Six-step management of hypertension in patients with rheumatoid arthritis

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Hypertension is one of the major risk factors for cardiovascular disease. Its prevalence in patients with rheumatoid arthritis is equal to, if not higher than, that in the general population, as is the attributable risk to the development of future cardiovascular events. Despite its serious complications, control of hypertension is far from adequate in the general population and even more so in rheumatoid arthritis patients. The constellation of inflammation, physical inactivity, polypharmacy and difficulties implementing primary prevention render the management of hypertension in rheumatoid arthritis patients a very challenging task. In this article we attempt to unravel the complexity of managing hypertension in rheumatoid arthritis patients and make practical recommendations that may be useful in clinical practice.

Hypertension is the blood pressure (BP) value above which treatment does more good than harm [1]. In line with this definition, BP thresholds for initiation of antihypertensive treatment are lower when an individual's risk for a cardiovascular event is high [2]. In general, BP thresholds for the diagnosis of hypertension are greater than or equal to 140/90 mmHg when using the auscultatory method in the clinic (with BP having been measured on at least three to six visits, spaced over a period of weeks to months [3]); greater than or equal to 130/80 mmHg for ambulatory BP monitoring; and greater than or equal to 135/85 mmHg for self BP monitoring at home [2]. Algorithms for diagnosis and management are predominantly based on clinic measurements, with the higher value used for classification if systolic and diastolic values fall into different categories [4]. The European [2] and WHO guidelines [5] are virtually identical, but the American Joint National Committee guidelines [6] are slightly different through use of the term prehypertension to encompass normal and high normal BP, and by merging grade 2 and grade 3 hypertension into a single stage.

The excessive cardiovascular morbidity and mortality in patients with rheumatoid arthritis (RA) [7,8] has been the subject of intense research in the last few years. Suggested explanations for the increased burden of cardiovascular disease (CVD) among these patients include an increased prevalence of traditional (dyslipidemia, hypertension and smoking) [9–12], novel (raised serum uric acid levels) [13] and RA-related (extra-articular disease, Health Assessment Questionnaire score, rheumatoid factor and glucocorticoid use) [14,15] CVD risk factors. Increased prevalence of hypertension in RA has been demonstrated in many [11,16], but not all studies [17,18]. Prevalence of hypertension in secondary-care cohorts of RA patients may be as high as 70% [19], higher than the highest prevalence in England observed in those over 75 years [20]. Recently, Gonzalez *et al.* showed that the impact of hypertension on cardiovascular outcome is similar in subjects with RA to those who do not have RA [17]; since cardiovascular mortality is higher in RA patients compared with non-RA controls [7,21], the number of deaths attributed to hypertension must be higher amongst RA patients. The risk of CVD in the general population increases in parallel with increases in systolic or diastolic BP, approximately doubling for every 20/10 mmHg incremental increase in BP that occurs within the range of 115–185/75–115 mmHg [22]. Despite its high prevalence and the impact of its complications, control of the disease is far from adequate both in the general population [6,23,24] and in RA [19]. In a recent study [19], the control rate of hypertension in RA was significantly lower, at 13.2%, than the 21–23% observed in the general population [25]. Antihypertensive therapy has been associated with mean reductions of 40% in stroke incidence, 20% in myocardial infarction and over 50% in heart failure [26], thus emphasizing the importance of optimal BP control in any population, including patients with RA.

One of the characteristic features of RA is the presence of chronic systemic inflammation [27]. Inflammation is an established risk factor for development of arterial stiffness [28,29] and hypertension [30] in the general population. It is

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thought that the increased inflammatory load in RA leads to impaired microcirculatory reactivity, endothelial dysfunction, increased arterial stiffness [31–33] and, thus, elevated BP levels [34,35]. Therefore, cardiovascular medications with anti-inflammatory properties, such as statins and ezetimibe [36] or inhibitors of the renin–angiotensin–aldosterone axis [37], may exhibit enhanced antihypertensive properties, particularly when administered to RA patients [38].

Treatment of hypertension in RA is a particularly challenging task. Multiple factors, including the extent of inflammation, comorbidities, physical inactivity and antirheumatic drugs with a hypertensive potential, may affect both BP levels and the effectiveness of antihypertensive treatment. Familiarity of primary-care health professionals with antirheumatic treatment and of rheumatology health professionals with antihypertensive therapy, as well as RA patient education on cardiovascular health and disease, are further issues of importance. In this article, we aim to present a systematic approach to the management of hypertension in RA patients by discussing three common clinical scenarios and summing up the main treatment pathways. Our approach is based on answering the following six questions:

- Does the patient have hypertension?
- What is the cause?
- Does the patient need antihypertensive treatment?
- Can the cause be removed?
- Is BP high enough in the context of overall CVD risk?
- If yes, what type and why?
- Is there a need for any more investigations or treatment for CVD or other relevant comorbidities?
- What monitoring does he/she require?

