGHT REVIEW

Therapeutic targeting of inflammation in hypertension: from novel mechanisms to translational perspective

Eleanor C. Murray [1], Ryszard Nosalski[1,2], Neil MacRitchie[3], Maciej Tomaszewski [4,5], Pasquale Maffia [1,3,6], David G. Harrison [7], and Tomasz J. Guzik [1,2]*

[1]Institute of Cardiovascular and Medical Sciences, College of Medical, Veterinary and Life Sciences, University of Glasgow, G12 8TA Glasgow, UK; [2]Department of Internal Medicine, Collegium Medicum, Jagiellonian University, 31-008 Kraków, Poland; [3]Centre for Immunobiology, Institute of Infection, Immunity and Inflammation, College of Medical, Veterinary and Life Sciences, University of Glasgow, G12 8TA Glasgow, UK; [4]Division of Cardiovascular Sciences, Faculty of Medicine, Biology and Health, University of Manchester, M13 9PL Manchester, UK; [5]Manchester Heart Centre and Manchester Academic Health Science Centre, Manchester University NHS Foundation Trust, M13 9WL Manchester, UK; [6]Department of Pharmacy, University of Naples Federico II, 80131 Naples, Italy; and [7]Division of Clinical Pharmacology, Department of Medicine, Vanderbildt University Medical Centre, Nashville, 37232 TN, USA

Received 3 October 2021; revised 14 October 2021; editorial decision 15 October 2021; accepted 21 October 2021; online publish-ahead-of-print 26 October 2021

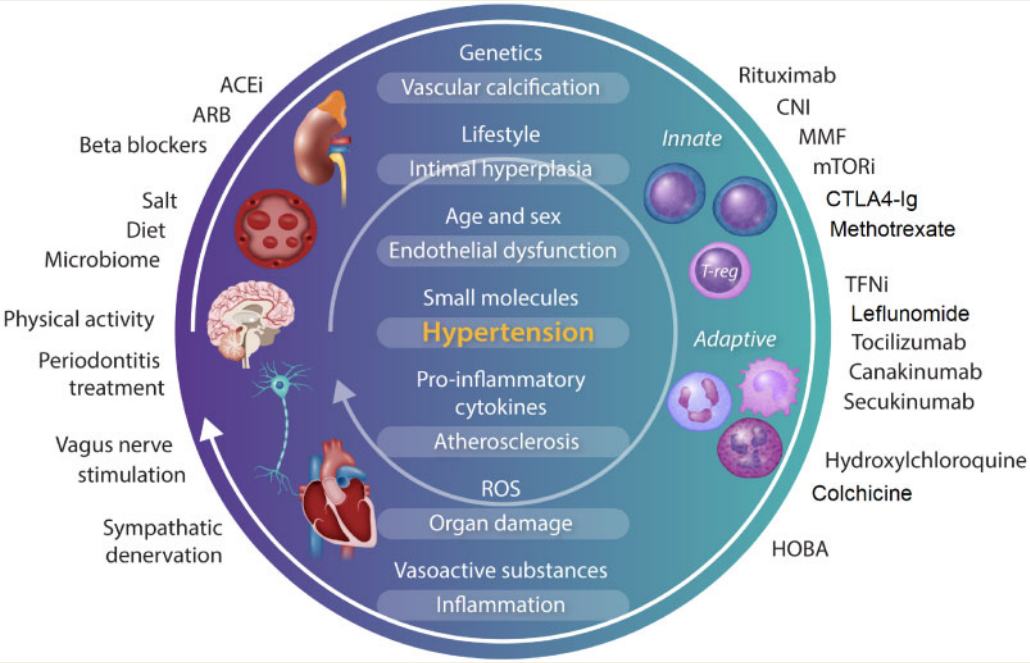
Tomasz Guzik and Pasquale Maffia have positions within CVR; the manuscript was handled by a consulting editor.

Abstract

Both animal models and human observational and genetic studies have shown that immune and inflammatory mechanisms play a key role in hypertension and its complications. We review the effects of immunomodulatory interventions on blood pressure, target organ damage, and cardiovascular risk in humans. In experimental and small clinical studies, both non-specific immunomodulatory approaches, such as mycophenolate mofetil and methotrexate, and medications targeting T and B lymphocytes, such as tacrolimus, cyclosporine, everolimus, and rituximab, lower blood pressure and reduce organ damage. Mechanistically targeted immune interventions include isolevuglandin scavengers to prevent neo-antigen formation, co-stimulation blockade (abatacept, belatacept), and anti-cytokine therapies (e.g. secukinumab, tocilizumab, canakinumab, TNF-α inhibitors). In many studies, trial designs have been complicated by a lack of blood pressure-related endpoints, inclusion of largely normotensive study populations, polypharmacy, and established comorbidities. Among a wide range of interventions reviewed, TNF-α inhibitors have provided the most robust evidence of blood pressure lowering. Treatment of periodontitis also appears to deliver non-pharmacological anti-hypertensive effects. Evidence of immunomodulatory drugs influencing hypertension-mediated organ damage are also discussed. The reviewed animal models, observational studies, and trial data in humans, support the therapeutic potential of immune-targeted therapies in blood pressure lowering and in hypertension-mediated organ damage. Targeted studies are now needed to address their effects on blood pressure in hypertensive individuals.

* Corresponding author. Tel: +44 141 3307590; fax: +44 141 3307590, E-mail: tomasz.guzik@glasgow.ac.uk

Graphical Abstract



Keywords Hypertension • Inflammation • Immune system • Immunomodulatory • Blood pressure

This article is part of the Spotlight Issue on Cardiovascular Immunology.

1. Introduction

In atherosclerosis, the role of inflammation is well defined,[1–5] and a co-existing chronic inflammatory condition such as rheumatoid arthritis (RA), inflammatory bowel disease, ankylosing spondylitis, or psoriasis is considered an additional risk factor, including in ESC Cardiovascular Disease Prevention guidelines.[6–8] Anti-inflammatory therapies are recommended in such patients,[6] and targeting inflammation to improve cardiovascular outcomes has been supported by recent clinical trials such as CANTOS, COLCOT, and LoDoCo2.[9–12] Hypertension is the most common cardiovascular risk factor worldwide.[13] For more than half a century, immune cells have been observed to infiltrate the kidney and vasculature of hypertensive humans and animals with experimental hypertension, and increasing evidence indicates that immune and inflammatory mechanisms promote this disease. It is therefore essential to identify the clinically permissible therapeutic interventions that address inflammatory targets in hypertension, and patient populations that would benefit from such treatment. While basic and translational evidence suggests that interfering in immune-inflammatory processes may aid in control of blood pressure (BP) and prevention of target organ damage,[14–17] the clinical evidence for these interventions has not been systematically analysed. Accordingly, we review potential immune therapeutic targets to identify approaches for which well-designed clinical studies may prove fruitful.

2. Immune and inflammatory targets for treatment of hypertension

Inflammation and immune activation were first implicated as being involved in hypertension through the work of Grollman, Okuda, Svendsen,[18–21] and Olsen.[22,23] In the last decade, new research has begun to reveal the mechanisms that explain this.[17] Using animal models of genetic and pharmacological targeting, the regulatory role of T cells,[24–34] γδ cells,[35] monocytes/macrophages,[36–39] dendritic cells (DC),[40] B cells,[41,42] NK cells,[43] as well as other components of a complex immuno-inflammatory network have been assessed.[17,44–48] The initiation of inflammation in hypertension appears to be associated with oxidative stress and redox-dependent mechanisms within the vascular and renal tissues.[49,50] These lead to generation of neo-antigens,[51] damage-associated molecular patterns,[52] and neuroimmune mechanisms[53,54] that trigger maladaptive immune responses, which compound hypertension and its' associated organ damage. Although antigen(s) responsible for activation of adaptive immunity have not been definitively identified, potential candidates are isolevuglandin (isoLG) adducted proteins. IsoLGs are oxidation products of arachidonic acid that rapidly ligate lysines on self-proteins and accumulate in antigen-presenting cells and are presented within major histocompatibility complexes. These activate a subset of $CD4^+$ and $CD8^+$ T cells. Importantly, the selective isoLG scavenger 2-

hydroxybenzylamine can prevent immune activation and lower BP in several animal models of hypertension.[51] Data from both animal and human studies also identify HSP70 as a potential auto-antigen.[55] Numerous animal studies in a wide range of models, reviewed previously,[56–58] highlight that immunomodulating inflammatory activation and effector cytokine release may curb BP increases and lessen development of vascular, cardiac, and renal damage.[59–66] Many of these studies have employed germline knockout animals. In addition, small molecule or neutralizing antibodies that target immune mediators have been used to determine the effect of selective blockade on experimental hypertension (*Table 1*). These have targeted both the innate (e.g. IL-1, TLR4) and adaptive (e.g. IL-17, CD80/86) immune system. Careful analysis of these studies helps identify potential therapeutic targets, but also highlights the impact of treatment protocol and animal model selection for BP and target organ damage outcomes (*Table 1* and *Figure 1*).

3. Clinical evidence

Epidemiological and observational human data supports a relationship between the immune system and hypertension, including the observation that humans with hypertension are at increased risk of COVID-19 infection-related death.[103,104] Inflammatory biomarkers[105–107] correlate with systolic BP (SBP) in acute stroke, each 10 mmHg BP elevation increasing the odds of an elevated C-reactive protein level by 72%.[108] Similarly, observational and clinical trial data demonstrate BP increases with each C-reactive protein quartile.[109,110] A nested case–control study of 400 normotensive women indicated that the risk of developing hypertension during follow-up increases with higher quartiles of IL-6 and C-reactive protein.[111] In addition to C-reactive protein and IL-6, TNF-α, IL-1β, IL-18, and CCL2 cytokine levels also appear to be increased in hypertension and may confer risk of developing the disease.[112–118] These cytokines likely promote cell infiltration, affect renal sodium transport,[75] and alter vascular function and structure, ultimately leading to sodium and volume retention, increased systemic vascular resistance, and the phenotype of hypertension.

Circulating leucocytes, which are important cellular components of the immune system, show significant perturbations in hypertension. Data from NHANES III demonstrate higher numbers of circulating leucocytes are associated with hypertension.[107] UK Biobank data similarly indicate that quintile distribution of lymphocyte, monocyte, neutrophil, and eosinophil count is positively associated with BP.[119] Other studies show that an increased neutrophil to lymphocyte ratio (NLR) predicts development of hypertension.[120–122] Intermediate and non-classical monocytes are associated with inflammatory states and endothelial dysfunction and are also increased in hypertensive patients.[123–125] A recent study has shown that signals from the activated endothelium in hypertension induces conversion of classical $CD14^{++}/CD16^{low}$ monocytes to $CD14^{++}CD16^{+}$ intermediate monocytes. This seems to be mediated by STAT3 activation and associated with increases in IL-6, IL-1β, IL-23, CCL4, and TNF-α.[123] Monocytes from hypertensive patients also express higher TLR4, and BP control reverses this.[126]

A causal role of lymphocytes in human hypertension is supported by large-scale Mendelian randomization genetic evidence.[119] T lymphocytes of hypertensive individuals are activated, with increased IL-17A and interferon γ (IFN-γ) production and proportionally higher memory T cells ($CD45RO^{+}$) in adults.[127] Youn *et al.*[128] have shown that patients with hypertension have an increased fraction of immunosenescent, proinflammatory, cytotoxic $CD8^{+}$ T cells. Even among hypertensive adolescents, a subset of pro-inflammatory $CD4^{+}$ T cells is associated with SBP and arterial stiffness.[129] Increased circulating effector memory $CD4^{+}/CD8^{+}$ T cells and $CD8^{+}CD28$ null T cells are also present at this early time point in hypertension.[129,130]

In summary, clinical studies identify greater proportions of activated pro-inflammatory monocytes and lymphocytes in hypertension. This may promote their infiltration into target organs, leading to perturbations in vascular and renal function, and ultimately modulating BP.

4. Genetic and multi-omics evidence

Data from Genome-Wide Association Studies (GWAS) and the transcriptome link hypertension with immune cellular defence and inflammatory responses.[130,131] This link is supported by integrative network analysis[132] and Mendelian randomization approaches,[119] and is important, considering that heritability of BP is between 33% and 57%.[133–135]

Several GWAS have implicated *SH2B3/LNK* gene in hypertension and myocardial infarction.[130,132,136,137] SH2B3 encodes a docking protein that seems to be a modulator of T cell activation. Variants of this gene are linked to autoimmune diseases such as multiple sclerosis, coeliac disease, and type 1 diabetes.[137] Single nucleotide polymorphism (SNP) rs3184504 in SH2B3 is evidential or its' trans-regulatory role in gene expression; regulating 6 out of the 34 BP-related signature genes identified by meta-analysis of GWAS reporting gene expression profiles from 7017 individuals not on anti-hypertensive treatment. All regulated genes are expressed in leucocytes.[138] Integrative network analysis of BP GWAS with mRNA expression profiles from 3679 participants not on anti-hypertensive agents confirms molecular interactions between key drivers such as SH2B3 and hypertension-related genes.[132] Mechanistically, T cells from *LNK* knockout mice produce high levels of type I cytokines and these mice exhibit increased sensitivity to angiotensin II (Ang II), leading to hypertension, endothelial and renal dysfunction, increased inflammatory cell infiltrate, and oxidative stress.[139,140] Mendelian randomization evidence based on 120 SNPs predictive of leucocyte subpopulations demonstrates a clear, potentially causal, relationship between lymphocyte count and systolic and diastolic BP, while BP itself appears to affect monocyte and neutrophil counts.[119] Finally, the recent multi-omic kidney analysis uncovered many immunity-related genes (such as IRF5, IRAK1, BP1, TRAF1) whose expression, splicing, and/or methylation ostensibly demonstrate causal relationships with BP.[141]

5. Effects of immunomodulatory drugs on BP

Clinically available immunomodulatory drugs employ heterogeneous mechanisms of action, and hence their impact on BP regulatory systems is likely to be diverse. Agents reviewed below are selected to illustrate this breadth.

5.1 Selected anti-cytokine therapies

5.1.1 TNF-α inhibitors

Using a systematized search, we identified 20 studies reporting BP in patients prescribed adalimumab, infliximab, etanercept, golimumab, and six papers with a mix of TNF-α inhibitors used (see *Table 2*).

Table 1 Key findings relevant to the relationship between the immune system and hypertension arising from animal models

Immune target and therapeutic agent	Model	Result relative to non-treated mice	References
TNF-α	SHR rat	↓ BP	Filho *et al.*[67]
Infliximab (anti-TNF-α neutralizing Ab)		↓ Cardiac hypertrophy	
		↓ Vascular inflammation	
Etanercept (TNF-inhibitor)	Rat (8% NaCl diet + 14 days ang-II)	↓ Renal inflammation/damage	Elmarakby *et al.*[68]
		Slowed but did not prevent rise in BP	
Etanercept	Mice infused with ang-II for 14 days	↓ BP	Guzik *et al.*[25]
Etanercept	Spontaneously hypertensive dTGR rats	↓ Renal inflammation/damage	Muller *et al.*[69]
		↓ Mortality	
		↔ BP	
Etanercept	Dahl salt-sensitive rat with renal interstitial administration of etanercept	↓ BP	Huang *et al.*[49]
		↓ renal damage	
Etanercept	High fructose-fed rats	↓ BP	Tran *et al.*[70]
		↓ Endothelial dysfunction	
Etanercept	Mouse model of SLE	↓ BP	Venegas-Pont *et al.*[71]
		↓ Renal inflammation/damage	
PEG-sTNFR1 (TNF inhibitor)	Renal mass reduction induced renal failure in rats	↓ BP	Therrien *et al.*[72]
		↓ Renal inflammation/damage	
NLRP3	Uni-nephrectomized wild-type mice treated with DOCA-salt up to 28 days	↓ BP	Krishnan *et al.*[73]
MCC950 (NLRP3 inhibitor)		↓ Cardiac hypertrophy	
		↓ Renal inflammation/damage	
NF-κb	SHR rats	↓ BP	Rodríguez-Iturbe *et al.*[44]
PDTC		↓ Renal inflammation	
PDTC	2K1C rats	↓ BP	Cau *et al.*[74]
		↓ Cardiac hypertrophy/fibrosis	
IL-1R	Mice treated with ang-II for 21 days	↓ BP	Zhang *et al.*[75]
Anakinra (IL-1R antagonist)		↓ Cardiac hypertrophy	
Anakinra	Uni-nephrectomized mice treated with DOCA-salt in drinking water for 21 days	↓ BP	Ling *et al.*[76]
		↓ Renal fibrosis	
IL-6	Dahl salt-sensitive rats fed 4% NaCl for up to 11 days	↓ BP	Hashmat *et al.*[77]
Neutralizing anti-IL-6 Ab		↓ Renal inflammation/damage	
T cells	Mouse model of SLE	↓ BP	Mathis *et al.*[78]
Anti-CD3 Ab		↓ Autoantibodies	
		↓ BP	
CD8 T cells	Mice treated with ang-II for 14 days	↔ BP	Ma *et al.*[79]
Anti-CD8 Ab		↓ Cardiac inflammation and fibrosis	
γδ T cells	Mice treated with ang-II for 7 or 14 days	↓ BP	Caillon *et al.*[35]
Anti-γδ T cell Ab		↓ Endothelial dysfunction	
Tregs	Mice treated with ang-II for 14 days	↔ BP	Majeed *et al.*[80]
IL-2/Anti-IL-2 Ab complex		↓ Aortic remodelling	
		↓ Aortic stiffness	
IL-2/Anti-IL-2 Ab complex	Transverse aortic constriction (TAC) in mice	↔ BP	Wang *et al.*[81]
		↓ Cardiac hypertrophy and dysfunction	
IFN-γ	Wild-type mice treated with ang-II for 14 days	↔ BP	Guzik *et al.*[25]
Neutralizing anti-IFN-γ Ab			
Neutralizing anti-IFN-γ Ab	Mice with T-cell restricted overexpression of mineralocorticoid receptor (TMROV mice) treated with ang-II for 21 days	↓ BP	Sun *et al.*[82]
IL-17	Wild-type mice treated with ang-II for 14 days	↔ BP and cardiac hypertrophy	Markó *et al.*[83]
Neutralizing anti-IL-17A Ab			
Neutralizing anti-IL-17A Ab	Rats treated with anti-IL-17A Ab for 28 days using the DOCA-salt model	↓ BP	Amador *et al.*[84]
		↓ Target organ damage	

