

# Pathogenesis and pathophysiology of aortic valve stenosis in adults

Maria Olszowska

Department of Social Cardiology, Department of Cardiac and Vascular Diseases, Institute of Cardiology, Jagiellonian University, Medical College, Kraków, Poland

## KEY WORDS

calcific aortic stenosis, valvular heart disease

## ABSTRACT

Aortic stenosis (AS) is the most common form of valvular heart disease. AS of degenerative etiology is predominant. It is a persistent disease associated with the activation of 3 processes: lipid accumulation, inflammation, and calcification. Recent studies suggest that valve calcification is an actively regulated process that involves extracellular matrix remodeling, angiogenesis, and inflammation leading to bone formation. Many mechanisms and risk factors involved in the pathogenesis of AS are similar to those observed in atherosclerosis. The knowledge of these processes may play a significant role in adequate prevention and therapy of patients with AS, especially at an early stage.

**Introduction** Left ventricular outflow tract obstruction in adults is most often caused by aortic stenosis (AS). However, obstruction may also occur above the valve (supravalvular stenosis) or below the valve (subvalvular stenosis). AS is the most common heart valve disease in adults. It is the third cause of cardiovascular diseases after arterial hypertension and coronary artery disease. According to the Euro Heart Survey on Valvular Heart Disease, AS is the most common among single native left-sided valve diseases (43.1%). It presents primarily as degenerative AS in adults of advanced age: 2% to 7% of the patients are older than 65 years. Degenerative changes of aortic valve are observed in 20% to 30% of the patients aged more than 65 years and in about 50% of those aged more than 85 years. In 15% of the patients aged less than 65 years, AS develops within 7 years.<sup>1</sup>

**Etiology and pathogenesis** There are 3 primary causes of AS:

- 1 calcific disease of a trileaflet valve
- 2 congenital abnormal valve with calcification (unicuspid or bicuspid)
- 3 rheumatic valve disease.

Rare causes of AS include metabolic syndromes (Fabry disease), nonspecific infectious diseases, lupus erythematosus, Paget disease, hyperuricemia, changes due to medication, and after-

-radiation therapy. Calcific AS develops in patients with end-stage renal disease.

According to the Euro Heart Survey on Valvular Heart Disease, degenerative etiology in AS is predominant (81.9%), followed by rheumatic origin (11.2%); endocarditis accounts for 0.8% of the cases; congenital AS with bicuspid aortic valve occurs in 5.4% of the patients; while other causes are observed in 0.6% of the patients.<sup>1</sup>

**Calcific disease** Normal aortic valve is a structure consisting of several layers: valvular endothelial cells at blood-contacting surface, valvular interstitial cells, and valvular extracellular matrix including collagen, elastin, and amorphous extracellular matrix with glycosaminoglycans. Valvular interstitial cells play a crucial role in valve function. They synthesize extracellular matrix and regulate matrix enzymes, which mediate remodeling of collagen and other matrix components.

Degenerative aortic valve disease is characterized by aortic valve leaflet thickening and calcification with normal function at the beginning. It is called aortic valve sclerosis. Progression of degenerative process is characterized by formation of calcium nodules, including the formation of actual bone and new blood vessels. In end-stage disease, large nodular calcific masses are observed in aortic leaflets. Risk factors and mediators leading to calcific AS are similar for atherosclerosis (older age,

Correspondence to:  
 Maria Olszowska, MD, PhD,  
 Pracownia Kardiologii Społecznej,  
 Klinika Chorób Serca i Naczyń,  
 Instytut Kardiologii, Uniwersytet  
 Jagielloński, Collegium Medicum,  
 ul. Prądnicka 80, Kraków, Poland,  
 phone: +48-12-614-22-87,  
 fax: +48-12-423-43-76, e-mail:  
 molszowska@szpitalp2.krakow.pl  
 Received: November 13, 2011.  
 Revision accepted:  
 November 21, 2011.  
 Conflict of interest: none declared.  
 Pol Arch Med Wewn. 2011;  
 121 (11): 409-413  
 Copyright by Medycyna Praktyczna,  
 Kraków 2011

male sex, hypercholesterolemia, hypertension, smoking, and diabetes).<sup>2</sup>