Clinical scenario one

A 53-year-old accountant with a 15-year history of RA was recently prescribed ibuprofen for persistent joint pains not controlled by analgesics (including opioid analogues). He attends regular check up visits. Apart from his long-standing RA he is in good health and has no personal or family history of hypertension, CVD or renal disease. He drinks alcohol in moderation (1–2 units a day) and is a current smoker of 20 cigarettes a day. Repeated BP measurements in previous visits (prior to ibuprofen use) revealed BP levels within the high normal range (130–139/85–89 mmHg). On physical examination he is mildly overweight (BMI: 26 kg/m^2; waist circumference: 98 cm), his BP is 155/85 mmHg at both arms, without a postural drop and with normal femoral pulses. The rest of the examination, including fundoscopy, was unremarkable. Urinalysis was normal and biochemistry results revealed: glucose: 4.6 mmol/l; total cholesterol: 6.4 mmol/l; HDL: 1.1 mmol/l; creatinine: 95 µmol/l; and serum potassium: 4.4 mmol/l. ECG was normal. What is the plan for managing this patient's hypertension and why?

Does the patient have hypertension?

Clinical assessment and investigations have not revealed any evidence of target-organ damage (such as renal impairment, retinopathy or ECG changes), so diagnosis of hypertension needs to be confirmed, based on at least two to three further measurements in more than two visits [2].

What is the cause?

As soon as the presence of hypertension (BP ≥ 140/90 mmHg) is established, the physician should consider withdrawing the NSAID, since the history suggests that BP was raised after its initiation. In a recent systematic review of the hypertensive effects of NSAIDs used for at least 4 weeks, ibuprofen was associated with a 2.9 mmHg increase in systolic BP (95% confidence interval [CI]: 0.28–6.08; $p < 0.001$) and a 1.16 mmHg increase in diastolic BP (95% CI: 0.68–1.64; $p < 0.001$) compared with placebo [39]. Similar results were obtained with indomethacin, whereas no significant differences in BP were observed with diclophenac, naproxen, sulindac or nabumetone [39]. In a meta-analysis of 38 placebo-controlled and 12 head-to-head randomized, controlled trials (RCTs) of NSAIDs [40], these drugs elevated supine mean BP by 5.0 mmHg (95% CI: 1.2–8.7). This would be sufficient to cause a 15% increase in the risk for heart disease and a 67% increase in the risk for cerebrovascular accident [41]. Piroxicam, indomethacin and naproxen had the most marked effect, while anti-inflammatory aspirin, sulindac and flubiprofen caused the smallest BP elevation. The hypertensive effect of NSAIDs was more marked in hypertensive than in normotensive patients taking antihypertensive therapy [40]. However, it is clear that there is a range of individual responses to an NSAID, from significant increases of BP in some individuals (e.g., those with a low circulatory volume)

to reductions (e.g., in a young patient who is relieved from pain). Therefore, close monitoring after commencement of those drugs (Box 1) is of vital importance in order to avoid potential side effects accompanying significant BP changes.

Selective inhibition of the COX-2 isoenzyme was proposed to be a solution to the noxious gastroenterological effects of nonselective inhibition of the older NSAIDs. However, in recent years, their absolute and relative contribution to adverse cardiovascular outcomes has been the subject of much controversy and multiple literature reviews [42–44]. In the meta-analysis of 114 RCTs by Zhang *et al.*, only rofecoxib was associated with hypertension (relative risk [RR]: 1.55; 95% CI: 1.29–1.85), whereas celecoxib was associated with a slightly lower risk of hypertension (RR: 0.83; 95% CI: 0.71–0.97), and the other agents (valdecoxib/parecoxib, etoricoxib and lumiracoxib) demonstrated no significant association [45]. A COX-2 inhibitor class effect was not evident, as only rofecoxib, but not other coxibs were associated with increased risk of hypertension. However, in the recently published Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) trial, patients receiving etoricoxib showed higher rates of discontinuation due to hypertension [46]. The above evidence suggests an association of sulfone coxibs, (e.g., rofecoxib and etoricoxib) with hypertension that could be explained by the pro-oxidant effects of these agents, which result in vasoconstriction and subsequent BP elevation [47]. Interestingly, celecoxib improves nitric oxide bioavailability and endothelium-dependent vasodilation and reduces vascular inflammation and oxidative stress in patients with CVD or hypertension [48,49]. Therefore, if COX-2 treatment cannot be withheld, physicians should consider substituting any other coxib with celecoxib, but we would still recommend close monitoring for ensuing/continuing hypertension.

Box 1. Recommendations for management of hypertension in patients with rheumatoid arthritis.

Step 1. Does the patient have hypertension?

- Establish diagnosis of hypertension as per new European Society of Hypertension/European Society of Cardiology guidelines
- Provide lifestyle advice to all RA patients, irrespective of BP status

Step 2. What is the cause?

- Screen for current use of NSAIDs, coxibs, glucocorticosteroids, leflunomide and cyclosporine

Step 3. Does the patient need antihypertensive treatment?

- Remove cause, if possible, and reassess
- Provide lifestyle advice and reassess
- Decide on requirement for pharmacological therapy and target BP according to risk stratification (as per **Figure 1**).

Step 4. What type of antihypertensive & why?

- If essential hypertension, use ACE-I/ARBs as first choice antihypertensive treatment*
- If hypertension is due to a NSAID/coxib that cannot be withdrawn, use CCB as an initial treatment option. If patient is on glucocorticosteroids, consider tapering the dose
- If insulin resistance is present, avoid β-blockers/diuretics
- If Raynaud's phenomenon is present avoid β-blockers and use CCB/ACE-Is/ARBs as initial antihypertensive treatment
- Educate patient and healthcare provider
- Facilitate lifestyle modification

Step 5. Is there a need for any more investigations or treatment for CVD or other relevant comorbidities?

