Raised erythrocyte sedimentation rate signals heart failure in patients with rheumatoid arthritis

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EXTENDED REPORT

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Background: Inflammatory markers are associated with heart failure. Patients with rheumatoid arthritis have twice the risk of heart failure compared with people without rheumatoid arthritis.
Objective: To assess whether heart failure in patients with rheumatoid arthritis is preceded by an inflammatory activation as shown by erythrocyte sedimentation rate (ESR), a systemic marker of inflammation.
Methods: A population-based inception cohort of 575 patients with rheumatoid arthritis, free of heart failure at their rheumatoid arthritis incidence date, was followed up longitudinally until death or 2001. During 15 years of follow-up, they had a median of 15 ESR tests, and 172 patients had new-onset heart failure (Framingham Heart Study criteria). The follow-up period, beginning with the rheumatoid arthritis incidence date and ending with date of the last follow-up, was divided into 6-month intervals. The proportions of patients with at least one ESR value ⩾40 mm/h and with anaemia (haemoglobin <11 g/dl) within each 6-month interval were plotted against time from fulfilment of heart failure criteria. A binomial test was used to compare proportions.
Results: In patients with rheumatoid arthritis who developed heart failure, the proportion with ESR ⩾40 mm/h was highest (23%) during the 6-month period immediately preceding the new-onset heart failure, as compared with the average ESR during the entire remaining follow-up period, both before and after heart failure (10.6%; $p<0.01$). The proportion of patients with anaemia peaked (54%) during the 6-month period after heart failure.
Conclusions: Inflammatory stimuli may be involved in the initiation of heart failure among patients with rheumatoid arthritis.

Rheumatoid arthritis is a chronic systemic inflammatory disease, and patients with rheumatoid arthritis have twice the risk of developing heart failure than a comparable group of people without rheumatoid arthritis.[1] The mechanism for the increased risk of heart failure in rheumatoid arthritis is unknown, but it seems to be independent of the traditional risk factors, suggesting that the persistent inflammatory state in rheumatoid arthritis may have an important pathological role.[2] Indeed, several lines of evidence support our observation by showing the pathogenic role for inflammation in the initiation and progression of heart failure.[3]

The disease course in rheumatoid arthritis is characterised by flares and remissions corresponding to fluctuations in disease activity. Disease activity in rheumatoid arthritis is assessed by examining symptoms of inflammatory joint disease, functional status and various laboratory tests of immune activation, such as erythrocyte sedimentation rate (ESR) and C reactive protein.[4] Although the ESR is not diagnostic of any particular disease, it is an inexpensive and a practical indicator of response of acute phase proteins in plasma.[5] Introduced in the 1920s, it has been commonly used to monitor disease activity and response to treatment in various inflammatory diseases, including rheumatoid arthritis.[5 6]

The significance of ESR is also examined in the setting of heart failure. Although earlier studies suggested a worse prognosis of chronic heart failure with low ESR,[7] a more recent study on patients with chronic heart failure treated with angiotensin-converting enzyme inhibitors showed that a high ESR may be an unfavourable prognostic sign, independent of patients' symptomatology and ventricular function.[8] ESR is also positively correlated with pro-inflammatory cytokines[8] that have been shown to predict heart failure even in asymptomatic people, and that seem to be associated with worse prognosis in patients with heart failure.[9–11]

In our population-based cohort of patients with rheumatoid arthritis, the ESR was often measured as part of their medical care. We capitalised on these serial ESR tests in patients with rheumatoid arthritis to test the hypothesis that heart failure in patients with rheumatoid arthritis is preceded by an inflammatory activation, as shown by ESR values.

METHODS

Study population and data collection

This is a retrospective longitudinal study that was conducted using the data resources of the Rochester Epidemiology Project medical records linkage system.[12 13] This system allows ready access to the complete medical records (covering inpatient and outpatient care) from all healthcare providers for the local population in Olmsted County, Minnesota, USA. The potential of this system for population-based research has been described previously.[13] The population for this study included a previously described[1 14] population-based incidence cohort of Rochester, Minnesota residents ⩾18 years of age who were first diagnosed with rheumatoid arthritis between January 1955 and January 1995. All subjects fulfilled the 1987 American College of Rheumatology criteria for rheumatoid arthritis.[15] The incidence date was defined as the first date of fulfilment of four of the seven classification criteria.

