Review

Hypertension in rheumatoid arthritis

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RA associates with an increased burden of cardiovascular disease, which is at least partially attributed to classical risk factors such as hypertension (HT) and dyslipidaemia. HT is highly prevalent, and seems to be under-diagnosed and under-treated among patients with RA. In this review, we discuss the mechanisms that may lead to increased blood pressure in such patients, paying particular attention to commonly used drugs for the treatment of RA. We also suggest screening strategies and management algorithms for HT, specific to the RA population, although it is clear that these need to be formally assessed in prospective randomized controlled trials designed specifically for the purpose, which, unfortunately, are currently lacking.

KEY WORDS: Systematic review, Rheumatoid arthritis, Cardiovascular, Hypertension, Inflammation, Physical inactivity, Medication, Non-steroidal anti-inflammatory drugs, Recommendations, Glucocorticosteroids.

Introduction and methods

RA associates with excessive morbidity and mortality from cardiovascular disease (CVD) [1], which may be due to multiple causes [2–6]. Several risk factors, such as hypertension (HT) [7–10], smoking [11–13], dyslipidaemia [14], as defined by National Cholesterol Education Program [15] and insulin resistance [16, 17] are thought to be more prevalent in RA and may be important contributors.

HT is one of the most important modifiable risk factors for the development of CVD in the general population [18]. It affects ~1 billion individuals worldwide [19], ~30% of the adult population in the United States [20, 21] and the United Kingdom [22]. HT may be a very important CVD risk factor in RA. Several studies among patients with RA have demonstrated that it associates with subclinical atherosclerosis [7, 23, 24] and is one of the most significant independent predictors of CVD, with relative risk ranking from 1.49 to 4.3 [1, 25, 26]. Using data from the Framingham Heart Study in the United States and the Third (US) National Health and Nutrition Examination Survey (NHANES III), Singh et al. [27] projected that a 20 mmHg increase in systolic blood pressure (SBP) in RA patients would associate with 1572 additional ischaemic heart disease events and 602 additional stroke events over 1 yr. The impact of HT on cardiovascular outcome is thought to be similar among patients with RA to those who do not have RA [28], but since CV mortality is higher in RA patients compared with matched, non-RA controls [29–31], the number of deaths attributed to HT may be higher amongst RA patients.

The reported prevalence of HT among patients with RA varies from 3.8% [32] to 73% [33]. In view of this very wide range, we conducted a systematic review of all studies reporting HT prevalence in patients with RA (Table 1). After taking into consideration an evidence-based tool for literature searching specifically for RA [34], the databases Medline, Cochrane Library, Cumulative Index to Nursing and Allied Health research database (CINAHL) and Excerpta Medica database (EMBASE) were searched to identify publications from 1990 to 18 November 2007 in English regarding RA and HT. The Medical Subject Heading (MeSH) term 'rheumatoid arthritis' was employed in combination with 'hypertension' and 'blood pressure (BP)'. Initial searches identified 465 articles (i.e. 336 for 'rheumatoid arthritis' and 'hypertension' and 129 articles for 'rheumatoid arthritis' and 'BP'). Full articles were retrieved for assessment if the study fulfilled the following criteria: (i) studying HT prevalence in RA; (ii) studying risk factors for CVD, including HT; or (iii) studying BP changes in response to any intervention in RA, as part of the methodology. The final search revealed 48 articles of which 13 were excluded because of lack of reporting HT prevalence (as a categorical variable) [8, 35–46], 1 because of lack of HT definition [47] and 3 because of high selection bias due to very strict inclusion criteria {new onset coronary artery disease [48] and RA patients starting on DMARDs [49] or biologic agents [50]}. The final 31 studies included are listed in Table 1.

The very wide range of reported prevalence of HT in RA is explained by the different populations assessed, the varied sample sizes and significant differences in the definition of HT used. When using the current definition of HT [51] [i.e. SBP ≥140 and/or diastolic BP (DBP) ≥90 and/or the use of anti-hypertensive medication] prevalence of HT in RA in most large studies of unselected, community-based, RA populations lies between 52% and 73% [28, 33]: this appears to depend on the mean age, which ranges from 51 to 66 yrs. In the larger studies of RA samples from secondary care with a similar mean age (56–61.5 yrs), HT prevalence is slightly higher, from 62% to 70.5% [10, 52, 53]. In one of these studies [53], the reported prevalence of HT of 62% would have been higher if patients on lipid-lowering agents and therapy for diabetes had not been excluded. The above figures suggest that the prevalence of HT in the overall RA population is equal to, if not higher than the prevalence observed in the over 65 yrs population of England [22].

Direct evidence as to whether the prevalence of HT is greater among patients with RA than in the general population is contradictory [1,9, 54, 55]; several studies support an increased prevalence amongst RA patients [7–9, 33, 36, 39, 43, 47], but in some cases this could be due to the higher age of the RA group compared with the controls used [33, 36, 43] or due to the bias arising from comparing RA patients recruited from secondary

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TABLE 1. Detailed characteristics of the studies included in the systematic review