- Always calculate 10-year risk for future cardiovascular events; never treat hypertension in isolation if full primary prevention is warranted
- If there is suspicion of established CVD, refer to cardiologist

Step 6. What monitoring do RA patients require?

- Systematic BP monitoring every time a patient attends primary or secondary care, or at least every 6 months
- If known hypertensive, monthly monitoring until BP optimal; thereafter, as above
- Review of continuing requirement for any antirheumatic therapy with BP-raising potential at every clinical visit, irrespective of whether patient is hypertensive or not. If not required, stop. If alternatives available, change. If continuing requirement, monitor BP as above

**Inflammation does not affect pharmacokinetics of these drugs; RA associates with increased sympathetic activity, which may lead to an increased renin state; they have additional anti-inflammatory properties.*
ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin II receptor blocker; BP: Blood pressure; CCB: Calcium-channel blocker; CVD: Cardiovascular disease; RA: Rheumatoid arthritis.

We believe that substitution of one NSAID with another, or with a coxib, is unlikely to have any significant beneficial effect on BP control, although there is no direct evidence to support this statement. Therefore, if NSAID/coxib therapy cannot be withdrawn (for example owing to patient preference), the need for antihypertensive therapy needs to be considered.

Does the patient need antihypertensive treatment?

A cardiovascular risk assessment is necessary to guide the requirement and type of antihypertensive treatment. Target-organ damage and associated clinical conditions have been excluded from history, physical examination and investigations, so risk stratification is based on the number of risk factors as per the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines (Figure 1) [2]. In the previous ESH/ESC guidelines [50], levels of C-reactive protein (CRP) of 1 mg/dl or more were considered a risk factor; such levels would virtually always be present in patients with RA. Even though CRP is not included in the panel of risk factors in the most recent ESH/ESC guidelines [2], we would still recommend that RA should be considered an additional risk factor, in view of the evidence of increased carotid-wall thickening [51] and arterial stiffness [31] as a result of background inflammation in these patients compared with healthy controls (Figure 1). On this basis, this patient has grade 1 hypertension and three CVD risk factors (e.g., smoking, dislipidemia and RA); thus, he could be considered at 'high risk' according to ESH/ESC guidance [2]. Therefore, in addition to lifestyle changes, drug treatment should be promptly initiated.

What type of antihypertensive therapy does this patient need & why?

Lifestyle changes are important in all cases. They include:

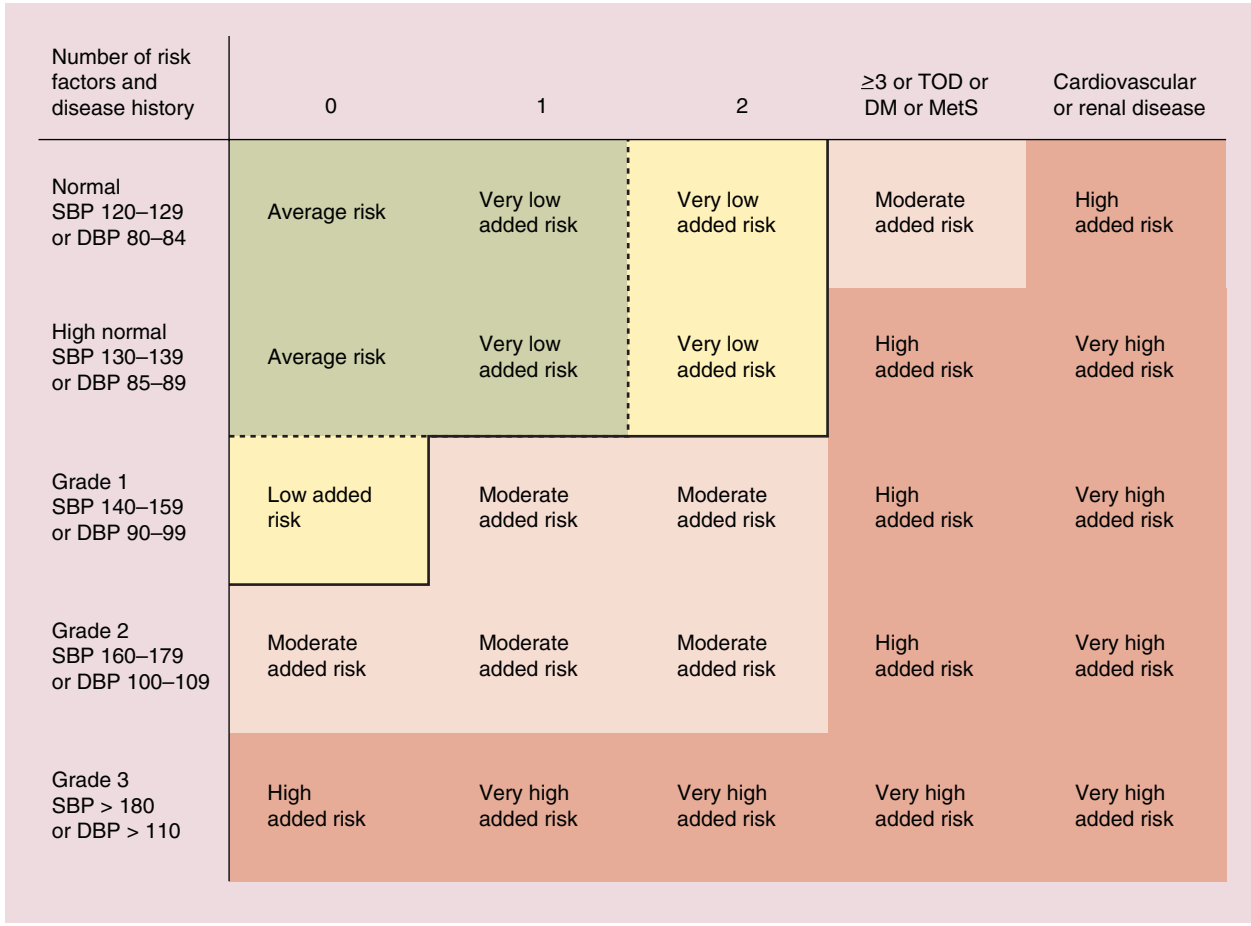
- Weight loss (ideal BMI for patient with RA is <23 kg\m^2) [19,52];
- Smoking cessation [53];
- Moderation of alcohol consumption (20–30 g ethanol per day for men and 10–20 g for women) [54];
- Daily sodium intake of less than 60 mmol/l (3.8 g/day) [55];
- Increased potassium, calcium and magnesium intake (even though more trials are needed to establish the benefits [56,57]) and dietary patterns based on the Dietary Approaches to Stop Hypertension 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) [58];
- High-dose omega-3 polyunsaturated fatty acid supplements [59];
- Regular aerobic exercise [60], which is particularly beneficial for patients with a sedentary lifestyle, such as this one.