The complete medical records of all patients were reviewed longitudinally, starting at 18 years of age (or date of migration to Olmsted County if >18 years) and continuing until death,

Abbreviations: ESR, erythrocyte sedimentation rate; IQR, interquartile range

migration from Olmsted County or January 2001 (end of study follow-up). Detailed information was collected regarding rheumatoid arthritis disease characteristics, clinically documented occurrence of cardiovascular risk factors, cardiovascular events and the results of laboratory tests. Details of data collection and definitions of rheumatoid arthritis disease characteristics, cardiovascular risk factors and cardiovascular events have been described previously.[1 14] In brief, rheumatoid arthritis disease characteristics included the presence of tender or swollen joints and the use of disease-modifying antirheumatic drugs and corticosteroids. A clinical disease flare was defined as the initiation of a new disease-modifying antirheumatic drug or glucocorticoid treatment, or the presence of tender or swollen joints.

Heart failure was defined according to validated criteria from the Framingham Heart Study[16] (table 1), diabetes mellitus according to the World Health Organization 1998 criteria[17] and hypertension according to the criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure.[18] The earliest recorded date of fulfilment of these criteria was considered the incidence date for each.

Results of laboratory tests were collected from the complete medical records available through the Rochester Epidemiology Project medical records linkage system that also includes the electronically available laboratory data after 1 July 1983. Results of all rheumatoid factor tests (considered positive if ⩾40 Iu/ml and ESR tests (Westergreen method) were obtained for all study subjects. To examine the influence of anaemia (a potential confounder for ESR) on our findings, we accessed the electronically available laboratory data on a subset of our study subjects. All haemoglobin, haematocrit values, erythrocyte and reticulocyte counts, mean corpuscular volume and mean corpuscular haemoglobin values after 1 July 1983 were retrieved. Anaemia was defined as haemoglobin concentration <11 g/dl. All of the laboratory tests were performed as part of the routine clinical care of the patients using standard laboratory methods.

Statistical analysis

Descriptive statistics (means, medians, percentages, etc) were used to summarise the data. Patients with rheumatoid arthritis having a validated diagnosis of heart failure before fulfilment of American College of Rheumatology 1987 criteria (28 of the 603 patients with incident rheumatoid arthritis) were excluded from the analysis. Analyses were conducted as follows. Firstly, patients with rheumatoid arthritis who developed heart failure (n = 172) during the entire follow-up period were identified. The follow-up period preceding heart failure was divided into 6-month intervals beginning with the heart failure incidence date and ending with the rheumatoid arthritis incidence date (fig 1). Similarly, the follow-up period after heart failure was divided into 6-month intervals beginning with the heart failure incidence date and ending with the date of last follow-up (or death). Secondly, among patients without heart failure (n = 403), we randomly chose a visit date from among all visits for medical care any time between the rheumatoid arthritis incidence date and the date of last follow-up. As we did with patients who developed heart failure, we divided the follow-up time into 6-month intervals, beginning with the random visit date and ending with the date of last follow-up. We also split the follow-up time preceding the random visit into 6-month intervals, beginning with the random visit date and ending with the rheumatoid arthritis incidence date. The proportion of patients with rheumatoid arthritis and at least one ESR value ⩾40 mm/h (and ⩾60 mm/h) within each 6-month interval was determined by dividing the number of patients with at least one ESR value ⩾40 mm/h by the number of patients under observation within the interval (fig 1). For the 172 patients with heart failure, these proportions were plotted against time both before and after the heart failure incidence date. Similarly, for patients without heart failure, the proportion of patients with rheumatoid arthritis with at least one ESR value ⩾40 mm/h (and ⩾60 mm/h) within each 6-month interval was plotted against time both before and after the random visit date. Sensitivity analyses were performed by conducting similar analyses for hypertension and diabetes mellitus incidence dates. The purpose of these sensitivity analyses was to assess whether the association observed between ESR and heart failure was due to an increase in the intensity of laboratory testing around the time of chronic disease diagnosis. If the association was not real but due to an increase in the intensity of testing around the time of diagnosis of heart failure, we would have expected to observe the same pattern preceding other diagnoses, such as hypertension and diabetes. Mean proportions were estimated by averaging the observed proportions across several 6-month intervals. A binomial test was used to compare an observed proportion for a specific 6-month interval to the mean proportion.

