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Review of Literature Investigating the Correlation between Prevalence of Risk Factors Associated with Both Rheumatoid Arthritis and Cardiovascular Diseases

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Abstract

The increased risk of cardiovascular morbidity and mortality in rheumatoid arthritis has been increasingly acknowledged in past decades, with accumulating evidence that rheumatoid arthritis is an independent cardiovascular risk factor. We will discuss the latest evidence in this respect. Cardiovascular disease risk management for patients with rheumatoid arthritis is essential. Clinical guidelines and implementation of cardiovascular risk management in daily clinical practice. One of the most applied forms of literature reviews is systematic reviews, which prioritizes real-world applicability over strict methodological constraints, making it ideal for public health and clinical decision-making. These reviews focus on clinical relevance, seeking to inform policy and practice by integrating findings in a way that directly translates into decision-making. An example is a recent review evaluating correlation between the prevalence of rheumatoid arthritis and cardiovascular diseases. **Objectives:** To review the literature that examines rheumatoid arthritis (RA)-cardiovascular diseases (CVD) association using statistical and epidemiological concepts from studies that are concerned with these important issues. In this Review, we will discuss epidemiological data on cardiovascular disease in rheumatoid arthritis, not only for atherosclerotic disease but also for venous thrombotic disease and heart failure, as clinical and subclinical prevalence of the two diseases is higher than previously thought. The underlying pathophysiology of increased cardiovascular risk relevant to inflammatory arthritis, as well as the observed effect of anti-inflammatory and disease modifying treatments, will be reviewed and discussed. **Methods:** We followed the main steps in writing a systematic review and scientifically formulated cardiovascular research questions addressing epidemiological and pathophysiological aspects of rheumatoid arthritis, cardiovascular effects of drug treatment, and management of cardiovascular risk. References for this Review were identified

through searches of PubMed with the terms "rheumatoid arthritis", "cardiovascular disease", "cardiovascular event", "myocardial ischemia", "stroke", "coronary disease", "congestive heart failure", "cardiac dysfunction", and "cardiovascular risk management" from January 1, 1998, to April 1, 2022. Only papers published in English were reviewed. The final reference list was generated based on originality and relevance to the broad scope of this Review. In Figure 1, we use PRISMA to map our review strategy. The inclusion-exclusion criteria are: *Inclusion criteria*: Adults aged > 25 years with a diagnosis of RA. Studies had to report on one or more factors associated with incident CVD in RA patients. Only studies written in English were included. *Exclusion criteria*: Children aged ≤ 25 years, studies that did not include any subjects with an RA diagnosis, prevalent CVD (cases with a prior history of CVD) and/or studies that did not assess risk factors associated with incident. **Findings:** There are several risk factors that are linked to both diseases. The literature confirmed that the increased risk of cardiovascular events in patients with RA is multifactorial. The traditional risk factors, such as smoking, hypertension, and hyperlipidemia, are of course still important, and the presence of RA exerts an additional independent risk. We emphasize the importance of precision medicine to address conflicting evidence of the treatment effect on stroke among RA patients.

Keywords

Autoimmune Diseases, Heart Diseases, Rheumatoid Arthritis, Cardiovascular Diseases, Common Risk Factors, Precision Medicine