Some of these lifestyle modifications, for example, exercise [60], smoking cessation [61] and omega-3 polyunsaturated fatty acids [62], may also have beneficial effects on RA control. The choice of the best antihypertensive agent needs careful consideration. Many studies have shown that NSAIDs attenuate the antihypertensive effects of diuretics [40,63], β-blockers [40,64], angiotensin-converting enzyme inhibitors (ACE-Is) [65,66], angiotensin II receptor blockers (ARBs) [65] and other vasodilators, such as prazosin [40]. Furthermore, concomitant use of ACE-Is and NSAIDs should be avoided, particularly in the elderly; when these agents are used together, close monitoring of renal function is essential. In the case of coxibs, a meta-analysis of 19 RCTs published before May 2004 suggests that their effects on BP are modest [67], and since sodium retention is presumed to be the mechanism causing hypertension, the authors suggest (in the absence of direct trial evidence) that diuretic therapy may be effective. However, studies in an animal model suggest that coxibs, like NSAIDs, counteract the effects of diuretics in rats [68]. Neither NSAIDs nor coxibs have any effect on dipyridamole calcium-channel blockers (CCBs), suggesting that this class of antihypertensives is the most appropriate initial treatment choice for this particular patient [69,70].

Is there a need for any further investigations or treatment for CVD or other relevant comorbidities?

Of vital importance is the estimation of the total cardiovascular risk (either using the Framingham [201] or the Joint British Societies [202] calculator). Primary-prevention treatment (including low-dose aspirin and a statin) should be initiated if the risk of CVD in the next 10 years exceeds 20% [71]. In this case this is necessary, as the calculated risk was 29%.

Figure 1. Risk stratification and cut-off levels for treatment initiation in the general (bold line) and the rheumatoid (dashed line) population.



RA patients have a lower threshold for antihypertensive treatment initiation (dashed bold line) compared with the general population (continuous bold line) owing to their increased inflammatory background. Highlighted with yellow are RA patients who need antihypertensive treatment and would have escaped attention if conventional cut-offs were used.

Risk factors: age (males: >55 years; females: >65 years), smoking, dyslipidemia (total cholesterol >5 mmol/l or low-density lipoprotein >3 mmol/l or high-density lipoprotein <1 mmol/l [males] or <1.2mmol/l [females] or triglycerides >1.7 mmol/l), fasting plasma glucose 5.6–7 mmol/l, abnormal glucose tolerance test, family history of premature cardiovascular disease (males: <55; females: <65), abdominal obesity (males: >102 cm; females: >88 cm).

Target organ damage: left ventricular hypertrophy, ultrasound evidence of arterial-wall thickening (carotic intima media thickness ≥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 (males: 115–133 mmol/l; females: 107–124 mmol/l), low estimated glomerular filtration rate (<60 ml/min/1.73 m^2) microalbuminuria.

Cardiovascular or renal disease: cerebrovascular accident, heart disease, renal disease (diabetic nephropathy, renal impairment and proteinuria), peripheral vascular disease, and advanced retinopathy.

DBP: Diastolic blood pressure; DM: Diabetes mellitus; MetS: Metabolic syndrome; RA: Rheumatoid arthritis; SBP: Systolic blood pressure; TOD: Target-organ damage.

What monitoring does this patient require?

A follow-up appointment should be given after 1 month in order to monitor BP control. If BP is well controlled then we would recommend BP monitoring in every rheumatology outpatient visit, or at least every 6 months. If BP remains uncontrolled, monthly BP monitoring should be recommended followed by titration of antihypertensive therapy, until BP levels are optimal.

