# An ultrasound automated method for non-invasive assessment of carotid artery pulse wave velocity

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Accepted 30 July 2017
Published Online First 2 September 2017

## ABSTRACT

To validate the clinical applicability and feasibility of an automated ultrasound (US) method in measuring the arterial stiffness of patients with chronic inflammatory rheumatic diseases, comparing automated measurements performed by a rheumatologist without experience in vascular sonography with those obtained by a sonographer experienced in vascular US, using a standardized manual method. Twenty subjects affected by different chronic inflammatory rheumatic disorders were consecutively recruited. For each patient, the arterial stiffness of both common carotids was manually calculated. Subsequently, the measure of the pulse wave velocity (PWV) was obtained using an US device called Radio Frequency - Quality Arterial Stiffness (RF-QAS), provided by the same US system (ie, My Lab 70 XVG, Esaote SpA, Genoa, Italy) equipped with a 4–13 MHz linear probe. The reliability comparison between the two US methods was calculated using the intraclass correlation coefficient (ICC). ICC between the values obtained with the two methods for calculating the arterial stiffness resulted 0.789. A significant positive correlation between the two methods was also established with Pearson's ($r=0.62$, $p<0.0001$) and Spearman's analysis ($r=0.66$, $p=0.001$). A significant performance comparison was seen using Bland-Altman plot. The acquisition of the arterial stiffness parameter with the automated method required about 2 min for each patient. Clinical applicability of this US automated method to assess PWV at common carotid level by a rheumatologist is reliable and feasible in comparison with a conventional manual method.

## Significance of this study

### What is already known about this subject?

- In the last decade, growing interest and attention have been given by rheumatologists to the relationship between chronic inflammatory rheumatic diseases and accelerated atherosclerosis.
- Non-invasive methods to recognize endothelial dysfunction, arterial stiffness and intima-media thickness may facilitate the work of an unskilled operator.
- The arterial stiffness can be measured both using the carotid diameter change and distensibility and the pulse wave velocity (PWV).

### What are the new findings?

- Clinical applicability validation of a new ultrasound device for the measurement of carotid PWV.
- An unskilled operator and an expert sonographer, using this device, obtained similar values for vascular stiffness.

### How might these results change the focus of research or clinical practice?

- Patients with chronic inflammatory rheumatic diseases have an increased risk for developing accelerated atherosclerosis and the use of this device, even by an unskilled operator, may favor an early diagnosis of arterial stiffness, reducing the risk of a cerebrovascular accident.

## INTRODUCTION

An increased risk of developing premature cardiovascular disease (CVD) has been observed among patients affected by chronic inflammatory rheumatic diseases with consequent higher morbidity and mortality than in general population.[1–21] For instance, it was asserted that the impact of an inflammatory arthritis on the prevalence and severity of preclinical atherosclerosis may be similar to that observed in patients with well-known conditions associated with CVD, such as diabetes mellitus.[22]

Nowadays, it is clear that chronic inflammation plays a key role in the atherosclerosis pathogenesis, together with traditional risk factors. Nevertheless, a multitude of non-traditional additional factors has been claimed to contribute to the premature CVD, such as immunologic abnormalities, quantity and quality of lipoproteins, presence of platelets bearing complement protein C4d, reduced number and function of endothelial progenitor