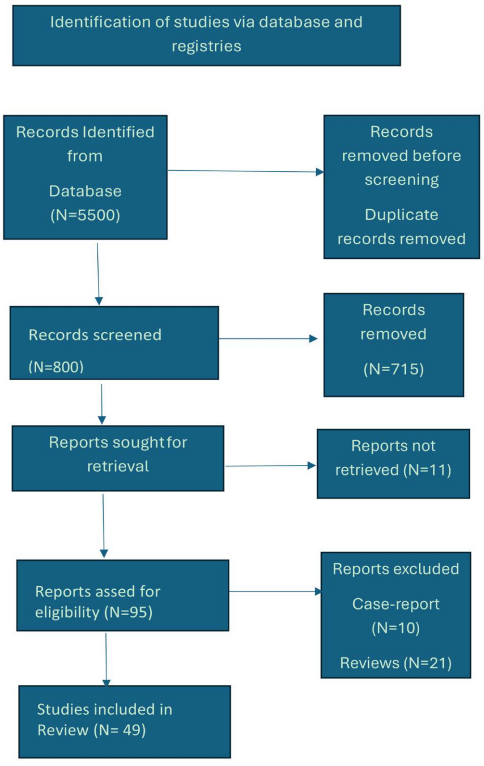

Figure 1. PRISMA diagram outlining study selection procedures.

1. Introduction

Cardiovascular disease is the most frequent cause of death worldwide. The 2017 Global Burden of Disease Study showed that 17·8 million people died of cardiovascular disease globally, accounting for 21% of all deaths [1]. Well-established, traditional risk factors for cardiovascular disease comprise age, sex, race, hypertension, diabetes, smoking, and hyperlipidemia, all of which are included in various prediction models. However, over the past 20 years, several non-traditional risk factors, such as chronic inflammation, have emerged as amplifiers of cardiovascular disease risk [2].

Rheumatoid arthritis is the most common autoimmune arthritis, with a prevalence of up to 1% or 2% and is characterized by a symmetrical polyarthritis with possible systemic manifestations. Rheumatoid arthritis is an accepted independent risk factor for cardiovascular disease, driven by the underlying chronic inflammatory process. However, traditional cardiovascular risk factors remain important [3].

2. Epidemiology: Key Common Risk Factors Influencing RA and CVD Rates

Two factors come together to increase your risk: chronic inflammation and shared risk factors.

Inflammatory substances called cytokines fuel joint destruction in RA and blood vessel damage in cardiovascular disease (CVD). Inflammation causes plaque build-up in the arteries, which slowly narrows blood vessels and blocks blood flow, and is the main cause of heart attack and stroke.

The other reason people with RA are more likely to develop heart disease is shared risk factors, which we group into main risk factors and other risk factors.

2.1. Main Risk Factors

High blood pressure—A number of factors increase blood pressure in people with RA, including a lack of exercise and drugs used to treat the disease (such as NSAIDs and steroids). People with RA also have less elastic arteries that can narrow, which lets less blood through and increases blood pressure.

Metabolic syndrome—Nearly 40% of people with RA have metabolic syndrome, compared to less than 20% of people overall. This collection of symptoms, which includes obesity, high triglycerides and cholesterol, high blood pressure, and elevated blood sugar, doubles the risk for CVD.

Obesity—Sore joints make it hard to exercise, and a lack of physical activity can lead to weight gain. Obesity is linked to CVD risk itself, as well as to cardiovascular risk factors like high blood pressure and high blood sugar. Fat cells release inflammatory substances that contribute to body-wide inflammation and CVD risk.

Smoking—People with RA are more likely to smoke than those without the

disease. Not only has this habit been linked to more aggressive joint destruction, but smoking also accelerates blood vessel damage and contributes to artery narrowing. Smokers with RA have a 50% higher risk for cardiovascular events than do nonsmokers with RA.

Abnormal lipids—RA have an unusual effect on lipids or fats in the blood. Experts call it the "lipid paradox." People with RA have high levels of triglycerides, low levels of low-density lipoproteins (LDL or "bad" cholesterol), and low levels of high-density lipoproteins (HDL or "good" cholesterol). Although low LDL is good for the heart, low HDL cholesterol and high triglycerides contribute to cardiovascular disease.

Infection—It is a possible initiator for inflammatory types of arthritis, particularly RA.