Continued

Table I *Continued*

Immune target and therapeutic agent	Model	Result relative to non-treated mice	References
Neutralizing anti-IL-17A Ab	Calcineurin-inhibitor treated mice	↓ BP ↓ Endothelial dysfunction ↓ Renal damage	Chiasson *et al.*[85]
Neutralizing anti-IL-17A, IL-17F or Il-17RA	Wild-type mice treated for 28 days with ang-II (14 days with Ab treatment)	IL-17A/IL-17R: ↓ BP ↓ Renal inflammation/damage Il-17F: No significant change	Saleh *et al.*[86]
IL-17 soluble receptor C	Preeclampsia rat model	↓ BP ↓ Oxidative stress	Cornelius *et al.*[87]
IL-23 Neutralizing anti-IL-21R Ab	Wild-type mice treated with ang-II for 14 days	↔ BP and cardiac hypertrophy	Marko *et al.*[83]
TGF-β Neutralizing anti-TGF-β Ab (1D11)	Dahl salt-sensitive rat fed 4% NaCl for 21-28 days	↓ BP ↓ Renal injury ↓ Cardiac damage	Murphy *et al.*[88]
B cells Anti-CD20 Ab	Wild-type mice treated with ang-II for 28 days	↓ BP	Chan *et al.*[41]
CCR2 INCB3344 (CCR2 antagonist)	Wild-type mice were uni-nephrectomized and treated with DOCA-salt for 21 days	↓ BP ↓ Vascular inflammation	Chan *et al.*[89]
INCB3344	Wild-type mice treated with ang-II for 28 days (21 days with CCR2 antagonist)	↓ BP ↓ Vascular inflammation/fibrosis ↓ Cardiac hypertrophy	Moore *et al.*[37]
CCR5 Met-RANTES (CCR5 antagonist)	Wild-type mice infused with ang-II for 14 days.	↓ Vascular inflammation and dysfunction ↔ BP	Mikolajczyk *et al.*[90]
TLR-4 TAK-242 (TLR-4 antagonist)	Rats infused with Aldo-salt for 28 days	↓ BP ↓ Cardiac hypertrophy ↓ Renal damage	De Batista *et al.*[91]
Neutralizing anti-TLR4 Ab	Wild-type mice treated with ang-II for 14 days	↓ BP ↓ Vascular inflammation and remodelling	Hernanz *et al.*[92]
Neutralizing anti-TLR4 Ab	SHR rat	↓ BP ↓ Vascular reactivity	Bomfin *et al.*[93]
Neutralizing anti-TLR4 Ab	Mice treated for 28 days with ang-II (14 days with Ab treatment)	↓ Vascular dysfunction ↔ BP	Nunes *et al.*[94]
Neutralizing anti-TLR4 Ab	SHR rat	↔ BP ↓ Cardiac hypertrophy ↓ Cardiac inflammation	Echem *et al.*[95]
TLR-9 Chloroquine (TLR-9 inhibitor + pleiotropic effects)	SHR rat	↓ BP ↓ Vascular and systemic inflammation	McCarthy *et al.*[96]
CD80/CD86 CTLA4-Ig (Abatacept) (CD80/86 inhibitor)	Wild-type mice infused with ang-II for 14 days, or uni-nephrectomized and treated with DOCA-salt for 21 days	↓ BP ↓ Vascular and systemic inflammation	Vinh *et al.*[24]
CD40L Anti-CD40L Ab	Preeclampsia rat model	↓ BP ↓ Oxidative stress ↓ Endothelin-1 release	Cornelius *et al.*[97]
Isoketals 2-Hydroxybenzylamine (2-HOBA) (isoketal scavenger)	Wild-type mice were infused with ang-II for 14	↓ BP ↓ renal inflammation/damage	Kirabo *et al.*[51]
mTOR Rapamycin (mTOR inhibitor)	Dahl salt-sensitive rats fed a 4% NaCl diet for up to 21 days	↓ BP ↓ renal inflammation/damage	Kumar *et al.*[98]
IMPDH MMF	SHR Rat	↓ BP ↓ Renal inflammation/damage	Rodríguez-Iturbe *et al.*[99]
MMF	Uni-nephrectomized rats implanted with DOCA-salt pellets + 0.9% NaCl drinking water for up to 21 days.	↓ BP ↓ Renal inflammation/damage	Boesen *et al.*[100]

Continued

Table I *Continued*

Immune target and therapeutic agent	Model	Result relative to non-treated mice	References
MMF	Mouse model of SLE	↓ BP ↓ Renal inflammation/damage	Taylor and Ryan[101]
Purine metabolism Azathioprine	DOCA-salt in pregnant rats	↓ BP ↓ Proteinuria ↓ Endothelial dysfunction ↓ Systemic inflammation	Tinsley *et al.*[102]

Ab, antibody; ang-II, angiotensin II; BP, blood pressure; CCR, CC motif chemokine receptor; CD, cluster of differentiation; CNI, calcineurin inhibitor; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; DOCA, deoxycorticosterone acetate; dTGR, double transgenic rats; IL, interleukin; IFN-γ, interferon γ; IMPDH, Inosine-5′-monophosphate dehydrogenase; mTOR: mammalian target of rapamycin; MTX: methotrexate; NF-κb, nuclear factor kappa b; NLRP3, NOD-like receptor family pyrin domain containing 3; PDTC; pyrrolidine dithiocarbamate; SHR, spontaneously hypertensive rat; SLE, systemic lupus erythematosus; TGF-β, transforming growth factor beta; TLR, Toll-like receptor; TNF, tumour necrosis factor.

Study populations included those with RA, ankylosing spondylitis, psoriasis, and combined rheumatological diseases. Follow-up was from 2 weeks to 12 months and cohort sizes varied from 9 to 5408. Only 5 of the 20 studies were randomized and/or placebo controlled.[148,149,156,159] Seventeen of these studies contained data adequate for meta-analysis (see Supplementary material online, methods and *Figure 2*): the combined estimate from 13 studies comparing average BP before and after TNF-α blockade was a 3.5 mmHg reduction in SBP (95% CI: –5.7 to –1.3), $P = 0.001$. Five randomized trials with placebo or other pharmacotherapy comparators produce a combined estimate of 4.1 mmHg SBP lowering (95% CI: –7.0 to –1.1), $P < 0.001$. Only two studies used the gold standard of ambulatory BP monitoring (ABPM), Yoshida *et al.*[146] demonstrating a SBP reduction of 7.3 mmHg. In contrast Grossman *et al.*[160] showed that TNF-α blockade caused an increase of 1.7 mmHg. Elevated BP was not an inclusion criterion in any of the studies and hypertension was reported inconsistently. Two of the studies reported only mean arterial pressure,[153,162] six studies did not report prevalence or use of antihypertensives,[144,145,153,156,158,161] and one specified no antihypertensive use.[143] Hypertension prevalence in the remaining studies ranged between 7% and 53%.[142,146–152,157,159,160] In some studies, good BP control was an inclusion criteria.[142,147,150,160] Finally, individual level data was not available, thus any effect in hypertensive participants may be masked through reporting of average BP across whole study cohorts, though despite this, combined estimates from observational and randomized trials do suggest a BP-lowering effect of anti-TNF-α agents (*Figure 2*). Observational data on incident rates of hypertension offer additional insight. In comparison with non-biologic anti-inflammatory medications, 4822 anti-TNF-α initiators demonstrated no difference in crude or adjusted rates of incident hypertension (HR: 0.95, 95% CI: 0.74–1.2),[163] results supported by a smaller Korean cohort of 996 patients with RA.[164] Paradoxically, previous meta-analysis suggested higher rates of incident hypertension as adverse events in TNF-α inhibitor recipients (OR: 1.89, 95% CI: 1.35–2.65).[165] This disparity indicates need for targeted studies in hypertensive populations.

5.1.2 IL-1β inhibition (CANTOS trial)

In a large RCT of patients with prior myocardial infarction and elevated high-sensitivity C-reactive protein, the IL-1β antagonist canakinumab 150 mg demonstrated benefit vs. placebo for a composite end point of myocardial infarction, stroke, or cardiovascular death. Largest effect size was in the quartile demonstrating greatest high-sensitivity C-reactive protein and IL-6 reductions.[10,166] Rates of incident hypertension, however, did not differ by high-sensitivity C-reactive protein tertiles; nor did canakinumab demonstrate a reduction in incident hypertension [HR: 0.96 (0.85–1.08), $P > 0.2$]. Ostensibly, this suggests that BP may not be the mechanism by which benefit was exerted; however, baseline prevalence of hypertension was 80%, thus only 20% of participants were 'at risk' from incident hypertension.[167] In the canakinumab arm, only subgroups with baseline BP (SBP ≥130 mm Hg) demonstrated BP lowering, as well as protection from major adverse cardiac events (MACE).[167] Fatal infections were increased with canakinumab, highlighting the importance of selecting permissible targets.[10]

5.1.3 Anti-IL-17

Considering other cytokine inhibitor approaches, we focused on pharmacotherapies with both animal study evidence and use in clinical practice: secukinumab and tocilizumab. We identified the FIXTURE trial of IL-17 antagonist secukinumab (150 and 300 mg groups) in patients with psoriasis. Despite BP being the primary outcome, this trial reported no change at 1 year, though patients were not hypertensive at baseline.[156] In contrast, a study of 50 patients with psoriasis commenced on secukinumab demonstrated a 6 mmHg reduction of SBP (130–124 mmHg, $P = 0.3$).[168] This is particularly important as psoriasis, like RA, appears to be associated with increased prevalence of hypertension and cardiovascular disease.[165,169,170]

5.1.4 Anti-IL-6

Three papers were identified reporting BP data with IL-6 antagonist tocilizumab, two used in combination with methotrexate (MTX).[171,172] SBP increase was demonstrated by Elmedany *et al.*[171] (116 ± 16 vs. 129 ± 17 mmHg, $P = 0.001$), the other two papers reporting no change in BP with IL-6 blockade,[172,173] though the average baseline BP values were normal range. Overall, the minimally available evidence (detailed in Supplementary material online, *Table*) does not support an association with BP lowering.

5.2 Immunosuppressant agents

5.2.1 Mycophenolate mofetil

Mycophenolate mofetil (MMF) inhibits nucleotide synthesis and thus prevents lymphocyte proliferation. In an early study, Herrera *et al.* demonstrated a reduction in average BP from 152/92 to 137/83 mmHg at 12 weeks in eight patients with psoriasis. Notably, BP increased following

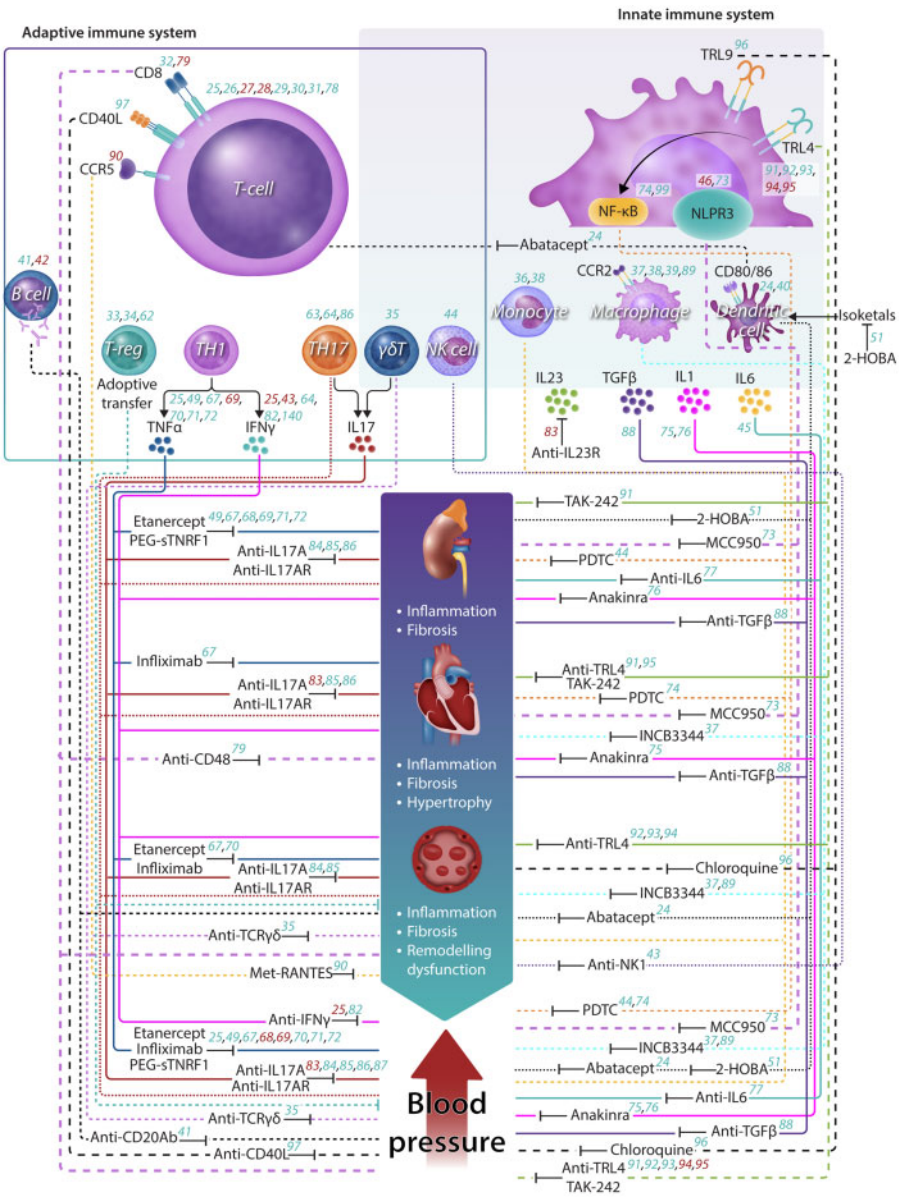


Figure 1 Role of the immune system in the pathogenesis of experimental hypertension and potential immunomodulators for the treatment of hypertension and cardiovascular organ damage. Animal studies implicate virtually all immune cell subsets (dash lines) and cytokines (solid lines) in the pathogenesis of hypertension and target organ damage. Initially, classical immunosuppressants such as mycophenolate[59,60] or rapamycin[58] showed improvement in renal damage and blood pressure regulation, by non-specific mechanisms. The introduction of cell/cytokine-specific immunomodulators (small-molecule inhibitors, antibodies, antagonists or scavengers) with beneficial effect in hypertension and hypertension-mediated organ damage, emphasize the potential use of immunomodulators as a pharmacological tool. More details about the inhibitors are presented in Table1. Numbers indicate references represent a positive (green) or negative (red) effect.

Legend: CD, cluster of differentiation; CCR, chemokine receptor; Treg, T-regulatory cell; TH, T-helper cell; IL, interleukin; TNF-α, tumour necrosis factor alfa; NF-κB, Nuclear factor kappa B; IFN-γ, interferon γ; NLPR3, NOD-like receptor family, pyrin domain-containing protein 3; TGF-β, transforming growth factor beta; TLR, Toll-like receptor; PEG-sTNFR1, PEGylated soluble tumour necrosis factor receptor 1; TAK-242, inhibitor of TLR4 signalling; 2-HOBA, 2-hydroxybenzylamine; MCC950, small-molecule inhibitor of the NLRP3 pathway; INCB3344, CCR2 antagonist; Met-RANTES, CCR5 antagonist.

MMF cessation in this study. The authors also demonstrated a reduction in urinary TNF-α was during MMF therapy.[174] Other studies reporting BP data are confounded by the presence of nephropathy, with concomitant anti-hypertensive treatment to achieve target BP under 130/80 mmHg, or organ transplantation in which improvement in volume status could obscure any independent impact of MMF on BP. With these caveats in mind, two trials of MMF in IgA nephropathy report BP reduction of –7 to –14 mmHg.[175,176] In two other studies of patients with lower enrolment BP, MMF did not reduce SBP beyond treatment with angiotensin-converting enzyme inhibitors (ACEi) alone, or ACEi plus placebo.[177,178] Head-to-head trials in transplantation showed that treatment with tacrolimus/MMF lowered SBP by 4 mmHg ($P = 0.08$) and

Table 2 Human studies pertaining to TNF-α inhibitor use and reporting data on BP outcomes

References	Population F=female	Design/comparator/ follow-up	SBP Baseline mmHg	Δ SBP mmHg *P* value	Notable and confounding features
Gonzalez-Juanatey *et al.*[142]	*n* = 34 (30 F) RA Age 55	Observational: Pre-/post-ADL 52 weeks	136 ± 17.8	–9.1 (–20, 2) *P* = 0.1	9/34 had controlled HTN. Other DMARDs/anti-hypertensives permitted, but no alterations to concomitant medication during study.
Bozkirli *et al.*[143]	*n* = 30 (7 F) Ank Spond Age 34	Pre-/post-IFX 12 weeks	119 ± 9.9	–9 (–14, –4) *P* = 0.001	No anti-hypertensive use. Lower NSAID use at follow up.
Komai *et al.*[144]	*n* = 15 (13F) RA Age 50	Pre-/post-IFX +MTX 6 weeks	127.9 ± 5.6	–8.6 *P* value not reported	Rates of baseline HTN/BP medications unknown. Concomitant MTX/prednisolone doses unknown.
Sandoo *et al.*[145]	*n* = 23 (15 F) RA Age 55	Anti-TNF's. Control group, *n* = 17 12 weeks	127 ± 15	–7.7 (–20, 5) *P* = 0.007	Rates of baseline HTN/BP medications unknown. Control group (stable on DMARD): no change in BP.
Yoshida *et al.*[146]	*n* = 16 (10 F) RA Age 57	Pre-/post-IFX ± MTX 2 weeks	127.4 ± 21.8	–7.3 (–10, –4) *P* < 0.001	24 h BP. 7/16 HTN; no hypotensive drug administered during study. All on MTX concomitantly, 10/16 on prednisolone.
Galarraga *et al.*[147]	*n* = 26 (22 F) RA Age 57	Pre-/post-ETN: Vs MTX (*n* = 21): 16 weeks	135 ± 16 139 ± 19	–5 (–13, 3) *P* = 0.22 –9 (–18, 0) *P* = 0.06	7/26 controlled HTN. Comparator group on MTX showed no change in BP.
Klarenbeek *et al.*[148]	*n* = 128 (85 F) RA	IFX + MTX Vs sequential monotherapy (*n* = 126) 52 weeks	136 ± 20	–4.8 (–8, –2)* *P* = 0.001	7% of IFX group on anti-hypertensive. *Adjusted for Δ DAS, baseline SBP, age, gender, anti-hypertensive use and Δ BMI. DAS >2.4 associated with higher BP. BP reduction in IFX responders –6.8, non-responders –4.9 mmHg.
Tam *et al.*[149]	*n* = 20 (19 F) RA Age 53	Pre-/post-IFX + MTX: Pre-/post-MTX (*n* = 20): 26 weeks	129 ± 16 130 ± 24	–4.2 ± 13.4 *P* value not reported –3 ± 15 *P* = 0.78*	6/20 HTN. Steroids and other DMARD use permitted. *Between groups comparison of Δ SBP
Daïen *et al.*[150]	N = 28 (28 F) RA Age 57	Pre-/post-ETN 26 weeks	124 ± 15	–3.1 (–22, 16) *P* = 0.55	5/28 controlled HTN. 89% on other sDMARDs. sDMARD group (*n*=20) Δ SBP -1.9 ± 10.9 (NS)
van den Oever *et al.*[151]	*n* = 23 (20 F) RA Age 53	Pre-/post-ADL 26 weeks	126 ± 17	–3.0 (–5, –1) *P* = 0.19	4/28 HTN Osteoarthritis group (*n* = 25), Δ SBP –4 ± 11 (NS)
Peters *et al.*[152]	*n* = 171 (135 F), RA Age 54	Pre-/post-ADL ± DMARD 16 weeks	130 ± 30	–2 (–7, 3) *P* = 0.44	46/171 HTN 133/171 also on MTX and/or other DMARDs

Continued

Table 2 *Continued*

References	Population F=female	Design/comparator/ follow-up	SBP Baseline mmHg	Δ SBP mmHg *P* value	Notable and confounding features
Mäki-Petäjä *et al.*[153]	*n* = 9 RA Age 54	Pre-/post-anti-TNF 12 weeks	MAP 100 ± 9	–2 (–5, 1) *P* = 0.2	Rates of baseline HTN/BP medications unknown. Concomitant drugs: 6/9 steroid, 4/9 DMARD
Rho *et al.*[154]	*n* = 35 RA Age 54	Anti-TNF's vs. other DMARDs (*n* = 134) Cross-sectional	133.6 ± 21.2	–1.4 (–26, 23) *P* = 0.91	53% of whole cohort (90/169) had HTN, not broken down by drug class.
Angel *et al.*[155]	*n* = 17 (9 F) RA, PsA, Ank Spond Age 54	Pre-/post-anti-IFX 8 weeks	MAP 90 ± 9.1	–1.2 (–4, 2) *P* = 0.37	2/17 HTN (BP had to be well controlled for 6 months). 10/17 on MTX concurrently.
Thaci *et al.*[156]	*n* = 303 Plaque psoriasis	Pre-/post-ETN 52 weeks	126.3	–0.7 *P* value not reported	Rates of baseline HTN/BP medications unknown. Secukinumab and placebo arms, but data only reported for former.
Baker *et al.*[157]	*n* = 5408 RA	Observational pre-/post-anti-TNFs 52 weeks	131 ± 16	–0.6 (–19, 18) *P* value not reported	Data derived from administrative database. 73% HTN and 68% on BP medication at baseline.
Mäki-Petäjä *et al.*[158]	*n* = 17 (11 F) RA Age 58	Pre-/post-ADL or ETN 8 weeks	MAP 104 ± 11	0 *P* = 0.9	9/17 treated HTN
Tam *et al.*[159]	*n* = 20 (92 F) Ank Spond Age 36	GOL: Placebo (*n* = 21): 52 weeks	116 ± 10.4 116 ± 10.1	0.20 ±9.8 0.98 ±8.8 0.8 (–6.6, 5.1)* *P* = 0.79*	2/20 HTN. 7/20 concomitant MTX or sulfasalazine *Between groups comparison of Δ SBP
Grossman *et al.*[160]	*N* = 15 (9 F) RA, PsA, Ank Spond Age 46	Pre-/post-ADL, ETN, or IFX 12 weeks	120.9 ± 11.8	1.7 (–22, 25) *P* = 0.88	ABPM. 2/15 HTN: included if stable for 3 months and BP controlled. 7/15 on other DMARDs.
van Doornum *et al.*[161]	*n* = 14 (8 F) RA Age 55	Pre-/post-anti-TNFs 6 weeks	140 ± 6	4 (–4, 12) *P* = 0.3	Rates of baseline HTN and BP medications not reported. Concurrent DMARD use (MTX 11/14, leflunomide 9/14, HCQ 5/14)

ADL, Adalimumab, ank spod, ankylosing spondylitis; IFX, infliximab; ETN, etanercept; GOL, golimumab; MAP, mean arterial pressure; PsA, psoriatic arthritis; RA, rheumatoid arthritis.
Asterix (*) is used to indicate a comment in the final column relating specifically to the asterixed result.

diastolic BP by 3 mmHg (*P* = 0.02) at 6 months compared to transplanted patients receiving tacrolimus/sirolimus. Ninety percent of these subjects had hypertension at baseline.[179] In a smaller study, no change in BP occurred in 58 liver transplant patients treated with a tacrolimus/MMF (*P* = 0.88, baseline average 129/70 mmHg) whilst a group treated with tacrolimus/steroid showed an 8 mmHg rise in SBP.[180] Overall, the clinical evidence favours association of MMF with BP reduction in hypertension (see *Figure 3*); however, no data specifically pertaining to hypertensive patients are available.

