Cardiac strain in patients on Janus Kinase inhibitors for rheumatic diseases: a 1-year echocardiographic study

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Abstract

Objective

Janus kinase inhibitors (JAKi) are increasingly used to treat autoimmune rheumatic diseases (ARDs), despite concerns regarding their potential cardiovascular risks. Cardiac strain, a sensitive marker for subclinical myocardial dysfunction, can predict the risk of heart failure. This study aims to evaluate the effect of JAKi on cardiac strain and function in patients with ARDs in routine clinical practice.

Methods

This prospective Greek cohort study enrolled patients diagnosed with RA, PsA, or axSpA initiating treatment with a JAKi (baricitinib, tofacitinib, or upadacitinib). Comprehensive assessments were performed at baseline, 6 months, and 12 months including disease-specific scores and laboratory tests. Transthoracic speckle-tracking echocardiography was used to assess global longitudinal strain (GLS), left ventricular ejection fraction (EF), and right ventricular function (including RV GLS, TAPSE, and S'RV). Diastolic function was evaluated through the E/A and E/E' ratios.

Results

Thirty patients completed the study: 12 with axSpA, 10 with RA, and 8 with PsA. Disease activity significantly improved across all cohorts. No significant changes in GLS, EF, E/A, E/E', TAPSE, S'RV or heart rate were observed from baseline to 12 months. Additionally, the GLS of the left ventricle did not show a decline.

Conclusion

In this cohort, JAKi did not result in significant changes in cardiac strain or function over one year in patients with ARDs, suggesting that JAKi may not have a detrimental impact on cardiac function in the short term. However, longer-term studies with larger cohorts are necessary to evaluate potential delayed effects and confirm the cardiovascular safety of JAKi.

Key words

cardiovascular disease, global longitudinal strain, cardiac function, autoimmune rheumatic diseases

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Introduction

Autoimmune rheumatic diseases (ARDs), including rheumatoid arthritis (RA), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA), are chronic autoimmune conditions that significantly impact patients' quality of life (1-4). These diseases are characterised by systemic inflammation that can lead to joint and spine damage, disability, and cardiovascular disease (CVD). Cardiovascular complications, such as heart failure, ischaemic heart disease, and stroke, are recognised as major contributors to morbidity and mortality in individuals with ARDs, with these patients having a higher incidence of cardiovascular events compared to the general population (5-7). The underlying mechanisms linking chronic inflammation and cardiovascular risk in ARDs include endothelial dysfunction, accelerated atherosclerosis, and increased systemic inflammation, which are thought to contribute to subclinical and overt cardiovascular damage (8-10).

Janus kinase inhibitors (JAKi), including tofacitinib, baricitinib, filgotinib and upadacitinib, have emerged as effective therapies for managing a wide spectrum of autoimmune diseases (11). These small molecules target intracellular signalling pathways involved in the pathogenesis of these diseases, particularly the Janus Kinases - Signal Transducer and Activator of Transcription (JAK-STAT) pathway, leading to a reduction in inflammation and improvement in disease activity (12). The rapid onset of action and oral administration make JAKi an attractive alternative to biologics in certain patient populations. However, concerns regarding the cardiovascular safety of JAKi have emerged due to their potential impact on lipid profiles, blood pressure, and other cardiovascular risk factors (13-15).

Despite the growing use of JAKi, the effect of these agents on cardiac function, particularly on cardiac strain, remains inadequately studied. Cardiac strain, assessed through echocardiographic techniques such as global longitudinal strain (GLS), is a sensitive marker of myocardial deformation and early-stage myocardial dysfunction, often before overt changes in ejection fraction or symptoms of heart failure are detectable (16). Strain imaging has gained recognition as a tool to identify subclinical cardiac dysfunction, making it an important parameter to evaluate when considering the cardiovascular safety of new therapies in populations at risk of heart disease (17-20).