Reference	Group	HT definition	Group	No.	Age (yrs)	Female (%)	DD	GC (%)	HT (%)	Comments—exclusion criteria (or inclusion criteria where specified)
Dessein et al. [245, 246]	S	≥130/85 and/or on anti-HT	RA	74	57	86.5	11	15	49	Cross-sectional: lipid-lowering agents, anti-DM
Kravounaris et al. [247]	S	≥130/85 mmHg or	RA	200	63	73.5	9.6	24	66††	Matched case–control
	C	self-reported anti-HT	C	400	63	73.5			77.5	
Chung et al. [33]	C	≥130/85 and/or on anti-HT OR	E-RA	88	51†	64	<2	53.2	56/39†	Case–control: <18 yr
		≥140/90 and/or on anti-HT	L-RA	66	59†	73	20		73/68†	
			Ct	52	52†	65			55/38†	
Dessein et al. [53]	S	≥140/90 and/or on anti-HT	RA	92	56	80.4	11	20	62	Cross-sectional: lipid-lowering agents, anti-DM
Dessein et al. [16]	S	≥140/90 and/or on anti-HT	RA	79	52	83.5	8.5	13	50	Matched case-control: lipid-lowering agents, anti-DM
			OA	39	56				59	
Dessein and Jaffe [248]	S	≥140/90 and/or on anti-HT	RA	21	59	66	6	14	57.1	Cross-sectional: lipid-lowering agents, anti-DM and GC>3 months
Maradit-Kremers et al. [249–251]	C	≥140/90 and/or on anti-HT	RA	603	58	73.1	0	24.5	51.7	Matched case–control: RA incidence cohort
Gonzalez et al. [28]			Ct	603	58	73.1			49	
del Rincon et al. [52]	S	≥140/90 and/or anti-HT	RA	631	58	72.3	14.1		62.8	Cross-sectional: data source: Outcome of RA Longitudinal Evaluation (ORALE)
Roman et al. [23]	S	≥140/90 and/or anti-HT	RA	98	48	98	12	71*	18	Matched case-control: age<18, Creatinine >270 μmol/l, creatinine clearance ≤ 0.5 ml/s, current or recent (3 months) pregnancy
			Ct	98	47	98			22	
La Montagna et al. [252]	S	≥140/90 and/or on anti-HT	RA	45	54	93.3	12.4	51.1	22.2	Matched case–control
			C	48	52	88.9			12.5	
Pamuk et al. [253]	S	≥140/90 and/or on anti-HT	RA	63	51	93.8	6	63.5	30.2	Matched case–control: atherosclerotic complications haemodialysis, malignancy, infections, DM
			Ct	61	53	88.9			32.4	
Gerli et al. [7]	S	≥140/90 and/or on anti-HT	RA	101	63	73	11	45.5	37†	Case–control: CVD, HF, IHD, CVA, PVD
			Ct	75	61	71			23†	
Panoulas et al. [10, 254]	S	≥140/90 and/or on anti-HT	RA	400	61.5	73	10	31.3	70.5	Cross-sectional
Dessein et al. [255]	S	≥140/90 and/or on anti-HT	RA	94	55	66	6	14	51	Cross-sectional: impaired Glc metabolism prior RA onset, lipid- and glucose-lowering agents, hypothyroidism
Dessein et al. [256]	S	≥140/90 and/or on anti-HT	RA	77	54	83.1		14.2	44	Matched case–control: patients with raised ALT, AST or Hep B/Hep C, evidence of auto-immune hepatitis, lipid- or glucose-lowering agents or medication that can affect aminotransferase levels
Van Halm et al. [69]	S	On antiHT	RA	613	62.6	70.3	9.6	30.3	22.5	Case–control
Singh et al. 2003 [54]	C	On anti-HT	RA	30 million					34	Cross-sectional
			OA						41	
Assous et al. [25]	S	On anti-HT (Q)	RA	239	56	82	11.6	88	34	Retrospective cohort
Wallberg-Jonsson et al. [26]	S	On anti-HT (at any point from baseline to death)	RA	211	52	59.7	<1	47**	32	Retrospective cohort: DD<1 yr at presentation included only
Wallberg-Jonsson et al. [257]	S	On anti-HT (at least for >1 yr)	RA	606	55	68	12.5	53**	29	Retrospective cohort: sero-positive RA included only
Erb et al. [68]	S	On anti-HT	RA	150	60.8	65.3	11.2		28	Matched case–control
			Ct	100	61.7	61			24	
Roman et al. [258]	S	Physician's diagnosis	RA	80	45	99			3.8	Case–control
			Ct	105	47†	95			4.8	
Wolfe et al. [1]	C	Physician's diagnosis (self-reported Q)	RA	9093	60†	76.9			28.1†	Cross-sectional
			OA	2479	66†				37.4†	
Solomon et al. [55]	C	Physician's diagnosis (self-reported Q)	RA	287	56†	100			31.4	Case–control: data from: Nurses Health Study
			Ct	87019	58†	100			29	
Wolfe and Michaud [259]	C	Physician's diagnosis (self-reported Q)	RA	13171	61	77	14.9	39	47	Cross-sectional
Han et al. [9]	C	ICD-9 401×	RA	28208	52	72.5			31†	Matched case–control: <17, no interaction with health system
			Ct	11232	52	72.5			23.4†	

S: secondary care; C: community; No.: number of participants; Ct: controls; F: female; DD: disease duration; E-RA: early RA; L-RA: long-standing RA; Q: questionnaire; DM: diabetes mellitus; HF: heart failure; IHD: ischaemic heart disease; CVA: cerebrovascular accident; PVD: peripheral vascular disease; ALT: alanine aminotransferase; AST: aspartate aminotransferase; †$P < 0.05$, *past/current use, **>1 yr use.

care (S) with community-derived controls (C) [8]. The most convincing evidence, comes from the large population study by Han *et al.* [9] on over 28 000 RA patients *vs* almost 113 000 age-matched controls in which prevalence of HT {defined as International Classification of Diseases 9th Revision, Clinical Modification (ICD-9) code CM 401× [56]} was significantly higher in RA (34% *vs* 23.4%). The lower overall rates in this, compared with other studies, are clearly due to the significantly different definitions used (physicians' diagnoses) [56] and the younger mean age of the participants.

Threshold BP levels for the diagnosis of HT are ≥140/90 mmHg when using the auscultatory method in the clinic (with BP having been measured on at least 3–6 visits, spaced over a period of 3 months [57]); ≥125/80 mmHg for ambulatory monitoring and ≥135/85 mmHg for self-reported BP monitoring at home [58]. Algorithms for diagnosis and management are predominantly based on clinical measurements, with the higher value used for classification if systolic and diastolic values fall into different categories. According to British Hypertension Society (BHS) guidance, SBP/DBP thresholds in millimetres of mercury are as follows: optimal <120/<80, normal <130/<85, 'high normal' 130–139/85–89, Grade 1 (mild HT) 140–159/90–99, Grade 2 (moderate HT) 160–179/100–109 and Grade 3 (severe HT) >180/>110. Isolated systolic HT is classified as Grade 1 (140–159/<90) or Grade 2 (>160/<90). The European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [58] and World Health Organization (WHO) guidelines [59] are virtually identical but the American Joint National Committee (JNC) [60] are slightly different by introducing the term 'pre-hypertension' to encompass normal and 'high normal' BP, and by merging Grades 2 and 3 HT in a single stage. This was based on evidence from the Framingham study [61, 62], which suggested an increased risk of future development of HT amongst individuals in the latter group(s). This classification was not adapted by the ESH/ESC [58] because it was felt that tagging individuals with a term of potentially ominous significance to the layman (i.e. 'pre-hypertension') may lead to an increased number of unnecessary visits and examinations [63].

Despite its high prevalence and the impact of its complications, control of HT is far from adequate both in the general population [60, 64–66] and in RA [10]. The poor control rates in the general population, where only a third of the people with HT have their BP under control [67], is attributed to poor access to health care and medications, and lack of adherence to long-term therapy for an usually asymptomatic condition. In a recent study [10], the rate of controlled HT in RA was significantly lower at 13.2%, than the 21–23% observed in the general population [65]. This is in line with several studies on RA patients, which report prevalence of treated HT between 22–34% [25, 26, 50, 54, 68, 69], a figure much lower than the aforementioned prevalence of HT in RA. Uncontrolled HT associates with premature CVD [20], increased risk for coronary heart disease (CHD) [70, 71], heart failure [23], cerebrovascular disease [71] and peripheral vascular disease (PVD). Left ventricular hypertrophy (LVH), a direct consequence of long-term increases in afterload due to HT, associates with increased incidence of heart failure, ventricular arrhythmias, fatal myocardial infarction (MI) or sudden cardiac death. In the general population, anti-hypertensive therapy has been associated with a 40% reduction in strokes, 20% in MIs and >50% in heart failure [72]: this emphasizes the importance of optimal BP control in any population, including RA. However, it must be emphasized that currently there are neither randomized controlled trials of the treatment of HT, nor any studies of the magnitude of benefit (if any) of HT control, specifically in patients with RA.