Clinical scenario two

A 45-year-old teacher with RA and long-standing, well-controlled essential hypertension (on amlodipine) had inadequate response to a combination therapy of methotrexate, hydroxychloroquine and low-dose (5 mg) daily oral prednisolone. She has a past history of exposure to TB and sulfasalazine intolerance and has also been started on leflunomide. She has a 2-year

history of Raynaud's phenomenon. She has never smoked and drinks only a glass of wine every other night. Her father is hypertensive and her mother died of a heart attack at the age of 63 years. Several previous BP recordings revealed were mostly, but not always, less than 140/90 mmHg. On physical examination she is lean (BMI: 21 kg/m^2) with cold extremities, a BP of 158/95 mmHg and no signs of secondary hypertension. The rest of the cardiovascular examination is normal. Urinalysis revealed positive protein and biochemistry results were as follows: fasting glucose: 6.7 mmol/l; total cholesterol: 4.3 mmol/l; high density lipoprotein (HDL): 1.1 mmol/l; creatinine: 95 µmol/l; and serum potassium: 3.9 mmol/l. ECG was normal. What is the further plan of management of this patient?

Does the patient have hypertension?

Diagnosis of hypertension requiring therapy has previously been established in the case of this patient.

What is the cause?

The history suggests that BP control destabilized with the introduction of leflunomide. Leflunomide is an isoxazole often used between methotrexate and biologic agents in the 'DMARD ladder' [72]. Hypertension is found in 2–4.7% of leflunomide-treated RA patients [73–75]. A recent longitudinal study of 30 consecutive RA patients on stable doses of glucocorticosteroids or NSAIDs revealed significant increases in systolic BP and diastolic BP, by both conventional and ambulatory BP monitoring, within the first 2–4 weeks of leflunomide therapy [76].

Does the patient need antihypertensive treatment?

Removing the possible cause of uncontrolled hypertension may be difficult in several cases. This patient requires further escalation of disease-modifying therapy for better control of her RA. She is already quite far down the DMARD ladder, with several of these drugs no longer being an option owing to intolerance, and biologics being a difficult (but not impossible) choice owing to the history of TB exposure. Reduction of leflunomide dose should be initially attempted if possible.

Dipstick testing showed proteinuria, suggesting the possibility of target-organ damage. There was no history of use of penicillamine or gold, both of which have been associated with proteinuria and nephropathy in RA [77]. Further evaluation included repeat dipstick tests at weekly intervals and urine albumin:creatinine ratio from an early morning urine specimen [78] confirming microalbuminuria, which, in the context of the history and clinical examination, was thought to be secondary to chronic hypertension. Therefore, this patient has uncontrolled grade 1 hypertension with evidence of target-organ damage; she requires immediate optimization of antihypertensive therapy.

What type of antihypertensive therapy does this patient need & why?

There are several factors that need to be taken into account in this case, including: microalbuminuria, fasting glucose, Raynaud's phenomenon and current antihypertensive therapy with a CCB (amlodipine), which may be beneficial for Raynaud's [79]. The ideal treatment for microalbuminuria is lowering BP to less than 125/75 mmHg, using either ACE-Is or ARBs, the beneficial effects of which have been demonstrated in many large population studies [80,81]. Fasting glucose levels in this patient suggest the presence of insulin resistance, a common feature in RA patients [82], especially among those on glucocorticosteroid treatment [83]. In this setting, β-blockers and thiazide diuretics should be avoided owing to their dyslipidemic and diabetogenic effects; ACE-I, ARBs or CCBs would be preferable for lowering BP [84,85]. ACE-Is may also be helpful in improving local blood flow in Raynaud's phenomenon by increasing kinins [86]. Although the role of ACE-Is/ARBs in severe Raynaud's is not well studied, one placebo-controlled trial, which included both patients with primary Raynaud's and patients with scleroderma, found that losartan reduced the severity and frequency of attacks [87]. All of the above suggest that the best approach for this particular patient includes the use of an ACE-I or ARB, and, if necessary, increase of the CCB dose.

Is there a need for any further investigations or treatment for cardiovascular disease or other relevant comorbidities?

Hypertension should never be addressed in isolation, but in the context of the overall cardiovascular risk of the individual. This patient also has chronic hypertension with target-organ damage, family history of premature CVD and may have insulin resistance. Repeat fasting glucose estimation and/or oral glucose-tolerance

test should be performed to rule out the occult presence of diabetes mellitus or to establish the diagnosis of glucose intolerance. If she is diabetic, or if her calculated 10-year risk exceeds 20% [71], she should also be treated with low-dose aspirin (or an alternative antiplatelet drug such as clopidogrel [88]) and a statin (irrespective of the fact that her cholesterol levels look reasonable) [38], in addition to optimal antihypertensive therapy.

What monitoring does the patient require?

Monthly BP measurements with appropriate adjustments of therapy are necessary until optimal BP levels have been achieved (in this case <125/75 mmHg owing to the microalbuminuria). Thereafter, BP monitoring at every clinical appointment or at least every 6 months may be sufficient. Annual review of overall cardiovascular risk is advocated by the Arthritis and Musculoskeletal Alliance standards of care [203].