While previous studies have suggested an increased risk of cardiovascular events in patients treated with JAKi, the impact of these therapies on cardiac strain is not well characterised. Understanding the potential effects of JAKi on cardiac strain could help clarify their cardiovascular safety profile and guide clinical decision-making. Therefore, the aim of this study was to evaluate the effect of JAKi on cardiac strain and function in patients with RA, PsA, and axSpA over a one-year follow-up period in routine clinical practice.

Methods

Study design and participants

This was a prospective cohort study conducted at Hippokration and Papanikolaou hospitals in Thessaloniki, Greece between September 2023 and December 2024. Patients were eligible for inclusion if they met the following criteria:

1. Diagnosed with RA according to the 2010 ACR/EULAR classification criteria (21), PsA as defined by the 2006 CASPAR criteria (22), or axSpA as it is outlined by the 2009 ASAS classification criteria (23).
2. Initiating treatment with one of the following JAKi according to national treatment guidelines: baricitinib, tofacitinib, or upadacitinib.
3. Aged 18 years or older.
4. Provided informed consent to participate in the study.

Exclusion criteria included:

1. History of prior or current heart failure or significant CVD (*e.g.* myocardial infarction, stroke).
2. Severe uncontrolled comorbidities (*e.g.* chronic renal disease, active cancer).

Ethical approval and informed consent

The study was approved by the local institutional review board (IRB) at

both hospitals and all participants provided written informed consent prior to enrolment. The study was conducted in accordance with the Declaration of Helsinki.

Treatment protocol

Patients were treated according to standard care protocols for RA, PsA, or axSpA. The choice of JAKi (tofacitinib, baricitinib, or upadacitinib) was made based on national treatment guidelines and individual patient considerations. Dosing regimens followed the existing recommendations: Tofacitinib; (5 mg twice daily), Baricitinib; (4 mg once daily), Upadacitinib; (15 mg once daily) (21–24). Patients were monitored for adverse events and efficacy throughout the study period. In case of treatment failure or adverse events, the patients continued the follow-up until the period of 12 months, regardless of the new treatment.

Echocardiographic assessment

Cardiac function was assessed by transthoracic echocardiography (TTE) at baseline, 6 months, and 12 months of follow-up. All echocardiograms were performed by a single experienced operator using a GE Vivid E95 ultrasound machine and analysed offline using the GE EchoPAC software. The following parameters were measured:

1. Global longitudinal strain (GLS) of the left ventricle (LV) using speckle-tracking echocardiography. GLS was measured by averaging the strain values from 18 myocardial segments of the LV, and values less than -20% were considered indicative of subclinical myocardial dysfunction (10).
2. Left ventricular ejection fraction (EF): measured using the Simpson's biplane method.
3. Right ventricular strain (RV GLS): assessing RV function using speckle-tracking echocardiography.
4. Tricuspid annular plane systolic excursion (TAPSE): measured in the apical four-chamber view as an index of RV systolic function.
5. Systolic velocity of the right ventricle (S'RV): assessed by tissue Doppler imaging.
6. Diastolic function: evaluated using. Doppler-derived parameters, including the early diastolic flow peak velocity of the mitral valve (m/s)/diastolic flow peak velocity of the mitral valve (m/s) (E/A) ratio and early diastolic flow peak velocity of the mitral valve (m/s)/early diastolic peak velocity of mitral valve annulus (m/s) (E/E') ratio. These echocardiographic measurements were chosen as they are sensitive to early changes in myocardial function and are predictive of adverse cardiovascular outcomes, such as heart failure (16).

Disease activity and laboratory assessments

At baseline, 6 months, and 12 months, disease activity was evaluated using the following scores:

1. Rheumatoid Arthritis Disease Activity Score (DAS28-CRP) for RA (25);
2. Axial Spondyloarthritis Disease Activity Score (ASDAS) for axSpA (26);
3. Disease Activity Index for Psoriatic Arthritis (DAPSA) for PsA (27).

Laboratory assessments included inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and other routine blood tests to assess liver function, renal function, and lipid profile.