In the following sections, we discuss the multiple factors that may affect BP and its control in RA, particularly inflammation, physical inactivity and drugs. We then present the latest guidelines for the management of HT in the general population and suggest an adaptation for their use in patients with RA.

Inflammation

The first suspicion of an association between low-grade systemic inflammation and HT was raised in studies in the general population. Cross-sectional studies initially demonstrated higher levels of CRP measured by high-sensitivity (hs) assays amongst people with HT [73–78], while a prospective cohort study showed that increased hsCRP levels associated with future risk of developing HT [79]. A study in an asymptomatic sample of the general population [80] suggests that hsCRP associates inversely with large artery elasticity, thus increasing the systolic component of BP. Interestingly, vascular function is abnormal in RA compared with age- and sex-matched controls, with RA patients demonstrating reduced small- and large-artery elasticity and greater systemic vascular resistance [81]. Chronic inflammatory diseases, including RA, have been associated with increased arterial stiffness [32, 82, 83], which may subsequently lead to increased arterial BP [84] and partly explain the high prevalence of HT in RA.

There are several mechanisms by which systemic inflammation (reflected by high CRP levels) may promote the development of HT. High CRP can reduce nitric oxide production in endothelial cells (ECs), resulting in vasoconstriction, increased production of endothelin-1 [85, 86], leucocyte adherence, platelet activation, oxidation and thrombosis [87]. It can also lead to induction of plasminogen activator inhibitor-1 (PAI-1), which has been found raised in people with HT [88, 89], and may contribute to impaired fibrinolysis and atherothrombosis [86, 90]. CRP can also up-regulate the expression of angiotensin type-1 receptor, affect the renin–angiotensin system and further contribute to high BP [91].

However, the inverse has also been proposed. High BP, especially particular patterns of haemodynamic flow with low average but high oscillatory shear stress, are thought to cause greater expression of adhesion molecules and inflammatory genes by EC and initiate the inflammatory cascade in the arterial wall [92], including the production of pro-inflammatory cytokines; these may leak in the systemic circulation and may consequently induce an acute-phase response, including an elevation of CRP [93] (Fig. 1).

The relationship between systemic inflammation and BP has yet to be investigated in any detail in RA. In a recent cross-sectional study [10], there was no significant difference in RA activity and severity between hypertensive and normotensive RA patients. It is interesting to note that long-term (>6 months) oral daily prednisolone of ≥7.5 mg (i.e. medium dose according to recent nomenclature [94]), was significantly and independently associated with HT [95]. Given the cross-sectional design of the study, a causal relationship between long-term glucocorticosteroid (GC) and HT cannot be inferred nor can it be assumed that this association simply mirrors an association between severe cases of RA (which are more likely to be treated with steroids) and HT. It remains unknown whether good control of RA disease activity reduces the risk of developing HT in normotensive RA patients or contributes to improved BP control in hypertensives. Prospective longitudinal studies are required to answer these questions.

Physical inactivity

A prospective study of Harvard University male alumni started in the 1960s, demonstrated that the lack of moderately vigorous sports activities, being overweight and a parental history of HT independently increased the risk of developing HT, and this was a strong predictor of premature death [96]. The intensity of physical activity was more important than the quantity of energy output in deterring HT and preventing premature mortality, a finding that was confirmed for men but not for women in another cohort [97]. Several manifestations of RA, such as pain, stiffness and permanent joint damage [98], may compromise the physical activity and fitness levels of these patients compared with people
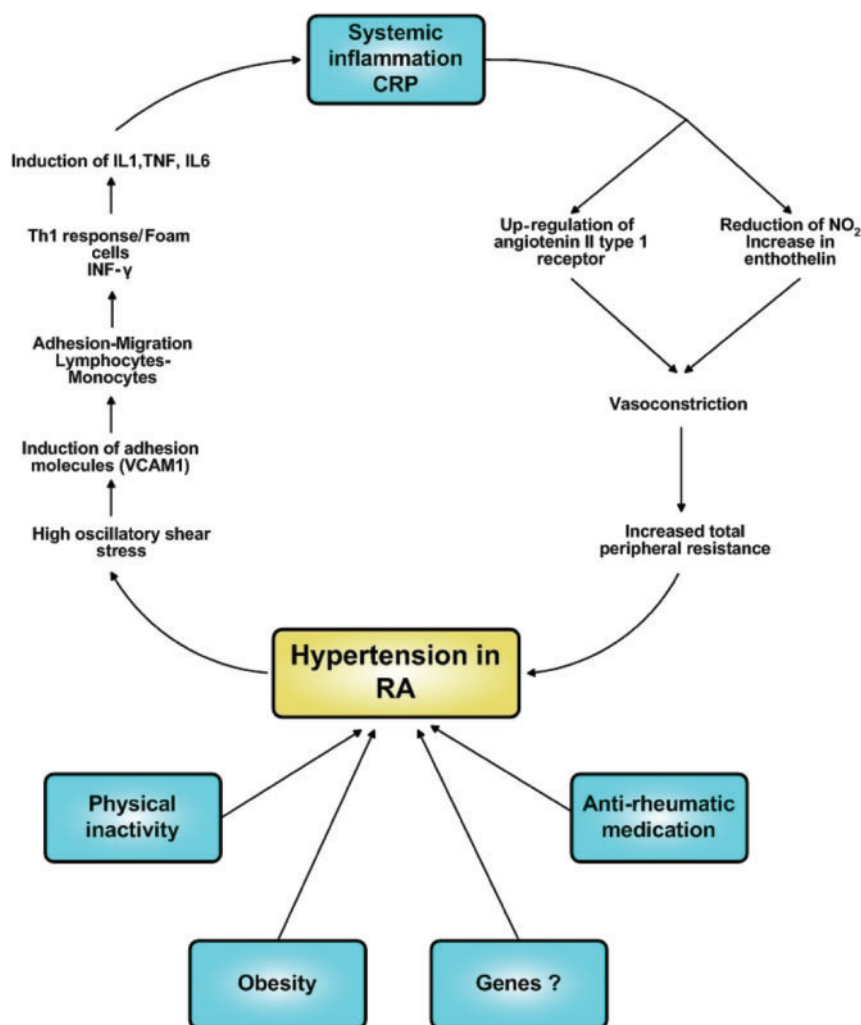
FIG. 1. Hypertension pathways in RA. Raised BP, particularly patterns of high oscillatory shear stress, initiate the inflammation cascade in the vascular wall which eventually leads to the production of acute-phase reactants from the liver, such as serum amyloid A and CRP. In turn, raised CRP levels lead to reduced NO/endothelin ratio and subsequent vasoconstriction, completing the vicious circle. Physical inactivity and obesity lead to increased propensity for the metabolic syndrome and subsequent BP elevations, whereas several anti-rheumatic medications (Fig. 2) have been associated with HT in RA. Even though the genetic element contribution to BP variation ranges from 30% to 50%, modern molecular approaches have not yet produced and substantiated any causative link between specific genes and HT neither in the general population, nor in RA. NO: nitric oxide; VCAM: vascular cell adhesion molecule; Th: T-helper lymphocytes.