Clinical scenario three

A 64-year-old lady with seropositive long-standing RA requiring combination DMARD therapy (methotrexate, sulphasalazine and hydroxychloroquine [89]) developed symptoms suggestive of polymyalgia rheumatica, and her GP started her on oral glucocorticosteroids with an excellent clinical and laboratory response. Steroid dose ranged from 20 mg of prednisolone daily (at symptom onset 8 months ago) to a current 7.5-mg daily, which remains sufficient for control of her symptoms and her acute-phase response. On review at the hospital, she mentions an episode of minor, dull chest pain, which lasted for 30 min 2 months ago but settled on its own. Her father died of a heart attack at the age of 65 years. She has been a smoker of 20 cigarettes a day for 40 years and drinks only during the weekends. On physical examination she is overweight (BMI: 29 kg/m^2) and has a resting BP of 175/100 mmHg. No previous BP readings are available but fundoscopy shows evidence of grade II hypertensive retinopathy. The rest of the cardiovascular examination is normal. Urinalysis was normal and biochemistry results showed: fasting glucose: 4.2 mmol/l; total cholesterol: 4.9 mmol/l; creatinine: 80µmol/l; and serum potassium: 4.1 mmol/l. ECG revealed evidence of left ventricular hypertrophy and deep Q waves in leads II, III and aV_F. What is the further plan of management for this patient?

Does this patient have hypertension?

The patient presents with increased BP but also has a history and ECG evidence of a recent, unrecognized myocardial infarction (MI). There is no need for further BP measurements in this case to establish a diagnosis of hypertension. Although there is no record of previous BP measurements, the presence of left ventricular hypertrophy on ECG and retinopathy on fundoscopy suggests long-term, uncontrolled hypertension that went unnoticed, and this is unfortunately common in RA patients [19]. More importantly, this patient has suffered an MI, so she would require secondary prevention including antihypertensive therapy even if her BP was optimal. As it happens, her BP is in the stage 2 range with evidence for target-organ damage and a recent acute event, indicating an urgent need for optimal BP control with an aggressive target of less than 130/80 mmHg [71].

What is the cause?

Corticosteroid use may relate to hypertension [90] (see detailed discussion below), but is unlikely to be the cause in this case as the ECG findings suggest long-standing, uncontrolled hypertension. There are no other obvious causes of secondary hypertension, so the assumption is that this patient suffers from essential hypertension. Essential hypertension is by far the most common type of hypertension in the general population [2] and in patients with RA [19].

What type of antihypertensive therapy does this patient need & why?

Because of existing evidence of a past MI, the patient requires an aggressive secondary-prevention approach, which includes antihypertensive therapy. A combination of ACE-Is/ARBs and β-blockers is recommended [2], if not contraindicated, with a target BP of less than 130/80 mmHg [71]. Interestingly, the combination of ACE-Is and a statin in patients such as this one may provide additional benefits. ACE-Is have well-established effects on heart remodeling after an MI [91], and may be particularly suited to patients with active RA since they have increased sympathetic activity [92,93], which may put them in a high-renin state [94,95]. However, 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 NFκB) [37]. Statins, on the other hand, are the

cornerstone of both primary and secondary prevention for CVD and also have anti-inflammatory effects that may be of relevance to arthritis control [38,96,97]. A recent meta-analysis suggests a significant antihypertensive effect of statins in non-RA patients with high BP [98]. The BP-lowering and anti-inflammatory effects of statins may be amplified in the context of the high-grade inflammation seen in RA [38]. Recent reports have shown improvement of endothelial function [99,100] and arterial stiffness [101] in RA patients treated with statins. The inter-relation of endothelial dysfunction and hypertension [102] and the bidirectional relationship between arterial stiffness and hypertension [34], in addition to the above studies in RA patients, suggest that statins may have an enhanced BP-lowering effect in these patients. However, no clinical trials to date have shown a potentially increased antihypertensive effect of ACE-Is or statins in RA patients, and this should be investigated in future research.

Is there a need for any further investigations or treatment for cardiovascular disease or other relevant comorbidities?

This patient has suffered an MI and requires full and aggressive secondary-prevention therapy and referral to a specialist cardiologist for further management. In RA there is an increased prevalence of unrecognized MIs, probably owing to a different perception of pain [103]. However, there is an increased risk of recurrence with fatal outcome [104], which renders immediate secondary-preventive therapy (including in the absence of contraindications of low-dose aspirin, β-blocker, ACE-I and a statin as per Joint British Societies guidance [71]) of utmost importance. There is also evidence that patients with RA may not be properly risk-assessed after an acute event [104,105] and may not have sufficient revascularization interventions [103]; thus, a combined approach between rheumatologists and cardiologists may be of importance. This patient requires further investigation with an ECG, exercise-tolerance test or, if this is not possible, a myocardial perfusion scan [106], and, most likely, also a coronary angiogram. Optimization of drug therapy and control of risk factors is also likely to be necessary in the long term. Again this may be a particular challenge owing to the multiple comorbidities and polypharmacy that characterize many patients with RA [107].