AS is a persistent disease connected with activation of 3 processes: lipid accumulation, inflammation, and calcification.<sup>3,4</sup> Mechanical stress (e.g., elevated stretch, shear stresses) on aortic valve leads to valvular endothelial dysfunction, followed by deposition of low-density lipoprotein, lipoprotein A, with evidence of lipoprotein oxidation, as well as inflammatory cells with T-lymphocytes and macrophages, which in turn activate valvular interstitial cells resulting in their osteoblastic transformation.<sup>5-11</sup> Cytokines, such as interleukin-1 and tumor necrosis factor- $\alpha$ , are markedly elevated in stenotic valves.<sup>5,6</sup> Recent studies suggest that valve calcification is an actively regulated process, which involves local production of proteins that promote tissue calcification. Several extracellular matrix proteins typically found in bones, for example osteocalcin, osteopontin, osteonectin, bone morphogenetic protein, and metalloproteinases, are present in cardiovascular calcification, including cardiac valves.<sup>12-16</sup> Osteopontin expression has been demonstrated in the mineralization zones of calcified aortic valves obtained during necropsy or surgery.<sup>7</sup> There is a complex interaction between the receptor activator of nuclear factor  $\kappa$ B (RANK) and its ligand (RANKL) and osteoprotegerin in relation to oxidative stress and inflammation.<sup>17,18</sup> This interaction plays an important role in calcification.

Pathological angiogenesis has been observed in calcific AS. Inflammatory mediators cause an increase in vascular endothelial growth factor-A (VEGF-A) and transforming growth factor- $\beta$  (TGF- $\beta$ ).<sup>19-21</sup> VEGF-A and TGF- $\beta$  induce fibrosis and contribute to the progression of calcific AS. TGF- $\beta$ 1 may contribute to the progression of calcific AS by initiating apoptosis-associated mineralization of aortic valve interstitial cells.<sup>22</sup> A number of authors have reported that the activation of angiogenesis in aortic valves occurs in a close association with valvular stenosis. Angiogenesis is involved in remodeling of the aortic valve and formation of calcified valves.<sup>23</sup>

In later stages, the aortic valve shows extensive thickening and matrix remodeling due to increasing cell proliferation, matrix synthesis, and activation of matrix metalloproteinases. They degrade all components of the extracellular matrix including fibrillar collagen.<sup>24</sup> A recent study suggested that metalloproteinases lead not only to matrix degradation, but may also directly promote the proliferation of fibroblasts to cause tissue thickening.<sup>25</sup>

The authors underline the role of the renin-angiotensin system. Angiotensin II leads to oxidative stress and inflammation and contributes to accelerated degeneration of valve leaflets.<sup>26</sup> Angiotensin-converting enzyme (ACE) and angiotensin I have been found to be increased in stenotic valves. A retrospective clinical study suggested that angiotensin type I receptor blockers,

but not ACE inhibitors, slow down calcific process at an early stage of AS.<sup>27</sup>

Oxidative stress has been demonstrated in abnormal endothelial nitric oxide synthase function, which decreases normal physiological levels of nitric oxide along the valve endothelium.<sup>28,29</sup> In calcific AS, the levels of superoxide and hydrogen peroxide are markedly increased.

The presence or progression of calcific AS has been associated with several clinical, genetic, and anatomic factors. Genetic factors play a role in selected patients. Mutations of NOTCH1 are associated with abnormal aortic valve (bicuspid aortic valve with or without aortic aneurysm) and severe aortic calcification.<sup>30</sup> Apolipoprotein E gene polymorphism, interleukin-10, vitamin D receptor, and ACE are factors predisposing to the development of aortic calcification.<sup>31,32</sup>

Increasing age is one of the strongest predictors of cardiovascular calcification. Several regulatory mechanisms decay to exhaustion. Normal endothelial cells are damaged by blood flow; however, the endothelial surface is preserved and encrusted with dividing endothelial cells and circulating progenitor cells. The number of progenitor cells and the ability of endothelial cells to divide decrease during aging. The lack of appropriate repair processes leads to calcific AS.<sup>33,34</sup> The degenerative process spreads from the basal attachment of the leaflets to their edges.