of the same age and gender [99]. Together with fear for disease aggravation and the exercise restriction often recommended (unjustifiably) by rheumatology health professionals, this may account for the inactive, sedentary lifestyle of many RA patients [100]. Physical inactivity in turn may lead to obesity [101], which is highly prevalent [102] and associates independently with HT in RA [10]. Recent studies in the general population suggest that even mild physical exercise, such as walking to work, associates with a lower incidence of HT [103]. This could be recommended to patients with RA as part of the lifestyle changes required to reduce their CVD risk [104] while involvement in structured exercise programmes may provide even more pronounced benefits [99]. In the updated guidelines of the ACR [105] it is clearly stated that dynamic exercise is a safe and effective intervention for patients with RA of recent onset [106], or those with long-standing disease that is active [107] or inactive [108].

Medications

Polypharmacy is a characteristic of RA [109]: many of the drugs used routinely for the treatment of this disease may cause HT or interfere with its effective control. These include the non-selective NSAIDs, cyclo-oxygenase II inhibitors (coxibs), GCs and some

DMARDs. The use of these drugs in RA should always be considered in the context of co-morbid HT and its control.

Non-selective NSAIDs and coxibs

Since non-selective NSAIDs and coxibs are commonly used in RA, their effects on renal function and BP should be considered, especially for patients with pre-existing HT, renal impairment and in the elderly in whom side-effects are most pronounced [110]. In recent years, the absolute and relative contribution of non-selective NSAIDs/coxibs to adverse cardiovascular outcomes has been the subject of much controversy and multiple literature reviews [111–114]. In the present article, we concentrate only on published effects of non-selective NSAIDs/coxibs on BP and its control in people with RA.

A recent systematic review of randomized controlled trials (RCTs) [115] that has studied the effects on BP of non-selective NSAIDs used for at least 4 weeks, showed that there was a significant increase (from baseline to end of study) in mean BP values in ibuprofen (SBP/DBP: 3.54/1.16 mmHg) and indomethacin (SBP/DBP: 2.9/1.58 mmHg) users compared with placebo. Changes from baseline in SBP were positive but not statistically significant for naproxen, sulindac and nabumetone, while diclofenac users showed similar changes to placebo. Compared
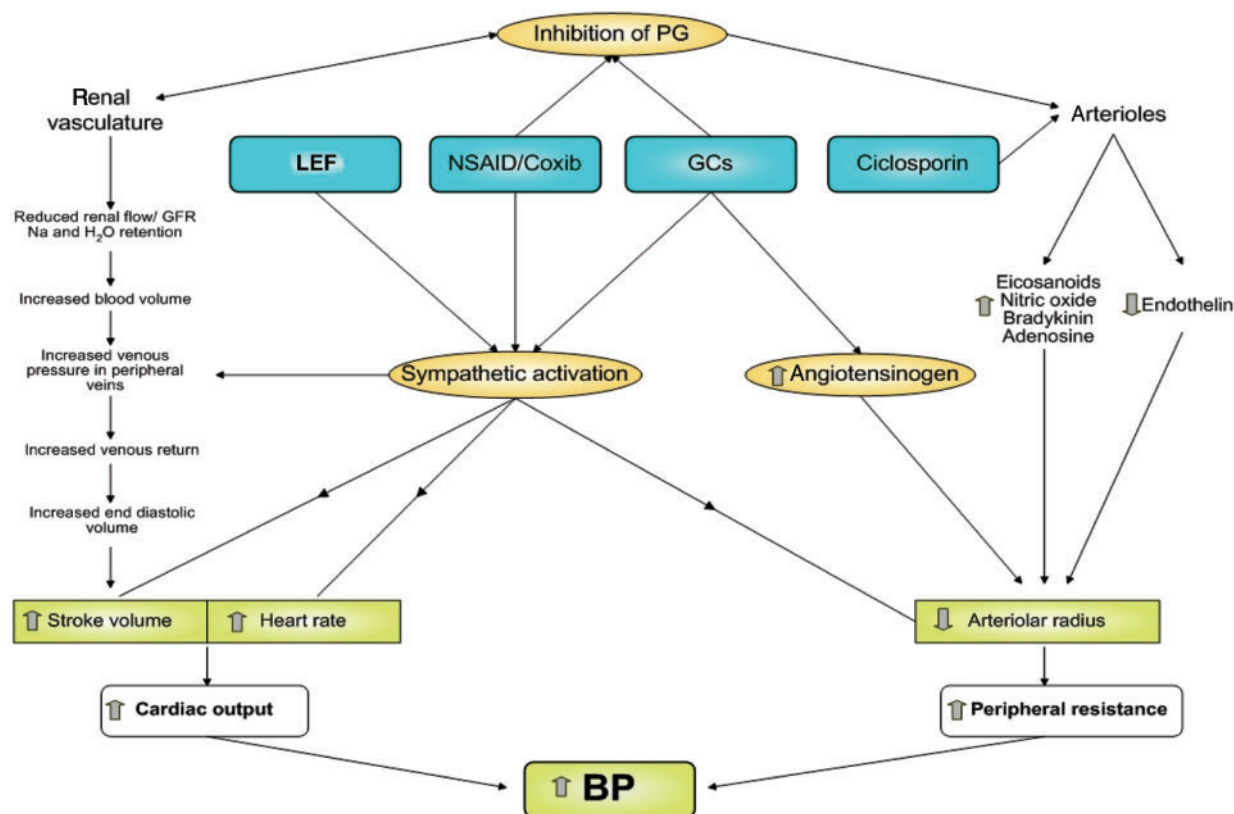
Fɪɢ. 2. Mechanisms through which drugs used in RA affect BP. PG: prostaglandin.

with placebo, the risk ratio (95% CI) of HT was 2.85 (95% CI 1.44, 5.65; $P = 0.003$) in two ibuprofen trials. In a large meta-analysis of 38 placebo-controlled and 12 head-to-head RCTs of non-selective NSAIDs, the latter, overall, have been shown to elevate the supine mean BP by 5 mmHg (95% CI 1.2, 8.7 mm Hg) [116]. This would be sufficient to cause a 15% increase in the risk for IHD and 67% for cerebrovascular accident [117]. In the latter meta-analysis, piroxicam, indomethacin and naproxen had the most marked effect, while aspirin (at anti-inflammatory doses), sulindac and flubiprofen caused the smallest BP elevation. The hypertensive effect of non-selective NSAIDs was more marked in people with HT taking anti-hypertensive therapy than in normotensive people [116].