In supplementary analyses, we examined the proportion of patients with clinically documented disease flares and the

Table 1 Framingham Heart Study Criteria for the diagnosis of heart failure[16]

Criterion	Number of subjects who fulfilled the criteria (%)*
Major criteria	
Paroxysmal nocturnal dyspnoea or orthopnea	28 (16)
Neck vein distention	104 (60)
Rales	155 (90)
Cardiomegaly	90 (56)
Acute pulmonary oedema	42 (26)
S3 gallop	39 (23)
Hepatojugular reflux	21 (12)
Minor criteria	
Ankle oedema	106 (62)
Night cough	67 (39)
Dyspnoea on exertion	121 (70)
Hepatomegaly	22 (13)
Pleural effusion	73 (45)
Tachycardia rate of ⩾120 beats/min	26 (16)

*Of the 172 subjects with heart failure and rheumatoid arthritis, each subject may have fulfilled more than one criterion. Heart failure was considered present with two major criteria or one major and two minor criteria.

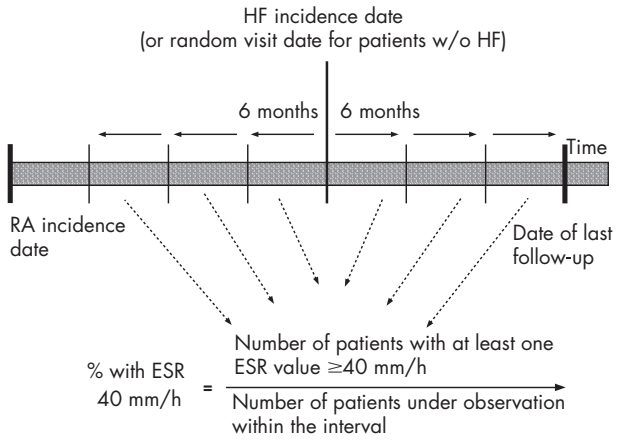

Figure 1 Study design. HF, heart failure; RA, rheumatoid arthritis; ESR, erythrocyte sedimentation rate.

proportion of patients with anaemia within the same 6-month intervals, both before and after the heart failure incidence date.

RESULTS

The study population comprised 575 incident cases of rheumatoid arthritis free of heart failure at rheumatoid arthritis incidence date. Over a median follow-up of 15 years (total 6785 person-years) after the rheumatoid arthritis incidence date, these 575 patients with rheumatoid arthritis had a median of 15 (interquartile range (IQR) 9–25) ESR tests. As reported previously,[14] the mean (standard deviation) recorded ESR values with the first year after diagnosis of rheumatoid arthritis was 46.7 (30.1) mm/h. Similarly, almost one third of the patients had ⩾3 recorded ESR values at ⩾60 mm/h during follow-up. During the same follow-up period, 172 patients had new-onset heart failure. Table 1 shows the distribution of the 172 patients by each Framingham criterion. The median (IQR) number of ESR tests among the 172 patients with rheumatoid arthritis with heart failure was 17 (10–28) and among the remaining 403 patients with rheumatoid arthritis without heart failure, it was 14 (8–24).

Among the 172 patients with rheumatoid arthritis with heart failure, the proportion of patients with ESR values ⩾40 mm/h was highest during the 6-month period immediately preceding the fulfilment of diagnostic criteria for new-onset heart failure, as compared with the entire remaining follow-up period (fig 2). The follow-up periods before and after the heart failure incidence date were approximately 10 and 5 years, respectively (fig 2). During the 6-month period immediately preceding the new-onset heart failure, the proportion of patients with rheumatoid arthritis ESR values ⩾40 mm/h was 23%, whereas the same proportion was, on average, 10.6% in other 6-month intervals, both before and after the heart failure incidence date ($p<0.01$, fig 2). By contrast, among 403 patients with rheumatoid arthritis with no clinical heart failure, the proportion with ESR values ⩾40 mm/h was relatively stable at 8.2%, on average, during the entire follow-up (fig 3). The same analyses were repeated considering patients with rheumatoid arthritis with ESR values ⩾60 mm/h, and the patterns were similar to those observed in figs 2 and 3 (data not shown).

