Atherosclerosis in Systemic Sclerosis: a Modern Controversy

Stefania L. MAGDA, Raluca I. MINCU, Carmen M. MIHAI, Mircea CINTEZA, Dragos VINEREANU

ABSTRACT

Systemic sclerosis (SSc) is a chronic disease of unknown etiology. The main feature of SSc is microvascular disease, but contemporary studies in the field have confirmed the presence of macrovascular affection. Due to its inflammatory background, and higher cardio- and cerebrovascular death rates, it is presumed that SSc is more frequently associated to accelerated atherosclerosis, similarly to other autoimmune diseases, such as systemic lupus erythematosus or rheumatoid arthritis.

The assessment of subclinical atherosclerosis in patients with SSc through different methods (such as intima media thickness, echo-tracking, wave intensity, pulse wave velocity, flow mediated dilation, nitroglycerin mediated dilation, ankle brachial pressure index or coronary angiotomography) has failed to show concordant results, regardless of the used tool.

In this review, we try to synthesise the most recent evidence about atherosclerotic involvement in SSc, reviewing the association between SSc and risk factors and also performing a summary of studies that compared atherosclerosis in SSc to controls.

Our research leads to the conclusion that in order to elucidate the extent of atherosclerosis and its consequences in SSc, further investigations are needed, combining atherosclerosis assessment tools and larger number of patients.

Keywords: systemic sclerosis, atherosclerosis, evaluation methods, discordance

INTRODUCTION

Atherosclerosis is a chronic, multifactorial process, which develops in medium and large arteries. It represents the main underlying cause of vascular disease in all territories. Atherosclerosis is considered an inflammatory disease, in which, amongst others, monocytes, macrophages and T-cells as well as autoantibodies, autoantigens and cytokines play a role (1-3).

Data from literature show that several autoimmune diseases, such as rheumatoid arthritis (RA) (1,4-8) or systemic lupus erythematosus (SLE) (1,9-14) are frequently associated to accelerated atherosclerosis, and have consequently increased cardiovascular morbidity.

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and mortality. This process is mediated by classical cardiovascular risk factors, as well as by chronic inflammation characteristic to autoimmune disease, and sometimes by certain treatments with atherogenic potential (such as corticosteroids in high doses).

Systemic sclerosis (SSc), chronic disease of unknown origin, characterized by skin fibrosis, microvascular abnormalities and multiple organ involvement, has been shown to present endothelial dysfunction in capillaries and arterioles, interdependently connected to a deficient vasomotor regulation.

During the past 4 decades, there has been a switch between death rates in SSc: those due to disease-related complications have decreased, while death rates due to atherosclerotic cardio- and cerebrovascular disease have gradually increased. Nowadays, cardiovascular related deaths are responsible for a 20–30% mortality rate in SSc patients (15,16).

Studies from the last two decades, investigating subclinical atherosclerosis in SSc produced discordant results. It remains still unclear whether accelerated atherosclerosis occurs in SSc, and if present, it has higher prevalence than in healthy individuals.

In this review, we try to synthetise the most recent evidence about atherosclerotic involvement in SSc, reviewing the association between SSc and risk factors and also performing a summary of studies that compared atherosclerosis in SSc to controls.

**RISK FACTORS FOR ATHEROSCLEROSIS IN SSc**

Similarly to other autoimmune disease, classical cardiovascular risk factors alone do not explain atherosclerotic disease in SSc, being evenly distributed between patients and age and sex-matched healthy individuals (17,18). In 2012, Zeng et al reported higher blood pressure and fasting plasma glucose in SSc patients compared to controls, but, at the same time, similar lipid profile and a lower body mass index in the control group (19). Other studies contradict an increased prevalence of obesity, dislipidemia, diabetes mellitus or hypertension in SSc (20-22).