Low (anti-platelet) doses of aspirin are not associated with BP elevation [118]. Two large prospective cohort studies [119, 120] of women in the 1976 Harvard Nurses' Health Study cohort [121] have shown that compared with non-users, regular non-selective NSAID and interestingly also acetaminophen users were twice as likely to be hypertensive. It was suggested that such analgesic use is responsible for the development of HT in 15% of middle-aged women [120]. However, in a large prospective cohort study of apparently healthy men in the 1982 Harvard Physicians' Health Study, analgesic use (non-selective NSAIDs, acetaminophen and aspirin) was not associated with subsequent HT [122]. As well as being gender-limited, these samples have narrow occupational group inclusion criteria that limit the generalizability, particularly given the effects of work status on subsequent CVD [123]. Even though several non-selective NSAIDs used in the above studies (such as indomethacin or piroxicam) are not any more frequently used in everyday clinical practice, overall data would suggest caution in the use of these agents, especially in the elderly, those who already have HT [124], patients with heart failure [125] or patients with renal impairment [126]. Patients belonging to these groups have increased activation of the renin–angiotensin and sympathetic nervous systems [127] and increased plasma concentrations of prostaglandin E2 [128, 129], and are therefore more prone to BP increases when treated with non-selective NSAIDs. The concurrent use of non-selective NSAIDs with diuretics, angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) can be particularly nephrotoxic in the elderly [130]. Therefore, if the above combinations cannot be avoided, they should be accompanied by close clinical and biochemical monitoring. Sulindac was thought to be a better choice in patients at high risk, as in the past it had been shown to have little effect on BP, although this has recently been questioned [110].

Many studies have shown that non-selective NSAIDs attenuate the anti-hypertensive effects of diuretics [116, 131, 132], β-blockers [116, 132], ACE-I [133, 134], ARBs [133] and other vasodilators, such as prazosin [116, 135]. However, non-selective NSAIDs do not have an effect on the BP-decreasing effect of calcium channel blockers (CCBs) [136, 137], which may therefore be an appropriate choice of anti-hypertensive if a non-selective NSAID is necessitated and worsening HT is noted.

The picture is quite similar with regard to coxibs and HT. The UK National Institute of Health and Clinical Excellence (NICE) guidance recommends that these agents should not be used routinely in patients with RA or OA [138]. They should be used in preference to non-selective NSAIDs only in patients at 'high risk' of developing gastrointestinal adverse effects and should be avoided in patients with concomitant CVD [138]. A meta-analysis [139] of 19 RCTs compared the hypertensive effects of coxibs (celecoxib, rofecoxib and etoricoxib) with a non-selective NSAID (naproxen) and placebo. The relative risk for developing HT was higher for coxibs *vs* non-selective NSAID or placebo but not significantly so. However, with coxib use, there appears to be a disproportionate rise in SBP compared with DBP, which may increase CHD risk [140]. Rofecoxib caused more increase in BP compared with celecoxib or etoricoxib, a result seen in many studies [141–143]. In agreement with these findings are the results

of the most recent meta-analysis of 114 RCTs of coxib use by Zhang *et al.* [144]. Only rofecoxib was associated with HT (RR = 1.55; 95%CI 1.29, 1.85) whereas celecoxib was associated with a slightly lower risk of HT (RR = 0.83; 95%CI 0.71, 0.97), and the other agents (valdecoxib/parecoxib, etoricoxib and lumiracoxib) demonstrated no significant association [144]. A coxib class effect was not evident, as only rofecoxib, but not other coxibs were associated with increased risk of HT. However, in the recently published Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) trial, participants receiving etoricoxib showed higher rates of discontinuation because of HT [145]. Taken together, this evidence would suggest an association of sulphone coxibs (rofecoxib, etoricoxib) with HT that could be explained by the pro-oxidant effects of these agents, which result to vasoconstriction and subsequent BP elevation [146].

Other studies have focused on non-selective NSAID and coxib effects on ambulatory BP and showed significant increases in SBP by rofecoxib but not celecoxib or naproxen [147]. The proportion of people with controlled HT at baseline who developed ambulatory HT by week 6 of the Sowers *et al.*'s [147] study was greater with rofecoxib (30%) than celecoxib (16%). In two other studies where ACE-I-treated people with HT were evaluated, the effects of celecoxib were comparable with placebo [148], whereas rofecoxib induced significant BP increases over placebo or indomethacin [149].

COX-2 is constitutively expressed in the kidney and expression is up-regulated during salt restriction indicating that COX-2 may be important in regulating renal function [150, 151], particularly in patients with low effective circulating volume, such as those with congestive heart failure, cirrhosis, renal insufficiency or users of diuretics [152]. In a comparative study of celecoxib *vs* naproxen, all participants experienced transient reduction in sodium and potassium excretion. Celecoxib at a dose of 400 mg BD lowered the glomerular filtration rate and renal plasma flow in contrast to naproxen, which had no such effect [153]. However, the Celecoxib Long-Term Arthritis Safety Study (CLASS) [154] in 7968 subjects, 2183 with RA and 5785 with OA, suggested an improved safety profile, regarding the renal effects of celecoxib compared with standard doses of ibuprofen or diclofenac. In cases with mild pre-renal azotemia, significantly fewer participants taking celecoxib exhibited clinically important reductions in renal function compared with diclofenac or ibuprofen. Celecoxib was associated with a similar incidence of HT or oedema to diclofenac, but significantly lower than ibuprofen [154]. However, despite the seemingly safe hypertensive profile of celecoxib, several studies have shown an association of the latter with increased risk of MI, consistent with a class effect for COX-2 specific inhibitors [155–157]. Therefore, use of celecoxib or any other coxib, should ideally be avoided in patients with RA, particularly when CVD factors or established CVD is present [158].

In the general population, concomitant use of low-dose aspirin is present in >20% of all people taking either non-selective NSAIDs or coxibs [159]. The interaction of non-selective NSAIDs/coxibs with low-dose aspirin may be of great importance: there is some evidence to suggest that ibuprofen (but not rofecoxib, diclofenac or acetaminophen) may antagonize the anti-platelet effect of aspirin and limit its cardioprotective effects [160]. There may also be an interaction between naproxen and aspirin, with naproxen inhibiting platelet COX-1 [161]. Pharmacodynamic data indicating an interaction between aspirin and NSAIDs have not translated to a consistent clinical effect in observational studies [162]. It remains unknown, currently, whether anti-platelet doses of aspirin decrease the cardiovascular risks afforded by chronic usage of coxibs or non-selective NSAIDs, although it may potentiate their gastrointestinal side-effects. [159]. For now, according to an FDA advisory [163] patients taking immediate release low-dose aspirin (not enteric coated) and ibuprofen 400 mg should take the latter at least 30 min after aspirin ingestion or at least 8 h before aspirin ingestion to avoid any potential interaction. Expert recommendation is also that patients should take a non-enteric coated aspirin at least 15–30 min (if chewed) or 2 h (if swallowed) prior to taking an NSAID, and at least 6–8 h after the last dose of ibuprofen or 36–48 h after naproxen [164]. It would be reasonable to suggest that concomitant use of low-dose aspirin and NSAIDs should be avoided if at all possible, and the lowest NSAID dose should be used for the shortest period of time.