5.2.2 Methotrexate

MTX is a chemotherapy agent and disease-modifying anti-rheumatic drug (DMARD). Five studies involving between 20 and 8065 participants were identified, reporting average baseline SBP between 121 and

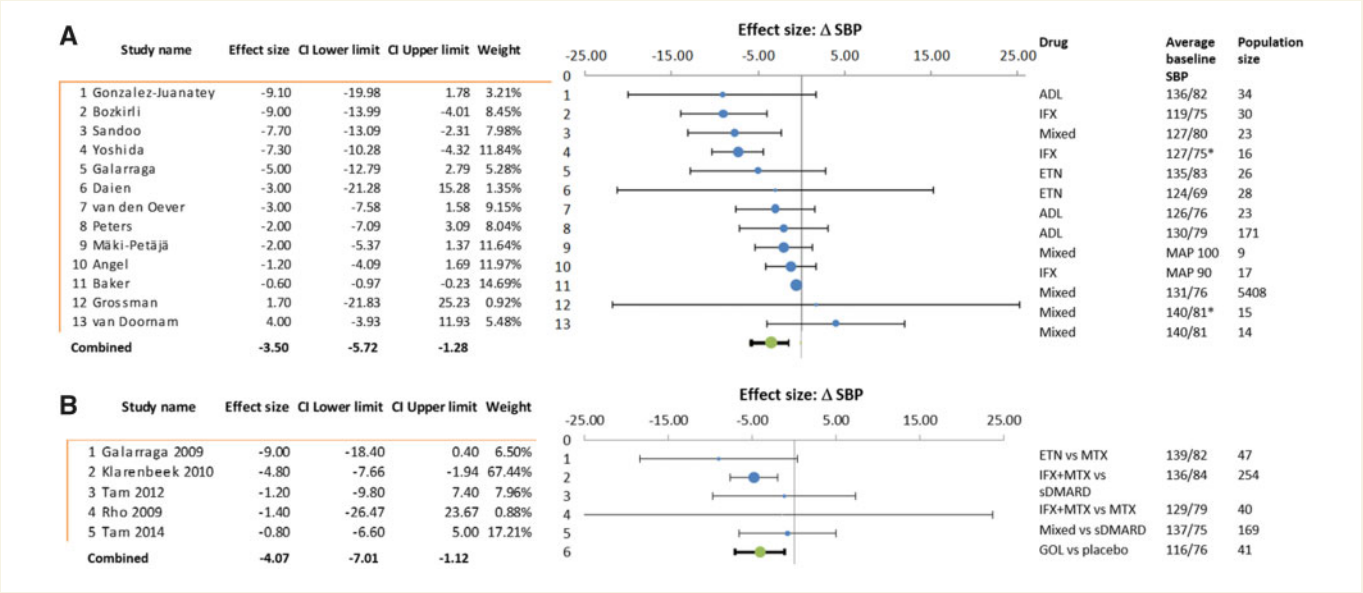


Figure 2 Meta-analysis and Forest Plot using random effect model, of TNF-α inhibitor studies reporting SBP outcomes, with reference to average baseline SBP, population size, and study weighting. Effect size reports average change in SBP in mmHg; * indicates ambulatory BP monitoring and MAP indicates only mean arterial pressure data available. Panel A includes cohort studies reporting average SBP prior and subsequent to drug initiation; panel B includes randomized trials with comparison to placebo or other pharmacotherapy. Overall change in average SBP accompanied by 95% confidence interval. ADL, adalimumab; ETN, etanercept; GOL, golimumab; IFX, infliximab; Mixed, different TNF-α inhibitors within the study; SBP, systolic blood pressure; sDMARD, conventional synthetic disease modifying anti-rheumatic; TNF-α, tumour necrosis factor alpha.

137.5 mmHg. Only one of these employed ABPM. Average SBP lowering ranged from 1.4 to 5.9 mmHg, and diastolic blood pressure (DBP) reduction of up to 4.4 mmHg (see Supplementary material online, *Table* and *Figure 3*).[149,154,157,181,182] Conversely, Makavos *et al.*[168] and CIRT[183] RCTs in psoriasis and patients with established cardiovascular risk, respectively, did not demonstrate average BP reduction with MTX. Considering the discrepancy, although 90% of the CIRT cohort had hypertension diagnoses, baseline BP values were not reported, precluding assessment of BP effects in individuals with uncontrolled hypertension.

5.2.3 Hydroxychloroquine

Hydroxychloroquine is an antimalarial agent that is used as a DMARD, and experimentally in IgA nephropathy.[154,157,184] This agent has been shown to reduce circulating dendritic cells (DCs) and reduces IFN-α, IL-6, and TNF-α levels.[185] Three studies of hydroxychloroquine have demonstrated BP lowering. The largest of these involved 7147 patients with RA and showed that hydroxychloroquine lowered BP by 1.2 mmHg systolic/0.6 mmHg diastolic from a baseline of 130/75 mmHg at 6 months.[157] Two smaller studies report SBP lowering of 3–8.8 mmHg (see Supplementary material online, *Table*).

5.2.4 Leflunomide

Leflunomide is a pyrimidine synthesis inhibitor used in active RA and psoriatic arthritis. In three studies, in which the subjects had an average baseline SBP ranging from 128 to 133 mmHg, a small increase of 1.44–4.3 mmHg systolic and 0.57–4.8 mmHg diastolic in office and ambulatory BP was observed.[154,157,186]

5.2.5 Calcineurin inhibitors

Calcineurin inhibitors (CNIs) block the earliest steps of T cell activation, but also have substantial off-target effects, including stimulation of endothelin production, increases in sympathetic outflow, renal vasoconstriction, salt retention, and hypertension (*Figure 4*).[187,188] Eight studies with BP data following 12–36 months of CNI treatment are reviewed (see Supplementary material online). In four of these, the baseline BP was in the hypertensive range.[189–192] Six reported lowering of BP (range −1 to −13 mmHg),[189–194] while two demonstrated a rise in BP of 5–11 mmHg.[168,195] Further detail is available in the Supplementary material online and reviewed elsewhere,[188] but in summary, limitations of trial design, and CNI off target effects make interpretation of BP effects of CNIs difficult (*Figure 4*).

5.2.6 Mammalian target of rapamycin inhibitors

Mammalian target of rapamycin (mTOR) inhibitors such as sirolimus and everolimus regulate cellular metabolism, growth, and proliferation, offering alternative immunosuppression following transplantation. Of six studies we found reporting BP values, the three reporting an average baseline SBP >140 mmHg all suggested a reduction in BP of between 3 and 8 mmHg,[189,190,192] though only one achieved statistical significance.[189] ABPM was only measured in the SCHEDULE trial of heart transplant patients treated with everolimus. An 8 mmHg fall in SBP ($P = 0.05$), and no change in DBP occurred from 2 weeks post-transplant to 12 months follow-up. This was dominated by reduction in nocturnal SBP in both the everolimus and cyclosporine arms.[189] BP lowering was not observed when the average baseline BP for the study was in the normotensive range.[195] mTOR inhibitors in comparison with other agents reported SBP outcomes that were neutral or elevated (0 or +4 mmHg

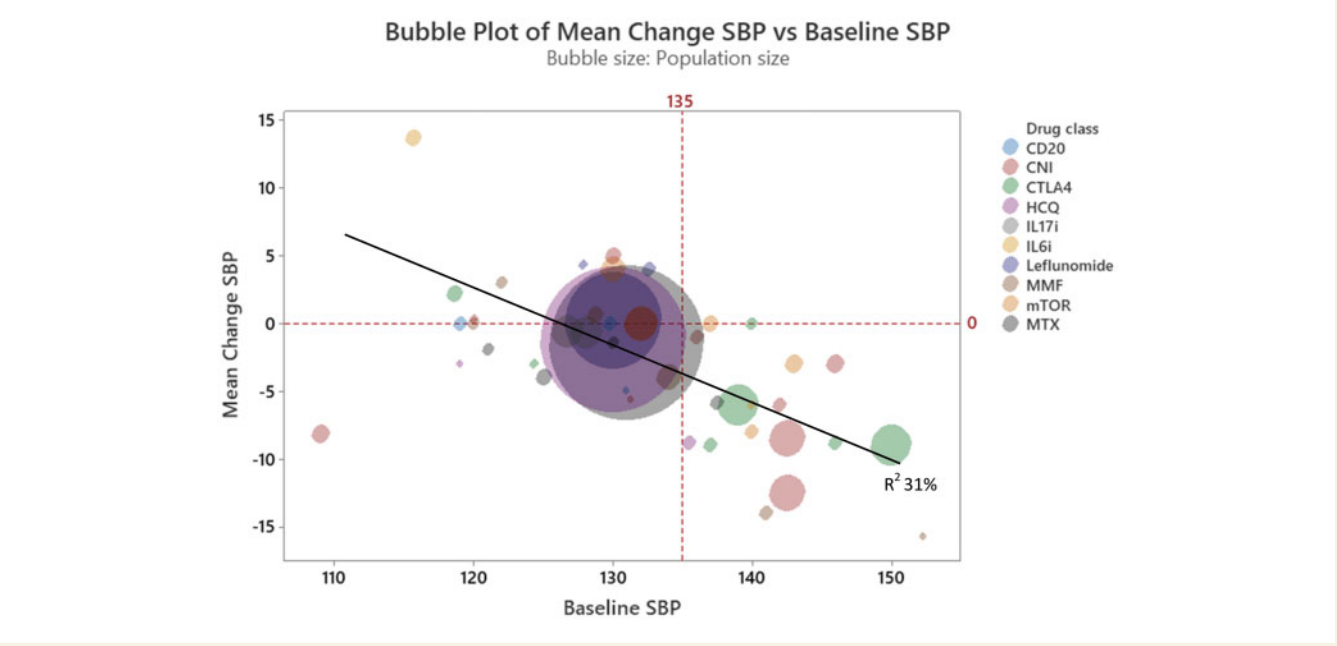


Figure 3 Bubble plot illustrating immunomodulatory agents plotted by baseline SBP (*x*-axis) and average change in SBP (*y*-axis), both in mmHg, with bubble area representing cohort size. R^2 = 31% fpr average change in SBP by average baseline SBP. CNI, calcineurin inhibitor; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; HCQ, hydroxychloroquine; IL, interleukin; MMF, mycophenolate mofetil; mTOR: mammalian target of rapamycin; MTX: methotrexate; SBP, systolic blood pressure; TNF, tumour necrosis factor.

change).[179,195,196] These studies are complicated by the concomitant use of multiple other drugs (see Supplementary material online).

5.2.7 Cytotoxic T-lymphocyte-associated protein 4-Ig

Abatacept is composed of the Fc region of the immunoglobulin IgG1 fused to the extracellular domain of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). This agent targets T cell co-stimulation and is commonly used in transplant and rheumatologic diseases. In five studies of RA patients reporting BP outcomes with abatacept, specific values were not available for two and none of the others reported a statistically significant effect on BP.[171,173,197–199] Seven studies reporting BP outcomes using Belatacept, an alternative CTLA-Ig, were identified. All of these were in transplant recipients and were compared to patients receiving CNIs. Two of these studies involved cross over from CNI to Belatacept and showed a SBP reduction of 5.4 and 8.8 mmHg ($P = 0.38$ and 0.03, respectively).[200,201] A case–control study reported a 9 mmHg lower SBP in subjects treated with this agent ($P = 0.68$).[202] Three RCTs showed a reduction in SBP between –2.4 and –9 mmHg,[203–205] but only one of these reached statistical significance[204] (see Supplementary material online, *Table*). One RCT reported no difference in mean SBP.[206] In only two studies did the subjects have an average baseline SBP in the hypertensive range,[199,201] and no studies employed ABPM. The apparent BP benefit with belatacept but not abatacept likely reflects population differences (transplant vs. RA, respectively), potential physiological changes post-transplantation, and the cross-over effect from CNI, which as noted above, has off-target effects that can raise BP.

5.2.8 Rituximab

Rituximab is a monoclonal antibody against CD20, resulting in B cell apoptosis and depletion. It is used in lymphoid and blood malignancies and diverse autoimmune diseases. Trials reporting BP that are not confounded by polypharmacy were sparse. We identified four such studies, and none involved patient groups with uncontrolled hypertension—the average participant baseline SBP being 131/83 mmHg or lower.[173,207–209] An early reduction in BP is common, but data reporting longer-term trends were discordant. No BP effect was seen in RA[173,207,208]; but a BP reduction was observed in membranous nephropathy at 4 weeks, though not sustained to 20 weeks.[209]

5.3 Determinants of the BP effects of immunosuppressants

In summary, trials in rheumatic, autoimmune, and transplant patients indicate a possible BP-lowering effect of selected anti-inflammatory therapies targeting diverse pathways previously identified by pre-clinical studies. The evidence appears to be most consistent in relation to anti-TNF-α agents, while other therapies such as hydroxychloroquine, MMF, and mTORs all suggest BP-lowering effect (*Figures 3 and 5*). Data are however conflicting, and hypertension was rarely a pre-specified outcome measure. Trials often involved normotensive populations in which BP lowering is difficult to observe. A combined analysis of studies discussed in this paper shows that cohorts with higher average baseline SBP appear to achieve greater BP-lowering effect (*Figure 3*), an association also reported for anti-hypertensive drugs.[210–212]

5.4 Non-pharmacological interventions

Several *non-pharmacological treatment* approaches have shown beneficial effects in reducing inflammation and therefore improving patient outcomes in the context of hypertension.

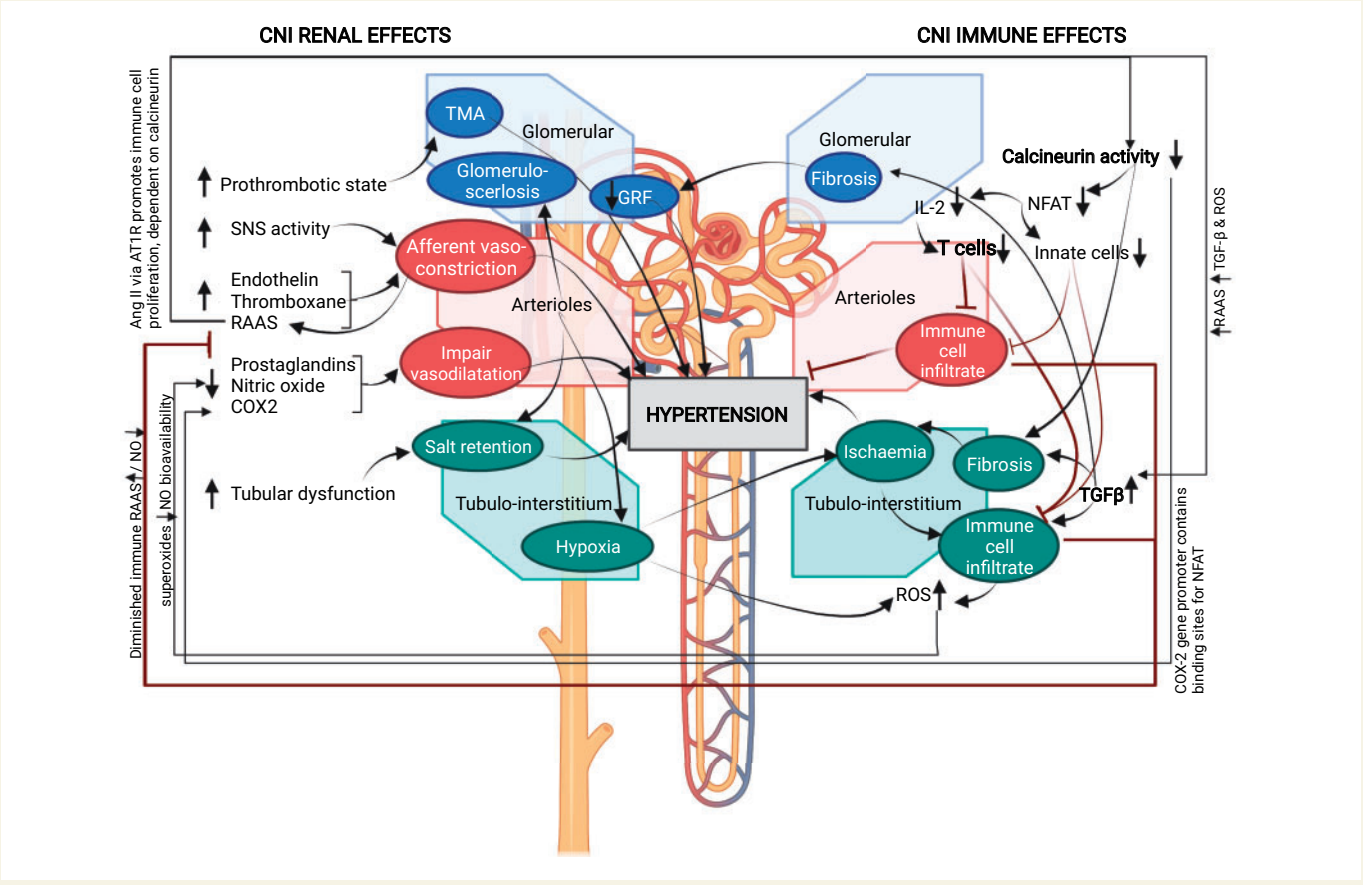


Figure 4 Renal and immune system effects of calcineurin inhibitors influencing blood pressure. COX2, cyclooxygenase-2; GFR, glomerulofiltration rate; IL-2, interleukin-2; NFAT, nuclear factor of activated T cells; NO, nitric oxide; TMA, thrombotic microangiopathy; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TGF-β, transforming growth factor beta. Created in BioRender.