We have evaluated recent literature regarding the association between risk factors and biological markers of atherosclerosis and we have found several studies reporting in patients with SSc higher levels of: a. LDL cholesterol; b. homocysteine; c. C reactive protein (CRP) (23); d. lipoprotein (a) (24) and e. anti oxidized-LDL antibodies (25) than in age, sex, and classical cardiovascular risk factors matched controls. The studies of Khurma et al (26) and Borba et al (27) have shown f. lower levels of HDL cholesterol in the SSc population compared to healthy controls.

Also, there are data showing that in patients with SSc there is g. an activation of coagulation and a reduction of fibrinolysis (28).

Some authors suggest that in SSc there is a rise of heat shock protein HSP70, associated with pulmonary fibrosis, skin sclerosis, renal vascular damage, oxidative stress, and inflammation (29), but at the other end, there is evidence that HSP70 has protective role against coronary events (30).

**MACROVASCULAR INVOLVEMENT IN SSc**

At cardiovascular level, SSc affects not only the heart and the small vessels, but also determines a series of arterial, macrovascular abnormalities.

Many studies conducted in the nineties have demonstrated the existence of macrovascular peripheral disease in SSc, in the upper (31) as well as in the lower limbs (16,32,33), with a prevalence, estimated clinically and angiographically of 4 to 58% (34).

Atherosclerotic involvement of the renal arteries in SSc has been shown to occur with a prevalence of until 26%, with higher percentage of intimal thickening and luminal occlusion in SSc patients compared to controls, found at autopsy (35,36).

Data about the prevalence of stroke are contradictory: Wan et al have reported in 2001 the occurrence of stroke in 3/119 SSc with a follow up of several years (37). Two other studies, published in 2013, suggest a high risk of stroke in patients with SSc: the first, conducted on 865 individuals with SSc, reported an incidence rate of stroke of 4.8 per 1000 person-years, versus 2.5 per 1000 person years in the comparison cohort (38), while in the second study, on 1238 SSc patients, ischemic stroke had an incidence of 16.5 per 1000 vs 11.5 per 1000 person-years when compared with controls (39). The study of Hettema et al, published in 2008 has not identified any association between SSc and stroke (1).
A frequent arterial modification in SSc, with a prevalence of until 81% is erectile dysfunction (40,41), which has an unclear mechanism, being uncertain if it is due to atherosclerosis or to miointimal proliferation of small arteries and to local fibrosis, without atherosclerosis (16, 42).

EVIDENCE FOR AND AGAINST SUBCLINICAL ATHEROSCLEROSIS IN SYSTEMIC SCLEROSIS – DIFFERENT METHODS OF EVALUATION

Modern studies evaluate the presence of atherosclerosis in SSc through different methods, regarding different arterial territories.

Intima media thickness is measured using B-mode ultrasound performed on the last two centimeters of the common carotid artery, prior to its bifurcation. The far wall IMT, identified as the region between the lumen-intima interface and the media-adventitia interface, is determined usually 1 cm below the bulb of the common carotid artery (43). Contemporary international cardiovascular practice guidelines mention IMT as a reliable index for the evaluation of subclinical atherosclerosis, and as an independent prediction factor for cardiovascular events due to its good correlation to traditional atherosclerosis risk factors. Values over 0.9 mm indicate a high cardiovascular risk (44).

There are many studies which aimed to identify subclinical atherosclerosis in subjects with SSc by using IMT, a non-invasive, cheap, feasible and reproducible tool. Results are distributed evenly between the two possibilities. 8 studies, including 317 patients with SSc and 258 controls showed a higher IMT in SSc than in matched healthy individuals. The studies of Bartoli et al (45), Sherer et al (46) and Kaloudi et al (47) in 2007, and later, in 2011, the study of Piccione et al (48), have also reported IMT values of over 0.9 mm in the SSc population compared to controls (Table 1).

At the other end, 11 studies, including more subjects, 510 SSc patients and 436 controls, contradict the hypothesis of subclinical atherosclerosis demonstrated by IMT in SSc. They report normal values of IMT in SSc patients, without any statistically significant difference compared to controls (Table 2).