In summary, current evidence and common sense would indicate that non-selective NSAIDs and coxibs have largely similar effects on BP control and renal function, and their use in RA should be avoided. These agents should be particularly avoided in conditions with diminished intravascular volume or oedema, such as congestive heart failure, nephrotic syndrome or cirrhosis, and in patients with serum creatinine levels ≥2.5 mg/dl [126]. A recent statement from the American Heart Association (AHA) [165] recommends that for patients with known CVD or at risk for IHD and concomitant musculoskeletal symptoms, the least risky medication should be tried first (acetaminophen, acetylsalicylic acid, tramadol, short-term narcotic analgesics) with escalation only if the latter are ineffective (with order of preference: non-COX-2 selective NSAIDs being preferable to NSAIDs with some COX-2 activity, and these being preferable to COX-2 selective NSAIDs) and with realization that effective pain relief may come at the cost of a small but real increase in risk for cardiovascular or cerebrovascular complications. We suggest that if NSAID use is unavoidable, BP (and renal function) should be closely monitored and in cases of developing new or uncontrolled HT with a continuing requirement for non-selective NSAIDs/coxibs, anti-hypertensive treatment should be instituted, possibly with CCBs.

DMARDs

Some of the DMARDs can induce HT, so if RA is diagnosed in a person with HT (or indeed the converse, when a person with established RA develops HT), the choice of DMARD must be carefully considered. The concurrent use of NSAIDs/coxibs and/or steroids may further exacerbate these side-effects.

LEF

LEF-related HT is found in 2–4.7% of people who were prescribed LEF [166–168], in the absence of renal function abnormalities. A small longitudinal study of consecutive patients on stable doses of NSAIDs and corticosteroids [169] revealed significant increases in SBP and DBP occurring within the first 2–4 weeks of LEF therapy.

The mechanisms by which LEF induces HT include an increase in sympathetic drive and displacement of free fraction of concomitant diclofenac or ibuprofen from protein binding, increasing the NSAID's effect on the distribution of renal blood flow and retention of salt and water [170]. The latter is thought to be because the active malononitrilamide metabolite A77 1726 of LEF, which is formed in the intestinal mucosa and plasma, and is highly protein bound in plasma [171].

The British Society for Rheumatology (BSR) monitoring guidelines [172] recommend fortnightly BP measurements for the first 6 months of LEF therapy and every 2 months thereafter. Though LEF is not contraindicated in HT, other DMARD options should be considered first, while if HT occurs after commencing LEF, anti-hypertensives may be used, but a dose reduction or cessation of therapy may be required if BP control is not attained.

Cyclosporin

Cyclosporin has a number of side-effects including HT and nephrotoxicity [173–178] and is contraindicated in people with abnormal renal function or uncontrolled HT [172].

Several mechanisms have been suggested to explain cyclosporin-induced HT [179, 180], including: increased peripheral vascular resistance as a result of widespread endothelin-related vasoconstriction; impaired vasodilation due to a reduction in nitric oxide levels or suppression of vasodilatory prostaglandins such as prostacyclin; vasoconstriction in the renal circulation resulting in reduced glomerular filtration rate; and increased sodium retention.

After commencing cyclosporin, serum creatinine and BP should be measured fortnightly until the dose has been stable for 3 months, and continued at monthly intervals thereafter. A 30% rise in creatinine requires urgent adjustment or even cessation of therapy [181]. The new discovery of HT while on cyclosporin also requires action. CCBs, other than diltiazem, verapamil and nicardipine (that increase plasma cyclosporin levels), are the drugs of choice in this situation as they antagonize the vasoconstrictive effects and control effectively cyclosporin-induced HT [182]. A reduction in cyclosporin dose or even complete withdrawal may be necessary in cases of resistant HT.

Biologic anti-TNF-α therapies and other DMARDs

The ultimate effect of biologic anti-TNF therapies on cardiovascular risk is not yet known [183], although initial reports appear promising [184]. There are no reports of HT occurring in association with TNF-α blockers, even though in a minority of patients with RA they can cause or exacerbate heart failure [185]. Some DMARDs may have overall favourable effects on CVD risk factors and may therefore be particularly suitable for hypertensive RA patients. HCQ, for example, may be associated with a favourable lipid profile [186–188] and thus eliminate another potential risk factor for HT [189] among people with RA, but this remains to be proven.

GCs

In the general population, therapeutic use of supraphysiological doses of oral GCs (≥ 7.5 mg/day) may associate with increased rates of MI, stroke, heart failure and all-cause mortality [190, 191]. However, unmeasured confounders may be very important in all observational studies of this type, so such results should be seen with great caution.

It is widely held that GC therapy may raise BP in both normotensive and hypertensive people, but good quality evidence for this is limited and the possible mechanisms are not well understood [192, 193]. Endogenous plasma or urine cortisol levels are increased in hypertensive subjects compared with controls, implying potential hypertensive properties of this hormone when administered orally [194, 195] and there is a positive correlation between plasma cortisol and 'white-coat' HT [196]. Most of the reviews on GC side-effects [197–199] or on mechanisms of GC-induced HT [200] are citing very old references [201–203] when discussing the association of HT with exogenous steroid use. The regimes used and the design of these studies do not provide sufficient evidence to support such an association. This lack of evidence is also reported in the recent European League Against Rheumatism (EULAR) recommendations on the management of systemic GC therapy in rheumatic disease [204]; for Recommendation 5, which is referring to BP monitoring, authors state that 'There is no direct evidence from appropriately designed studies to support this proposition (category IV)'. A study from the early 1970s [205] reported that radiologically visible arteriosclerosis in the ankle joint region in RA patients on long-term GC was three times more frequent than in RA patients not receiving GC or in healthy controls. There was no information on GC dose and duration, and no adjustment for age, disease activity or severity. A prospective longitudinal study from the 1980s suggested that in people receiving 'low doses of GCs' (defined in that study as prednisone <20 mg/day!), significant HT may be explained by age and initial BP rather than by the use of

GCs [206]. However, new thresholds were recently set to define 'low', 'medium' and 'high' dose prednisolone [94]. Participants in that study [206] could belong to the 'modern' low- or medium-dose category and this may have influenced the results. A recent small RCT [207] of GC use in RA, assessed the effects of low-dose prednisolone use (≤ 7.5 mg) on atherosclerosis, endothelial function and risk factors including HT. There was a trend for increased BP among participants who had been treated for at least 4 yrs with prednisolone 7.5 mg (157 ± 29 mmHg) compared with untreated participants (141 ± 28 mmHg, $P = 0.06$). A recent large cross-sectional study in RA [95] showed an increased prevalence of HT in patients on medium-dose (prednisolone ≥ 7.5 mg/day), long-term (>6 months) GCs, with GCs appearing to be a risk factor for HT independent of other HT risk factors, RA activity or severity, but this finding needs to be confirmed in prospective longitudinal studies.