**To cite:** Zardi EM, Di Geso L, Afeltra A, *et al. J Investig Med* 2018;**66**:973–979.

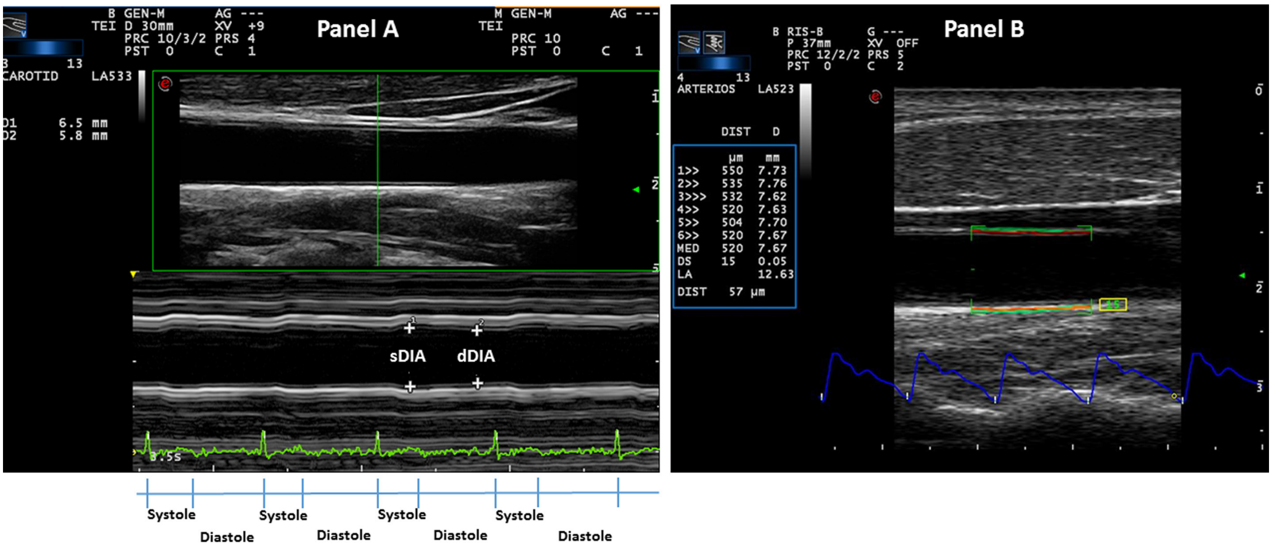


**Figure 1** (A) Measurement of the vascular stiffness adopting the manual method. Longitudinal scan of the common carotid. Carotid vascular wall excursion are measured by means of calipers, according to the diastolic and systolic phase of the cardiac cycle. dDIA, diastolic diameter (5.8 mm); sDIA, systolic diameter (6.5 mm). (B) Measurement of the vascular stiffness adopting the automated method (RF-QAS). Longitudinal scan of the common carotid. The grey box includes the values of the common carotid diameter (in mm) and its distention (in µm) during six consecutive cardiac cycles and the average value of them (MED). DS is the SD (the same value is also reported in the grey box at the common carotid level where it appears in grey color when this value is sufficiently low to provide accurate values). The light grey curve indicates the distention waveform of the common carotid during consecutive cardiac cycles.

cells, apoptosis of endothelial cells, hyperuricemia, hypothyroidism and vitamin D deficiency.[7 23–26]

Detection of signs indicative of atherosclerosis during the early stages could be crucial to plan an effective strategy of treatment. Thus, the knowledge and adoption of non-invasive methods for the assessment of early and subclinical atherosclerosis, such as the assessment of endothelial dysfunction, arterial stiffness and intima-media thickness (IMT), are gaining a growing interest among the rheumatologists.[27–32]

Arterial stiffness describes a reduced expansion and contraction capability of an artery in response to blood pressure changes and its use has entered the European Society of Hypertension/European Society of Cardiology guidelines for the management of hypertension.[33] It can be measured using several parameters, mainly based on the carotid diameter change and distensibility and on measurements of pulse wave velocity (PWV).[32] The acquisition of these parameters is operator-dependent and may be time-consuming.[34 35]

Automated devices for measuring PWV in several vascular districts have been proposed and tested in the past[36]; interestingly, PWV may be performed with accuracy using the cardiovascular magnetic resonance phase contrast imaging through which values of aortic distance can be obtained from two-dimensional and three-dimensional images.[37] However, due to the lack of patients compliance and to excessive running costs, there is nothing routine about its use in the cardiovascular field. Several manual or automated methods measuring carotid distensibility and PWV have been compared and are used to detect arterial stiffness.[32] These PWV methods are characterized by measurements of the pulse transit time between two different locations in aorta or in aorta-femoral artery, carotid-femoral artery and femoral-tibial artery.[38]

The absence of a validated automated method for assessing carotid PWV pushed us to perform this study comparing this method with a standardized manual method for measuring vascular stiffness (VSF).

## Aim of the study

To validate the clinical applicability of an automated ultrasound (US) device, used by a rheumatologist without experience in vascular US, for measuring carotid stiffness through the PWV detection within a box area located in the middle segment of common carotid; to this purpose, this automated method was compared with a manual standardized US method used by an expert vascular sonographer.

## METHODS

### Patients

Twenty patients affected by chronic inflammatory rheumatic diseases were consecutively recruited at Hospital Outpatient Clinic of the Rheumatology Department-Università Politecnica delle Marche.