**Congenital abnormal valve** The most frequent cause of congenital AS is bicuspid valve accounting for about 1% to 2% of the cases worldwide. Most frequently, it arises from right coronary and noncoronary leaflet fusion. Patients with bicuspid aortic valve are more often exposed to degenerative changes and more often develop AS and aortic regurgitation. These valve diseases are observed in the 4th or 5th decade of life. They usually occur in isolation but are associated with other abnormalities in 20% of the cases, the most common being coarctation of the aorta or patent ductus arteriosus.<sup>35</sup>

**Rheumatic valve disease** Rheumatic valve disease results from adhesion and fusion of the commissures between the leaflets with small central orifice. Nowadays, rheumatic fever is very rare. Contrary to degenerative aortic valve, rheumatic changes spread from the edges of leaflets and their commissures. Rheumatic disease nearly always affects the mitral valve first, so that rheumatic aortic valve disease is accompanied by rheumatic mitral valve changes.<sup>35</sup>

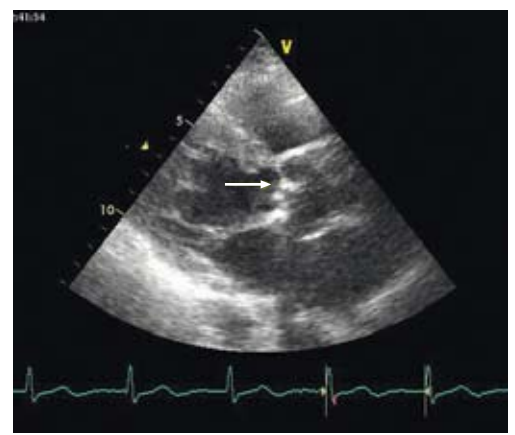
**Pathophysiology** AS, regardless of the etiology, results in the obstruction in the left ventricular emptying. Left ventricular pressure is much greater than aortic pressure during the left ventricular ejection. Normally, the pressure gradient across the aortic valve during ejection is very low (a few mmHg); however, it can become high during stenosis. The high pressure gradient across

the stenotic valve results from increased resistance (related to the narrowing of the valve opening) and turbulence distal to the valve. The magnitude of the pressure gradient is determined by the severity of stenosis and the flow rate across the valve. Obstruction of the left ventricular outflow results in pressure overload, with compensatory hypertrophy of the left ventricle to maintain normal wall stress, preserving systolic function. Narrowing of the aortic orifice to half its size causes little obstruction to the left ventricular outflow and only a small pressure gradient exists across the valve. Reduced valve area results in progressively greater left ventricular pressure overload and the development of left ventricular hypertrophy as a major compensatory mechanism. As hypertrophy continues to develop, the left ventricle becomes less compliant and left ventricular end-diastolic pressure can become elevated even though the ventricular size remains normal. Left ventricular diastolic function is reduced. Excessive hypertrophy may cause decreased coronary blood flow reserve. Long-lasting hypertrophy leads to increased collagen synthesis, interstitial fibrosis, and myocyte degeneration. In some patients, hypertrophy fails to normalize afterload allowing the abnormal afterload to reduce ventricular ejection performance, reducing cardiac output, adding to the heart failure syndrome.<sup>36</sup>

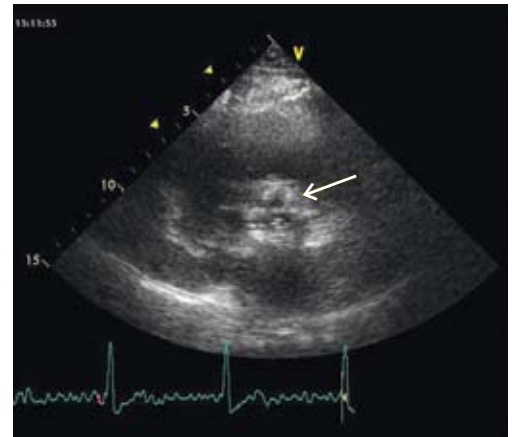
**Classification** The normal aortic valve orifice is 3.0 to 4.0 cm<sup>2</sup>. AS becomes hemodynamically significant when the area is about 1 cm<sup>2</sup>. The European Society of Cardiology categorizes AS severity as mild, moderate, or severe to provide guidance for clinical decision-making. The simplest measure of the extent of stenosis is the forward velocity across the aortic valve. This velocity is about 1.0 m/s in normal state and increases to 2.6 to 2.9 m/s in mild stenosis, 3.0 to 4.0 m/s in moderate stenosis, and more than 4.0 m/s severe stenosis (FIGURES 1, 2, 3).<sup>37</sup>