GC-induced HT is likely to be multifactorial [192, 193]. GCs inhibit extraneuronal uptake and catechol-*O*-methyltransferase (which breaks down noradrenaline) and thus raise noradrenaline levels in the synaptic cleft [208, 209]; they can also increase the number of α-1 adrenergic receptors [210] with the overall effect of increased peripheral vascular sensitivity to adrenergic agonists. GCs can also increase angiotensinogen production from adipose tissue [211] and inhibit prostaglandin production, thus leading to renal sodium retention and increase in blood volume [212].

So far, evidence suggests that GCs, when given in low doses (<7.5 mg daily prednisolone) probably do not cause clinically significant BP increases [95, 199]; however, RA patients on higher doses of prednisolone should be regularly screened for HT and adequately treated, should the latter occur.

Guidelines for the management of HT

Risk assessment

People with high BP do not necessarily require treatment: in the general population, requirement for intervention is guided by risk stratification. There are several systems for this, including the ESH/ESC [58], which best lend themselves for adaptation in RA (Table 2). In the general population, the link between HT and inflammation has been established in prospective studies [79]. RA *per se*, a chronic disease of high inflammatory state, leads to increased arterial stiffness and carotid wall thickening compared with healthy controls [82, 213, 214] and could therefore be considered an independent risk factor for HT [84], although direct evidence for this is currently lacking. Furthermore, raised CRP levels (≥ 1 mg/dl), which are almost universally observed among RA patients, were considered an additional risk factor in the previous ESC/ESH guidelines [215]. We therefore recommend that, when stratifying the risk of a person with RA who is hypertensive (as per ESH/ESC), physicians should add '+1' in the total sum of risk factors and treat accordingly [58] (Table 2).

It is extremely important to remember that HT should not be addressed in isolation, but must be considered in the context of the overall cardiovascular risk of an individual. This risk can be calculated on the basis of risk factors (including HT), using risk calculators, such as the Joint British Societies calculator [216]. Table 3 outlines an overall therapeutic strategy for a patient, on the basis of their BP levels, 10-yr CVD risk and the presence of relevant comorbidity. RA patients who have 'compelling indications', including those with heart failure, post-MI, high CHD risk, diabetes, stroke or chronic kidney disease [19], require detailed consideration of their anti-hypertensive treatment and further management [140] by a cardiology specialist.

Next, we consider specific aspects to consider when managing HT in people with RA.

TABLE 2. Proposed risk stratification for RA patients according to BP levels and other CVD risk factors

Risk factors and disease history	Normal SBP 120–129 or DBP 80–84	High normal SBP 130–139 or DBP 85–89	Grade 1 SBP 140–159 or DBP 90–99	Grade 2 SBP 160–179 or DBP 100–109	Grade 3 SBP >180 or DBP >110
No other risk factor	Very low added risk	Very low added risk	Moderate added risk	Moderate added risk	Very high added risk
1 risk factor	Very low added risk	Very low added risk	Moderate added risk	Moderate added risk	Very high added risk
2 or more other risk factors	Moderate added risk	High added risk	High added risk	High added risk	High added risk
3 or more other risk factors or TOD or diabetes or MetS	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CVD or renal disease	High added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

RA patients in the shaded cells (bold line cut-off) may require prompt treatment. The dashed line represents cut-off levels for treatment initiation in the general population.
Risk factors: age (M>55, F>65), smoking, dyslipidaemia (TChol>5 mmol/l or LDL>3 mmol/l or HDL <1 mmol/l M or <1.2 mmol/l F or TG>1.7 mmol/l), fasting plasma glucose 5.6<FPG<7 mmol/l, abnormal glucose tolerance test, family history of premature CVD disease (<55 M, <65 F), abdominal obesity (>102 cm M, >88 cm F) Target organ damage (TOD): LVH, U/S evidence of arterial wall thickening (carotic IMT≥0.9 mm or atherosclerotic plaque), carotid-femoral pulse wave velocity >12 m/s, ankle/brachial BP index <0.9, slight increase in serum creatinine (M: 115–133 μmol/l, F: 107–124 μmol/l), low estimated GFR (<60 ml/min/1.73m^2), microalbuminuria. CVD or renal disease: CVA, heart disease, renal disease (diabetic nephropathy, renal impairment, proteinuria), PVD, advanced retinopathy. M: Males; F: Females; TChol: Total Cholesterol; TG: triglycerides; LDL: low density lipoprotein; HDL: high density lipoprotein; US: ultrasound; IMT: intima–media thickness; GFR: glomerular filtration rate; CVA: cerebrovascular accident.

TABLE 3. Risk factors and therapeutic targets for CVD prevention among people with RA

CVD risk <20% over the next 10 yrs		CVD risk >20% over the next 10 yrs		Atherosclerotic cardiovascular disease		Diabetes	
Normal BP (<140/90)	Raised BP (≥140/90)	Normal BP (<140/90)	Raised BP (≥140/90)	Normal BP (<130/80)	Raised BP (≥130/80)	Normal BP (<130/80)	Raised BP (≥130/80)
Lifestyle advice Monitoring at every clinical visit (at least 6 monthly) Anti-HT[a]	Lifestyle advice Anti-HT[a]	Lifestyle advice Aspirin Statin[c] Anti-HT[a]	Lifestyle advice Aspirin[b] Statin[c] Anti-HT	Lifestyle advice Aspirin[b] Statin[c] ACE-I/ARBs[d,e] β-Blockers	Lifestyle advice Aspirin[b] Statin[c] ACE-I/ARBs β-Blockers Other anti-HT[g]	Lifestyle advice Aspirin[b] Statin[c] ACE-I/ARBs[e,f]	Lifestyle advice Aspirin[b] Statin[c] ACE-I/ARBs[f] Other anti-HT[g]

[a]Anti-hypertensive therapy only if required from Table 2 risk stratification (see Table 4 for anti-hypertensive choice). [b]Avoid concomitant use of aspirin and NSAIDs. If no realistic alternative then use lowest dose possible and consider PPI use and *Helicabacter pylori* eradication. Anti-HT: anti-hypertensives; LDL: low density lipoprotein; PPI: protein pump inhibitor. [c]Targets are: total cholesterol <4 mmol/l or 25% reduction and LDL-C <2 mmol/l or 30% reduction. [d]In people with heart failure or LV dysfunction and consider in people with coronary disease and normal LV function. [e]According to Table 2, these people fall into the high/moderate risk category. Therefore BP treatment should be initiated immediately. ACE-Is/ARBs are a good initial choice because they also serve the compelling indication, diabetes and atherosclerosis. Consider CCB if the patient is on NSAIDs and unable to discontinue use. [f]In people with renal dysfunction and microalbuminuria. [g]Consider if BP target not achieved with ACE-Is, ARBs, β-blockers.