Arterial stiffness

There are different methods of assessing arterial stiffness, most of them non-invasive and easily applicable in the clinical setting. Several techniques give information on systemic arterial stiffness (such as pulse wave velocity), while others only give information on local stiffness of the vessel being studied (such as parameters derived from echo-tracking or wave intensity analysis). Arterial stiffness in SSc subjects was measured frequently using pulse wave velocity, but there are also some studies based on echo-tracking and wave intensity analysis at carotid level.

Pulse wave velocity (PWV) is the speed at which the forward pressure wave is transmitted from the heart, through the aorta, into the vascular system. It is calculated by measuring the time needed by the arterial waveform to travel between two points a measured distance apart, and involves taking readings from the two sites simultaneously. Various methods have been used, such as Complior and Sphygmocor for carotid–femoral PWV, Arteriograph for calculating aortic PWV or echo-tracking and wave intensity analysis for local carotid PWV. New guidelines of the European Society of Hypertension recommend measurements of arterial stiffness, quantified through PWV in patients with arterial hypertension. A threshold of carotid–femoral PWV greater than 10 m/s suggests subclinical organ damage (44).

Echo-tracking is an ultrasonographic method for evaluating vascular stiffness, in which a radio frequency (RF) signal is used to provide a high accuracy of 0.01 mm resolution at 10 MHz transmission/reception. Changes in the common carotid artery diameters, before carotid bifurcation, are evaluated by measuring the distance between two tracking gates. The value of blood pressure (systolic and diastolic), is included in the system and the value of arterial stiffness parameters is adjusted by it (49).

Wave intensity is a hemodynamic index, evaluating ventriculo-arterial interaction and can be measured real-time by means of a double beam ultrasound technique, through simultaneous recording of carotid arterial blood flow velocity and diameter (50).

Studies confirming the presence of subclinical atherosclerosis in SSc subjects through echo-tracking, wave intensity analysis and/or local/aortic pulse wave velocity are presented in table 1. They totalize a number of 141 SSc
patients and 131 controls and have shown higher arterial stiffness in SSc (such as \( \beta \) index, augmentation index, local and central PWV) compared to age, sex and cardiovascular risk factors matched controls.

The study of Domsic et al, published in 2014, assessed vascular and endothelial function parameters in 15 diffuse SSc patients and 15 cardiovascular risk factors matched controls, and shows similar aortic PWV in SSc vs. healthy subjects (Table 2).