5.4.1 Periodontitis targeting and BP

Animal studies suggest that periodontal *Porphyromonas gingivalis* infection increases IFN-γ and TNF-α production through modulation of Th1 responses, leading to BP elevation, endothelial dysfunction, and vascular inflammation.[213] This link is supported by Mendelian randomization,[214] observational data, and meta-analysis.[215–218] Data from well-controlled trials demonstrate that intense treatment of periodontitis can improve endothelial function,[219] lower inflammatory markers, and BP as measured by ABPM, with a reduction in SBP of 5 mmHg ($P < 0.01$).[220] A meta-analysis of eight studies involving intensive periodontal treatment showed an average decrease of SBP of -4.3 mm Hg (95% CI: –9.1 to –0.5) and DBP –3.16 mm Hg (95% CI: –6.5 to –0.2), though none of these achieved statistical significance. As in the case of pharmacological interventions, BP reductions were not observed in normotensive individuals.[221]

5.4.2 Energy metabolism, microbiome, and salt

Physical activity has an established role in BP regulation, with 3 months of exercise lowering SBP by approximately 5 mmHg and DBP by 3 mmHg.[222] Physical activity also has demonstrable immune effects.[223] Exercise can both increase circulating numbers of T cells[224] and improve response to influenza vaccination.[225]

For dietary interventions, most research has focused on CVD risk reduction, though BP lowering has also been demonstrated in both normotensive and hypertensive cohorts,[226,227] at least in part immune-mediated via effects of diet on the microbiome.[228] Metagenome-wide association evidence of gut dysbiosis in hypertension includes restricted sample diversity, higher lipopolysaccharide synthesis, membrane transport, and steroid degradation; suggesting low-grade inflammatory stimuli may be the mechanism.[229] Evidence is accumulating that plant-based dietary protein may promote bacterial species associated with anti-inflammatory effects, while meat consumption is linked to CVD and inflammatory bowel disease.[230]

Dietary salt is another dominant driver of hypertension, primarily through activation of renin–angiotensin–aldosterone system[231]; at higher concentration, salt also favours pro-inflammatory monocyte[232] and T cell phenotypes with increased tissue infiltration[233] and microvascular dysfunction.[234] Highly controlled experimental reduction in salt intake lowers pro-inflammatory IL-6 and IL-23, and increases IL-10 levels,[235] though this effect was not detected in a larger observational study.[236]

5.4.3 Neuronal manipulations

The central nervous system regulates vascular and kidney function through sympathetic innervation but is also a potent modulator of

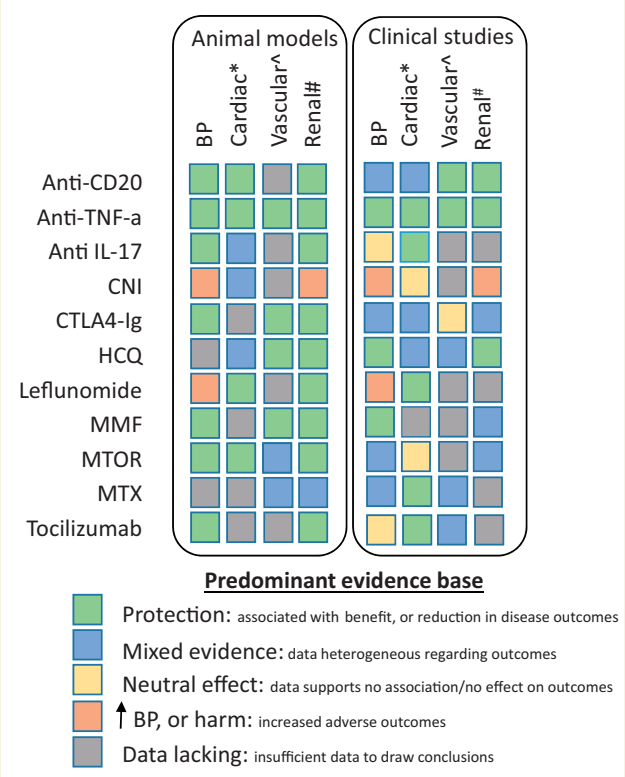


Figure 5 Immunomodulatory drugs and the level of animal and clinical evidence available regarding blood pressure and organ system outcomes. Summarized according to the aggregated weight of the available evidence. BP, blood pressure; CD, cluster of differentiation; CNI, calcineurin inhibitor; CTLA4-Ig, cytotoxic T-lymphocyte-associated protein 4 immunoglobulin; HCQ, hydroxychloroquine; IL, interleukin; MMF, mycophenolate mofetil; mTOR: mammalian target of rapamycin; MTX: methotrexate; TNF, tumour necrosis factor. *Cardiovascular outcomes. ^Includes arterial stiffness, endothelial function, and cerebrovascular outcomes. #Includes chronic kidney disease, end-stage kidney disease, fibrosis, and inflammation.

immune responses. Animal and human studies demonstrate the role of neuroimmune axis in the pathogenesis of hypertension,[237,238] with murine renal denervation (RDN) inducing a reduction in BP,[239–242] and reduction in renal inflammation, T cell activation, and pro-inflammatory cytokine production.[240,243] However, SIMPLICITY, SPYRAL, and RADIANCE human clinical trials demonstrate inconsistent results, mostly favouring sustained BP reduction.[244,245] Some but not all[246] of these were sham-controlled RDN designs.[247–249] The effect of RDN on immune activation in humans is less clear. One trial demonstrated reductions in TNF-α and IL-1β, and up-regulation of IL-10 one day after RDN; however, this did not persist to day 3,[250] and was not corroborated elsewhere.[251,252]

An alternative approach to sympathetic denervation is augmentation of parasympathetic activity through vagus nerve stimulation (VNS). This approach has proven effective in hypertensive rodent models.[253–255] VNS limits hypertension-induced endothelial dysfunction[256] and reduces levels of systemic cytokines and mRNA expression in target organs,[257] with both afferent and efferent VNS protecting mice from kidney injury.[258] Anti-inflammatory effects of VNS are abolished in immune-deficient and β2 adrenergic receptor-deficient mice.[259] When stimulated by Ang II or bioelectronic signals, a splenic neuroimmune cascade is triggered via α-adrenergic receptors. In response, $CD8^+$ effector T cells with a role in hypertension[25] egress from the spleen.[260] VNS has not yet been tested in human hypertension, but has been used in epilepsy and in RA, demonstrating lowering of circulating TNF-α, IL-1-β, and IL-6 levels and improvement in disease activity.[261]

5.5 Hypertension-mediated organ damage

Hypertension-mediated organ damage (HMOD) correlates with BP values in hypertension[262,263]; however, genetics, lifestyle, and co-morbid conditions may also contribute to end-organ damage independently of BP levels. Similarly, the target organ benefit of immunomodulation might be partially independent of BP effects. The strength of evidence regarding the effects of immunomodulatory therapy on HMOD in experimental and clinical settings is summarized in *Figure 5*. Registry data of active RA, with 30% hypertension prevalence, suggested no difference in myocardial infarction rates in response to TNF-α inhibitors vs. DMARDs. However, 60% fewer events did occur in the TNF-α inhibitor responder subgroup vs. non-responders.[264] The observational QUEST-RA study included subjects with hypertension prevalence of 32% and was adjusted for traditional risk factors. This study reported a reduction in cardiovascular risk in response to numerous immunomodulatory drugs, including biologic agents (HR: 0.42; 95% CI: 0.21–0.81), MTX (HR: 0.85; 95% CI: 0.81–0.89), sulfasalazine (HR: 0.92; 95% CI: 0.87–0.98), and leflunomide (HR: 0.59; 95% CI: 0.43–0.79); $P < 0.05$.[265] Baseline BP values were not reported in either paper. Nurmohamed *et al.* reviewed 90 studies reporting cardiovascular risk outcomes in rheumatological conditions treated with abatacept, TNF-α inhibitors, rituximab, secukinumab, tocilizumab, and tofacitinib. They report a neutral effect on BP, on surrogate markers of cardiovascular risk, and on MACE, though authors emphasise the variation in quantity and quality of evidence.[266]

Observational data based on 13 000 matched pairs from Medicare and MarketScan patients with RA and newly treated with abatacept or a TNF-α inhibitor found benefit of abatacept in MACE restricted to the subgroup with diabetes [HR: 0.74 (95% CI: 0.57–0.96)].[267] Potential confounding arose from higher rates of hypertension in the diabetic subgroups, again supporting potential benefit of TNF-α inhibitors in hypertension.[167] Finally, a meta-analysis of 14 studies in patients with RA, adjusted for hypertension, concluded that DMARDs were associated with an increased risk of MACE relative to TNF-α inhibitor therapy [OR: 1.58 (95% CI: 1.16–2.15); I2 = 16%], effect maintained in presence or absence of MTX.[268]

Colchicine is hypothesized to inhibit microtubular polymerization, assembly of the NLRP3 inflammasome, and IL-1β and IL-18 production. In acute coronary syndrome, colchicine abrogates local increases in IL-1β, IL-18, and IL-6 levels,[269] and its addition to aspirin and statin reduces high-sensitivity C-reactive protein.[270] Colchicine 0.5 mg daily has been demonstrated to reduce MACE by 67% compared to placebo in LoDoCo RCT of 532 patients with stable coronary artery disease,[271] though the similarly sized COPS trial found no benefit in cardiovascular outcomes.[272] The larger COLCOT trial of 4745 participants recruited within 30 days of acute coronary syndrome reported composite cardiovascular end-point occurrences in 5.5% of the colchicine group vs. 7.1% of the placebo group (HR: 0.77; 95% CI: 0.61–0.96; $P = 0.02$).[9] Half of these patients had hypertension. Similarly, LoDoCo2 randomized 5522

chronic coronary disease patients to low-dose colchicine, with composite end-point events in 6.8% of the colchicine group vs. 9.6% of placebo group (HR: 0.69; 95% CI: 0.57–0.83; $P < 0.001$).[11]

Overall, we would conclude that there is evidence of improvement in MACE for TNF-α inhibitors, MTX, tocilizumab, secukinumab, leflunomide and colchicine, though heterogeneity of study designs and outcomes limits the strength of this statement, and we have not explored the relationship between reduction in inflammation and MACE suggested by CANTOS and TNF-α inhibitor responders in the registry data above. HMOD outcomes beyond MACE are surmised in *Figure 5* for common immunomodulatory drugs.

6. Conclusions

While experimental, genetic, and clinical evidence supports the role of inflammation and immune system involvement in hypertension and associated vascular, renal, and cardiac pathology, immunomodulatory approaches are not currently considered therapeutic options in BP lowering and cardiovascular disease reduction. Indeed, clinical evidence reviewed in this paper shown a highly heterogeneous effect of immune targeting on BP and cardiovascular events across a wide range of patients mainly with various underlying immune-mediated diseases. Going forward, there are several important considerations. As is the case with traditional anti-hypertensive medications, the BP-lowering effects of anti-inflammatory agents appear to be limited to those with uncontrolled hypertension. This is not surprising as numerous compensatory mechanisms make lowering beyond normal BP difficult. It is also important to consider that the effects may be limited to patients with active pro-hypertensive inflammatory mechanisms. The lesson from CIRT, TNF-α inhibitor responders vs. non-responders, CANTOS, and the body of the evidence presented is that there must be *active* inflammation. Hence, cardiovascular risk reduction with immune modulation is mediated not through BP alone, but via broader mechanisms of oxidative stress, endothelial function, vascular remodelling, and endocrine regulation, that are the 'common denominators' of a dysfunctional relationship. Secondly, we must target the optimal checkpoint in the inflammation–hypertension relationship to optimize benefit without adverse effect, and so far, this has remained elusive at a population level. Finally, it is important to consider that virtually all of the preclinical studies investigating the anti-hypertensive effect of immune interventions on hypertension have involved treatment of animals at the onset on hypertension, often concomitantly with the onset of the disease. In contrast, these agents are usually given to humans with long-standing hypertension. It is possible, and even likely that once hypertension has been established, there are chronic changes in renal and vascular function and structure that render such treatment less effective. In this regard, treatment of younger individuals with early onset hypertension might yield different results than those observed in the studies summarized here.

Supplementary material

Supplementary material is available at *Cardiovascular Research* online.

Conflict of interest: none to declare.

Funding

This work was supported by the European Research Council (Project Identifier: 726318); the British Heart Foundation grants PG/19/84/34771, PG/21/10541, and RE/13/5/30177; the Marie Sklodowska Curie CIG Award 3631773; the Wellcome Trust grant 204820/Z/16/Z; and the University of Glasgow, Scottish Funding Council and the Global Challenges Research Fund.

Data availability

Data derived from sources in the public domain. Reference details are provided in full.

Acknowledgements

Statistical assistance was provided by Dr John McClure, University of Glasgow. Software used in the generating of this manuscript includes BioRender.com (figures), Minitab-19 Statistical Software, and Meta-essentials (meta-analysis).[273]

References

1. Libby P. The changing landscape of atherosclerosis. *Nature* 2021;**592**:524–533.
2. Liberale L, Montecucco F, Tardif JC, Libby P, Camici GG. Inflamm-ageing: the role of inflammation in age-dependent cardiovascular disease. *Eur Heart J* 2020;**41**:2974–2982.
3. Nus M, Mallat Z, Sage A. Beating (T-lymphocyte driven) atherosclerosis with B- and T-lymphocyte attenuator. *Cardiovasc Res* 2020;**116**:251–252.
4. van Kuijk K, Kuppe C, Betsholtz C, Vanlandewijck M, Kramann R, Sluimer JC. Heterogeneity and plasticity in healthy and atherosclerotic vasculature explored by single-cell sequencing. *Cardiovasc Res* 2019;**115**:1705–1715.
5. Douna H, Amersfoort J, Schaftenaar FH, Kröner MJ, Kiss MG, Slütter B, Depuydt MAC, Bernabé Kleijn MNA, Wezel A, Smeets HJ, Yagita H, Binder CJ, Bot I, van Puijvelde GHM, Kuiper J, Foks AC. B- and T-lymphocyte attenuator stimulation protects against atherosclerosis by regulating follicular B cells. *Cardiovasc Res* 2020;**116**:295–305.
6. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Bäck M, Benetos A, Biffi A, Boavida J-M, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337.
7. Steffens S, van LS, Sluijter JPG, Tocchetti CG, Thum T, Madonna R. Stimulating pro-reparative immune responses to prevent adverse cardiac remodelling: consensus document from the joint 2019 meeting of the ESC Working Groups of cellular biology of the heart and myocardial function. *Cardiovasc Res* 2020;**116**:1850–1862.
8. Elnabawi YA, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, Rodante J, Harrington CL, Teague HL, Baumer Y, Keel A, Playford MP, Sandfort V, Chen MY, Lockshin B, Gelfand JM, Bluemke DA, Mehta NN. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: results from a prospective observational study. *Cardiovasc Res* 2019;**115**:721–728.
9. Tardif J-CC, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, Pinto FJ, Ibrahim R, Gamra H, Kiwan GS, Berry C, López-Sendón J, Ostadal P, Koenig W, Angoulvant D, Grégoire JC, Lavoie M-AA, Dubé M-PP, Rhainds D, Provencher M, Blondeau L, Orfanos A, L'Allier PL, Guertin M-CC, Roubille F. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;**381**:2497–2499.
10. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker SD, Kastelein JJP, Cornel JH, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi PRF, Troquay RPT, Libby P, Glynn RJ, Krum H, Varigos J. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;**377**:1119–1131.
11. Nidorf SM, Fiolet ATL, Mosterd A, Eikelboom JW, Schut A, Opstal TSJ, The SHK, Xu X-F, Ireland MA, Lenderink T, Latchem D, Hoogslag P, Jerzewski A, Nierop P, Whelan A, Hendriks R, Swart H, Schaap J, Kuijper AFM, van Hessen MWJ, Saklani P, Tan I, Thompson AG, Morton A, Judkins C, Bax WA, Dirksen M, Alings M, Hankey GJ, Budgeon CA, Tijssen JGP, Cornel JH, Thompson PL; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;**383**:1838–1847.
12. Weber BN, Blankstein R. Something old, something new: a paradigm for considering immune therapies for cardiovascular disease. *Cardiovasc Res* 2020;**116**:e51–e53.
13. GBD 2017 Risk Factor Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018;**392**:1923–1994.