Patients with rheumatoid arthritis have up to a two-times higher risk of developing atherosclerotic cardiovascular disease than the general population, similar to patients with diabetes. [4] The risk of ischemic heart disease is increased in patients with early rheumatoid arthritis and symptom duration of less than 1 year, and probably even in the subclinical stage. [5] The risk of cerebrovascular incidents is increased by about 50% (relative risk 1.48, 95% CI 0.70 - 3.12). We suspect that the confidence interval included unity may be either due to inadequate sample size, or presence of heterogeneity among the subjects that might have affected the variance of the estimated relative risk. In the meantime, the risk of myocardial infarction is doubled (relative risk 2.00, 1.23 - 3.29). Moreover, patients with rheumatoid arthritis have almost twice the risk of developing congestive heart failure (rate ratio = 1.7, 95% CI 1.3 - 2.1), including both heart failure with preserved ejection fraction and heart failure with reduced ejection fraction.

Several factors contribute to increased cardiovascular risk, including comorbidities such as diabetes, dyslipidemia, and hypertension; [6] [7] albeit the data for hypertension are somewhat conflicting. [8] [9] Lipids seem to have paradoxical associations with cardiovascular risk in rheumatoid arthritis. During active disease, low total cholesterol and LDL cholesterol are associated with increased cardiovascular risk (the so-called lipid paradox). [10] Effective antirheumatic therapies resulting in reduced disease activity of rheumatoid arthritis reverse the cholesterol reduction, thus leading to increased lipid concentrations [11]-[13]. Furthermore, patients with rheumatoid arthritis also have more than a two-times increased risk of venous thrombotic disease compared with the general population (cumulative incidence of 67% vs 28% [11], $p = 0.005$).

Studies show that cause mortality among patients with rheumatoid arthritis was 54% higher than in the general population, primarily because of cardiovascular disease (32%) [13] with a median shortened life expectancy of 6 - 7 years [14]. Different underlying pathophysiological mechanisms, such as systemic inflammation, elevated oxidative stress, endothelial dysfunction, and changes in lipid profiles, might contribute to a substantially higher cardiovascular risk in these patients. The increased cardiovascular risk includes not only a higher rate of is-

chemic cardiovascular disease but also subclinical heart failure, which seems far more prevalent than previously thought. Early therapeutic intervention with current antirheumatic treatment in rheumatoid arthritis has shown favorable effects on cardiovascular disease risk. Figure 2 shows the interaction between CVD and RA risk factors.

2.2. Other Risk Factors

Age: Arthritis can develop at any age. The risk of developing most types of arthritis increases with age.

Sex: Most types of arthritis are more common in women; an estimated 64% of all people with arthritis are women. Ankylosing spondylitis (AS) and gout are more common in men.

Hormones: There is a possible hormonal link for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) with evidence of disease changes occurring around menopause and pregnancy (particularly in RA). Hormones have also been found to be associated with disease progression.

Genetic Predisposition: Specific genes are associated with a higher risk of certain types of arthritis, such as RA, SLE, and AS. Specific genes influence the severity of RA.

Diet: It plays an important role in healthy weight maintenance, which is a key factor in the prevention/reduction of disease progression. It is also an identified risk factor for gout development and management.

Overweight and Obesity: Excess weight can contribute to both the onset and progression of knee, hip and hand osteoarthritis (OA). It is also associated with severity/progression of several types of arthritis.