We then conducted several sensitivity analyses to examine the robustness of our findings. Specifically, the incidence dates for diabetes mellitus and hypertension were chosen (instead of the heart failure incidence date) and the same analyses were conducted by aligning the 6-month intervals around the diabetes mellitus and hypertension incidence dates. We examined the proportion of patients with at least one ESR value ⩾40 mm/h within each 6-month interval before and after diabetes (fig 4A) and hypertension (fig 4B). No increase in the proportion of patients with ESR values ⩾40 mm/h was observed at any time during follow-up in either instance. The mean proportion was relatively stable both before and after the diabetes and hypertension incidence dates, 8.3% and 10.0%, respectively. This analysis was repeated considering ESR values ⩾60 mm/h, and the results were unchanged.

In an effort to determine whether the increased ESR preceding heart failure was accompanied by a clinically documented rheumatoid arthritis flare, we examined the proportion of patients with a flare within the 6-month intervals surrounding the new-onset heart failure. The proportion of patients with a flare during the 6-month period before heart failure was 30%, whereas the average proportion for the 5-year period before the 6-month window before heart failure was 24%. This difference was marginally significant ($p = 0.05$).

We then conducted the same analyses with anaemia (fig 5). The proportion of patients with anaemia (haemoglobin <11 g/dl) was highest (54%) during the 6-month period immediately *after* the fulfilment of diagnostic criteria for heart failure, as compared with the entire remaining follow-up period (fig 4). In addition, the average proportion of patients with anaemia started to increase before heart failure; the mean proportion was 9.8% prior to the 6-month window before heart failure, and increased to 32.3% within the 6-month window before heart failure (fig 5). The mean proportion of anaemia also remained high following the 6-month window after heart failure (23.6%, $p<0.01$).

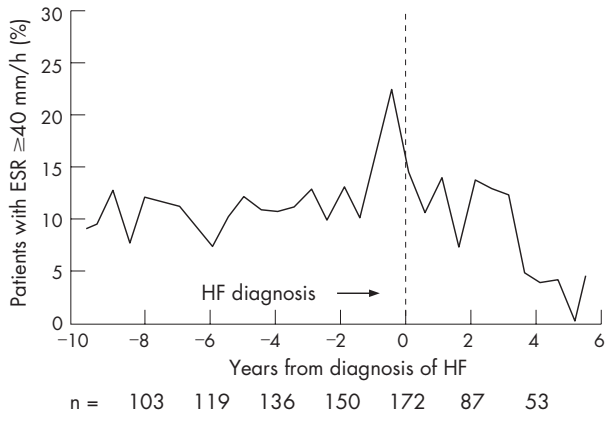

Figure 2 Proportion of patients with rheumatoid arthritis with erythrocyte sedimentation rate (ESR) >40 mm/h during the 6-month intervals before and after the heart failure (HF) incidence date (among 172 patients with rheumatoid arthritis who developed heart failure). n, the number of patients under observation within the interval.

DISCUSSION

In this population-based incidence cohort of patients with rheumatoid arthritis who developed new-onset heart failure, the proportion with significantly increased ESR (⩾40 and ⩾60 mm/h) was highest during the 6-month period immediately before diagnosis of heart failure as compared with any other period over their entire follow-up time, both before and after heart failure. Further, the proportion of patients with anaemia peaked (54%) during the 6-month period after heart failure. These findings suggest that inflammatory mechanisms may be involved in the initiation or exacerbation of heart failure and anaemia among patients with rheumatoid arthritis.