14. Markó L, Park J-K, Henke N, Rong S, Balogh A, Klamer S, Bartolomaeus H, Wilck N, Ruland J, Forslund SK, Luft FC, Dechend R, Müller DN. B-cell lymphoma/leukaemia 10 and angiotensin II-induced kidney injury. *Cardiovasc Res* 2020;**116**:1059–1070.
15. Grabie N, Lichtman AH, Padera R. T cell checkpoint regulators in the heart. *Cardiovasc Res* 2019;**115**:869–877.
16. Peet C, Ivetic A, Bromage DI, Shah AM. Cardiac monocytes and macrophages after myocardial infarction. *Cardiovasc Res* 2020;**116**:1101–1112.
17. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. *Nat Rev Immunol* 2019;**19**:517–532.
18. Okuda T, Grollman A. Passive transfer of autoimmune induced hypertension in the rat by lymph node cells. *Tex Rep Biol Med* 1967;**25**:257–264.
19. Svendsen U. The role of thymus for the development and prognosis of hypertension and hypertensive vascular disease in mice following renal infarction. *Acta Pathol Microbiol Scand A* 1976;**84**:235–243.
20. Svendsen UG. Influence of neonatal thymectomy on blood pressure and hypertensive vascular diseases in rats with renal hypertension. *Acta Pathol Microbiol Scand A* 1975;**83**:199–205.
21. Svendsen UG. Thymus dependency of periarteritis nodosa in DOCA and salt treated mice. *Acta Pathol Microbiol Scand A* 1974;**82**:30–34.
22. Olsen F. Transfer of arterial hypertension by splenic cells from DOCA-salt hypertensive and renal hypertensive rats to normotensive recipients. *Acta Pathol Microbiol Scand C* 1980;**88**:1–6.
23. Olsen F. Evidence for an immunological factor in the hypertensive vascular disease. *Acta Pathol Microbiol Scand A* 1971;**79**:22–26.
24. Vinh A, Chen W, Blinder Y, Weiss D, Taylor WR, Goronzy JJ, Weyand CM, Harrison DG, Guzik TJ. Inhibition and genetic ablation of the B7/CD28 T-cell costimulation axis prevents experimental hypertension. *Circulation* 2010;**122**:2529–2537.
25. Guzik TJ, Hoch NE, Brown KA, McCann LA, Rahman A, Dikalov S, Goronzy J, Weyand C, Harrison DG. Role of the T cell in the genesis of angiotensin II–induced hypertension and vascular dysfunction. *J Exp Med* 2007;**204**:2449–2460.
26. Pollow DP, Uhrlaub J, Romero-Aleshire M, Sandberg K, Nikolich-Zugich J, Brooks HL, Hay M. Sex differences in T-lymphocyte tissue infiltration and development of angiotensin II hypertension. *Hypertension* 2014;**64**:834–890.
27. Seniuk A, Thiele JL, Stubbe A, Oser P, Rosendahl A, Bode M, Meyer-Schwesinger C, Wenzel UO, Ehmke H. B6.Rag1 Knockout mice generated at the Jackson Laboratory in 2009 show a robust wild-type hypertensive phenotype in response to Ang II (angiotensin II). *Hypertension* 2020;**75**:1110–1116.
28. Ji H, Pai AV, West CA, Wu X, Speth RC, Sandberg K. Loss of resistance to angiotensin II-induced hypertension in the Jackson Laboratory recombination-activating gene null mouse on the C57BL/6J background. *Hypertension* 2017;**69**:1121–1127.
29. Mattson DL, Lund H, Guo C, Rudemiller N, Geurts AM, Jacob H. Genetic mutation of recombination activating gene 1 in Dahl salt-sensitive rats attenuates hypertension and renal damage. *Am J Physiol Regul Integr Comp Physiol* 2013;**304**:R407–R414.
30. Crowley SD, Song Y-S, Lin EE, Griffiths R, Kim H-S, Ruiz P. Lymphocyte responses exacerbate angiotensin II-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**:1089–1097.
31. Wu J, Thabet SR, Kirabo A, Trott DW, Saleh MA, Xiao L, Madhur MS, Chen W, Harrison DG. Inflammation and mechanical stretch promote aortic stiffening in hypertension through activation of p38 mitogen-activated protein kinase. *Circ Res* 2014;**114**:616–625.
32. Trott DW, Thabet SR, Kirabo A, Saleh MA, Itani H, Norlander AE, Wu J, Goldstein A, Arendshorst WJ, Madhur MS, Chen W, Li C-I, Shyr Y, Harrison DG. Oligoclonal CD8+ T cells play a critical role in the development of hypertension. *Hypertension* 2014;**64**:1108–1115.
33. Kvakan H, Kleinewietfeld M, Qadri F, Park J-K, Fischer R, Schwarz I, Rahn H-P, Plehm R, Wellner M, Elitok S, Gratze P, Dechend R, Luft FC, Muller DN. Regulatory T cells ameliorate angiotensin II-induced cardiac damage. *Circulation* 2009;**119**:2904–2912.
34. Barhoumi T, Kasal DA, Li MW, Shbat L, Laurant P, Neves MF, Paradis P, Schiffrin EL. T regulatory lymphocytes prevent angiotensin II-induced hypertension and vascular injury. *Hypertension* 2011;**57**:469–476.
35. Caillon A, Mian MOR, Fraulob-Aquino JC, Huo K-G, Barhoumi T, Ouerd S, Sinnaeve PR, Paradis P, Schiffrin EL. γδ T cells mediate angiotensin II-induced hypertension and vascular injury. *Circulation* 2017;**135**:2155–2162.
36. Wenzel P, Knorr M, Kossmann S, Stratmann J, Hausding M, Schuhmacher S, Karbach SH, Schwenk M, Yogev N, Schulz E, Oelze M, Grabbe S, Jonuleit H, Becker C, Daiber A, Waisman A, Münzel T. Lysozyme M-positive monocytes mediate angiotensin ii-induced arterial hypertension and vascular dysfunction. *Circulation* 2011;**124**:1370–1381.
37. Moore JP, Vinh A, Tuck KL, Sakkal S, Krishnan SM, Chan CT, Lieu M, Samuel CS, Diep H, Kemp-Harper BK, Tare M, Ricardo SD, Guzik TJ, Sobey CG, Drummond GR. M2 macrophage accumulation in the aortic wall during angiotensin II infusion in mice is associated with fibrosis, elastin loss and elevated blood pressure. *Am J Physiol Heart Circ Physiol* 2015;**309**:H906–H917.
38. De Ciuceis C, Amiri F, Brassard P, Endemann DH, Touyz RM, Schiffrin EL. Reduced vascular remodeling, endothelial dysfunction, and oxidative stress in resistance arteries of angiotensin II-infused macrophage colony-stimulating factor-deficient mice: evidence for a role in inflammation in angiotensin-induced vascular injury. *Arterioscler Thromb Vasc Biol* 2005;**25**:2106–2113.
39. Huang L, Wang A, Hao Y, Li W, Liu C, Yang Z, Zheng F, Zhou M-S. Macrophage depletion lowered blood pressure and attenuated hypertensive renal injury and fibrosis. *Front Physiol* 2018;**9**:e473.
40. Hevia D, Araos P, Prado C, Luppichini Rojas FE, Alzamora M, Cifuentes-Araneda R, Gonzalez F, Amador AA, Pacheco CA, Michea R. L. Myeloid CD11c^{+} antigen-presenting cells ablation prevents hypertension in response to angiotensin II plus high-salt diet. *Hypertension* 2018;**71**:709–718.
41. Chan CT, Sobey CG, Lieu M, Ferens D, Kett MM, Diep H, Kim HA, Krishnan SM, Lewis CV, Salimova E, Tipping P, Vinh A, Samuel CS, Peter K, Guzik TJ, Kyaw TS, Toh BH, Bobik A, Drummond GR. Obligatory role for B cells in the development of angiotensin II-dependent hypertension. *Hypertension* 2015;**66**:1023–1033.
42. Chen Y, Dale BL, Alexander MR, Xiao L, Ao M, Pandey AK, Smart CD, Davis GK, Madhur MS. Class switching and high-affinity immunoglobulin G production by B cells is dispensable for the development of hypertension in mice. *Cardiovasc Res* 2021;**117**:1217–1228.
43. Kossmann S, Schwenk M, Hausding M, Karbach SH, Schmidgen MI, Brandt M, Knorr M, Hu H, Kröller-Schön S, Schönfelder T, Grabbe S, Oelze M, Daiber A, Münzel T, Becker C, Wenzel P. Angiotensin ii-induced vascular dysfunction depends on interferon-γ- driven immune cell recruitment and mutual activation of monocytes and NK-cells. *Arterioscler Thromb Vasc Biol* 2013;**33**:1313–1319.
44. Rodríguez-Iturbe B, Ferrebuz A, Vanegas V, Quiroz Y, Mezzano S, Vaziri ND. Early and sustained inhibition of nuclear factor-kappaB prevents hypertension in spontaneously hypertensive rats. *J Pharmacol Exp Ther* 2005;**315**:e51–e57.
45. Brands MW, Banes-Berceli AKL, Inscho EW, Al-Azawi H, Allen AJ, Labazi H. Interleukin 6 knockout prevents angiotensin II hypertension: role of renal vasoconstriction and janus kinase 2/signal transducer and activator of transcription 3 activation. *Hypertension* 2010;**56**:879–884.
46. Wen Y, Liu Y, Tang T, Lv L, Liu H, Ma K, Liu B. NLRP3 inflammasome activation is involved in Ang II-induced kidney damage via mitochondrial dysfunction. *Oncotarget* 2016;**7**:54290–54302.
47. Huang B, Cheng Y, Usa K, Liu Y, Baker MA, Mattson DL, He Y, Wang N, Liang M. Renal tumor necrosis factor α contributes to hypertension in Dahl salt-sensitive rats. *Sci Rep* 2016;**6**:21960.
48. McShane L, Tabas I, Lemke G, Kurowska-Stolarska M, Maffia P. TAM receptors in cardiovascular disease. *Cardiovasc Res* 2019;**115**:1286–1295.
49. Nosalski R, Mikolajczyk T, Siedlinski M, Saju B, Koziol J, Maffia P, Guzik TJ. Nox1/4 inhibition exacerbates age dependent perivascular inflammation and fibrosis in a model of spontaneous hypertension. *Pharmacol Res* 2020;**161**:105235.
50. MacRitchie N, Grassia G, Noonan J, Cole JE, Hughes CE, Schroeder J, Benson RA, Cochain C, Zernecke A, Guzik TJ, Garside P, Monaco C, Maffia P. The aorta can act as a site of naïve CD4+ T-cell priming. *Cardiovasc Res* 2020;**116**:306–316.
51. Kirabo A, Fontana V, de Faria APC, Loperena R, Galindo CL, Wu J, Bikineyeva AT, Dikalov S, Xiao L, Chen W, Saleh MA, Trott DW, Itani HA, Vinh A, Amarnath V, Amarnath K, Guzik TJ, Bernstein KE, Shen XZ, Shyr Y, Chen S-C, Mernaugh RL, Laffer CL, Elijovich F, Davies SS, Moreno H, Madhur MS, Roberts J, Harrison DG. DC isoketal-modified proteins activate T cells and promote hypertension. *J Clin Invest* 2014;**124**:4642–4656.
52. Krishnan SM, Dowling JK, Ling YH, Diep H, Chan CT, Ferens D, Kett MM, Pinar A, Samuel CS, Vinh A, Arumugam TV, Hewitson TD, Kemp-Harper BK, Robertson AAB, Cooper MA, Latz E, Mansell A, Sobey CG, Drummond GR. Inflammasome activity is essential for one kidney/deoxycorticosterone acetate/salt-induced hypertension in mice. *Br J Pharmacol* 2016;**173**:752–765.
53. Carnevale D, Perrotta M, Pallante F, Fardella V, Iacobucci R, Fardella S, Carnevale L, Carnevale R, De LM, Cifelli G, Lembo G. A cholinergic-sympathetic pathway primes immunity in hypertension and mediates brain-to-spleen communication. *Nat Commun* 2016;**7**:13035.
54. Carnevale D, Pallante F, Fardella V, Fardella S, Iacobucci R, Federici M, Cifelli G, De Lucia M, Lembo G. The angiogenic factor PlGF mediates a neuroimmune interaction in the spleen to allow the onset of hypertension. *Immunity* 2014;**41**:737–752.
55. Rodriguez-Iturbe B, Lanaspa MA, Johnson RJ. The role of autoimmune reactivity induced by heat shock protein 70 in the pathogenesis of essential hypertension. *Br J Pharmacol* 2019;**176**:1829–1838.
56. Idris-Khodja N, Mian MOR, Paradis P, Schiffrin EL. Dual opposing roles of adaptive immunity in hypertension. *Eur Heart J* 2014;**35**:1238–1244.
57. Madhur MS, Kirabo A, Guzik TJ, Harrison DG. From rags to riches: moving beyond Rag1 in studies of hypertension. *Hypertension* 2020;**75**:930–934.
58. Xiao L, Harrison DG. Inflammation in hypertension. *Can J Cardiol* 2020;**36**:635–647.
59. Nosalski R, Siedlinski M, Denby L, McGinnigle E, Nowak M, Cat AND, Medina-Ruiz L, Cantini M, Skiba D, Wilk G, Osmenda G, Rodor J, Salmeron-Sanchez M, Graham G, Maffia P, Graham D, Baker AH, Guzik TJ. T-cell-derived miRNA-214 mediates perivascular fibrosis in hypertension. *Circ Res* 2020;**126**:988–1003.
60. Hoyer FF, Nahrendorf M. Interferon-γ regulates cardiac myeloid cells in myocardial infarction. *Cardiovasc Res* 2019;**115**:1815–1816.
61. Abdellatif M, Zirlik A. Immunometabolism: a key target to improve microcirculation in ageing. *Cardiovasc Res* 2020;**116**:e48–e50.
62. Matrougui K, Abd Elmageed Z, Zakaria AE, Kassan M, Choi S, Nair D, Gonzalez-Villalobos RA, Chentoufi AA, Kadowitz P, Belmadani S, Partyka M. Natural

regulatory T cells control coronary arteriolar endothelial dysfunction in hypertensive mice. *Am J Pathol* 2011;**178**:434–441.
63. Madhur MS, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, Harrison DG. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunction. *Hypertension* 2010;**55**:500–507.
64. Kamat N. V, Thabet SR, Xiao L, Saleh MA, Kirabo A, Madhur MS, Delpire E, Harrison DG, McDonough AA. Renal transporter activation during angiotensin-II hypertension is blunted in interferon-γ-/- and interleukin-17A-/- mice. *Hypertension* 2015;**65**:569–576.
65. Zhang J, Patel MB, Griffiths R, Mao A, Song Y, Karlovich NS, Sparks MA, Jin H, Wu M, Lin EE, Crowley SD. Tumor necrosis factor-α produced in the kidney contributes to angiotensin II-dependent hypertension. *Hypertension* 2014;**64**:1275–1281.
66. Yvan-Charvet L, Bonacina F, Guinamard RR, Norata GD. Immunometabolic function of cholesterol in cardiovascular disease and beyond. *Cardiovasc Res* 2019;**115**: 1393–1407.
67. Filho AG, Kinote A, Pereira DJ, Rennó A, Dos Santos RC, Ferreira-Melo SE, Velloso LA, Bordin S, Anhê GF, Junior HM. Infliximab prevents increased systolic blood pressure and upregulates the AKT/eNOS pathway in the aorta of spontaneously hypertensive rats. *Eur J Pharmacol* 2013;**700**:201–209.
68. Elmarakby AA, Quigley JE, Pollock DM, Imig JD. Tumor necrosis factor alpha blockade increases renal Cyp2c23 expression and slows the progression of renal damage in salt-sensitive hypertension. *Hypertension* 2006;**47**:557–562.
69. Muller DN, Shagdarsuren E, Park J-K, Dechend R, Mervaala E, Hampich F, Fiebeler A, Ju X, Finckenberg P, Theuer J, Viedt C, Kreuzer J, Heidecke H, Haller H, Zenke M, Luft FC. Immunosuppressive treatment protects against angiotensin II-induced renal damage. *Am J Pathol* 2002;**161**:1679–1693.
70. Tran LT, MacLeod KM, McNeill JH. Chronic etanercept treatment prevents the development of hypertension in fructose-fed rats. *Mol Cell Biochem* 2009;**330**: 219–228.
71. Venegas-Pont M, Manigrasso MB, Grifoni SC, LaMarca BB, Maric C, Racusen LC, Glover PH, Jones AV, Drummond HA, Ryan MJ. Tumor necrosis factor-alpha antagonist etanercept decreases blood pressure and protects the kidney in a mouse model of systemic lupus erythematosus. *Hypertension* 2010;**56**:643–649.
72. Therrien FJ, Agharazii M, Lebel M, Larivière R. Neutralization of tumor necrosis factor-alpha reduces renal fibrosis and hypertension in rats with renal failure. *Am J Nephrol* 2012;**36**:151–161.
73. Krishnan SM, Ling YH, Huuskes BM, Ferens DM, Saini N, Chan CT, Diep H, Kett MM, Samuel CS, Kemp-Harper BK, Robertson AAB, Cooper MA, Peter K, Latz E, Mansell AS, Sobey CG, Drummond GR, Vinh A. Pharmacological inhibition of the NLRP3 inflammasome reduces blood pressure, renal damage, and dysfunction in salt-sensitive hypertension. *Cardiovasc Res* 2018;**61**:776–787.
74. Cau SBA, Guimaraes DA, Rizzi E, Ceron CS, Gerlach RF, Tanus-Santos JE. The nuclear factor kappaB inhibitor pyrrolidine dithiocarbamate prevents cardiac remodelling and matrix metalloproteinase-2 up-regulation in renovascular hypertension. *Basic Clin Pharmacol Toxicol* 2015;**117**:234–241.
75. Zhang J, Rudemiller NP, Patel MB, Karlovich NS, Wu M, McDonough AA, Griffiths R, Sparks MA, Jeffs AD, Crowley SD. Interleukin-1 receptor activation potentiates salt reabsorption in angiotensin II-induced hypertension via the NKCC2 Co-transporter in the nephron. *Cell Metab* 2016;**23**:360–368.
76. Ling YH, Krishnan SM, Chan CT, Diep H, Ferens D, Chin-Dusting J, Kemp-Harper BK, Samuel CS, Hewitson TD, Latz E, Mansell A, Sobey CG, Drummond GR. Anakinra reduces blood pressure and renal fibrosis in one kidney/DOCA/salt-induced hypertension. *Pharmacol Res* 2017;**116**:77–86.
77. Hashmat S, Rudemiller N, Lund H, Abais-Battad JM, Van Why S, Mattson DL. Interleukin-6 inhibition attenuates hypertension and associated renal damage in Dahl salt-sensitive rats. *Am J Physiol Renal Physiol* 2016;**311**:F555–F561.
78. Mathis KW, Taylor EB, Ryan MJ. Anti-CD3 antibody therapy attenuates the progression of hypertension in female mice with systemic lupus erythematosus. *Pharmacol Res* 2017;**120**:252–257.
79. Ma F, Feng J, Zhang C, Li Y, Qi G, Li H, Wu Y, Fu Y, Zhao Y, Chen H, Du J, Tang H. The requirement of CD8+ T cells to initiate and augment acute cardiac inflammatory response to high blood pressure. *J Immunol* 2014;**192**:3365–3373.
80. Majeed B, Tawinwung S, Eberson LS, Secomb TW, Larmonier N, Larson DF. Interleukin-2/anti-interleukin-2 immune complex expands regulatory T cells and reduces angiotensin II-induced aortic stiffening. *Int J Hypertens* 2014;**2014**:126365.
81. Wang H, Hou L, Kwak D, Fassett J, Xu X, Chen A, Chen W, Blazar BR, Xu Y, Hall JL, Ge J-B, Bache RJ, Chen Y. Increasing regulatory T cells with interleukin-2 and interleukin-2 antibody complexes attenuates lung inflammation and heart failure progression. *Hypertension* 2016;**68**:114–122.
82. Sun X-NN, Li C, Liu YY, Du L-J, Zeng M-RR, Zheng X-JJ, Zhang W-CC, Liu YY, Zhu M, Kong D, Zhou L, Lu L, Shen Z-XX, Yi Y, Du L-J, Qin M, Liu X, Hua Z, Sun S, Yin H, Zhou B, Yu Y, Zhang Z, Duan S-ZZ. T-cell mineralocorticoid receptor controls blood pressure by regulating interferon-gamma. *Circ Res* 2017;**120**: 1584–1597.
83. Markó L, Kvakan H, Park JK, Qadri F, Spallek B, Binger KJ, Bowman EP, Kleinewietfeld M, Fokuhl V, Dechend R, Müller DN. Interferon-γ signaling inhibition ameliorates angiotensin ii-induced cardiac damage. *Hypertension* 2012;**60**: 1430–1436.
84. Amador CA, Barrientos V, Peña J, Herrada AA, González M, Valdés S, Carrasco L, Alzamora R, Figueroa F, Kalergis AM, Michea L. Spironolactone decreases DOCA-salt-induced organ damage by blocking the activation of T helper 17 and the down-regulation of regulatory T lymphocytes. *Hypertension* 2014;**63**:797–803.
85. Chiasson VL, Pakanati AR, Hernandez M, Young KJ, Bounds KR, Mitchell BM. Regulatory T-cell augmentation or interleukin-17 inhibition prevents calcineurin inhibitor-induced hypertension in mice. *Hypertension* 2017;**70**:183–191.
86. Saleh MA, Norlander AE, Madhur MS. Inhibition of interleukin 17-A but not interleukin-17F signaling lowers blood pressure and reduces end-organ inflammation in angiotensin II-induced hypertension. *JACC Basic Transl Sci* 2016;**1**:606–616.
87. Cornelius DC, Hogg JP, Scott J, Wallace K, Herse F, Moseley J, Wallukat G, Dechend R, LaMarca B. Administration of interleukin-17 soluble receptor C suppresses TH17 cells, oxidative stress, and hypertension in response to placental ischemia during pregnancy. *Hypertension* 2013;**62**:1068–1073.
88. Murphy SR, Dahly-Vernon AJ, Dunn KMJ, Chen CCA, Ledbetter SR, Williams JM, Roman RJ. Renoprotective effects of anti-TGF-β antibody and antihypertensive therapies in Dahl S rats. *Am J Physiol Regul Integr Comp Physiol* 2012;**303**:R57–R69.
89. Chan CT, Moore JP, Budzyn K, Guida E, Diep H, Vinh A, Jones ES, Widdop RE, Armitage JA, Sakkal S, Ricardo SD, Sobey CG, Drummond GR. Reversal of vascular macrophage accumulation and hypertension by a CCR2 antagonist in deoxycorticosterone/salt-treated mice. *Hypertension* 2012;**60**:1207–1212.
90. Mikolajczyk TP, Nosalski R, Szczepaniak P, Budzyn K, Osmenda G, Skiba D, Sagan A, Wu J, Vinh A, Marvar PJ, Guzik B, Podolec J, Drummond G, Lob HE, Harrison DG, Guzik TJ. Role of chemokine RANTES in the regulation of perivascular inflammation, T-cell accumulation, and vascular dysfunction in hypertension. *FASEB J* 2016; **30**:1987–1999.
91. De Batista PR, Palacios R, Martín A, Hernanz R, Médici CT, Silva MASC, Rossi EM, Aguado A, Vassallo DV, Salaices M, Alonso MJ. Toll-like receptor 4 upregulation by angiotensin II contributes to hypertension and vascular dysfunction through reactive oxygen species production. *PLoS One* 2014;**9**:e104020.
92. Hernanz R, Martínez-Revelles S, Palacios R, Martín A, Cachofeiro V, Aguado A, García-Redondo L, Barrús MT, De Batista PR, Briones AM, Salaices M, Alonso MJ. Toll-like receptor 4 contributes to vascular remodelling and endothelial dysfunction in angiotensin II-induced hypertension. *Br J Pharmacol* 2015;**172**:3159–3176.
93. Bomfim GF, Echem C, Martins CB, Costa TJ, Sartoretto SM, Dos Santos RA, Oliveira MA, Akamine EH, Fortes ZB, Tostes RC, Webb RC, Carvalho MHC. Toll-like receptor 4 inhibition reduces vascular inflammation in spontaneously hypertensive rats. *Life Sci* 2015;**122**:1–7.
94. Nunes KP, Bomfim GF, Toque HA, Szasz T, Clinton Webb R. Toll-like receptor 4 (TLR4) impairs nitric oxide contributing to Angiotensin II-induced cavernosal dysfunction. *Life Sci* 2017;**191**:219–226.
95. Echem C, Bomfim GF, Ceravolo GS, Oliveira MA, Santos-Eichler RA, Bechara LR, Veras MM, Saldiva PHN, Ferreira JC, Akamine EH, Fortes ZB, Dantas AP, de Carvalho MHC. Anti-toll like receptor 4 (TLR4) therapy diminishes cardiac remodeling regardless of changes in blood pressure in spontaneously hypertensive rats (SHR). *Int J Cardiol* 2015;**187**:243–245.
96. McCarthy CG, Wenceslau CF, Goulopoulou S, Baban B, Matsumoto T, Webb RC. Chloroquine suppresses the development of hypertension in spontaneously hypertensive rats. *Am J Hypertens* 2017;**30**:173–181.
97. Cornelius DC, Castillo J, Porter J, Amaral LM, Campbell N, Paige A, Thomas AJ, Harmon A, Cunningham MW, Wallace K, Herse F, Wallukat G, Dechend R, LaMarca B. Blockade of CD40 ligand for intercellular communication reduces hypertension, placental oxidative stress, and AT1-AA in response to adoptive transfer of CD4+ T lymphocytes from RUPP rats. *Am J Physiol Regul Integr Comp Physiol* 2015;**309**:R1243–R1250.
98. Kumar V, Wollner C, Kurth T, Bukowy JD, Cowley AW. Inhibition of mammalian target of rapamycin complex 1 attenuates salt-induced hypertension and kidney injury in Dahl salt-sensitive rats. *Hypertension* 2017;**70**:813–821.
99. Rodríguez-Iturbe B, Quiroz Y, Nava M, Bonet L, Chávez M, Herrera-Acosta J, Johnson RJ, Pons HA. Reduction of renal immune cell infiltration results in blood pressure control in genetically hypertensive rats. *Am Jf Physiol Renal Physiol* 2002; **282**:F191–F201.
100. Boesen EI, Williams DL, Pollock JS, Pollock DM. Immunosuppression with mycophenolate mofetil attenuates the development of hypertension and albuminuria in deoxycorticosterone acetate-salt hypertensive rats. *Clin Exp Pharmacology Physiol* 2010;**37**:1016–1022.
101. Taylor EB, Ryan MJ. Immunosuppression with mycophenolate mofetil attenuates hypertension in an experimental model of autoimmune disease. *J Am Heart Assoc* 2017;**6**:1–11.
102. Tinsley JH, Chiasson VL, South S, Mahajan A, Mitchell BM. Immunosuppression improves blood pressure and endothelial function in a rat model of pregnancy-induced hypertension. *Am J Hypertens* 2009;**22**:1107–1114.
103. Guzik TJ, Mohiddin SA, Dimarco A, Patel V, Savvatis K, Marelli-Berg FM, Madhur MS, Tomaszewski M, Maffia P, D'Acquisto F, Nicklin SA, Marian AJ, Nosalski R, Murray EC, Guzik B, Berry C, Touyz RM, Kreutz R, Wang DW, Bhella D, Sagliocco O, Crea F, Thomson EC, McInnes IB. COVID-19 and the cardiovascular system: implications for risk assessment, diagnosis, and treatment options. *Cardiovasc Res* 2020;**116**:1666–1687.