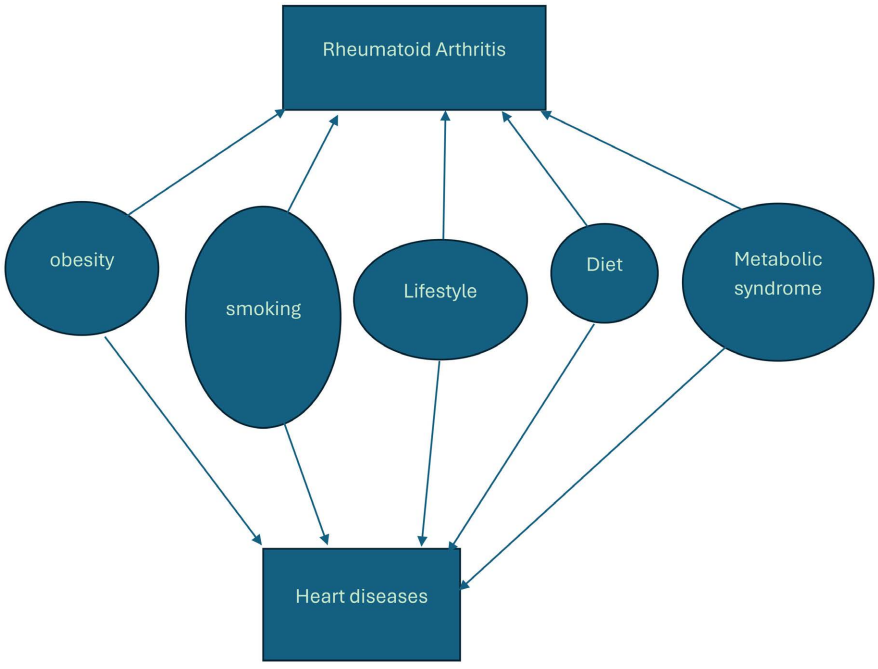

Figure 2. Important risk factors linked to both heart disease and rheumatoid arthritis.

3. Underlying Pathophysiology

There is an increased understanding of the pathogenesis of CV disease in RA, and it appears to be related to shared inflammatory and immune mediators. There is a consensus that a 1.5 multiplication factor is used when using cardiovascular disease (CVD) predictor algorithms in patients with RA [15] [16]. Furthermore, the management of RA involves a plethora of drugs that can directly or indirectly affect CV risk. Non-steroidal anti-inflammatory drugs (NSAIDs), for example, are associated with increased risk, but on the other hand, tumor necrosis factor (TNF) inhibitors and methotrexate are associated with a decreased risk [17].

3.1. Pathogenesis of Stroke

The pathogenesis of stroke in RA involves shared inflammatory and immune mediators that affect blood vessels in the brain [18]. Inflammatory cytokines released in the joints can enter the bloodstream and contribute to atherosclerosis and stroke [19]. RA can also lead to cardioembolic stroke through nervous system vasculitis and cardiac complications. Managing the risk of stroke in RA patients involves focusing on cardiovascular risk management, including lifestyle changes such as a nutritious diet, regular physical activity, and quitting smoking [20]. While the link between RA and the risk of stroke has been firmly established, it is worth noting that some studies have not demonstrated an increased risk of stroke in individuals with RA. This lack of association could be attributed to variations in the definitions of stroke used in various studies. Notably, despite clear distinctions in risk factor profiles and the differing pathogenesis of ischemic and hemorrhagic strokes, certain studies have chosen to use composite outcomes that encompass both types of strokes [21]. Given the fundamental disparities between ischemic and hemorrhagic strokes, it is imperative to classify stroke types separately and assess the risk for these two distinct entities rather than relying on a composite outcome. The involvement of the anti-CCP response in the pathogenesis of RA may be attributed to the established association between anti-CCP antibodies and the severity of RA. Additionally, numerous studies have indicated a link between anti-citrullinated protein antibodies (ACPAs) and an elevated risk of acute myocardial infarction, major adverse cardiovascular events, and stroke [22]. Consequently, an approach could be employed to effectively reduce the risk of stroke and other cardiovascular complications in individuals with RA. This approach encompasses monitoring anti-CCP antibodies, addressing conventional cardiovascular risk factors, and managing inflammation. Healthcare providers could potentially enhance cardiovascular well-being and overall quality of life for RA patients, ultimately reducing the burden of cardiovascular diseases, including stroke.