The importance of glucocorticosteroid therapy in the overall context of this case requires particular consideration. This patient has been on a medium dose of prednisolone for 8 months. New thresholds were recently set to define low-, medium- and high-dose prednisolone [108]. Doses of less than 7.5 mg daily are considered low since they occupy less than 50% of the glucocorticoid receptors: they are often used for maintenance therapy for many rheumatic diseases [109,110] with the expectation of relatively few adverse effects; doses between 7.5 and 30 mg daily are now termed medium and those above 30 mg daily are termed high. There is evidence to suggest increased mortality amongst medium- and high-dose steroid users. Among the 1165 Medicine Monitoring Unit cohort patients who had inflammatory joint disease, those receiving more than 7.5 mg/day had a higher risk of cardiovascular events (RR: 3.3; 95% CI: 1.56–6.96) than those on lower doses (RR: 1.5; 95% CI: 0.98–2.3) compared with those not on any steroids [111]. Similarly, in the 1515 RA patients of the GP Research Database [112], the odds ratios for MI, ischemic stroke and heart failure were 1.2 (1.11–1.29), 0.91 (0.84–0.99) and 2.66 (2.46–2.87), respectively, in the group receiving steroids, with no evidence of dose-dependency. Recently, Davis *et al*. suggested that steroid exposure increases the risk of cardiovascular events only in rheumatoid-factor-positive RA patients [113]. One of the pathways leading from increased steroid exposure to CVD could be via hypertension [90,114]; however, although hypertension is thought to be a well-known side effect of steroids, evidence is very limited and even contradictory [90,115]. On the basis of the available evidence, this patient would be better off with a gradual reduction and, if possible, complete withdrawal of steroid therapy.

Lifestyle modification is particularly important in view of her obesity and smoking habit. Diet (aiming for an ideal BMI of less than 23 [52]) and exercise [60] may be challenging, in view of her continuing steroid therapy and physical disability caused by her arthritis, but not contraindicated or impossible. Smoking is encountered more frequently in RA patients compared with the general population [18] and has been associated with increased basal metabolic rate [116] and adverse disease progression [117]. Smoking cessation is of vital importance, both for CVD prevention and hypertension control [118], although the latter has recently been questioned [119].

What monitoring does this patient require?

BP optimization in this case is only one of the (many) tasks of the cardiologist, her GP and the rheumatology team. Excellent communication and coordination are required between them in order to optimize this patient's management.

Other considerations

Pharmacokinetics, inflammation & antihypertensives

Of note is the influence of systemic inflammation on the pharmacokinetics of various antihypertensive drugs. Clearance of highly bound and efficiently metabolized drugs may be reduced in the presence of inflammation amounting to an increased circulating-drug concentration [120]. Inflammatory conditions and proinflammatory cytokines have been shown to depress CYP isoenzyme activities [121]. Proinflammatory mediators such as TNF-α, high levels of which are observed in RA [122,123], lead to elevation of plasma α1-acid glycoproteins responsible for drug–protein binding [124,125], hence reducing the unbound fraction and diminishing hepatic clearance of drugs. Although it may be expected that inflammation would increase levels of drugs such as β-blockers [126] or CCBs [120], this does not necessarily associate with an increased biological effect. The reason for this is that various cardiovascular receptors are downregulated by increased expression of proinflammatory mediators (e.g., TNF-α and IL-1), including the β-adrenergic [127] and L-type cardiac calcium channels [128]. The reduction in binding may be attributed to gene downregulation, resulting in reduced mRNA synthesis or post-translational alteration of the receptor. However, not all cardiovascular receptors are downregulated by inflammation. At least for the angiotensin II type 1 receptors, inflammation appears to have no downregulating effect and therefore does not alter the antihypertensive effect of ARBs such as valsartan [129] and losartan [130] in RA patients. On the contrary, a trend towards upregulation of the above receptors is evident, which favors treatment with ARBs in this patient.

Patient education

Translating this knowledge into clinical practice requires education not only of health professionals, but also of the patients themselves, in order to address such integral issues as adherence to medication [131,132] and relevant and necessary lifestyle changes. Multifactorial interventions, including both patient education and health-provider education, have been shown to result in improved BP control when compared with provider education alone [133].

Hypertension exemplifies the principle of primary prevention, and the education/communication required to convey the concept of therapy to prevent a future event is recognized as one of the most challenging facets of the patient–health professional relationship [134]. Poor compliance with antihypertensive treatment is well recognized [135,136], as is compliance with lifestyle measures [137] in the general population, and techniques to address this have been identified [136]. Although patient education alone seems unsuccessful [136], in newly diagnosed hypertensive patients it has been shown to improve adherence to lifestyle measures [138], and common sense suggests it is essential for all patients to complement other interventions. For patients with RA, the situation is more complex: the paradigm of the potential hypertensive effects of symptom-relieving medication such as NSAIDs and corticosteroids, or DMARDs such as leflunomide and cyclosporin, versus the silent benefits of antihypertensive medication with potential side effects, means effective communication and patient education has never been more critical. In addition, exercise [60] and maintaining an appropriate body weight [52] may be harder for patients with RA owing to their physical disabilities, and so requires appropriate encouragement and resource provision to support these necessary lifestyle modifications.

There are no specific patient-education resources for a patient with RA and hypertension to refer to. Existing material, such as the British Heart Foundation Heart Information Series [204], or the Blood Pressure Association website [205], may provide helpful information, but these may not be so personally relevant for a patient with RA as they do not address the specific challenges described above. Therefore, in addition to disseminating advice for best practice for hypertension in RA to healthcare professionals, there is a pressing need for disease-specific patient-education material to be developed.