104. Bienvenu LA, Noonan J, Wang X, Peter K. Higher mortality of COVID-19 in males: sex differences in immune response and cardiovascular comorbidities. *Cardiovas Res* 2020;**116**:2197–2206.
105. Bautista LE, Vera LM, Arenas IA, Gamarra G. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-α) and essential hypertension. *Jf Hum Hypertens* 2005;**19**:149–154.
106. Puszkarska A, Niklas A, Głuszek J, Lipski D, Niklas K. The concentration of tumor necrosis factor in the blood serum and in the urine and selected early organ damages in patients with primary systemic arterial hypertension. *Medicine (Baltimore)* 2019;**98**:e15773.
107. Chan SP, Kim HY, Park HJ, Jang SW, Ihm SH, Lee JM, Yoo KD, Jeon DS, Baek SH, Youn HJ, Seung KB, Kim JH, Choi KB. Association between the JNC 7 classification of the stages of systolic hypertension and inflammatory cardiovascular risk factors. *Korean Circ J* 2007;**37**:623–662.
108. Di Napoli M, Papa F. Association between blood pressure and C-reactive protein levels in acute ischemic stroke. *Hypertension* 2003;**42**:1117–1123.
109. Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, Ridker PM, MacFadyen JG, Everett BM, Libby P, Thuren T, Glynn RJ, Kastelein J, Koenig W, Genest J, Lorenzatti A, Varigos J, Siostrzonek P, Sinnaeve P, Fonseca F, Nicolau J, Gotcheva N, Yong H, Urina-Triana M, Milicic D, Cifkova R, Vettus R, Anker SD, Manolis AJ, Wyss F, Forster T, Sigurdsson A, Pais P, Fucili A, Ogawa H, Shimokawa H, Veze I, Petrauskiene B, Salvador L, Cornel JH, Klemsdal TO, Medina F, Budaj A, Vida-Simiti L, Kobalava Z, Otasevic P, Pella D, Lainscak M, Seung K-B, Commerford P, Dellborg M, Donath M, Hwang J-J, Kultursay H, Flather M, Ballantyne C, Bilazarian S, Chang W, East C, Forgosh L, Harris B, Ligueros M. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. *Lancet* 2018;**391**:319–328.
110. Stuveling EM, Hillege HL, Bakker SJL, Gans ROB, De Jong PE, De Zeeuw D. C-reactive protein is associated with renal function abnormalities in a non-diabetic population. *Kidney Int* 2003;**63**:654–661.
111. Sesso HD, Wang L, Buring JE, Ridker PM, Gaziano JM. Comparison of interleukin-6 and C-reactive protein for the risk of developing hypertension in women. *Hypertension* 2007;**49**:304–310.
112. Schnabel R, Larson MG, Dupuis J, Lunetta KL, Lipinska I, Meigs JB, Yin X, Rong J, Vita JA, Newton-Cheh C, Levy D, Keaney JF, Vasan RS, Mitchell GF, Benjamin EJ. Relations of inflammatory biomarkers and common genetic variants with arterial stiffness and wave reflection. *Hypertension* 2008;**51**:1651–1657.
113. Swerdlow DI, Holmes MV, Kuchenbaecker KB, Engmann JEL, Shah T, Sofat R, Guo Y, Chung C, Peasey A, Pfister R, Mooijaart SP, Ireland HA, Leusink M, Langenberg C, Li K, Palmen J, Howard P, Cooper JA, Drenos F, Hardy J, Nalls MA, Li YR, Lowe G, Stewart M, Bielinski SJ, Peto J, Timpson NJ, Gallacher J, Dunlop M, Houlston R. The interleukin-6 receptor as a target for prevention of coronary heart disease: a Mendelian randomisation analysis. *Lancet* 2012;**379**:1214–1224.
114. Cai T, Zhang Y, Ho YL, Link N, Sun J, Huang J, Cai TA, Damrauer S, Ahuja Y, Honerlaw J, Costa L, Schubert P, Hong C, Gagnon D, Sun Y, Sun YV, Gaziano JM, Wilson P, Cho K, Tsao P, O'Donnell CJ, Liao KP, Gaziano MJ, Ramoni R, Breeling J, Chang KM, Huang G, Muralidhar S, Tsao PS, Moser J; VA Million Veteran Program. Association of interleukin 6 receptor variant with cardiovascular disease effects of interleukin 6 receptor blocking therapy: a phenome - Wide association study. *JAMA Cardiol* 2018;**3**:849–857.
115. Dalekos GN, Elisaf M, Bairaktari E, Tsolas O, Siamopoulos KC. Increased serum levels of interleukin-1β in the systemic circulation of patients with essential hypertension: additional risk factor for atherogenesis in hypertensive patients? *J Lab Clin Med* 1997;**129**:300–308.
116. Rabkin SW. The role of interleukin 18 in the pathogenesis of hypertension-induced vascular disease. *Nat Clin Pract Cardiovasc Med* 2009;**6**:192–199.
117. Madej A, Okopień B, Kowalski J, Haberka M, Herman ZS. Plasma concentrations of adhesion molecules and chemokines in patients with essential hypertension. *Pharmacol Rep* 2005;**57**:878–881.
118. Carranza-Leon DA, Oeser A, Wu Q, Stein CM, Ormseth MJ, Chung CP. Ambulatory blood pressure in patients with systemic lupus erythematosus: association with markers of immune activation. *Lupus* 2020;**29**:1683–1690.
119. Siedlinski M, Jozefczuk E, Xu X, Teumer A, Evangelou E, Schnabel RB, Welsh P, Maffia P, Erdmann J, Tomaszewski M, Caulfield MJ, Sattar N, Holmes MV, Guzik TJ. White blood cells and blood pressure: a Mendelian randomization study. *Circulation* 2020;**141**:1307–1317.
120. Tatsukawa Y, Hsu WL, Yamada M, Cologne JB, Suzuki G, Yamamoto H, Yamane K, Akahoshi M, Fujiwara S, Kohno N. White blood cell count, especially neutrophil count, as a predictor of hypertension in a Japanese population. *Hypertens Res* 2008; **31**:1391–1397.
121. Liu X, Zhang Q, Wu H, Du H, Liu L, Shi H, Wang C, Xia Y, Guo X, Li C, Bao X, Su Q, Sun S, Wang X, Zhou M, Jia Q, Zhao H, Song K, Niu K. Blood neutrophil to lymphocyte ratio as a predictor of hypertension. *Am J Hypertens* 2015;**28**:1339–1346.
122. Belen E, Sungur A, Sungur MA, Erdoğan G. Increased neutrophil to lymphocyte ratio in patients with resistant hypertension. *J Clin Hypertens* 2015;**17**:532–537.
123. Loperena R, Van Beusecum JP, Itani HA, Engel N, Laroumanie F, Xiao L, Elijovich F, Laffer CL, Gnecco JS, Noonan J, Maffia P, Jasiewicz-Honkisz B, Czesnikiewicz-Guzik M, Mikolajczyk T, Sliwa T, Dikalov S, Weyand CM, Guzik TJ, Harrison DG. Hypertension and increased endothelial mechanical stretch promote monocyte differentiation and activation: roles of STAT3, interleukin 6 and hydrogen peroxide. *Cardiovasc Res* 2018;**114**:1547–1563.
124. Urbanski K, Ludew D, Filip G, Filip M, Sagan A, Szczepaniak P, Grudzien G, Sadowski J, Jasiewicz-Honkisz B, Sliwa T, Kapelak B, McGinnigle E, Mikolajczyk T, Guzik TJ. CD14+CD16++ "nonclassical" monocytes are associated with endothelial dysfunction in patients with coronary artery disease. *Thromb Haemost* 2017;**117**: 971–980.
125. Mikołajczyk TP, Osmenda G, Batko B, Wilk G, Krezelok M, Skiba D, Sliwa T, Pryjma JR, Guzik TJ. Heterogeneity of peripheral blood monocytes, endothelial dysfunction and subclinical atherosclerosis in patients with systemic lupus erythematosus. *Lupus* 2016;**25**:18–27.
126. Marketou ME, Kontaraki JE, Zacharis EA, Kochiadakis GE, Giaouzaki A, Chlouverakis G, Vardas PE. TLR2 and TLR4 gene expression in peripheral monocytes in nondiabetic hypertensive patients: the effect of intensive blood pressure-lowering. *J Clin Hypertens (Greenwich)* 2012;**14**:330–335.
127. Itani HA, McMaster WG, Saleh MA, Nazarewicz RR, Mikolajczyk TP, Kaszuba AM, Konior A, Prejbisz A, Januszewicz A, Norlander AE, Chen W, Bonami RH, Marshall AF, Poffenberger G, Weyand CM, Madhur MS, Moore DJ, Harrison DG, Guzik TJ. Activation of human T cells in hypertension: studies of humanized mice and hypertensive humans. *Hypertension* 2016;**68**:123–132.
128. Youn JC, Yu HT, Lim BJ, Koh MJ, Lee J, Chang DY, Choi YS, Lee SH, Kang SM, Jang Y, Yoo OJ, Shin EC, Park S. Immunosenescent CD8+T clls and C-X-C cemokine receptor type 3 chemokines are increased in human hypertension. *Hypertension* 2013;**62**:126–133.
129. Gackowska L, Michałkiewicz J, Niemirska A, Helmin-Basa A, Kłosowski M, Kubiszewska I, Obrycki Ł, Szalecki M, Wierzbicka A, Kułaga Z, Wiese M, Litwin M. Loss of CD31 receptor in CD4+ and CD8+ T-cell subsets in children with primary hypertension is associated with hypertension severity and hypertensive target organ damage. *J Hypertens* 2018;**36**:2148–2156.
130. Litwin M, Kułaga Z. Obesity, metabolic syndrome, and primary hypertension. *Pediatr Nephrol* 2021;**36**:825–837.
131. Levy D, Ehret GB, Rice K, Verwoert GC, Launer LJ, Dehghan A, Glazer NL, Morrison AC, Johnson AD, Aspelund T, Aulchenko Y, Lumley T, Köttgen A, Vasan RS, Rivadeneira F, Eiriksdottir G, Guo X, Arking DE, Mitchell GF, Mattace-Raso FUS, Smith AV, Taylor K, Scharpf RB, Hwang S-J, Sijbrands EJG, Bis J, Harris TB, Ganesh SK, O'Donnell CJ, Hofman A, Rotter JI, Coresh J, Benjamin EJ, Uitterlinden AG, Heiss G, Fox CS, Witteman JCM, Boerwinkle E, Wang TJ, Gudnason V, Larson MG, Chakravarti A, Psaty BM, van Duijn CM. Genome-wide association study of blood pressure and hypertension. *Nat Genet* 2009;**41**:677–687.
132. Huan T, Meng Q, Saleh MA, Norlander AE, Joehanes R, Zhu J, Chen BH, Zhang B, Johnson AD, Ying S, Courchesne P, Raghavachari N, Wang R, Liu P, O'Donnell CJ, Vasan R, Munson PJ, Madhur MS, Harrison DG, Yang X, Levy D; International Consortium for Blood Pressure GWAS (ICBP). Integrative network analysis reveals molecular mechanisms of blood pressure regulation. *Mol Syst Biol* 2015;**11**:799.
133. Jermendy G, Horváth T, Littvay L, Steinbach R, Jermendy ÁL, Tárnoki ÁD, Tárnoki DL, Métneki J, Osztovits J. Effect of genetic and environmental influences on cardiometabolic risk factors: a twin study. *Cardiovas Diabetol* 2011;**10**:96.
134. Levy D, DeStefano AL, Larson MG, O'Donnell CJ, Lifton RP, Gavras H, Cupples LA, Myers RH. Evidence for a gene influencing blood pressure on chromosome 17: genome scan linkage results for longitudinal blood pressure phenotypes in subjects from the Framingham Heart Study. *Hypertension* 2000;**36**:477–483.
135. Mitchell GF, DeStefano AL, Larson MG, Benjamin EJ, Chen MH, Vasan RS, Vita JA, Levy D. Heritability and a genome-wide linkage scan for arterial stiffness, wave reflection, and mean arterial pressure: the Framingham heart study. *Circulation* 2005; **112**:194–199.
136. Rudemiller NP, Lund H, Priestley JRC, Endres BT, Prokop JW, Jacob HJ, Geurts AM, Cohen EP, Mattson DL. Mutation of SH2B3 (LNK), a genome-wide association study candidate for hypertension, attenuates Dahl salt-sensitive hypertension via inflammatory modulation. *Hypertension* 2015;**65**:1111–1117.
137. Devallière J, Charreau B. The adaptor Lnk (SH2B3): an emerging regulator in vascular cells and a link between immune and inflammatory signaling. *Biochem Pharmacol* 2011;**82**:1391–1402.
138. Huan T, Esko T, Peters MJ, Pilling LC, Schramm K, Schurmann C, Chen BH, Liu C, Joehanes R, Johnson AD, Yao C, Ying S-X, Courchesne P, Milani L, Raghavachari N, Wang R, Liu P, Reinmaa E, Dehghan A, Hofman A, Uitterlinden AG, Hernandez DG, Bandinelli S, Singleton A, Melzer D, Metspalu A, Carstensen M, Grallert H, Herder C, Meitinger T, Peters A, Roden M, Waldenberger M, Dörr M, Felix SB, Zeller T, Vasan R, O'Donnell CJ, Munson PJ, Yang X, Prokisch H, Völker U, van Meurs JBJ, Ferrucci L, Levy D; International Consortium for Blood Pressure GWAS (ICBP). A meta-analysis of gene expression signatures of blood pressure and hypertension. *PLOS Genet* 2015;**11**:e1005035.
139. McMaster W, Saleh M, Kirabo A, Itani H, Harrison D, Madhur M. Deficiency of LNK/SH2B3 promotes hypertension, endothelial dysfunction, and aortic dissection. *Angiogenesis* 2014;**17**:935–984.
140. Saleh MA, McMaster WG, Wu J, Norlander AE, Funt SA, Thabet SR, Kirabo A, Xiao L, Chen W, Itani HA, Michell D, Huan T, Zhang Y, Takaki S, Titze J, Levy D, Harrison DG, Madhur MS. Lymphocyte adaptor protein LNK deficiency exacerbates hypertension and end-organ inflammation. *J Clin Invest* 2015;**125**:1189–1202.