3.2. Microvascular Endothelial Dysfunction

Microvascular endothelial dysfunction is an early and/or seminal event in the development of cardiovascular diseases and associated organ damage and is also pre-

sent in patients with rheumatoid arthritis (RA) [23]. Microvascular endothelial dysfunction does not correlate with disease activity, disease duration, levels of C-reactive protein or the erythrocyte sedimentation rate. Antirheumatic drugs and other therapies can be used to treat microvascular endothelial dysfunction, but the effects of these therapies differ [24] [25].

It was reported that achieving remission in RA does not guarantee the normalization of microvascular endothelial function. Semiautomated methods for the measurement of microvascular endothelial dysfunction exist; therefore, the concept of endothelial-guided therapies in RA deserves attention.

4. Effect of Treatments Used in Rheumatoid Arthritis on Cardiovascular Disease Risk

Management of RA is multifactorial, and it usually follows a stepwise approach depending on the disease phase. Based on various observational studies, even low doses of 5 - 10 mg of prednisolone per day carry additional risk. There also seems to be an association between steroids and any-cause mortality, which is dose dependent, with a threshold starting from 8 mg/d of prednisolone [26].

4.1. Disease-Modifying Antirheumatic Drugs (DMARD)

The most common and most important DMARD is methotrexate. Others include sulfasalazine, hydroxychloroquine, leflunomide, and cyclosporine. Methotrexate has demonstrated survival benefits over other DMARDs, and it seems to reduce cardiovascular risk in RA, based on results from a meta-analysis [27]. While the mechanism is not fully elucidated, proposed pathways include effects on cholesterol, cytokines, and endothelial function.

There are reports that it relates to its effects on cholesterol and free radicals, as well as by blocking the effects of pro-atherosclerotic cytokines such as IL-11, IL-6 and TNF-α, resulting in improved endothelial function and vascular homeostasis. Animal studies have not confirmed a positive effect on endothelial function yet. Sulfasalazine is advocated as monotherapy in patients who cannot receive methotrexate, and as combination therapy with methotrexate. Studies on patients with coronary heart disease and ankylosing spondylitis indicate a beneficial effect with regard to cardiovascular risk, and earlier reports indicate that it reduces cardiovascular morbidity in patients with rheumatoid arthritis [27] [28]. A potential mechanism of action is the inhibition of platelet function [29]. Another drug is hydroxychloroquine, also used in combination with other DMARDs. It does not have the same benefit profile as other drugs. However, it seems to be associated with a better metabolic profile and reduced incidence of CVD morbidity [30] [31].

An association of leflunomide and cyclosporin with hypertension has been observed in some studies, although cyclosporin protects against atherosclerosis [32]. The actual cardiovascular risk profile of these drugs is still uncertain. Cardiac and vascular complications of rheumatoid arthritis.

4.2. Conflicting Evidence on Treatment Effect of Stroke

A comprehensive study analyzed stroke incidence among RA patients over five decades, revealing a significant decline in stroke rate, particularly for ischemic strokes. This suggests that management strategies are effective in reducing stroke. Conversely, another study examined the effects of anti-rheumatic medication on stroke risk. The study found that while sulfasalazine and hydroxychloroquine were associated with decreased risk of stroke, glucocorticoids and tocilizumab were linked to an increased risk. This indicates that the choice of treatment can significantly influence stroke among RA patients, leading to conflicting evidence regarding the overall risk associated with RA. This highlights the need for personalized treatment strategies among RA patients. While some treatments may mitigate stroke, others could exacerbate it. Therefore, it is necessary to carefully consider the medications selected for CVD patients.

This complexity underscores the importance of further research to clarify these relationships and optimize treatment protocols for RA patients at risk of stroke [33].