Statistical analysis

Descriptive statistics were used to summarise baseline characteristics, echocardiographic measurements, and disease activity scores. Continuous variables are expressed as means ± standard deviations (SD). Paired t-tests were used to compare mean values at baseline, 6 months, and 12 months. A p-value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 30 patients completed the study: 12 with AxSpA, 10 with RA, and 8 with PsA. 6 patients changed treatment due to inefficacy: 2 switched to another JAKi, and 4 to other biologics. The distribution of JAK inhibitors was: upadacitinib (n=18), tofacitinib (n=10), and baricitinib (n=4). Previous biologic treatments were reported as follows: 20 patients (67%) had used ≥1 biologic agent, and 12 patients (40%) had used ≥2 biologic agents prior to initiating JAK inhibitor therapy. The mean age was 47.6±12 years, and 47% of the participants were male. The majority of patients had a normal BMI (24.7±2.3), with 43% reporting current smoking. Comorbidities included hypertension in 20%, diabetes in 10%, and hyperlipidaemia in 40% (Table I). At baseline, patients demonstrated moderate disease activity, with a mean DAS28-CRP score of 4.6±1.0, ASDAS of 3.0±0.7, and DAPSA of 19.7±4.7.

Changes in Disease Activity Scores

Significant improvements in disease activity were observed over the course of the study. At 6 months, the mean DAS28-CRP decreased to 2.9±0.7, and at 12 months, it was further reduced to 3.0±0.7. A similar trend was noted for the ASDAS, which improved from 3.0±0.7 at baseline to 1.8±0.6 at 6 months, and 1.9±0.7 at 12 months. The DAPSA score also decreased significantly, from 19.7±4.7 at baseline to 9.3±3.9 at 6 months, and 8.8±3.9 at 12 months (Table II).

Echocardiographic findings

- Heart rate (HR)

There was no significant change in HR from baseline to 6 months (p=0.42). However, a statistically significant increase in heart rate was observed between baseline and 12 months (p=0.01), suggesting a mild elevation in heart rate over the course of treatment with JAK inhibitors.

- Global longitudinal strain (GLS)

No significant change in GLS was noted from baseline to 6 months (p=0.49). However, a significant improvement was observed from baseline to 12 months (p=0.0027), indicating a potential benefit of JAK inhibitor therapy on myocardial deformation in the longer term (Fig. 1).

- E/A ratio (diastolic function)

The E/A ratio remained stable from baseline to both 6 months (p=0.21) and 12 months (p=0.09), with no statistically significant changes, suggesting that diastolic function did not alter significantly during the study.

Table I. Baseline characteristics.

	All patients (n=30)
Age (mean ± SD)	47.6 ± 12
Male sex (n, %)	14 (47%)
Body mass index (mean ± SD)	24.7 ± 2.3
Smoking (n, %)	13 (43%)
Hypertension (n, %)	6 (20%)
Diabetes (n, %)	3 (10%)
Hyperlipidaemia (n, %)	12 (40%)

Table II. Echocardiographic findings and Disease Activity Scores.

	Baseline	6 months	12 months
HR (mean ± SD)	79.13 ± 11.12	80.83 ± 11.84	83.97 ± 9.31
GLS Full (mean ± SD)	18.37 ± 1.67	18.25 ± 1.79	19.00 ± 1.87
E/A (mean ± SD)	1.00 ± 0.31	1.05 ± 0.34	1.07 ± 0.31
E/E' (mean ± SD)	6.49 ± 2.12	6.95 ± 1.85	7.08 ± 2.00
TAPSE (mean ± SD)	2.38 ± 0.34	2.30 ± 0.26	2.35 ± 0.17
S'RV (mean ± SD)	0.14 ± 0.02	0.13 ± 0.02	0.14 ± 0.02
EF (mean ± SD)	63.10 ± 4.68	62.00 ± 3.88	63.40 ± 4.26
GLS RV (mean ± SD)	23.83 ± 2.79	24.03 ± 2.85	24.23 ± 2.63
DAS28-CRP (mean ± SD)	4.6 ± 1	2.9 ± 0.7	3 ± 0.7
ASDAS (mean ± SD)	3 ± 0.7	1.8 ± 0.6	1.9 ± 0.7
DAPSA (mean ± SD)	19.7 ± 4.7	9.3 ± 3.9	8.8 ± 3.9