141. Eales JM, Jiang X, Xu X, Saluja S, Akbarov A, Cano-Gamez E, McNulty MT, Finan C, Guo H, Wystrychowski W, Szulinska M, Thomas HB, Pramanik S, Chopade S, Prestes PR, Wise I, Evangelou E, Salehi M, Shakanti Y, Ekholm M, Denniff M, Nazgiewicz A, Eichinger F, Godfrey B, Antczak A, Glyda M, Król R, Eyre S, Brown J, Berzuini C, Bowes J, Caulfield M, Zukowska-Szczechowska E, Zywiec J, Bogdanski P, Kretzler M, Woolf AS, Talavera D, Keavney B, Maffia P, Guzik TJ, O'Keefe RT, Trynka G, Samani NJ, Hingorani A, Sampson MG, Morris AP, Charchar FJ, Tomaszewski M. Uncovering genetic mechanisms of hypertension through multi-omic analysis of the kidney. *Nat Genet* 2021;**53**:630–637.
142. Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Gomez-Acebo I, Testa A, Garcia-Porrua C, Sanchez-Andrade A, Llorca J, Gonzlez-Gay MA, González-Gay MA, Gonzlez-Gay MA. Anti-TNF-alpha-adalimumab therapy is associated with persistent improvement of endothelial function without progression of carotid intima-media wall thickness in patients with rheumatoid arthritis refractory to conventional therapy. *Mediators Inflamm* 2012;**2012**:674265.
143. Bozkirli EDE, Bozkirli E, Yucel AE. Effects of infliximab treatment in terms of cardiovascular risk and insulin resistance in ankylosing spondylitis patients. *Mod Rheumatol* 2014;**24**:335–339.
144. Komai N, Morita Y, Sakuta T, Kuwabara A, Kashihara N. Anti-tumor necrosis factor therapy increases serum adiponectin levels with the improvement of endothelial dysfunction in patients with rheumatoid arthritis. *Mod Rheumatol* 2007;**17**:385–390.
145. Sandoo A, Panoulas VF, Toms TE, Smith JP, Stavropoulos-Kalinoglou A, Metsios GS, Gasparyan AY, Carroll D, Veldhuijzen Van Zanten JJCS, Kitas GD. Anti-TNFα therapy may lead to blood pressure reductions through improved endothelium-dependent microvascular function in patients with rheumatoid arthritis. *J Hum Hypertens* 2011;**25**:699–702.
146. Yoshida S, Takeuchi T, Kotani T, Yamamoto N, Hata K, Nagai K, Shoda T, Takai S, Makino S, Hanafusa T. Infliximab, a TNF-α inhibitor, reduces 24-h ambulatory blood pressure in rheumatoid arthritis patients. *J Hum Hypertens* 2014;**28**:165–169.
147. Galarraga B, Khan F, Kumar P, Pullar T, Belch JJF. Etanercept improves inflammation-associated arterial stiffness in rheumatoid arthritis. *Rheumatology (Oxford)* 2009;**48**:1418–1423.
148. Klarenbeek NB, Van Der Kooij SM, Huizinga TJW, Goekoop-Ruiterman YPM, Hulsmans HMJ, Van Krugten MV, Speyer I, De Vries-Bouwstra JK, Kerstens PJSM, Huizinga TWJ, Dijkmans BAC, Allaart CF. Blood pressure changes in patients with recent-onset rheumatoid arthritis treated with four different treatment strategies: a post hoc analysis from the BeSt trial. *Ann Rheum Dis* 2010;**69**:1342–1335.
149. Tam LS, Shang Q, Li EK, Wang S, Li RJ, Lee KL, Leung YY, Ying KY, Yim CW, Kun EW, Leung MH, Li M, Li TK, Zhu TY, Chui RK, Tseung L, Yu SL, Kuan WP, Yu CM. Infliximab is associated with improvement in arterial stiffness in patients with early rheumatoid arthritis – a randomized trial. *J Rheumatol* 2012;**39**:2267–2275.
150. Daïen CI, Fesler P, Du Cailar G, Daïen V, Mura T, Dupuy AM, Cristol JP, Ribstein J, Combe B, Morel J. Etanercept normalises left ventricular mass in patients with rheumatoid arthritis. *Ann Rheum Dis* 2013;**72**:881–887.
151. van den Oever IAM, Baniaamam M, Simsek S, Raterman HG, van Denderen JC, van Eijk IC, Peters MJL, van der Horst-Bruinsma IE, Smulders YM, Nurmohamed MT. The effect of anti-TNF treatment on body composition and insulin resistance in patients with rheumatoid arthritis. *Rheumatol Int* 2021;**41**:319–328.
152. Peters MJL, Welsh P, McInnes IB, Wolbink G, Dijkmans BAC, Sattar N, Nurmohamed MT. Tumour necrosis factor α blockade reduces circulating N-terminal pro-brain natriuretic peptide levels in patients with active rheumatoid arthritis: results from a prospective cohort study. *Ann Rheum Dis* 2010;**69**:1281–1285.
153. Mäki-Petäjä KM, Hall FC, Booth AD, Wallace SML, Yasmin, Bearcroft PWP, Harish S, Furlong A, McEniery CM, Brown J, Wilkinson IB. Rheumatoid arthritis is associated with increased aortic pulse-wave velocity, which is reduced by anti-tumor necrosis factor-α therapy. *Circulation* 2006;**114**:1185–1192.
154. Rho YH, Oeser A, Chung CP, Milne GL, Stein CM. Drugs used in the treatment of rheumatoid arthritis: relationship between current use and cardiovascular risk factors. *Arch Drug Inf* 2009;**2**:34–40.
155. Angel K, Provan SA, Hammer HB, Mowinckel P, Kvien TK, Atar D. Changes in arterial stiffness during continued infliximab treatment in patients with inflammatory arthropathies. *Fundam Clin Pharmacol* 2011;**25**:511–517.
156. Thaci D, Girolomoni G, Philipp S, Qureshi A, You R, Fox T. Secukinumab treatment does not induce blood pressure change in subjects with moderate to severe plaque psoriasis: results from the FIXTURE study. *J Am Acad Dermatol* 2016;**74**:AB273.
157. Baker JF, Sauer B, Teng CC, George M, Cannon GW, Ibrahim S, Cannella A, England BR, Michaud K, Caplan L, Davis LA, O'Dell J, Mikuls TR. Initiation of disease-modifying therapies in rheumatoid arthritis is associated with changes in blood pressure. *J Clin Rheumatol* 2018;**24**:203–209.
158. Mäki-Petäjä KM, Elkhawad M, Cheriyan J, Joshi FR, Östör AJK, Hall FC, Rudd JHF, Wilkinson IB. Anti-tumor necrosis factor-α therapy reduces aortic inflammation and stiffness in patients with rheumatoid arthritis. *Circulation* 2012;**126**:2473–2480.
159. Tam L-SS, Shang Q, Kun EW, Lee K-LL, Yip M-LL, Li M, Li TK, Zhu TY, Pui MO, Li EK, Yu C-MM. The effects of golimumab on subclinical atherosclerosis and arterial stiffness in ankylosing spondylitis-a randomized, placebo-controlled pilot trial. *Rheumatology (Oxford)* 2014;**53**:1065–1074.
160. Grossman C, Bornstein G, Leibowitz A, Ben-Zvi I, Grossman E. Effect of tumor necrosis factor-α inhibitors on ambulatory 24-h blood pressure. *Blood Pressure* 2017;**26**:24–29.
161. Van Doornum S, McColl G, Wicks IP. Tumour necrosis factor antagonists improve disease activity but not arterial stiffness in rheumatoid arthritis. *Rheumatology (Oxford)* 2005;**44**:1428–1432.
162. Angel K, Provan SA, Gulseth HL, Mowinckel P, Kvien TK, Atar D. Tumor necrosis factor-α antagonists improve aortic stiffness in patients with inflammatory arthropathies: a controlled study. *Hypertension* 2010;**55**:333–338.
163. Desai RJ, Solomon DH, Schneeweiss S, Danaei G, Liao KP, Kim SC. Tumor necrosis factor-α inhibitor use and the risk of incident hypertension in patients with rheumatoid arthritis. *Epidemiology* 2016;**27**:414–422.
164. Kim SK, Kwak SG, Choe JY. Association between biologic disease modifying antirheumatic drugs and incident hypertension in patients with rheumatoid arthritis: results from prospective nationwide KOBIO Registry. *Medicine (Baltimore)* 2020;**99**:e19415.
165. Zhao Q, Hong D, Zhang Y, Sang Y, Yang Z, Zhang X. Association between anti-TNF therapy for rheumatoid arthritis and hypertension: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015;**94**:e731.
166. Everett BM, Cornel JH, Lainscak M, Anker SD, Abbate A, Thuren T, Libby P, Glynn RJ, Ridker PM. Anti-inflammatory therapy with canakinumab for the prevention of hospitalization for heart failure. *Circulation* 2019;**139**:1289–1299.
167. Rothman AMK, MacFadyen J, Thuren T, Webb A, Harrison DG, Guzik TJ, Libby P, Glynn RJ, Ridker PM. Effects of interleukin-1β inhibition on blood pressure, incident hypertension, and residual inflammatory risk: a secondary analysis of CANTOS. *Hypertension* 2020;**75**:477–482.
168. Makavos G, Ikonomidis I, Andreadou I, Varoudi M, Kapniari I, Loukeri E, Theodoropoulos K, Pavlidis G, Triantafyllidi H, Thymis J, Parissis J, Tsoumani M, Rafouli-Stergiou P, Katsimbri P, Papadavid E. Effects of interleukin 17A inhibition on myocardial deformation and vascular function in psoriasis. *Can J Cardiol* 2020;**36**:100–111.
169. Takeshita J, Wang S, Shin DB, Mehta NN, Kimmel SE, Margolis DJ, Troxel AB, Gelfand JM. Effect of psoriasis severity on hypertension control a population-based study in the United Kingdom. JAMA Dermatol 2015;**151**:161–169.
170. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, Troxel AB, Hennessy S, Kimmel SE, Margolis DJ, Choi H, Mehta NN, Gelfand JM. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. *Ann Rheum Dis* 2015;**74**:326–332.
171. Elmedany SH, Mohamed AE, Galil SMA. Efficacy and safety profile of intravenous tocilizumab versus intravenous abatacept in treating female Saudi Arabian patients with active moderate-to-severe rheumatoid arthritis. *Clin Rheumatol* 2019;**38**:2109–2117.
172. McInnes IB, Thompson L, Giles JT, Bathon JM, Salmon JE, Beaulieu AD, Codding CE, Carlson TH, Delles C, Lee JS, Sattar N. Effect of interleukin-6 receptor blockade on surrogates of vascular risk in rheumatoid arthritis: MEASURE, a randomised, placebo-controlled study. *Ann Rheum Dis* 2015;**74**:694–702.
173. Provan SA, Berg IJ, Hammer HB, Mathiessen A, Kvien TK, Semb AG. The impact of newer biological disease modifying anti-rheumatic drugs on cardiovascular risk factors: a 12-month longitudinal study in rheumatoid arthritis patients treated with rituximab, abatacept and tociliziumab. *PLoS One* 2015;**10**:e0130709.
174. Herrera J, Ferrebuz A, MacGregor EG, Rodriguez-Iturbe B. Mycophenolate mofetil treatment improves hypertension in patients with psoriasis and rheumatoid arthritis. *J Am Soc Nephrol* 2006;**17**:S218–S225.
175. Frisch G, Lin J, Rosenstock J, Markowitz G, Agati VD', Radhakrishnan J, Preddie D, Crew J, Valeri A, Appel G. Mycophenolate mofetil (MMF) vs placebo in patients with moderately advanced IgA nephropathy: a double-blind randomized controlled trial. *Nephrol Dial Transplant* 2005;**20**:2139–2145.
176. Liu X, Dewei D, Sun S, Xu G, Liu H, He L, Zhang P. Treatment of severe IgA nephropathy: mycophenolate mofetil/prednisone compared to cyclophosphamide/prednisone. *Int J Clin Pharmacol Ther* 2014;**52**:95–102.
177. Tang SCW, Tang AWC, Wong SSH, Leung JCK, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. *Kidney Int* 2010;**77**:543–549.
178. Maes BD, Oyen R, Claes K, Evenepoel P, Kuypers D, Vanwalleghem J, Damme B, Van C, Vanrenterghem YF, Vanrenterghem YFC. Mycophenolate mofetil in IgA nephropathy: results of a 3-year prospective placebo-controlled randomized study. *Kidney Int* 2004;**65**:1842–1849.
179. Gonwa T, Mendez R, Yang HC, Weinstein S, Jensik S, Steinberg S. Randomized trial of tacrolimus in combination with sirolimus or mycophenolate mofetil in kidney transplantation: results at 6 months. *Transplantation* 2003;1213–1220.
180. Cuervas-Mons V, Herrero JI, Gomez MA, González-Pinto I, Serrano T, de la Mata M, Fabregat J, Gastaca M, Bilbao I, Varo E, Sánchez-Antolín G, Rodrigo J, Espinosa MD. Impact of tacrolimus and mycophenolate mofetil regimen vs. a conventional therapy with steroids on cardiovascular risk in liver transplant patients. *Clin Transplant* 2015;**29**:667–677.
181. Mangoni AA, Baghdadi LR, Shanahan EM, Wiese MD, Tommasi S, Elliot D, Woodman RJ. Methotrexate, blood pressure and markers of arterial function in patients with rheumatoid arthritis: a repeated cross-sectional study. *Ther Adv Musculoskelet Dis* 2017;**9**:213–229.
182. Gyldenløve M, Jensen P, Løvendorf MB, Zachariae C, Hansen PR, Skov L. Short-term treatment with methotrexate does not affect microvascular endothelial function in patients with psoriasis. *J Eur Acad Dermatol Venereol* 2015;**29**:591–594.

183. Ridker PM, Everett BM, Pradhan A, MacFadyen JG, Solomon DH, Zaharris E, Mam V, Hasan A, Rosenberg Y, Iturriaga E, Gupta M, Tsigoulis M, Verma S, Clearfield M, Libby P, Goldhaber SZ, Seagle R, Ofori C, Saklayen M, Butman S, Singh N, Le May M, Bertrand O, Johnston J, Paynter NP, Glynn RJ; CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;**380**: 752–762.
184. Gao R, Wu W, Wen Y, Li X. Hydroxychloroquine alleviates persistent proteinuria in IgA nephropathy. *Int Urol Nephrol* 2017;**49**:1233–1241.
185. Sacre K, Criswell LA, McCune JM. Hydroxychloroquine is associated with impaired interferon-alpha and tumor necrosis factor-alpha production by plasmacytoid dendritic cells in systemic lupus erythematosus. *Arthritis Res Ther* 2012;**14**:R155.
186. Rozman B, Praprotnik S, Logar D, Tomšič M, Hojnik M, Kos-Golja M, Accetto R, Dolenc P. Leflunomide and hypertension. *Ann Rheum Dis* 2002;**61**:567–569.
187. Hoorn EJ, Walsh SB, McCormick JA, Fürstenberg A, Yang CL, Roeschel T, Paliege A, Howie AJ, Conley J, Bachmann S, Unwin RJ, Ellison DH. The calcineurin inhibitor tacrolimus activates the renal sodium chloride cotransporter to cause hypertension. *Nat Med* 2011;**17**:1304–1309.
188. Hošková L, Málek I, Kopkan L, Kautzner J. Pathophysiological mechanisms of calcineurin inhibitor-induced nephrotoxicity and arterial hypertension. *Physiol Res* 2017; **66**:167–180.
189. Andreassen AK, Broch K, Eiskjær H, Karason K, Gude E, Mølbak D, Stueflotten W, Gullestad L; SCHEDULE (SCandinavian HEart transplant everolimus De-novo stUdy with earLy calcineurin inhibitors avoidancE) Investigators. Blood pressure in de novo heart transplant recipients treated with everolimus compared with a cyclosporine-based regimen. *Transplantation* 2019;**103**:781–788.
190. Murbraech K, Massey R, Undset LH, Midtvedt K, Holdaas H, Aakhus S. Cardiac response to early conversion from calcineurin inhibitor to everolimus in renal transplant recipients - a three-yr serial echocardiographic substudy of the randomized controlled CENTRAL trial. *Clin Transplant* 2015;**29**:678–684.
191. Claes K, Meier-Kriesche HU, Schold JD, Vanrenterghem Y, Halloran PF, Ekberg H. Effect of different immunosuppressive regimens on the evolution of distinct metabolic parameters: evidence from the Symphony study. *Nephrol Dial Transplant* 2012; **27**:850–857.
192. van Dijk M, van Roon AM, Said MY, Bemelman FJ, Homan van der Heide JJ, de Fijter HW, de Vries APJ, Bakker SJL, Sanders JSF. Long-term cardiovascular outcome of renal transplant recipients after early conversion to everolimus compared to calcineurin inhibition: results from the randomized controlled MECANO trial. *Transpl Int* 2018;**31**:1380–1390.
193. Chamienia A, Biedunkiewicz B, Król E, Dębska-Ślizień A, Rutkowski B. One-year observation of kidney allograft recipients converted from cyclosporine microemulsion to tacrolimus. *Transplant Proc* 2006;**38**:81–85.
194. Rostaing L, Sánchez-Fructuoso A, Franco A, Glyda M, Kuypers DR, Jaray J. Conversion to tacrolimus once-daily from ciclosporin in stable kidney transplant recipients: a multicenter study. *Transpl Int* 2012;**25**:391–400.
195. Larson TS, Dean PG, Stegall MD, Griffin MD, Textor SC, Schwab TR, Gloor JM, Cosio FG, Lund WJ, Kremers WK, Nyberg SL, Ishitani MB, Prieto M, Velosa JA. Complete avoidance of calcineurin inhibitors in renal transplantation: a randomized trial comparing sirolimus and tacrolimus. *Am J Transplant* 2006;**6**:514–522.
196. de Fijter JW, Holdaas H, Øyen O, Sanders JS, Sundar S, Bemelman FJ, Sommerer C, Pascual J, Avihingsanon Y, Pongskul C, Oppenheimer F, Toselli L, Russ G, Wang Z, Lopez P, Kochuparampil J, Cruzado JM, van der Giet M, Gaite LE, Lopez VF, Maldonado R, Massari P, Novoa P, Palti G, Chadban S, Kanellis J, Masterson R, Oberbauer R, Saemann M, Kuypers D; the ELEVATE Study Group. Early conversion from calcineurin inhibitor- to everolimus-based therapy following kidney transplantation: results of the randomized ELEVATE trial. *Am J Transplant* 2017;**17**: 1853–1867.
197. Ursini F, Russo E, Hribal ML, Mauro D, Savarino F, Bruno C, Tripolino C, Rubino M, Naty S, Grembiale RD. Abatacept improves whole-body insulin sensitivity in rheumatoid arthritis: an observational study. *Medicine (Baltimore)* 2015;**94**:e888.
198. Kume K, Yamada S, Kanazawa T, Hatta K, Amano K. Abatacept does not improve subclinical atherosclerosis despite good response in rheumatoid arthritis: a cohort study. *Arthritis Rheumatology* 2015:1–4046.
199. Mathieu S, Couderc M, Glace B, Pereira B, Tournadre A, Dubost JJ, Soubrier M. Effects of 6 months of abatacept treatment on aortic stiffness in patients with rheumatoid arthritis. *Biologics* 2013;**7**:259–264.
200. Iasella CJ, Winstead RJ, Moore CA, Johnson BA, Feinberg AT, Morrell MR, Hayanga JWA, Lendermon EA, Zeevi A, McDyer JF, Ensor CR. Maintenance belatacept-based immunosuppression in lung transplantation recipients who failed calcineurin inhibitors. *Transplantation* 2018;**102**:171–177.
201. Malvezzi P, Fischman C, Rigault G, Jacob MC, Raskovalova T, Jouve T, Janbon B, Rostaing L, Cravedi P. Switching renal transplant recipients to belatacept therapy: results of a real-life gradual conversion protocol. *Transpl Immunol* 2019;**56**: 101207–101177.
202. Seibert FS, Steltzer J, Melilli E, Grannas G, Pagonas N, Bauer F, Zidek W, Grinyó J, Westhoff TH. Differential impact of belatacept and cyclosporine A on central aortic blood pressure and arterial stiffness after renal transplantation. *Clin Transplant* 2014; **28**:1004–1009.
203. Rostaing L, Massari P, Garcia VD, Mancilla-Urrea E, Nainan G, Rial MDC, Steinberg S, Vincenti F, Shi R, Di Russo G, Thomas D, Grinyó J. Switching from calcineurin inhibitor-based regimens to a belatacept-based regimen in renal transplant recipients: a randomized phase II study. *Clin J Am Soc Nephrol* 2011;**6**:430–439.
204. Durrbach A, Pestana JM, Pearson T, Vincenti F, Garcia VD, Campistol J, Del Carmen Rial M, Florman S, Block A, Di Russo G, Xing J, Garg P, Grinyó J. A phase III study of belatacept versus cyclosporine in kidney transplants from extended criteria donors (BENEFIT-EXT Study). *Am J Transplant* 2010;**10**:547–557.
205. Vincenti F, Charpentier B, Vanrenterghem Y, Rostaing L, Bresnahan B, Darji P, Massari P, Mondragon-Ramirez GA, Agarwal M, Di Russo G, Lin C-S, Garg P, Larsen CP. A phase III study of belatacept-based immunosuppression regimens versus cyclosporine in renal transplant recipients (BENEFIT study). *Am J Transplant* 2010;**10**:535–546.
206. Ferguson R, Grinyó J, Vincenti F, Kaufman DB, Woodle ES, Marder BA, Citterio F, Marks WH, Agarwal M, Wu D, Dong Y, Garg P. Immunosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *Am J Transplant* 2011;**11**:66–76.
207. Novikova DS, Popkova TV, Lukina GV, Luchikhina EL, Karateev DE, Volkov AV, Novikov AA, Aleksandrova EN, Nasonov EL. The effects of rituximab on lipids, arterial stiffness, and carotid intima-media thickness in rheumatoid arthritis. *J Korean Med Sci* 2016;**31**:202–207.
208. Mathieu S, Pereira B, Dubost JJ, Lusson JR, Soubrier M. No significant change in arterial stiffness in RA after 6 months and 1 year of rituximab treatment. *Rheumatology (Oxford)* 2012;**51**:1107–1111.
209. Remuzzi G, Chiurchiu C, Abbate M, Brusegan V, Bontempelli M, Ruggenenti P. Rituximab for idiopathic membranous nephropathy. *Lancet* 2002;**360**:923–924.
210. Runlin G, Junren Z, Guozhang L, Weizhong Z, Tingjie Z, Ningling S, Landen H. Efficacy and safety of nifedipine GITS in Asians with hypertension: results of a post-marketing surveillance study in China. *Clin Drug Investig* 2007;**27**:565–572.
211. Hu H, Zhang J, Wang Y, Tian Z, Liu D, Zhang G, Gu G, Zheng H, Xie R, Cui W. Impact of baseline blood pressure on the magnitude of blood pressure lowering by nifedipine gastrointestinal therapeutic system: refreshing the Wilder's principle. *Drug Des Devel Ther* 2017;**11**:3179–3186.
212. Ueng KC, Ningling S, El Maksod A, Hung KY, Yuehui Y. Efficacy and tolerability of long-acting nifedipine GITSOROS monotherapy or combination therapy in hypertensive patients: results of a 12-week international, prospective, multicentre, observational study. *Clinical Drug Investig* 2011;**31**:631–642.
213. Czesnikiewicz-Guzik M, Nosalski R, Mikolajczyk TP, Vidler F, Dohnal T, Dembowska E, Graham D, Harrison DG, Guzik TJ. Th1-type immune responses to *Porphyromonas gingivalis* antigens exacerbate angiotensin II-dependent hypertension and vascular dysfunction. *Br J Pharmacol* 2019;**176**:1922–1931.
214. Czesnikiewicz-Guzik M, Osmenda G, Siedlinski M, Nosalski R, Pelka P, Nowakowski D, Wilk G, Mikolajczyk TP, Schramm-Luc A, Furtak A, Matusik P, Koziol J, Drozdz M, Munoz-Aguilera E, Tomaszewski M, Evangelou E, Caulfield M, Grodzicki T, D'Aiuto F, Guzik TJ. Causal association between periodontitis and hypertension: evidence from Mendelian randomization and a randomized controlled trial of non-surgical periodontal therapy. *Eur Heart J* 2019;**40**:3459–3470.
215. Martin-Cabezas R, Seelam N, Petit C, Agossa K, Gaertner S, Tenenbaum H, Davideau JL, Huck O. Association between periodontitis and arterial hypertension: a systematic review and meta-analysis. *Am Heart J* 2016;**180**:98–112.
216. Muñoz Aguilera E, Suvan J, Buti J, Czesnikiewicz-Guzik M, Barbosa Ribeiro A, Orlandi M, Guzik TJ, Hingorani AD, Nart J, D'Aiuto F. Periodontitis is associated with hypertension: a systematic review and meta-analysis. *Cardiovasc Res* 2020;**116**: 28–39.
217. Pietropaoli D, Del Pinto R, Ferri C, Wright JT, Giannoni M, Ortu E, Monaco A. Poor oral health and blood pressure control among US hypertensive adults. *Hypertension* 2018;**72**:1365–1373.
218. Ahn YB, Shin MS, Byun JS, Kim HD. The association of hypertension with periodontitis is highlighted in female adults: results from the Fourth Korea National Health and Nutrition Examination Survey. *J Clin Periodontol* 2015;**42**:998–1005.
219. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, Suvan J, Hingorani AD, Vallance P, Deanfield J. Treatment of periodontitis and endothelial function. *N Engl J Med* 2007;**356**:911–920.
220. Vidal F, Cordovil I, Figueredo CMS, Fischer RG. Non-surgical periodontal treatment reduces cardiovascular risk in refractory hypertensive patients: a pilot study. *J Clin Periodontol* 2013;**40**:681–687.
221. Sharma S, Sridhar S, Mcintosh A, Messow C-M, Aguilera EM, del Pinto R, Pietropaoli D, Górska R, Siedlinski M, Maffia P, Tomaszewski M, Guzik TJ, D'aiuto F, Czesnikiewicz-Guzik M. Periodontal therapy and treatment of hypertension – alternative to the pharmacological approach. A systematic review and meta-analysis. *Pharmacol Res* 2021;**166**:e105511.
222. Herrod PJJ, Doleman B, Blackwell JEM, O'Boyle F, Williams JP, Lund JN, Phillips BE. Exercise and other nonpharmacological strategies to reduce blood pressure in older adults: a systematic review and meta-analysis. *J Am Soc Hypertens* 2018;**12**: 248–267.
223. Valdiglesias V, Sánchez-Flores M, Maseda A, Lorenzo-López L, Marcos-Pérez D, López-Cortón A, Strasser B, Fuchs D, Laffon B, Millán-Calenti JC, Pásaro E. Immune biomarkers in older adults: role of physical activity. *J Toxicol Environ Health A* 2017; **80**:605–620.
224. Sagiv M, Ben-Sira D, Goldhammer E. Beta-blockers, exercise, and the immune system in men with coronary artery disease. *Med Sci Sports Exerc* 2002;**34**:587–591.