**Natural history** AS is a chronic progressive disease. For a long time, patients remain asymptomatic despite the obstruction and increased pressure load on the left ventricle. However, the duration of asymptomatic phase varies widely among individuals. A recent study showed that the probability of living 5 years without cardiovascular events is below 50% in asymptomatic patients. Predictors of rapid progression of valve disease include age under 50 years, coronary artery disease, elevated brain natriuretic peptide, large calcific aortic valve, and increased velocity across the aortic valve under 4 m/s. Sudden cardiac death is a frequent cause of death in symptomatic patients but appears to be rare in the asymptomatic group. Clinical symptoms cause deterioration, and some authors have reported symptom-free survival at 2 years ranging from 20% to 50% of patients.

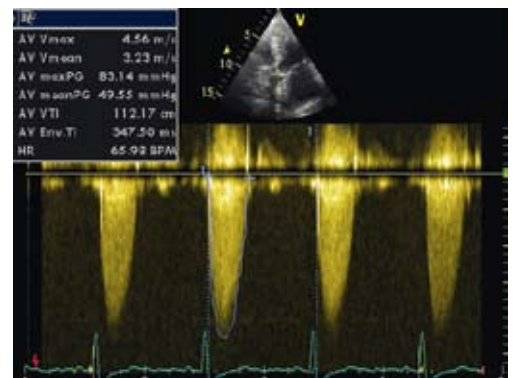
Patients with AS are at increased risk of bleeding. In some patients, it is due to angiodysplasia.



**FIGURE 1** Transthoracic echocardiography, parasternal long-axis view: calcified aortic leaflets (arrow)



**FIGURE 2** Transthoracic echocardiography, parasternal short-axis view: calcified aortic leaflets (arrow)



**FIGURE 3** Transthoracic echocardiography, continuous-wave Doppler of severe aortic stenosis, max pressure gradient 83 mmHg, mean pressure gradient 49 mmHg

The increased risk of bleeding appears to be due to pathological function of platelets and decreased concentration of the von Willebrand factor. This abnormality results from mechanical disruption of von Willebrand multimers during turbulent passage through the narrowed valve. The severity of the von Willebrand factor abnormality is directly related to the severity of AS and transvalvular gradient.<sup>38,39</sup>

**Conclusions** The knowledge of the pathogenesis and mechanisms of developing AS is particularly important. Reduction in risk factors of, for

example, hypercholesterolemia, diabetes, or hypertension, and suppressing the inflammatory process seem to be potential novel strategies for preventing the progression of calcific AS.