### Clinical assessment

A complete physical examination was made on each patient, including the measurement of blood pressure in the left arm. This parameter was obtained at rest with the patient in supine position for at least 5 min.

The study was carried out according to the Declaration of Helsinki and local regulations and the institutional ethics committee approved it (Comitato Etico dell'Azienda Sanitaria Unica Regionale di Ancona); informed consent was obtained from each patient.

**Table 1** Demographic and clinical data of the patients

| Characteristic | Mean value±SD (range) |
|---|---|
| Age (years) | 52.0±14 (23–74) |
| Gender: female/male | 11/9 |

Diagnosis, nine rheumatoid arthritis, three psoriatic arthritis, three systemic sclerosis, two undifferentiated chronic arthritis, one antiphospholipid antibody syndrome, one Behçet's disease, one undifferentiated connective tissue disease.

### US assessment

US examinations were conducted by two operators using a My Lab 70 XVG (Esaote SpA, Genoa, Italy) equipped with a linear probe (4–13 MHz) and with RF-QAS software. The two sonographers performed a standardized bilateral US examination placing the linear transducer on the patient's neck in order to visualize both common carotids in longitudinal scan, using the minimal pressure to allow the best visualization without compressing the artery; optimization B-mode settings of gain, depth, focal zone placement to enhance arterial wall structures and image quality were also obtained on each patient. The first sonographer, experienced in vascular US, scanned the middle segment of the common carotid artery, at a plaque-free site, measuring the minimum and maximum arterial diameter by B-mode-guided M-mode US with synchronous ECG and simultaneous blood pressure recording (figure 1A). Since semi-automated computer-assisted edge-detection methods were not applied, special care was taken in order to minimize this limitation; the manual measurement was made in each patient after a precise setting of the near and far wall edges used to determine vessel diameter (blood-intima).

The stiffness parameter (VSF) was calculated applying the equation shown below, according to the cited reference.[39]

VSf = [(sBP/dBP)]/(sDIA–dDIA)/dDIA, where sDIA is systolic carotid diameter; dDIA is diastolic carotid diameter; sBP is systolic blood pressure and dBP is diastolic blood pressure.

The mean value of two measurements from both the right and left side was used for statistical evaluation.

Subsequently, the second operator, a rheumatologist experienced in musculoskeletal US without experience in vascular US, unaware of the first sonographer results, scanned the middle segment of both common carotid arteries; differently from the first sonographer, the second one used an automated device able to calculate PWV [distance (m)/transit time (s)]. This US device (called RF-QAS), automatically obtained PWV measuring the pulse transit time in a single-point of the box area located in the middle segment of the common carotid; its estimate was based on the calculation of beta-stiffness index (figure 1B). The pulse wave velocity was obtained from brachial blood pressure and from the accurate measurements of diameter and change in diameter. The local blood pressure at the site of the US measurement was also taken.

Image data were directly acquired by the US system and then brought off-line for analysis of the arterial pulse wave. Similarly, the mean value of two measurements from the right and left side was used for statistical evaluation.

The time taken for each US assessment was used as a measure to evaluate the feasibility.

**Table 2** Blood pressure, systolic and diastolic diameter of right and left common carotid used for the manual measurement of vascular stiffness

| Systolic blood pressure (mm Hg) | Diastolic blood pressure (mm Hg) | Right common carotid sDIA (mm) | Right common carotid dDIA (mm) | Left common carotid sDIA (mm) | Left common carotid dDIA (mm) |
|---|---|---|---|---|---|
| 150.00 | 100.00 | 6.00 | 5.20 | 6.20 | 5.50 |
| 120.00 | 75.00 | 7.30 | 6.00 | 7.50 | 6.70 |
| 140.00 | 90.00 | 5.60 | 5.40 | 5.60 | 5.20 |
| 135.00 | 80.00 | 4.70 | 4.10 | 6.50 | 6.10 |
| 135.00 | 80.00 | 6.90 | 6.30 | 6.70 | 6.20 |
| 124.00 | 73.00 | 6.30 | 5.50 | 5.50 | 4.80 |
| 123.00 | 82.00 | 5.30 | 4.60 | 5.90 | 5.10 |
| 116.00 | 75.00 | 5.70 | 5.20 | 5.60 | 5.30 |
| 156.00 | 81.00 | 8.40 | 7.90 | 7.30 | 6.80 |
| 128.00 | 75.00 | 5.40 | 4.60 | 6.70 | 5.80 |
| 125.00 | 90.00 | 6.50 | 5.70 | 5.90 | 5.30 |
| 135.00 | 90.00 | 6.30 | 5.70 | 5.60 | 4.80 |
| 140.00 | 90.00 | 6.70 | 6.40 | 6.60 | 6.00 |
| 130.00 | 85.00 | 7.20 | 6.60 | 7.60 | 7.00 |
| 150.00 | 95.00 | 6.30 | 5.90 | 6.80 | 6.60 |
| 150.00 | 80.00 | 7.20 | 6.30 | 6.20 | 5.50 |
| 110.00 | 65.00 | 7.40 | 6.50 | 7.00 | 6.50 |
| 121.00 | 61.00 | 6.70 | 6.20 | 7.20 | 6.20 |
| 115.00 | 75.00 | 7.30 | 6.70 | 7.30 | 6.70 |
| 153.00 | 83.00 | 8.30 | 7.60 | 6.50 | 5.70 |