**Table 1.** Studies demonstrating atherosclerosis in SSc (different methods).

<table>
<thead>
<tr>
<th>Study, year</th>
<th>Number SSc</th>
<th>Number control</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intima media thickness (IMT)</td>
<td></td>
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<tr>
<td>Lekakis et al, 1998(^{62})</td>
<td>12</td>
<td>12</td>
<td>0.83 vs.0.46, ( p=0.002 )</td>
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<tr>
<td>Bartoli et al, 2007(^{45})</td>
<td>35</td>
<td>20</td>
<td>0.93 vs.0.77, ( p&lt;0.005 )</td>
</tr>
<tr>
<td>Sherer et al, 2007(^{46})</td>
<td>44</td>
<td>32</td>
<td>43% din SSc vs. 28% din control IMT&gt;0.9 mm</td>
</tr>
<tr>
<td>Bartoli et al, 2007(^{45})</td>
<td>53</td>
<td>53</td>
<td>0.85 vs.0.68, ( p&lt;0.03 )</td>
</tr>
<tr>
<td>Kaloudi et al, 2007(^{47})</td>
<td>66</td>
<td>20</td>
<td>0.90 vs.0.69, ( p&lt;0.01 )</td>
</tr>
<tr>
<td>Tsfetaki et al, 2010(^{48})</td>
<td>66</td>
<td>51</td>
<td>0.77 vs.0.59, ( p&lt;0.0001 )</td>
</tr>
<tr>
<td>Piccione et al, 2011(^{49})</td>
<td>21</td>
<td>20</td>
<td>1.1 vs. 1.0, ( p = NS )</td>
</tr>
<tr>
<td>Turiel et al, 2013(^{50})</td>
<td>20</td>
<td>20</td>
<td>Right IMT 0.69 vs. 0.55, left IMT 0.71 vs.0.46, for both ( p&lt;0.006 )</td>
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<tr>
<td>Echo-tracking, wave intensity analysis, pulse wave velocity (PWV)</td>
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<tr>
<td>Turiel et al, 2013(^{50})</td>
<td>20</td>
<td>20</td>
<td>Right PWV, 7.8 m/s vs 6.3 m/s; left PWV, 9.3 m/s vs. 6.6 m/s, for both ( p=0.0039 )</td>
</tr>
<tr>
<td>Liu et al, 2011(^{46})</td>
<td>25</td>
<td>25</td>
<td>Brachial-radial PWV 12.1 m/s vs. 8.3 m/s and carotid-radial PWV 7.9 m/s vs. 6.9 m/s, for both ( p&lt;0.05 )</td>
</tr>
<tr>
<td>Piccione et al, 2011(^{48})</td>
<td>21</td>
<td>20</td>
<td>( \beta ) stiffness index, 10.4 vs. 0.95, left ( \beta ) stiffness index, 13.0 vs. 0.89, for both ( p=0.0004 )</td>
</tr>
<tr>
<td>Colaci et al, 2012(^{47})</td>
<td>35</td>
<td>26</td>
<td>Aortic PWV 9.4 m/s vs.7.3 m/s; ( p = 0.002 )</td>
</tr>
<tr>
<td>Ngian et al, 2014(^{48})</td>
<td>40</td>
<td>40</td>
<td>Augmentation index 31% vs.23.8%, ( p&lt;0.001 ), PWV similar</td>
</tr>
<tr>
<td>Carotid ultrasound</td>
<td></td>
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<tr>
<td>Ho et al, 2000(^{52})</td>
<td>52</td>
<td>42</td>
<td>Carotid stenosis in 64% vs.35%</td>
</tr>
<tr>
<td>Frerix et al, 2014(^{45})</td>
<td>90</td>
<td>100 systemic lupus eritematosus patients</td>
<td>Atherosclerotic plaque lesions found frequently with normal IMT in both SSc and SLE</td>
</tr>
<tr>
<td>Schiopu et al, 2014(^{44})</td>
<td>46</td>
<td>46</td>
<td>Similar IMT, more carotid plaque in SSc; 45.6% vs 19.5%, ( p = 0.01 )</td>
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<tr>
<td>Ankle brachial pressure index (ABPI)</td>
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<tr>
<td>Ho et al, 2000(^{52})</td>
<td>54</td>
<td>43</td>
<td>17% vs.0% ABPI&lt;0.9</td>
</tr>
<tr>
<td>Wan et al, 2001(^{52})</td>
<td>119</td>
<td>0</td>
<td>12% ABPI&lt;1</td>
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<tr>
<td>Flow mediated dilation (FMD)</td>
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<tr>
<td>Lekakis et al, 1998(^{46})</td>
<td>12</td>
<td>12</td>
<td>3.6% vs. 11.9%; ( p=0.003 )</td>
</tr>
<tr>
<td>Szucs et al, 2007(^{23})</td>
<td>9</td>
<td>10</td>
<td>2.1% vs. 8.2%; ( p=0.001 )</td>
</tr>
<tr>
<td>Dándrea et al, 2007(^{70})</td>
<td>30</td>
<td>30</td>
<td>4.8% vs.7.8%; ( p&lt;0.001 )</td>
</tr>
<tr>
<td>Bartoli et al, 2007(^{45})</td>
<td>35</td>
<td>20</td>
<td>3.41% vs.7.66%; ( p&lt;0.037 )</td>
</tr>
<tr>
<td>Cypiene et al, 2008(^{71})</td>
<td>17</td>
<td>34</td>
<td>3.7% vs.9.2%; ( p=0.001 )</td>
</tr>
<tr>
<td>Rossi et al, 2010(^{72})</td>
<td>14</td>
<td>14</td>
<td>10.2% vs. 26.6%, ( p&lt;0.001 )</td>
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<tr>
<td>Nytraglicerin mediated dilation (NMD)</td>
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<tr>
<td>Lekakis et al, 1998(^{46})</td>
<td>12</td>
<td>12</td>
<td>14% vs. 23%; ( p=0.003 )</td>
</tr>
<tr>
<td>Lekakis et al, 1998(^{46})</td>
<td>9</td>
<td>10</td>
<td>17.6% vs. 26%; ( p=0.01 )</td>
</tr>
<tr>
<td>Rossi et al, 2010(^{72})</td>
<td>14</td>
<td>14</td>
<td>24.2% vs.33.3%, ( p&lt;0.001 )</td>
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<tr>
<td>Coronary atherosclerosis through multidetector CT</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Khurma et al, 2008(^{26})</td>
<td>17</td>
<td>17</td>
<td>Mean coronary calcium score through multidetector CT 126.6 vs.14.7, ( p=0.03 )</td>
</tr>
<tr>
<td>Mok et al, 2009(^{61})</td>
<td>19</td>
<td>0</td>
<td>31.6% patients with coronary calcifications through coronary multidetector CT</td>
</tr>
</tbody>
</table>