## REFERENCES

- 1 Bernard Lungu, Gabriel Baronb, Eric G, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003; 24: 1231-1243.
- 2 Rajamannan NM, Evans FJ, Aikawa E, et al. Calcific aortic valve disease: not simply a degenerative process: a review and agenda for research from the national heart and lung and blood institute aortic stenosis working group executive summary: calcific aortic valve disease - 2011 update. *Circulation*. 2011; 124: 1783-1791.
- 3 Freeman RV, Otto CM. Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. *Circulation*. 2005; 111: 3316-3326.
- 4 Yetkin E, Waltenberger J. Molecular and cellular mechanisms of aortic stenosis. *Int J Cardiol*. 2009; 135: 4-13.
- 5 Kaden JJ, Dempfle CE, Grobholz R, et al. Interleukin-1 beta promotes matrix metalloproteinase expression and cell proliferation in calcific aortic valve stenosis. *Atherosclerosis*. 2003; 170: 205-211.
- 6 Helske S, Kupari M, Lindstedt KA, Kovanen PT. Aortic valve stenosis: an active atheroinflammatory process. *Curr Opin Lipidol*. 2007; 18: 483-491.
- 7 Rajamannan NM. Calcific aortic stenosis: lessons learned from experimental and clinical studies. *Arterioscler Thromb Vasc Biol*. 2009; 29: 162-168.
- 8 Akat K, Borggreffe M, Kaden JJ. Aortic valve calcification: basic science to clinical practice. *Heart*. 2009; 95: 616-623.
- 9 Miller JD, Weiss RM, Heistad DD. Calcific aortic valve stenosis: methods, models, and mechanisms. *Circ Res*. 2011; 108: 1392-1412.
- 10 Kaden JJ, Kiliç R, Sarikoç A, et al. Tumor necrosis factor alpha promotes an osteoblast-like phenotype in human aortic valve myofibroblasts: a potential regulatory mechanism of valvular calcification. *Int J Mol Med*. 2005; 16: 869-872.
- 11 Winchester R, Wiesendanger M, O'Brien W, et al. Circulating activated and effector memory T cells are associated with calcification and clonal expansions in bicuspid and tricuspid valves of calcific aortic stenosis. *J Immunol*. 2011; 187: 1006-1014.
- 12 Liu AC, Joag VR, Gotlieb AI. The emerging role of valve interstitial cell phenotypes in regulating heart valve pathobiology. *Am J Pathol*. 2007; 171: 1407-1418.
- 13 Poggio P, Grau JB, Field BC, et al. Osteopontin controls endothelial cell migration in vitro and in excised human valvular tissue from patients with Calcific Aortic Stenosis and controls. *J Cell Physiol*. 2010 Dec 6. [Epub ahead of print].
- 14 Kaden JJ, Bickelhaupt S, Grobholz R, et al. Expression of bone sialoprotein and bone morphogenetic protein-2 in calcific aortic stenosis. *J Heart Valve Dis*. 2004; 13: 560-566.
- 15 Chen JH, Simmons CA. Cell-matrix interactions in the pathobiology of calcific aortic valve disease: critical roles for matricellular, matricrine, and matrix mechanics cues. *Circ Res*. 2011; 108: 1510-1524.
- 16 Yu PJ, Skolnick A, Ferrari G, et al. Correlation between plasma osteopontin levels and aortic valve calcification: potential insights into the pathogenesis of aortic valve calcification and stenosis. *J Thorac Cardiovasc Surg*. 2009; 138: 196-199.
- 17 Hofbauer LC, Schoppert M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. *JAMA*. 2004; 292: 490-495.
- 18 Lee NK, Choi YG, Baik JY, et al. A crucial role for reactive oxygen species in rankl-induced osteoclast differentiation. *Blood*. 2005; 106: 852-859.
- 19 Ferrara N, Davis-Smyth T. The biology of vascular endothelial growth factor. *Endocr Rev*. 1997; 18: 4-25.
- 20 Waltenberger J. Modulation of growth factor action: implications for the treatment of cardiovascular diseases. *Circulation*. 1997; 96: 4083-4094.
- 21 Chen JH, Chen WL, Sider KL, et al.  $\beta$ -catenin mediates mechanically regulated, transforming growth factor- $\beta$ 1-induced myofibroblast differentiation of aortic valve interstitial cells. *Arterioscler Thromb Vasc Biol*. 2011; 31: 590-597.
- 22 Jian B, Narula N, Li QY, et al. Progression of aortic valve stenosis: TGF-beta1 is present in calcified aortic valve cusps and promotes aortic valve interstitial cell calcification via apoptosis. *Ann Thorac Surg*. 2003; 75: 457-465.
- 23 Soini Y, Salo T, Satta J. Angiogenesis is involved in the pathogenesis of nonrheumatic aortic valve stenosis. *Hum Pathol*. 2003; 34: 756-763.
- 24 Satta J, Oiva J, Salo T, et al. Evidence for an altered balance between matrix metalloproteinase-9 and its inhibitors in calcific aortic stenosis. *Ann Thorac Surg*. 2003; 76: 681-688.
- 25 Kaden JJ, Dempfle CE, Grobholz R, et al. Inflammatory regulation of extracellular matrix remodeling in calcific aortic valve stenosis. *Cardiovasc Pathol*. 2005; 14: 80-87.
- 26 Helske S, Lindstedt KA, Laine M, et al. Induction of local angiotensin II-producing systems in stenotic aortic valves. *J Am Coll Cardiol*. 2004; 44: 1859-1866.
- 27 Rosenhek R, Rader F, Loho N, et al. Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. *Circulation*. 2004; 110: 1291-1295.
- 28 Cagirci G, Cay S, Karakurt O, et al. Paraoxonase activity might be predictive of the severity of aortic valve stenosis. *J Heart Valve Dis*. 2010; 19: 453-458.
- 29 Rajamannan NM. Bicuspid aortic valve disease: the role of oxidative stress in Lrp5 bone formation. *Cardiovasc Pathol*. 2011; 20: 168-176.
- 30 Garg V, Muth AN, Ransom JF, et al. Mutations in NOTCH1 cause aortic valve disease. *Nature*. 2005; 437: 270-274.
- 31 Novaro GM, Sachar R, Pearce GL, et al. Association between apolipoprotein E alleles and calcific valvular heart disease. *Circulation*. 2003; 108: 1804-1808.
- 32 Ortlepp JR, Hoffmann R, Ohme F, et al. The vitamin D receptor genotype predisposes to the development of calcific aortic valve stenosis. *Heart*. 2001; 85: 635-638.
- 33 Singh R, Strom JA, Ondrovic L, et al. Age-related changes in the aortic valve affect leaflet stress distributions: implications for aortic valve degeneration. *J Heart Valve Dis*. 2008; 17: 290-298.
- 34 Matsumoto Y, Adams V, Walther C, et al. Reduced number and function of endothelial progenitor cells in patients with aortic valve stenosis: a novel concept for valvular endothelial cell repair. *Eur Heart J*. 2009; 30: 346-355.
- 35 Vahanian A, Baumgartner H, Bax J, et al. Guidelines on the management of valvular heart disease. The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J* 2007; 28: 230-268.
- 36 Carabello BA, Paulus WJ. Aortic stenosis. *Lancet*. 2009; 373: 956-966.
- 37 Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr*. 2009; 22: 1-23.
- 38 Islam S, Islam E, Cevik C, et al. Aortic stenosis and angiodysplastic gastrointestinal bleeding: Heyde's disease. *Heart Lung*. 2011 Oct 11. [Epub ahead of print].
- 39 Vincentelli A, Susen S, Le Tourneau T, et al. Acquired vonWillebrand syndrome in aortic stenosis. *N Engl J Med*. 2003; 349: 343-349.