dDIA, diastolic diameter; sDIA, systolic diameter.

### Statistical analysis

Software MedCalc, V.11.2.0.0 for Windows XP was carried out for statistical analyses. Demographic values (ie, age and disease duration) were expressed as the mean±SD intraclass correlation coefficient (ICC) was adopted for the evaluation of the reliability of the two US techniques. Pearson's rank coefficient and Spearman's rank correlation were also carried out to explore the correlation between the two US methods; $p<0.05$ was considered to be statistically significant. Performance was also assessed by Bland-Altman plot.

## RESULTS

A total of 20 patients was the sample of the study. Table 1 shows demographic and clinical data of the enrolled patients. In table 2, blood pressure values and common carotid diameters are shown.

The measurements of carotid PWV with automated method and of VSF with manual method are shown in table 3.

ICC between data obtained by the two methods for calculating the arterial stiffness was 0.789, suggesting a substantial reliability. PWV and VSF measured with automated and manual method, respectively, were moderately correlated: Pearson's rank correlation coefficient was 0.624 (coefficient of determination ($R^2$)=0.39; $p<0.0001$) (figure 2) and Spearman's rank was 0.66 ($p=0.001$).

The range of Bland-Altman plot obtained from the comparison of the two methods varied from 3.69 to 9.33 (figure 3) showing a significant performance of the automated method.

**Table 3** Pulse wave velocity (PWV) (automated method) and vascular stiffness (VSF) (manual method) parameters

| Automated method Mean PWV (m/s) | Manual method Mean VSF | Patient's age (years) |
|---|---|---|
| 6.37 | 0.39 | 38 |
| 4.90 | 0.30 | 37 |
| 6.56 | 0.75 | 41 |
| 7.76 | 0.69 | 53 |
| 9.17 | 0.54 | 47 |
| 7.93 | 0.51 | 35 |
| 5.14 | 0.37 | 34 |
| 6.64 | 0.97 | 38 |
| 9.17 | 0.57 | 74 |
| 6.89 | 0.33 | 51 |
| 8.24 | 0.44 | 57 |
| 4.88 | 0.39 | 23 |
| 6.27 | 0.43 | 66 |
| 6.54 | 0.36 | 60 |
| 11.16 | 1.20 | 60 |
| 7.14 | 0.49 | 65 |
| 6.91 | 0.52 | 59 |
| 6.42 | 0.32 | 64 |
| 5.16 | 0.38 | 70 |
| 7.44 | 0.40 | 58 |

Mean and maximum times required for the acquisition of sonographic parameters for measuring arterial stiffness were 2.5 and 3.3 min for the conventional method, and 2.1 and 3.4 min for the automated method. Of note, the manual time required an additional time for the calculation of the PWV using the above reported formula.

## DISCUSSION

The present pilot study was mainly made to preliminarily investigate the clinical applicability and feasibility of an automated US method for the measurement of carotid PWV using the standardized manual one as reference method, in assessing carotid stiffness.

Previous studies demonstrated accuracy of automated devices to measure carotid-femoral PWV.[40 41] Manual and automated US methods may equally evaluate vascular stiffness through detection of arterial diameter, distention values and PWV.[32 42–44]

Indeed, the Moens-Korteweg equation links the value of the PWV to the Young's modulus of elasticity, allowing to obtain the value of the PWV starting from the knowledge of the vascular stiffness.[45 46] Conventional B-mode US, despite a much lower spatial and temporal resolution compared with radiofrequency methods, has long been used to measure arterial stiffness and in this study it represents the reference for the time needed and feasibility.