**Carotid ultrasound**

In order to quantify carotid atherosclerosis non-invasively, high-resolution B-mode ultrasound is used as a valid and reproducible method. Both ultrasound and autopsy studies have found that carotid atherosclerosis correlates well with atherosclerosis elsewhere in the circulation and can be used as a marker of general atherosclerosis. An atherosclerotic plaque is usually defined as a localized protrusion of the vessel wall into the lumen (51).
The quantification of atherosclerosis through carotid ultrasound in patients with SSc has also shown discordant results. There are 3 relevant studies confirming carotid atherosclerosis in SSc subjects (Table 1): the first, published in 2000, has included 52 subjects with SSc and 42 controls, and has reported the presence of carotid stenosis in 64% patients with SSc versus only 35% controls (52). The study of Frerix et al, dated 2014, has compared SSc to systemic lupus erythematosus (SLE) patients and has found frequent atherosclerotic plaque lesions with normal IMT in both diseases (53). Schiopu et al, also in 2014, have noticed the same (more carotid plaque, similar IMT) in 46 SSc subjects compared to 46 healthy controls (54).

Contradicting the hypothesis of more prevalent atherosclerosis in SSc, Hettema et al, in 2008, have observed the existence of atherosclerotic plaque in only 3 out of 49 patients with SSc, without statistically significant differences compared to the control group, matched in age, sex and distribution of classical cardiovascular risk factors (Table 2) (1).

### Ankle brachial pressure index

Ankle brachial pressure index is an easy to calculate, non-invasive parameter, represented by ratio of the systolic blood pressure measured at the ankle to that measured at the brachial artery. Initially it was proposed for the noninvasive diagnosis of peripheral artery disease (PAD), but eventually it was shown that the ABPI is an indicator of atherosclerosis, which can serve as a prognostic marker for cardiovascular events in the absence of symptoms of PAD. When the ABPI is used as a prognostic marker of cardiovascular events and mortality, the lower of the ABPIs of the left and right leg should be used.

According to the 2012 AHA Scientific Statement individuals with an ABI <0.90 or >1.40 should be considered at increased risk of cardiovascular events and mortality independently of the presence of symptoms of PAD and other cardiovascular risk factors (Class I; level of evidence A), while subjects with an ABPI between 0.91 and 1.00 are considered “borderline” and need further evaluation (Class IIa; level of evidence A) (55).
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The studies using ABPI in SSC are divided as follows: 2 studies, with 173 SSC patients and 43 controls have reported the alteration of ABPI in SSC (Table 1), while another 3, including 230 SSC patients and 178 controls, demonstrate a similar ABPI in the 2 groups, adjusted to traditional cardiovascular risk (Table 2).