# Patogeneza i patofizjologia stenozы aortalnej u dorosłych

Maria Olszowska

Pracownia Kardiologii Społecznej, Klinika Chorób Serca i Naczyń, Instytut Kardiologii, Uniwersytet Jagielloński, Collegium Medicum, Kraków

## SŁOWA KLUCZOWE

stenoza aortalna,  
wady zastawkowe  
serca

## STRESZCZENIE

Zwężenie zastawki aortalnej należy do najczęściej spotykanych wad zastawkowych serca. Obecnie dominuje postać degeneracyjna tej wady. Jest to przewlekła choroba związana z aktywacją 3 głównych procesów: gromadzenia lipidów, nacieczenia zapalnego i kalcyfikacji. Ostatnie badania sugerują, że zwężenie zastawki jest aktywnym procesem, w którym dochodzi do przebudowy w obrębie substancji pozakomórkowej, rozwoju angiogenezy, a także – w wyniku działania mediatorów zapalnych – do kostnienia. Wiele mechanizmów i czynników ryzyka biorących udział w patogenezie zwężenia zastawki aortalnej przypomina rozwój miażdżycy. Znajomość tych procesów może odgrywać ważną rolę w prewencji i zastosowaniu właściwej terapii u chorych, szczególnie w początkowym okresie rozwoju stenozы aortalnej.

Adres do korespondencji:  
dr hab. med. Maria Olszowska,  
Pracownia Kardiologii Społecznej,  
Klinika Chorób Serca i Naczyń,  
Instytut Kardiologii, Uniwersytet  
Jagielloński, Collegium Medicum,  
ul. Prądnicka 80, Kraków,  
tel.: 12-614-22-87, fax: 12-423-43-76,  
e-mail: molszowska@szpitaljp2.  
krakow.pl

Praca wpłynęła: 13.11.2011.

Przyjęta do druku: 21.11.2011.

Nie zgłoszono sprzeczności  
interesów.

Pol Arch Med Wewn. 2011;

121 (11): 409-413

Copyright by Medycyna Praktyczna,

Kraków 2011