4.3. Pericarditis

Pericarditis is one of the most common cardiac manifestations in RA. Although the incidence of pericarditis in echocardiographic or post-mortem studies is as high as 30% - 50%, clinically it is seen in <10% of patients with severe RA [34]. Pericarditis occurs most frequently in male patients with active rheumatoid disease and other extra-articular manifestations. There have been several reports associated with the development of acute and/or recurrent pericarditis in patients treated with anti-TNF agents [35]. Diagnosis is commonly made by echocardiography. Treatment for mild disease is aspirin or NSAIDs and GCs for moderate to severe disease. Severe cases associated with cardiac tamponade, hemodynamically significant pericardial effusion, or constrictive pericarditis may require surgical management, which may include pericardiocentesis, pericardiectomy, or pericardiotomy [36].

4.4. Other Cardiac Complications

One of the rare manifestations of systemic RA associated amyloid A amyloidosis is cardiac amyloidosis. The gold standard for diagnosis is a myocardial biopsy, but it is invasive, so other newer modalities, such as cardiac magnetic resonance imaging, are increasingly used. Prognosis is usually poor due to associated heart failure. Cytotoxic drugs and DMARDs can temporarily improve cardiac function, but progressive organ failure occurs despite aggressive treatment [37]. Non-infectious or autoimmune endocarditis is a rare but severe complication of RA. It can result in embolic disease or valvular dysfunction and may need valve repair or replacement. Myocardial ischemia can also occur in RA patients secondary to vasculitis, in addition to atherosclerotic disease [38].

Previous cohort studies conducted in western countries reported that RA was

linked to a higher risk of CVD, with a 1.4- to 3.7-fold increased risk for myocardial infarction (MI) and 1.3- to 2.7-fold increased risk for stroke [39]-[42]. However, research on modifiers associated with increased CVD in RA has yielded conflicting results. Some studies reported that younger age was associated with increased CVD in RA subjects [39]-[42]. A Korean nationwide cohort study of 2765 RA patients showed that increased MI risk in RA was associated with non-diabetes, and higher risk of stroke in RA was associated with female sex, non-diabetes, and non-dyslipidemia [43] [44]. In a large UK case-control study of 6591 RA patients, current smoking, body mass index (BMI), and diabetes were associated with higher CV risk in RA patients [44]. In a study of postmenopausal women, joint pain and WBC count were significantly associated with CVD [45]. Another study reported that anti-CCP positivity was associated with increased ischemic heart disease and fatal CVD [46]; however, a different study showed no association between coronary atherosclerosis and anti-CCP antibody positivity [47]. In contrast to data showing increased risk of MI among RA patients [39] [40], studies on the association of RA with stroke have found conflicting results [41] [42]. Some studies reported increased risk of stroke in RA [48]-[50], but others failed to demonstrate a difference [41] [42] [49]-[51]. In a Nurses' Health Study of 114,342 women, RA subjects had increased risk of MI, but a similar risk of ischemic stroke compared with subjects without RA [42]. Similarly, Turesson *et al.* reported a larger risk of incident stroke (combined ischemic and hemorrhagic stroke) in RA subjects, but the difference was not statistically significant. In a Swedish rheumatology cohort, the rate of ischemic stroke was approximately 30% higher in RA patients than in the general population (aHR 1.29, 95% CI 1.18 - 1.41).

Accumulating evidence has revealed that incident CV risk is higher in RA patients compared with the general population. However, the extent of the increase in CV risk differs among studies, and which characteristics of RA patients are mainly associated with increased CV risk remains unclear. Moreover, there is an increased risk of several cardiovascular events such as HF, IHD, CAD, ACS, VTE among RA patients.

To date, the largest sample size was 114,342 subjects, but the study only included female subjects and used self-reported questionnaires to define RA, CVD, and other covariates [43]. Another large-scale study of 160,000 postmenopausal women mainly reported the association between anti-CCP antibody and CVD [44] [45]. Unfortunately, many previous studies on association between RA and CVD were conducted on non-Asian groups. Only three epidemiological studies have investigated this issue in a South Korean population, but the data were evaluated in a cross-sectional manner or in models that were not fully adjusted with a small number of subjects. Therefore, we aimed to investigate associations between CV outcomes and RA and explore the characteristics of RA patients that are associated with higher CV risk in a large, nationwide, longitudinal population-based study after adjusting for various confounding factors and using validated definitions of variables [47] [48].