A: diastolic flow peak velocity of the mitral valve (m/s); ASDAS: Ankylosing Spondylitis Disease Activity Score; CRP: C-reactive protein; DAPSA: Disease Activity Index in PSoriatic Arthritis; DAS 28: Disease Activity Score 28; E: early diastolic flow peak velocity of the mitral valve (m/s); EF: ejection fraction; E': early diastolic peak velocity of mitral valve annulus (m/s); GLS: global longitudinal strain (- %); HR: heart rate (beats/min); S' RV: right ventricular systolic annular velocity (cm/s); SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion (cm).

- E/E' ratio (diastolic function)

Similarly, the E/E' ratio did not show significant changes from baseline to 6 months (p=0.19) or to 12 months (p=0.18), indicating no meaningful alterations in diastolic function during the study period.

- Tricuspid annular plane systolic excursion (TAPSE)

TAPSE showed a significant improvement from baseline to 6 months (p=0.048), but this change was not sustained at 12 months (p=0.43), suggesting a transient improvement in right ventricular function early on in the treatment course (Fig. 2).

- Right ventricular systolic velocity (S'RV)

There was a significant improvement in S'RV from baseline to 6 months (p=0.017), but this improvement did not persist at 12 months (p=0.49), indicating a transient change in right ventricular systolic velocity that stabilised over time.

- Ejection fraction (EF)

EF decreased significantly from baseline to 6 months (p=0.03), but no significant change was observed from baseline to 12 months (p=0.64). This suggests that the observed decrease in EF was transient, with no sustained change by the end of the study (Fig. 1).

- Right ventricular strain (GLS RV)

GLS RV did not show significant changes at either 6 months (p=0.56) or 12 months (p=0.38), indicating that right ventricular strain remained stable throughout the study period.

Discussion

The use of JAKi in patients with inflammatory rheumatic diseases (IRDs) has become an essential component of treatment due to their efficacy in controlling disease activity (21-24). However, concerns regarding their cardiovascular safety persist, particularly given their impact on immune modulation, which could influence cardiovascular risk factors (5-7, 13-15). Our study aimed to evaluate the effects of JAK inhibitors on cardiac strain and function in patients with RA, axSpA, and PsA over a one-year follow-up period. Despite significant improvements in disease activity, we found that JAK inhibitors did not induce significant changes in cardiac strain or other echocardiographic parameters, suggesting no substantial cardiovascular harm in this cohort.

Cardiac strain and function in JAKi therapy

Cardiac strain, especially GLS, is a sensitive marker of subclinical myocardial dysfunction, predicting future cardiovascular risk, including heart failure. Clinically meaningful changes in GLS are typically defined as ≥15% (31). Longitudinal studies suggest that significant changes can be detected over intervals as short as 3 to 6 months (32, 33). Although there was a statistical improvement in GLS over the 12-month period, the magnitude of change was modest; thus, its clinical impact should be interpreted cautiously, particularly given the lack of a comparator group (Table II, Fig. 1). Likewise, other echocardiographic parameters (ejection fraction, TAPSE, E/A ratio, E/E' ratio, and S'RV) showed no significant alterations throughout the study with one exception. A statistically significant decline in EF at 6 months was noticed, which normalised by 12 months. However, given the transient and small magnitude of this change, it is considered unlikely to be clinically relevant (Table II, Fig. 1). These findings suggest that JAK inhibitors do not lead to acute or subclinical cardiac dysfunction over the short term.