Recommendations

So far there are no evidence-based, RA-specific guidelines, so the general principles of hypertension management are the same as for the wider population. There are a number of RA-specific factors that should be taken into account when formulating the management plan for

hypertension in a patient with RA, and the three sample cases discussed above have demonstrated some of them. An overall approach with relevant recommendations for the management of hypertension in patients with RA is presented in Box 1. Of note is the lack of evidence regarding the efficacy of antihypertensive treatments in patients with RA. Future studies should aim to confirm and validate the recommendations presented in Box 1 (step 4), especially the potential multiple benefits from the use of ACE-Is/ARBs as first-line treatment.

Future perspective

The patient presented in clinical scenario one attends clinic in approximately 2025:

Does the patient have hypertension?

The patient (together with his whole family) are included in a health-state monitoring program at home, available to all from a very young age; this includes regular self-assessments of BP (sedentarity, obesity and their sequelae have taken epidemic proportions and there are active monitoring programs for relevant morbidities from early childhood onwards). Data have been electronically transferred and stored into his 'electronic patient record' and are available to his GP, as well as his secondary-care specialists.

What is the cause?

A warning, to him and his healthcare professionals, has been automatically triggered after six 'high' BP readings with an indication that they occurred soon after initiation of NSAID therapy. The patient is invited to a face-to-face review and assessment by his GP.

Does the patient need antihypertensive treatment?

Hypertension is confirmed and the timing suggests that NSAID therapy is responsible, at least in part. The patient's 10-year CVD-event risk is calculated, taking into account the extra risk conferred by his RA (RA-specific algorithms have been developed and are widely available, as is currently the case for diabetes); this indicates that BP control for risk reduction is essential. The patient sees a trained educator and is taken through a fully developed and validated education program outlining the possible long-term sequelae of hypertension (education has taken a central place in management and multiple programs have been developed and evaluated, some generic, some for specific patient groups). The association with NSAID therapy, and the possibility of discontinuing this therapy, are discussed in detail. The patient is not willing to withdraw from this therapy owing to what he perceives to be great benefits to his symptoms and functional capacity. Immediate commencement of antihypertensive therapy and inclusion in a lifestyle modification program are suggested instead, and the patient agrees to this course of action. A concordat is signed between him and his health professional team, clearly outlining what the patient and health professional undertake to do (the 'paternalistic' approach to patient care is no longer practised: compliance and adherence are not accepted as terms or concepts and not expected from the patient; instead, concordance is meant to be achieved between patients and health professionals in any and all models of care) [132].

What type of antihypertensive & why?

DNA microarray analysis shows a genetic pattern of a subject prone to suffer from salt-sensitive hypertension. Detailed analysis of his 'antihypertensive treatment genetic profile' revealed an increased number of diuretic receptors that show high affinity to bendroflumethiazide and a pharmacokinetic profile that suggests a low bendroflumethiazide-metabolism rate. Therefore, this patient is likely to respond to dietary salt restriction and 5 mg of bendroflumethiazide therapy. However, the NSAID may reduce the antihypertensive effect of diuretics, so if continuing monitoring does not indicate sufficient BP control, combination therapy with CCB may be required. In addition, lifestyle modification is very important in this case and the patient has agreed to attempt this. In subsequent visits, he is enrolled in a 6-week cognitive–behavioral program, specifically developed to address cardiovascular risk in patients with some physical disability due to arthritis. He has a detailed assessment of his physical ability and his aerobic fitness, on the basis of which he agrees to a personalized training program with an exercise physiologist; this is available in the community but remotely monitored. Finally, he has a full assessment of his dietary habits and is given nutritional guidance based on his current phenotype, genotype and clinical need. All advice is taking account of his perception of what he can achieve, and has a predetermined time limit for review.

Is there a need for any further investigations or treatment for cardiovascular disease or other relevant comorbidities?

The patient has a whole-body functional MRI scan, which provides a noninvasive assessment of body composition as well as vascular, cardiac and cerebral function. He also has a full metabolic screen on a proteomic microarray. Overall, cardiovascular risk is calculated on the basis of these tests, together with expected reductions of this risk if successful modification of the modifiable components (e.g., BP, metabolic and phenotypic abnormalities) is achieved. The result suggests that he would benefit from further primary prevention, and he is given polypill-x, which matches his risk profile most closely.

What monitoring does he require?

Monitoring is all proximal to the patient and is his responsibility. It involves weekly home BP measurements, weight and body-composition analyses (using bioelectrical impedance scales), resting heart rate, maximum heart rate during exercise and recovery time, and a mini metabolic screen including drug metabolites (using equipment similar to that currently used for blood-sugar monitoring). His retinal scan (used in the electronic lock of his property) is automatically analyzed at predetermined 6-monthly intervals for relevant changes. Results are transmitted real-time to the health professional team and, depending on progress, changes to the lifestyle-modification program and medications are suggested every 6 weeks.

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Executive summary

Background information

- Rheumatoid arthritis (RA) associates with increased cardiovascular morbidity and mortality.
- Hypertension, one of the major risk factors for cardiovascular disease, is common but often undiagnosed or insufficiently controlled in patients with RA.

Management of hypertension in rheumatoid arthritis

- Management of hypertension should always be seen in the context of the patient's overall cardiovascular risk.
- The continuing requirement of widely used antirheumatic drugs with hypertensive potential must be regularly reviewed.
- Lifestyle modification is always important and possible in RA patients, despite their arthritis.
- Pharmacological therapy in a patient with RA should be approached systematically and consider specific target blood pressure, as well as the potential impact of continuing antirheumatic therapy.

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