ESR is widely used as an indicator of acute-phase response in several immune-mediated inflammatory diseases, including rheumatoid arthritis.[4 6 19–22] Although the patterns of acute-phase response and cytokine production may differ in different inflammatory diseases, acute-phase changes essentially reflect the presence and intensity of inflammation. Consequently, ESR is an indirect, albeit non-specific, reflection of acute-phase protein concentrations in plasma and can be raised in any condition that leads to an acute-phase response, such as infection, surgery, trauma or advanced cancer.[5]

The transient increase in ESR immediately preceding new-onset heart failure in fig 2 possibly reflects an inflammatory activation or an acute-phase response, accompanied by raised levels of circulating pro-inflammatory cytokines and their receptors. This may happen at times of increased disease activity in rheumatoid arthritis. ESR values of 40 and 60 mm/h clearly indicate a state of heightened systemic inflammation among people who already have an inflammatory disease. We also examined whether the increase in ESR was accompanied with disease flares, and our results suggest that this may be the case. This observation is consistent with our findings regarding ESR as it implies that periods of active systemic inflammation,

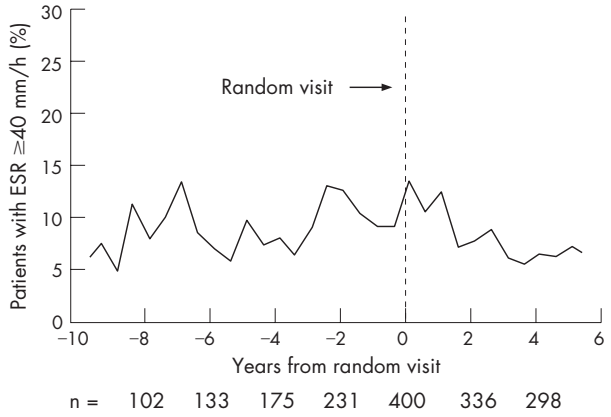

Figure 3 Proportion of patients with rheumatoid arthritis and erythrocyte sedimentation rate (ESR) >40 mm/h during the 6-month intervals before and after a random visit date (among 400 patients with rheumatoid arthritis without heart failure).

such as at times of disease flares, may signal heart failure in patients with rheumatoid arthritis.

Conceivably, the transient increase in ESR may be related to ongoing but yet preclinical or unrecognised heart failure. For example, heart failure commonly leads to extracellular fluid volume expansion and anaemia and consequently, the raised ESR may be a consequence of anaemia due to haemodilution from preclinical heart failure.[23] Alternatively, the ESR peak may truly reflect an inflammatory activation preceding a yet preclinical heart failure. Indeed, inflammation is implicated in the aetiology of heart failure. Raised levels of C reactive protein and cytokines are associated with the risk of heart failure even in asymptomatic people, and seem to be associated with worse prognosis in patients with heart failure.[9–11] Our observation is consistent with the inflammatory aetiology of heart failure.

Another important observation in our study is the high proportion of patients with anaemia within the 6-month period after the new-onset heart failure. Anaemia of chronic disease, also known as the anaemia of inflammation, is commonly observed in patients with chronic or acute immune activation, such as rheumatoid arthritis, heart failure, malignancies, infections and trauma.[24 25] It seems to be immune-driven, where the immune system alters the iron homoeostasis, decreased erythropoiesis and blunted erythropoietin response.[25] The chronology of events observed in our study (ie, raised ESR in the 6-month window preceding heart failure is followed by a high frequency of anaemia in the 6-month window after heart failure, as shown in figs 2 and 5) is consistent with the inflammatory aetiology of anaemia with acute immune activation.[24]

Potential limitations should be kept in mind in interpreting our findings. Firstly, ESR is a non-specific test and can be affected by many factors other than acute-phase response, including the patient's age, sex, the size, shape and number of erythrocytes, other plasma constituents, such as serum immunoglobulins, rheumatoid factor and various drugs such as salicylates, and even smoking.[26 27] Therefore, ESR captures changes in all these factors and, in turn, all these factors can potentially confound the association we observed in our study. Secondly, non-steroidal anti-inflammatory drugs are commonly used by patients with rheumatoid arthritis and they are also associated with increased risk of heart failure. It was not feasible to account for the use of non-steroidal anti-inflammatory drugs in this study because much of their use is over the counter, and therefore not documented in the medical