Disease activity and cardiovascular risk

While our primary goal was to assess the impact of JAK inhibitors on cardiac strain, we also observed significant reductions in disease activity scores across all disease cohorts. Both DAS28-CRP and DAPSA scores improved markedly at 6 and 12 months, reflecting effective disease control. This reduction in disease activity likely lowers systemic inflammation, a key contributor to cardiovascular risk in ARDs (8, 9). Previous research has shown that disease-modifying anti-rheumatic drugs (DMARDs), including JAK in-

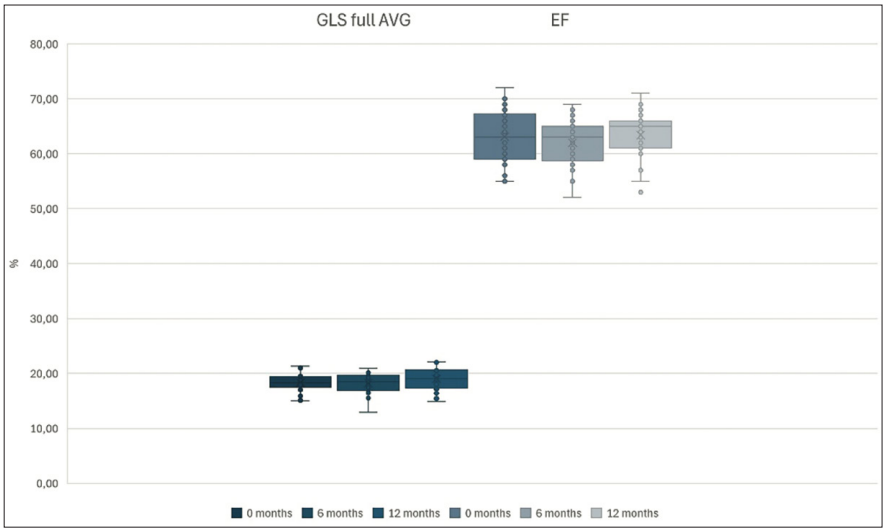

Fig. 1. Boxplot representation of GLS full AVG (global longitudinal strain, average) and EF (ejection fraction) at baseline (0 months), 6-month, and 12-month follow-up. Data are presented as median (central line), interquartile range (box), and range (whiskers), with individual outliers displayed as points. GLS values are shown on the left side while EF values are displayed on the right side of the plot. Comparisons reflect changes over the follow-up period.

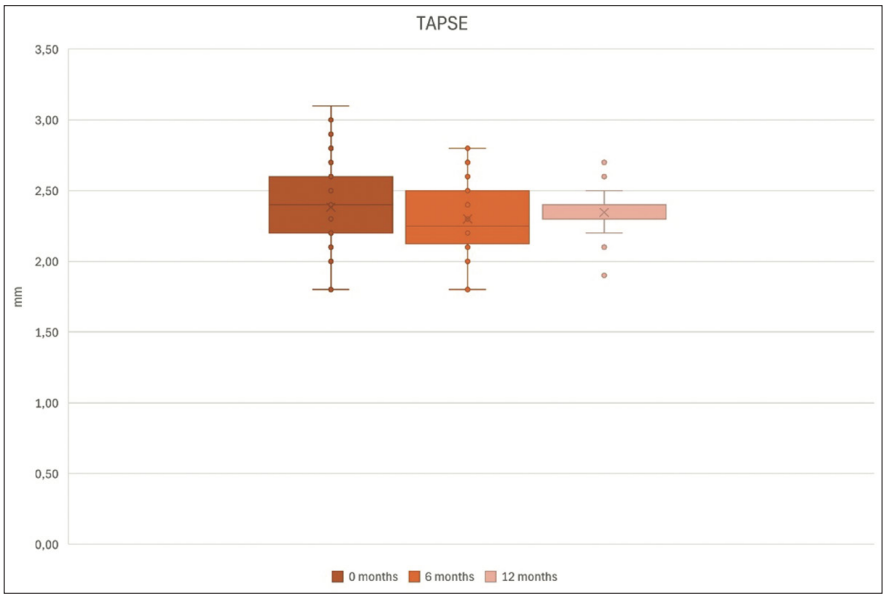

Fig. 1. Boxplot representation of TAPSE (tricuspid annular plane systolic excursion) at baseline (0 months), 6-month, and 12-month follow-up. TAPSE is expressed in millimeters. Data are shown as median (central line), interquartile range (box), and range (whiskers), with individual outliers depicted as points. Comparisons illustrate changes of TAPSE over time.

hibitors, help mitigate this inflammation, potentially improving cardiovascular outcomes (19, 20, 28, 29).