Lifestyle measures

Lifestyle modifications leading to improved BP control include maintenance of ideal weight (for RA patients to a BMI of <23 kg/m^2 for people with RA) [102], limiting daily sodium intake to <60 mmol/l (<3.8 g/day) [217] and alcohol consumption to 20–30 g ethanol per day for men and 10–20 g for women [218], smoking cessation [219], dietary patterns based on the Dietary Approaches to Stop HT (DASH) diet (rich in fruits and vegetables and low-fat dairy products, with a reduced content of dietary cholesterol as well as saturated and total fat) [220], high-dose omega-3-polyunsaturated fatty acid supplements [221], increased potassium, calcium and magnesium intake (even though more trials are needed to establish the benefits [222, 223] and last but not the least, regular aerobic exercise [99]. Relevant advice and leaflets can be found through the BHS [224] or British Heart Foundation [225] websites. Some of these lifestyle modifications, e.g. exercise [99] and smoking cessation [226] could also result in clear benefits in control of RA disease activity; there is no existing evidence that any of the other lifestyle modifications would precipitate adverse outcomes of RA.

Anti-hypertensive drugs

The recent joint NICE and BHS 2006 guidelines for HT management provide an excellent framework for initial drug treatment and stepwise escalation depending on response [227], which could be applied to people with RA either in primary care or in the rheumatology clinic. There are no RCTs to guide HT management specifically among patients with RA. There are, however, several issues that should be taken into account when making treatment decisions for a person with RA who is hypertensive:

(i) requirement for anti-hypertensive therapy should always be considered in the context of the patient's anti-rheumatic therapy (Table 4);

TABLE 4. A practical approach to the prevention, diagnosis and management of hypertension in patients with RA

(i) Diagnosis of hypertension
  Establish diagnosis of hypertension as per new ESH/ESC guidelines.
(ii) Identify the cause (essential or secondary)
  Screen for current use of non-selective NSAIDs, coxibs, GCs, LEF, cyclosporin.
(iii) Initial steps in hypertension management
  (a) Remove cause if possible (e.g. NSAID) and re-assess (within 3 months).
  (b) Provide lifestyle advice and re-assess (within 3–6 months).
  (c) Decide on requirement for pharmacological therapy and target BP according to risk stratification (as per Table 2).
(iv) Choice of anti-hypertensives
  (a) If essential hypertension present, use ACE-I/ARBs as first choice anti-hypertensive treatment. Monitor renal function closely, particularly in the elderly or those on nephrotoxic medication (e.g. NSAIDs, cyclosporin).
  (b) If hypertension is due to non-selective NSAID/coxib, which cannot be withdrawn, use CCB as initial treatment option. If the person is taking GCs consider tapering dose.
  (c) If insulin resistance is present, avoid β-blockers/diuretics.
  (d) If RP is present avoid β-blockers and use CCB/ACE-I/ARBs as initial anti-hypertensive treatment.
(v) Decide if other treatment is required in the context of calculated 10-yr CVD risk or presence of comorbidities (CVD or diabetes)
  (a) Treat as per Table 3. If suspicion of compelling indication (heart failure, post-MI, stroke, etc.) refer to cardiologist.
  (b) If concomitant use of low-dose aspirin and NSAID necessary, consider using the lowest possible NSAID dose, PPI and *Helicobacter pylori* eradication.
(vi) BP monitoring requirements in patients with RA
  (a) Systematic BP monitoring every time a patient attends primary or secondary care, or at least every 6 months.
  (b) If patient started on non-selective NSAIDs/coxibs or GCs, monthly follow-up (either at the primary or secondary setting) for the first 6 months, as above (a) thereafter.
  (c) If patient initiated on LEF/cyclosporin therapy, fortnightly follow-up for the first 6 months, 2 monthly thereafter.
  (d) Review of continuing requirement for any anti-rheumatic therapy with BP-raising potential at every clinic visit, irrespective of whether patient is hypertensive or not.
    • If not required: stop
    • If alternatives available: change
    • If continuing requirement: monitor BP as above
  (e) In case of incident hypertension, monthly monitoring until BP target is reached; thereafter as above (a).

Coxib: cyclo-oxygenase; PPI: protein pump inhibitor.

(ii) ACE-I may be particularly suited to patients with active RA, since they have increased sympathetic activity [228, 229], which may put them in a high renin state [230, 231]. Additionally, these agents may also have a beneficial effect on the course of RA disease *per se*, since they suppress mediators of inflammation, including reactive oxygen species and CRP and they increase the expression of inhibitory κB (inhibitor of nuclear factor-κB) [232];

(iii) Increased systemic inflammation (due to over-production of TNF-α and IL-1) leads to down-regulation of various cardiovascular receptors including β-adrenergic [233] and L-type cardiac calcium channel [234] receptors. No such effect has been reported for the angiotensin II type 1 receptors. This may, in theory, influence the efficacy of β-blockers and some CCBs, but the anti-hypertensive effect of ARBs, such as valsartan [235] and losartan [236], in RA patients should remain unaltered. There are no clinical trials in RA to support or refute this possibility;

(iv) Insulin resistance is a common feature in RA patients [237], especially among those on treatment with GCs [238]. In this setting, β-blockers and thiazide diuretics should be avoided, due to their dyslipidaemic and diabetogenic effects. ACE-I, ARBs or CCBs would be preferable for lowering BP [239, 240]; and

(v) If secondary RP is present then CCBs [241] or ACE-I/ARBs [242, 243] may be the preferred first-line anti-hypertensive treatment, while β-blockers should be avoided.

All of the above suggest that RA patients are more likely to benefit from ACE-I or ARBs, irrespective of their age, with CCBs being also useful in specific situations. An overall approach to the management of HT in patients with RA is presented in Table 4.

Summary

Awareness of the risk of CVD and aggressive screening and treatment strategies, including meticulous BP control [244], have greatly benefited patients with diabetes over the last decade. Over the same time period, awareness of the cardiovascular risk associated with RA has increased, but is yet to be translated in a systematic approach aiming to reduce comorbidity and mortality. Although direct evidence specifically in RA is lacking, it seems reasonable to suggest that early detection and aggressive management of HT in patients with RA should form part of such a systematic approach. There is a need for specifically designed trials to identify the best approaches for HT management in patients with RA, and quantify the beneficial effect of HT control (if any) on the cardiovascular outcome of this group of people.

Rheumatology key messages

- HT is highly prevalent in RA.
- Use of anti-inflammatory analgesics and disease-modifying drugs with hypertensive potential, physical inactivity and yet to be determined inflammatory pathways, and genetic factors may synergistically lead to HT in patients with RA.
- Aggressive screening and low BP thresholds for anti-hypertensive treatment may be helpful, but these strategies need to be confirmed in prospective studies designed specifically for the purpose.

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