225. Kohut ML, Arntson BA, Lee W, Rozeboom K, Yoon KJ, Cunnick JE, McElhaney J. Moderate exercise improves antibody response to influenza immunization in older adults. *Vaccine* 2004;**22**:2298–2306.
226. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N, Simons-Morton D, McCullough M, Swain J, Steele P, Evans MA, Miller ER, Harsha DW. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med* 1997;**336**:1117–1124.
227. Moore TJ, Vollmer WM, Appel LJ, Sacks FM, Svetkey LP, Vogt TM, Conlin PR, Simons-Morton DG, Carter-Edwards L, Harsha DW. Effect of dietary patterns on ambulatory blood pressure: results from the dietary approaches to Stop Hypertension (DASH) Trial. *Hypertension* 1999;**34**:472–474.
228. Meli AC. When immune cells are coached by intestinal microbiota. *Cardiovasc Res* 2020;**116**:e21–e22.
229. Yan Q, Gu Y, Li X, Yang W, Jia L, Chen C, Han X, Huang Y, Zhao L, Li P, Fang Z, Zhou J, Guan X, Ding Y, Wang S, Khan M, Xin Y, Li S, Ma Y. Alterations of the gut microbiome in hypertension. *Front Cell Infect Microbiol* 2017;**24**:381.
230. De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, Laghi L, Serrazanetti DI, Di Cagno R, Ferrocino I, Lazzi C, Turroni S, Cocolin L, Brigidi P, Neviani E, Gobbetti M, O'Toole PW, Ercolini D. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut* 2016;**65**:1812–1821.
231. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev* 2013:CD004937.
232. Zhou X, Zhang L, Ji WJ, Yuan F, Guo ZZ, Pang B, Luo T, Liu X, Zhang WC, Jiang TM, Zhang Z, Li YM. Variation in dietary salt intake induces coordinated dynamics of monocyte subsets and monocyte-platelet aggregates in humans: implications in end organ inflammation. *PLoS One* 2013;**8**:e60332.
233. De Miguel C, Das S, Lund H, Mattson DL. T lymphocytes mediate hypertension and kidney damage in Dahl salt-sensitive rats. *Am J Physiol Regul Integr Comp Physiol* 2010;**298**:R1136–R1142.
234. Marketou ME, Maragkoudakis S, Anastasiou I, Nakou H, Plataki M, Vardas PE, Parthenakis FI. Salt-induced effects on microvascular function: a critical factor in hypertension mediated organ damage. *J Clin Hypertens (Greenwich)* 2019;**21**:749–757.
235. Yi B, Titze J, Rykova M, Feuerecker M, Vassilieva G, Nichiporuk I, Schelling G, Morukov B, Choukèr A. Effects of dietary salt levels on monocytic cells and immune responses in healthy human subjects: a longitudinal study. *Transl Res* 2015;**166**:103–110.
236. Crouch SH, Botha-Le Roux S, Delles C, Graham LA, Schutte AE. Inflammation and salt in young adults: the African-PREDICT study. *Eur J Nutr* 2021;**60**:873–882.
237. Lob HE, Marvar PJ, Guzik TJ, Sharma S, McCann LA, Weyand C, Gordon FJ, Harrison DG. Induction of hypertension and peripheral inflammation by reduction of extracellular superoxide dismutase in the central nervous system. *Hypertension* 2010;**55**:277–283.
238. Marvar PJ, Thabet SR, Guzik TJ, Lob HE, McCann LA, Weyand C, Gordon FJ, Harrison DG. Central and peripheral mechanisms of T-lymphocyte activation and vascular inflammation produced by angiotensin II-induced hypertension. *Circ Res* 2010;**107**:263–270.
239. Ong J, Kinsman BJ, Sved AF, Rush BM, Tan RJ, Carattino MD, Stocker SD. Renal sensory nerves increase sympathetic nerve activity and blood pressure in 2-kidney 1-clip hypertensive mice. *J Neurophysiol* 2019;**122**:358–367.
240. Xiao L, Kirabo A, Wu J, Saleh MA, Zhu L, Wang F, Takahashi T, Loperena R, Foss JD, Mernaugh RL, Chen W, Roberts J, Osborn JW, Itani HA, Harrison DG. Renal denervation prevents immune cell activation and renal inflammation in angiotensin II-induced hypertension. *Circ Res* 2015;**117**:547–557.
241. Hart EC, Mcbryde FD, Burchell AE, Ratcliffe LEK, Stewart LQ, Baumbach A, Nightingale A, Paton JFR. Translational examination of changes in baroreflex function after renal denervation in hypertensive rats and humans. *Hypertension* 2013;**62**:533–541.
242. Banek CT, Gauthier MM, Baumann DC, Van Helden D, Asirvatham-Jeyaraj N, Panoskaltsis-Mortari A, Fink GD, Osborn JW. Targeted afferent renal denervation reduces arterial pressure but not renal inflammation in established DOCA-salt hypertension in the rat. *Am J Physiol Regul Integr Comp Physiol* 2018;**314**:R883–R891.
243. Banek CT, Gauthier MM, Van Helden DA, Fink GD, Osborn JW. Renal inflammation in DOCA-salt hypertension: role of renal nerves and arterial pressure. *Hypertension* 2019;**73**:1079–1086.
244. Krum H. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. *Hypertension* 2011;**57**:911–917.
245. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M, Mahfoud F, Sievert H, Wunderlich N, Rump LC, Vonend O, Uder M, Lobo M, Caulfield M, Erglis A, Azizi M, Sapoval M, Thambar S, Persu A, Renkin J, Schunkert H, Weil J, Hoppe UC, Walton T, Scheinert D, Binder T, Januszewicz A, Witkowski A, Ruilope LM, Whitbourn R. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. *Lancet* 2010;**376**:1903–1909.
246. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, Leon MB, Liu M, Mauri L, Negoita M, Cohen SA, Oparil S, Rocha-Singh K, Townsend RR, Bakris GL. A controlled trial of renal denervation for resistant hypertension. *N Engl J Med* 2014;**370**:1393–1401.
247. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA, Ewen S, Tsioufis K, Tousoulis D, Sharp ASP, Watkinson AF, Schmieder RE, Schmid A, Choi JW, East C, Walton A, Hopper I, Cohen DL, Wilensky R, Lee DP, Ma A, Devireddy CM, Lea JP, Lurz PC, Fengler K, Davies J, Chapman N, Cohen SA, DeBruin V, Fahy M, Jones DE, Rothman M, Böhm M, Aoki J, Batson B, Böhm M, Choi JW, Cohen DL, Dangas G, David S, Davies J, Devireddy CM, Kandzari D, Kario K, Lee DP, Lurz PC, Patel M, Patel K, Schmieder RE, Sharp ASP, Singh J, Tsioufis K, Walton A, Weber T, Weil J, Zeller T, Ziada K, Tanabe K, Wilkins R, Mahfoud F, East C, Wilensky R, Contreras J, Steigerwalt S, Chapman N, Lea JP, Reedus D, Hoshide S, Ma A, Fengler K, Svetkey L, Rao A, Schmid A, Watkinson AF, Brown A, Tousoulis D, Hopper I, Suppan M, Agdirlioglu T, Noory E, Chasen C. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. *Lancet* 2017;**390**:2160–2170.
248. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S, Tsioufis K, Tousoulis D, Choi JW, East C, Brar S, Cohen SA, Fahy M, Pilcher G, Kario K, Aoki J, Batson B, Böhm M, Choi JW, Cohen DL, Dangas G, David S, Davies J, Devireddy CM, Kandzari D, Kario K, Lee DP, Lurz PC, Papademetriou V, Patel M, Patel K, Schmieder RE, Sharp ASP, Singh J, Tsioufis K, Walton A, Weber T, Weil J, Zeller T, Ziada K, Tanabe K, Wilkins R, Mahfoud F, East C, Wilensky R, Contreras J, Steigerwalt S, Chapman N, Lea JP, Reedus D, Hoshide S, Ma A, Fengler K, Li P, Svetkey L, Rao A, Schmid A, Watkinson AF, Brown A, Tousoulis D, Hopper I, Suppan M, Agdirlioglu T, Noory E, Chasen C. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018;**391**:2346–2355.
249. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J, Basile J, Kirtane AJ, Wang Y, Lobo MD, Saxena M, Feyz L, Rader F, Lurz P, Sayer J, Sapoval M, Levy T, Sanghvi K, Abraham J, Sharp ASP, Fisher NDL, Bloch MJ, Reeve-Stoffer H, Coleman L, Mullin C, Mauri L; RADIANCE-HTN Investigators. Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. *Lancet* 2018;**391**:2335–2345.
250. Hilderman M, Qureshi AR, Abtahi F, Witt N, Jägren C, Olbers J, Delle M, Lindecrantz K, Bruchfeld A. The cholinergic anti-inflammatory pathway in resistant hypertension treated with renal denervation. *Mol Med* 2019;**25**:39.
251. Kampmann U, Mathiassen ON, Christensen KL, Buus NH, Bjerre M, Vase H, Møller N, Kaltoft A, Poulsen PL. Effects of renal denervation on insulin sensitivity and inflammatory markers in nondiabetic patients with treatment-resistant hypertension. *J Diabetes Res* 2017;**2017**:6915310.
252. Eikelis N, Hering D, Marusic P, Sari C, Walton A, Phillips S, Lambert E, Duval J, Krum H, Lambert G, Esler M, Schlaich M. The effect of renal denervation on endothelial function and inflammatory markers in patients with resistant hypertension. *Int J Cardiol* 2015;**188**:96–98.
253. Annoni EM, Van Helden D, Guo Y, Levac B, Libbus I, KenKnight BH, Osborn JW, Tolkacheva EG. Chronic low-level vagus nerve stimulation improves long-term survival in salt-sensitive hypertensive rats. *Front Physiol* 2019;**10**:10–25.
254. Annoni EM, Xie X, Lee SW, Libbus I, KenKnight BH, Osborn JW, Tolkacheva EG. Intermittent electrical stimulation of the right cervical vagus nerve in salt-sensitive hypertensive rats: effects on blood pressure, arrhythmias, and ventricular electrophysiology. *Physiol Rep* 2015;**3**:e12476.
255. Plachta DTT, Gierthmuehlen M, Cota O, Espinosa N, Boeser F, Herrera TC, Stieglitz T, Zentner J. Blood pressure control with selective vagal nerve stimulation and minimal side effects. *J Neural Eng* 2014;**11**:036011.
256. Chapleau MW, Rotella DL, Reho JJ, Rahmouni K, Stauss HM. Chronic vagal nerve stimulation prevents high-salt diet-induced endothelial dysfunction and aortic stiffening in stroke-prone spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol* 2016;**311**:H276–H285.
257. Inoue T, Abe C, Sung SSJ, Moscalu S, Jankowski J, Huang L, Ye H, Rosin DL, Guyenet PG, Okusa MD. Vagus nerve stimulation mediates protection from kidney ischemia-reperfusion injury through $\alpha7nAChR^{+}$ splenocytes. *J Clin Invest* 2016;**126**:1939–1952.
258. Tanaka S, Abe C, Abbott SBG, Zheng S, Yamaoka Y, Lipsey JE, Skrypnyk NI, Yao J, Inoue T, Nash WT, Stornetta DS, Rosin DL, Stornetta RL, Guyenet PG, Okusa MD. Vagus nerve stimulation activates two distinct neuroimmune circuits converging in the spleen to protect mice from kidney injury. *Proc Natl Acad Sci U S A* 2021;**118**:e2021758118.
259. Vida G, Peña G, Kanashiro A, del Thompson-Bonilla MR, Palange D, Deitch EA, Ulloa L. β2-Adrenoreceptors of regulatory lymphocytes are essential for vagal neuromodulation of the innate immune system. *FASEB J* 2011;**25**:4476–4485.
260. Carnevale L, Pallante F, Perrotta M, Iodice D, Perrotta S, Fardella S, Mastroiacovo F, Carnevale D, Lembo G. Celiac vagus nerve stimulation recapitulates angiotensin II-induced splenic noradrenergic activation, driving egress of CD8 effector cells. *Cell Rep* 2020;**33**:108494.
261. Koopman FA, Chavan SS, Miljko S, Grazio S, Sokolovic S, Schuurman PR, Mehta AD, Levine YA, Faltys M, Zitnik R, Tracey KJ, Tak PP. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in Rheumatoid arthritis. *Proc Natl Acad Sci U S A* 2016;**113**:8284–8289.

262. Flint AC, Conell C, Ren X, Banki NM, Chan SL, Rao VA, Melles RB, Bhatt DL. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N Engl J Med* 2019;**381**:243–251.
263. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;**14**:1903–1913.
264. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DPM, Maiden N, Price T, Hopkinson N, O'Reilly S, Hordon L, Griffiths I, Porter D, Capell H, Hassell A, Benitha R, Choy E, Walsh D, Emery P, Knight S, Bruce I, Taggart A, Scott D, Thompson P, McCrae F, Goodfellow R, Kitas G, Jubb R, Abernethy R, Sanders P; British Society for Rheumatology Biologics Register. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor α therapy: results from the British Society for Rheumatology Biologics Register. *Arthritis Rheum* 2007;**56**:2905–2912.
265. Naranjo A, Sokka T, Descalzo MA, Calvo-Alén J, Hørslev-Petersen K, Luukkainen RK, Combe B, Burmester GR, Devlin J, Ferraccioli G, Morelli A, Hoekstra M, Majdan M, Sadkiewicz S, Belmonte M, Holmqvist A-C, Choy E, Tunc R, Dimic A, Bergman M, Toloza S, Pincus T; the QUEST-RA Group. Cardiovascular disease in patients with rheumatoid arthritis: results from the QUEST-RA study. *Arthritis Res Ther* 2008;**10**:R30.
266. Nurmohamed M, Choy E, Lula S, Kola B, DeMasi R, Accossato P. *The Impact of Biologics and Tofacitinib on Cardiovascular Risk Factors and Outcomes in Patients with Rheumatic Disease: A Systematic Literature Review. Drug Safety*. Berlin, Germany: Springer International Publishing; 2018. p473–488.
267. Kang EH, Jin Y, Brill G, Lewey J, Patorno E, Desai RJ, Kim SC. Comparative cardiovascular risk of abatacept and tumor necrosis factor inhibitors in patients with rheumatoid arthritis with and without diabetes mellitus: a multidatabase cohort study. *J Am Heart Assoc* 2018;**7**:e007393.
268. Singh S, Fumery M, Singh AG, Singh N, Prokop LJ, Dulai PS, Sandborn WJ, Curtis JR. Comparative risk of cardiovascular events with biologic and synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Arthritis Care Res* 2020;**72**:561–576.
269. Martínez GJ, Robertson S, Barraclough J, Xia Q, Mallat Z, Bursill C, Celermajer DS, Patel S. Colchicine acutely suppresses local cardiac production of inflammatory cytokines in patients with an acute coronary syndrome. *J Am Heart Assoc* 2015;**4**:e002128.
270. Nidorf M, Thompson PL. Effect of colchicine (0.5 mg twice daily) on high-sensitivity C-reactive protein independent of aspirin and atorvastatin in patients with stable coronary artery disease. *Am J Cardiol* 2007;**99**:805–807.
271. Nidorf S, Eikelboom J, Budgeon C, Thompson P. Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013;**61**:404–410.
272. Tong DC, Quinn S, Nasis A, Hiew C, Roberts-Thomson P, Adams H, Sriamareswaran R, Htun NM, Wilson W, Stub D, van Gaal W, Howes L, Collins N, Yong A, Bhindi R, Whitbourn R, Lee A, Hengel C, Asrress K, Freeman M, Amerena J, Wilson A, Layland J. Colchicine in patients with acute coronary syndrome. *Circulation* 2020;**142**:1890–1900.
273. Suurmond R, van Rhee H, Hak T. Introduction, comparison and validation of Meta-Essentials: a free and simple tool for meta-analysis. *Res Synth Methods* 2017;**8**:537–553.