FMD (flow mediated dilation) is a non-invasive technique, developed for assessing endothelial function. It is calculated as the percent of maximal diameter change, usually at the right brachial artery level, observed during reactive hyperemia following deflation of a forearm occluding-cuff. This stimulus provokes the endothelium to release nitric oxide, with subsequent vasodilation that can be expressed as an index of vasomotor function (56). The procedure is complicated and time-consuming, reference values haven’t been established yet, due to the effects of technical aspects of the methodology on absolute values across various studies (57).

There are several studies which aimed to demonstrate, using FMD as a tool, the presence of endothelial dysfunction and atherosclerosis in subjects with SSC. Similarly to previously presented parameters, FMD studies also showed variable results: 7 studies, including 146 SSC patients and 149 controls, have reported statistically significant lower values of FMD in SSC (Table 1), while on the other side, 3 studies, on 95 SSC subjects vs. 86 controls, have found similar FMD in the 2 groups (Table 2).

Nitroglycerin mediated vasodilation (NMD) is a brachial ultrasound test, aimed to assess the arterial vasodilator response to nitroglycerin, which has direct effects on the smooth muscle and consequently produces endothelium independent vasodilation. NMD is expressed as percent of maximal diameter change of the brachial artery, after the sublingual administration of nitroglycerin (25-400 mcg). Lower NMD’s have been noticed in patients with coronary heart disease (58) and coronary heart disease risk factors (59, 60). Similarly to FMD, technical aspects of the method made it difficult to be implemented in current clinical practice.

Studies using NMD as marker of arterial stiffness in patients with SSC are divided as follows: 3 studies with 35 SSC patients and 36 controls have shown statistically significant lower values of NMD in SSC (Table 1), versus 6 studies (the most recent published in 2014), on 174 SSC patients and 179 healthy subjects, showing similar NMD in SSC and controls (Table 2).

Evaluation of coronary artery atherosclerosis

From the several well-known methods for assessing coronary atherosclerosis, such as coronary angiography, coronary intravascular ultrasound, cardiac magnetic resonance imaging or coronary angiotomography, most studies evaluating SSC patients use the latter, due to the fact that it’s non-invasive, fiable and cost-efficient. The studies of Khurma et al (17 SSC subjects vs.17 controls) in 2008 (26), and Mok et al (19 SSC subjects) (61), in 2009, have shown a higher calcium score and a higher prevalence of coronary artery disease in SSC compared to controls (Table 1).

**CONCLUSION**

The main feature of SSC is microvascular disease, but contemporary studies in the field have confirmed the presence of macrovascular affection. Due to its inflammatory background, and higher cardio- and cerebrovascular death rates, it is presumed that SSC is more frequently associated to accelerated atherosclerosis, similarly to other autoimmune diseases, such as systemic lupus erythematosus or rheumatoid arthritis.

The assessment of subclinical atherosclerosis in patients with SSC through different methods has failed to show concordant results, regardless of the used method. Unfortunately, most of the studies have a small number of patients and short follow up. There is high necessity of ample studies, with complex methodology and numerous patients, in order to solve this controversy. Until then, the utility of early and aggressive cardio-vascular preventive treatment remains uncertain.

**Abbreviations**

SSC- Systemic sclerosis  
RA- Rheumatoid arthritis  
SLE- Systemic lupus erythematosus  
CRP- C reactive protein  
HSP- Heat shock protein  
IMT- Intima media thickness  
ABPI- Ankle brachial pressure index  
PWV- Pulse wave velocity  
FMD- Flow mediated dilatation  
NMD- Nitroglycerin mediated dilatation
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REFERENCES


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44. The Task Force for the management of arterial hypertension of the European Society of Hypertension and of the European Society of Cardiology. 2013 ESH/ESC Guidelines for thermannagement of arterial hypertension. European Heart J 2013;34:2159-219


61. Maedica – Aortic pulse wave velocity measurement in systemic sclerosis patients. Reumatismo 2012;64:360-7


64. D’Andrea A, Castronuovo, Cuomo S, et al. – Myocardial and vascular dysfunction in systemic sclerosis: the potential role of noninvasive assessment in asymptomatic patients. Int J Cardiol 2007;121:298-301