Our study provides evidence data in favour of the fact that the measurement of arterial stiffness obtained by a rheumatologist using this US automated device has clinical applicability and feasibility; indeed, the results obtained from this automated method are not different from those obtained by the manual US method performed by a sonographer experienced in vascular US.

Previously, we already showed an encouraging positive correlation between manual and automated US methods in the measurement of IMT.[47]

The growing interest among rheumatologists for potential cardiovascular comorbidities is proved by the publication of recommendations for the cardiovascular risk management in patients affected by rheumatoid arthritis and other forms of inflammatory arthritis provided by the European League Against Rheumatism Standing Committee for Clinical Affairs.[34]

The use of non-invasive techniques may play a key role in early detection of patients with subclinical atherosclerosis.[48–50] This may lead to different strategies of treatment tailored to the characteristics of the single patient.

The evaluation of vascular stiffness may be particularly useful. There is some evidence that these parameters can be abnormal before an increase of IMT occurs.[22 23]

Arterial stiffness indicates the rigidity of the arterial wall and can be expressed using a wide spectrum of parameters (elastic modulus, distensibility, vascular impedance, etc), obtained with the use of several methods: even

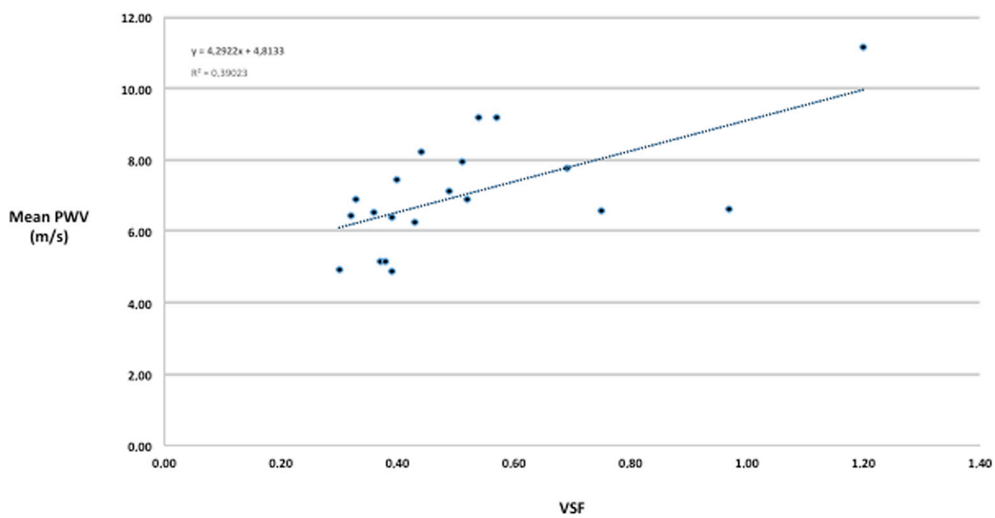


**Figure 2** Pearson's correlation between pulse wave velocity (PWV) parameters and vascular stiffness (VSF) (automated and manual methods, respectively).

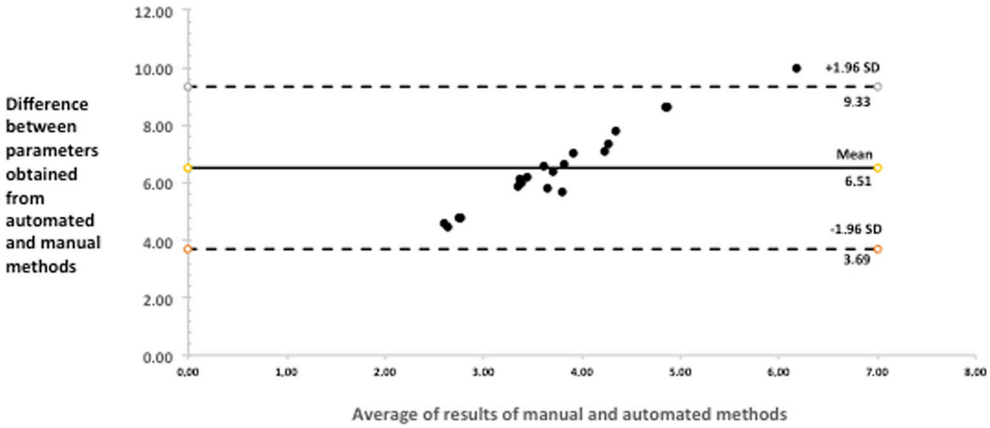


**Figure 3** Bland-Altman plot where differences are presented as units, showing agreement between automated and manual methods. The central horizontal continuous line represents the mean difference in values obtained with the two methods. The dashed horizontal lines below and above the central horizontal line represent the 95% lower and upper limits of agreement (±1.96 SD) (95% limits of agreement: 3.69–9.33).