Comparisons to previous studies

Few studies have directly assessed the effects of JAK inhibitors on cardiac function. In contrast, studies of biologics, like tocilizumab, have shown improvements in left ventricular function in RA patients (19). However, studies evaluating other DMARDs have indicated potential subclinical left ventricular dysfunction, particularly in conventional synthetic disease modifying anti-rheumatic drugs (cDMARDs) users compared to biologic disease modifying anti-rheumatic drugs (bDMARDs) (20). Our study is the first to examine specifically the effects of JAK inhibitors on cardiac function using echocardiography in a real-world setting, offering valuable insights into their cardiovascular safety profile.

Considerations of long-term cardiovascular risk

Some studies, such as the ORAL Surveillance study, have indicated a potential increased risk of major adverse cardiovascular events (MACE) with long-term tofacitinib use, particularly in older patients with cardiovascular comorbidities (15). Furthermore, a recent study from France highlights that JAKi warrant a cautious prescription in RA patients with risk factors for VTE, as JAKi are independently associated with the chance of sustaining VTE episodes with an OR of 5.54 (36). However, our study focused on a younger cohort with relatively low comorbidity burdens, and no significant adverse effects on cardiac strain were observed. These findings suggest that while JAK inhibitors appear safe in the short term for patients without significant cardiovascular risk factors, caution is warranted with long-term use, particularly in higher-risk populations.

Strengths and limitations

The strengths of our study include the prospective cohort design, which provides a more robust assessment of JAKi therapy in real-world clinical practice, and the use of advanced echocardiographic techniques to assess cardiac function and strain. Moreover, the inclusion of patients with different ARDs (RA, PsA, and axSpA) increases the generalisability of our findings to a broader population of patients receiving JAKi.

However, there are some limitations that must be considered. Firstly, this study is exploratory in nature and was not powered to detect small changes in echocardiographic findings of patients with ARD on JAKi. The sample size of 30 patients is relatively small, which limits the statistical power and generalisability of the findings. A larger sample, particularly one with a broader range of cardiovascular risk factors, would provide more comprehensive insights into the cardiovascular effects of JAK inhibitors. Additionally, the study duration of one year may not be long enough to fully capture potential long-term cardiovascular risks associated with JAKi therapy. Long-term

studies with extended follow-up are needed to better understand the impact of JAK inhibitors on cardiovascular health. Moreover, the absence of other cardiovascular risk markers, such as lipid profiles or arterial stiffness and the deficit of cardiovascular risk stratification, limits our ability to assess the full spectrum of cardiovascular effects of JAKi. Lastly, the absence of a case-by-case matched comparator group receiving other DMARDs hinders the ability to establish causality or attribute any echocardiographic changes to JAKi.

Conclusions

In conclusion, our study suggests that JAK inhibitors, when used in everyday clinical practice, do not have a negative impact on cardiac strain or function over one year of follow-up in patients with inflammatory rheumatic diseases. JAK inhibitors effectively reduce disease activity and inflammatory burden, and their short-term cardiovascular safety profile appears favourable, particularly in patients without significant comorbidities. However, the relatively short follow-up and small sample size limit the ability to fully assess long-term cardiovascular risks. Larger, long-term studies are necessary to understand the sustained cardiovascular effects of JAK inhibitors, particularly in populations with higher cardiovascular risk.

Take-home messages

- JAK inhibitors did not result in significant changes in cardiac strain or function over one year in patients with ARDs.
- JAK inhibitors effectively reduce disease activity and inflammatory burden, and their short-term cardiovascular safety profile appears favourable, particularly in patients without significant comorbidities.

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