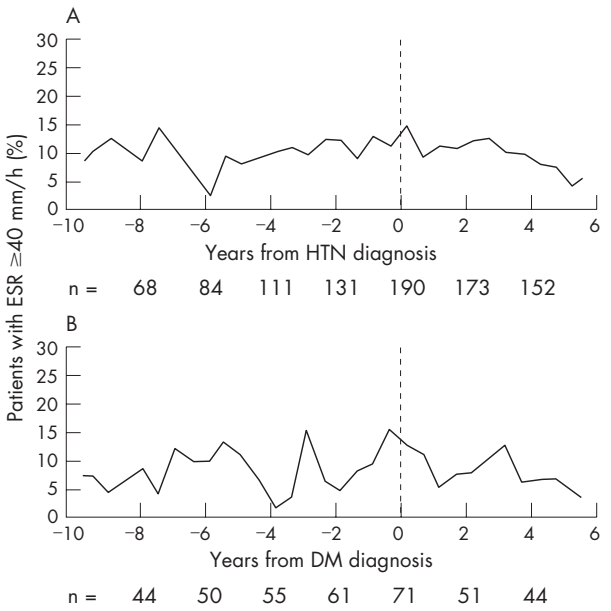

Figure 4 Proportion of patients with rheumatoid arthritis with erythrocyte sedimentation rate (ESR) >40 mm/h during the 6-month intervals before and after the hypertension (HTN) incidence date (A; among 190 patients with rheumatoid arthritis and hypertension) and the diabetes mellitus (DM) incidence date (B; among 71 patients with rheumatoid arthritis and diabetes mellitus).

records. Thirdly, all laboratory tests in our study were performed as needed for the clinical care of the patients, and at irregular intervals. Although we can examine the predictive importance of change in ESR values over time and the risk of heart failure, we have no direct measures of immune activation. On the other hand, the availability of repeated ESR tests over a long follow-up period (mean 15 years of follow-up) complemented by extensive and rigorously validated clinical and laboratory data is a unique strength of our study. Conducting such a study prospectively over such a long period is not feasible. Other important strengths of our study are the inclusion of a community-based cohort of patients with rheumatoid arthritis that reflect the entire spectrum of

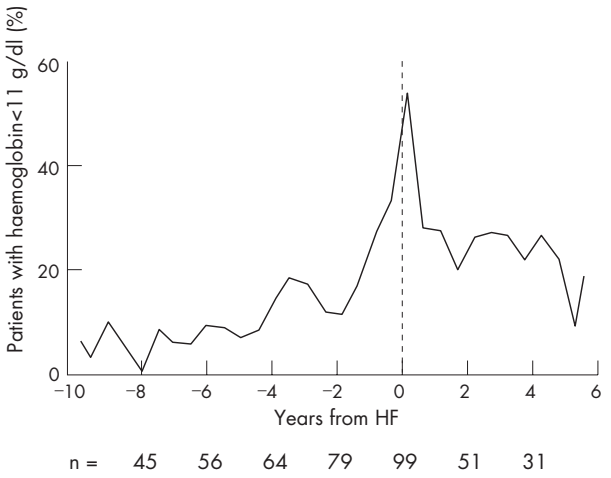

Figure 5 Proportion of patients with rheumatoid arthritis haemoglobin concentration <11 g/dl during the 6-month intervals before and after the heart failure incidence date (among 99 patients with rheumatoid arthritis with new-onset heart failure (HF) after 7 January 1983).

rheumatoid arthritis in the community, and the unique ability to start follow-up at the rheumatoid arthritis incidence date and identify all incident new-onset heart failure episodes, rather than chronic or prevalent heart failure. The results of our study provide important insights into the potential role of immune and inflammatory mechanisms in the aetiology of new-onset heart failure and anaemia in a disease setting characterised by chronic inflammation, and where inflammatory activity is monitored periodically over time.

In conclusion, among patients with rheumatoid arthritis who developed heart failure, the proportion with significantly raised ESR was highest during the 6-month period immediately before diagnosis of new-onset heart failure, as compared with any other period over their entire follow-up time (including both before and after heart failure). Further, the proportion of patients with anaemia peaked during the 6-month period after new-onset heart failure. These findings provide compelling evidence that inflammatory stimuli may be involved in the initiation of heart failure and anaemia among patients with rheumatoid arthritis. There may be a potential role for ESR and possibly other and more specific inflammatory markers, as evaluation tools for heart failure among patients with rheumatoid arthritis. These findings suggest that it is important for clinicians to carefully evaluate cardiovascular status in patients with raised ESR, irrespective of rheumatoid arthritis-associated clinical manifestations.

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Competing interests: None declared.

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