5. Discussion and Conclusions

This review investigated the increased risk of various CV events in RA patients. Since patients with RA are susceptible to early atherosclerosis, DL, HTN, and various risk factors, they are more prone to HF, IHD, CAD, ACS, VTE, and even valvular disorders. These risks have been concluded by many studies and should be taken seriously by health officials. Considering early prophylaxis in these patients is advisable, and hospitals and healthcare centers should incorporate protocols to consider these complications while handling patient care and treatment. These studies suggest that early and more frequent screening for these CV complications should be implemented. Screening for more severe complications such as ACS, stroke, and HF should be prioritized over less severe ones. Cardiac echocardiograms, lipid profiles, CT angiograms, and Doppler ultrasound must be performed in the early stages of the disease, and follow-up with these patients should be recommended to prevent the progression of these complications if diagnosed.

The recognition of an increased cardiovascular disease risk in arthritis prompted the European League Against Rheumatism (EULAR) to set out evidence-based recommendations for the management of cardiovascular disease risk in inflammatory arthritis, and these guidelines were updated in 2017. Rheumatoid arthritis is also now accepted as an independent cardiovascular disease risk factor by the European Society of Cardiology guidelines. To reduce the risk of cardiovascular disease in patients with rheumatoid arthritis, optimal disease control is necessary, and cardiovascular disease management should be the responsibility of the rheumatologist. Risk assessment. The increased cardiovascular risk includes not only a higher rate of ischemic cardiovascular disease but also subclinical heart failure, which seems far more prevalent than previously thought. Early therapeutic intervention with current antirheumatic treatment in rheumatoid arthritis has shown favorable effects on cardiovascular disease risk.

This comprehensive review sheds light on the complex relationship between genetic, molecular, and lifestyle variables influencing cardiovascular health by summarizing the current viewpoints on lipid diseases and cardiovascular risk. The synthesis highlights the numerous mechanisms involved in lipid metabolism and the dynamic nature of treatment interventions. It emphasizes the complexity of the topic and the importance of employing nuanced and tailored approaches. The consequences for clinical practice are significant. The introduction of precision medicine, which focuses on genetic and molecular profiling, requires a fundamental change in how therapeutic decisions are made. The customization of therapies based on individual risk profiles, considering pharmacogenomic factors, and adding lifestyle adjustments highlights the progression toward individualized cardiovascular care. Clinicians must skillfully traverse this field, utilizing progress to enhance patient results while tackling issues about availability, understanding, and ethical concerns. As we journey into the next phase of cardiovascular research, clear recommendations for future efforts emerge. Further investigation into genetic markers, molecular pathways, and the incorporation of new technologies

will enhance our comprehension of cardiovascular diseases [48]-[50].

There are future challenges that must be met to address the complex relationship between RA and CVD. Relatively concurrent explosions in data collection, genomics, computing and a multitude of advances in stroke research have prefaced the realization of precision medicine in stroke. Implementing this concept in practice, however, will require a multidisciplinary effort to bring together experts in traditionally disparate disciplines within the stroke field. True stroke precision medicine will require accurate clinical phenotyping, genomic and proteomic expertise, spatial and temporal imaging analysis, incorporation of new biological variables and the statistical and experiential knowledge to help assign the appropriate weight to each variable. Though daunting, patients already think of medical decision-making in personal terms that increasingly demand individualized precision. There is nothing more powerful than being able to convey to a patient a precise diagnosis and treatment plan, never more so than in stroke, when the outcome in question is not only mortality but physical and mental disability. Proper consideration of how one might apply the principles of precision medicine to stroke presages a new era of individualized therapy in stroke [51].

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Conflicts of Interest

None declared by the author.

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