blood pressure can be considered as a measure of arterial stiffness.[35]

An accurate measurement of vascular stiffness may be challenging. When using PWV that measures the pulse transit time in two locations in different arteries of the body, the presence of convoluted arterial path between the two arteries may be a bias to obtain a correct result.[51] Our automated method, evaluating the time delay of the pulse waveforms for a known distance, reduces or eliminates this bias, since the measurements were performed within the box area located in the middle segment of the common carotid.

There is some concern regarding the reproducibility of US-derived indices, because they are operator-dependent.[35] In particular, as for other US-derived parameters (eg, IMT), the measurement of vascular stiffness may be affected by subjective parameters, such as human eye ability to differentiate the layer interfaces and operator hand ability in positioning electronic calipers.[52 53] Furthermore, the multistep process in acquisition of the parameters needed to calculate the vascular stiffness is time-consuming and may be another source of errors. Direct measurement of vascular stiffness requires the accurate evaluation of arterial diameter changes, and of blood pressure, at the same time. Only the operator's experience and expertise can reduce these limitations and, sometimes, they may not be sufficient.

Taking into account these aspects, we compared an US conventional manual method to calculate the arterial stiffness with an automated one. A positive correlation between the two methods was established. The comparison was made about their performance, the time needed, the feasibility and the clinical applicability. The results of the present study support the use of the automated method, which is reliable compared with the manual one.

Indeed, the calculated mean time to complete the automated examination is in favour of the feasibility of this method. These results, in line with those obtained in assessing the common carotid IMT[47] and with previous studies on US automated methods in patients with cardiovascular risk factors,[43 44] may open the way to a widespread use of US in rheumatology, as a non-invasive method for detecting early signs indicative of atherosclerosis.

### Limitations

This is a preliminary study and the following limitations are to be considered in interpreting these data. First, the small cohort enrolled in the present study. Second, the intraoperator variability was not calculated but the value used for statistical evaluation was the mean of two measurements and the expert operator periodically undergoes training program and his performances are constantly controlled. Third, the manual evaluation of carotid stiffness was made with peripheral pressure.

## CONCLUSIONS

The values of the common carotid stiffness obtained by a rheumatologist using an US automated method were not different from those obtained by an expert vascular sonographer using the conventional manual method. Furthermore, the automated method resulted feasible being time saving compared with the conventional manual one. Even if these preliminary results have to be confirmed in larger cohorts of patients, they are encouraging and demonstrate the clinical applicability of this authomated method in patients with chronic inflammatory rheumatic diseases; this can further stimulate the attention of the rheumatologists in assessing the cardiovascular risk using US.

**Contributors** EMZ and LDG conception and design of research; EMZ and LDG performed sonography; DMZ, CG and AA analyzed data; FS, MC, EF and WG interpreted the results of the work; LDG and MG prepared the figure; EMZ, LDG and EF drafted manuscript; EMZ, AF, DMZ, CG, FS, MC, MG, EF and WG edited and revised manuscript; all authors approved final version of manuscript.

**Competing interests** EMZ, AA, DMZ, CG, FS, MC declare no competing interests. LDG has received speaking fees from Esaote Spa. EF has received speaking fees from AbbVie, UCB Pharma, Bristol-Myers Squibb, Merck Sharp & Dohme. WG has attended advisory board meetings and scientific consultancies and has received speaking fees from General Electric Medical System, Esaote Spa, Bristol-Myers Squibb, Merck Sharp & Dohme, Schering Plough, UCB Pharma, AbbVie, Savient, Pfizer, Menarini, Wyeth and Fidia.

**Ethics approval** Comitato Etico dell'Azienda Sanitaria Unica Regionale di Ancona.

**Provenance and peer review** Not commissioned; externally peer reviewed.



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