Degenerative valve disease and bioprostheses: risk assessment, predictive diagnosis, personalised treatments

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Received: 21 January 2011 / Accepted: 3 March 2011 / Published online: 3 April 2011 © European Association for Predictive, Preventive and Personalised Medicine 2011

Abstract Aortic stenosis (AS) is the most frequent valvular heart disease. Severe AS results in concentric left ventricular hypertrophy, and ultimately, the heart dilates and fails. During a long period of time patients remain asymptomatic. In this period a pathology progression should be monitored and effectively thwarted by targeted measures. A cascade of cellular and molecular events leads to chronic degeneration of aortic valves. There are some molecular attributes characteristic for the process of valvular degeneration with clear functional link between shifted cell-cycle control, calcification and tissue remodelling of aortic valves. Bioactivity of implanted bioprostheses is assumed to result in its dysfunction. Age, gender (females), smoking, Diabetes mellitus, and high cholesterol level dramatically shorten the re-operation time. Therefore, predictive and preventive measures would be highly beneficial, in particular for young female diabetes-predisposed patients. Molecular signature of valvular degeneration is reviewed here with emphases on clinical meaning, risk-assessment, predictive diagnosis, individualised treatments.

Keywords Degenerative valve disease · Bioprostheses · Risk assessment · Diabetes · Predictive diagnosis · Personalised medicine

Degenerative valve disease: clinical aspects and molecular signature

Clinical assessment of aortic stenosis

Aortic stenosis (AS) is the most frequent valvular heart disease. Its prevalence increases with age, and has been reported between 2–4% in a population ≥65 years old [1, 2]. Aortic sclerosis is the precursor of AS and has been found in 25–30% [3]. Calcific AS refers to a narrowing of the aortic valve lumen as a result of the deposition of calcium in the cusps and valve ring. Severe AS results in concentric left ventricular hypertrophy, and ultimately, the heart dilates and fails. During a long period with increasing outflow tract obstruction, which results in increasing left ventricular pressure load, patients remain asymptomatic, acute complications are rare. Therefore, these asymptomatic patients with AS should be monitored closely for the development of symptoms and progression of disease, especially by Doppler-echocardiography, an accurate non-invasive measurement of the stenosis severity (Fig. 1).

However, as soon as symptoms occur, such as exertional dyspnoea, angina, and syncope, outcome becomes poor. Average survival after the onset of symptoms has been reported to be less than 2–3 years [4]. In this situation, valve replacement does not only result in dramatic symptomatic improvement but also in good long term survival [5]. This holds true even for patients with already reduced left ventricular function, as long as functional impairment is, indeed, caused by AS. Thus, there is general
agreement that urgent surgery must be strongly recommended in symptomatic patients [5–7].

A cascade of cellular and molecular events leads to chronic degeneration of aortic valves

Mechanical stress is currently considered as the main cause that triggers degenerative processes. This is accompanied by a thickening of the valve cusps, and remodelling of the left ventricular geometry. Clinical-pathological studies of aortic stenosis have demonstrated an abundant deposition of extracellular matrix (ECM) proteins physiologically present in bones [6], and cuspal calcific deposits associated with mineralisation of devitalised cells [8]. Moreover, bone-marrow derived endothelial progenitor and dendritic cells have been identified in both native degenerative aortic valves and degenerative prostheses; the co-localisation of those cells with inflammatory infiltrates has been demonstrated [9]. A cascade of cellular and molecular events leading to the degeneration of aortic valves is summarised in Fig. 2.

Mineralisation of skeletal and dental tissue is genetically programmed and physiologically well-regulated. In contrast, non-physiological calcification occurs in numerous pathological cardiovascular conditions including atherosclerosis, valvular stenosis, and reperfused ischemic myocardium. This is proposed to be an undesired common feature of degenerative or / and inflammatory tissue changes throughout the body. Pathomechanisms leading to the calcification of heart valves are still largely unknown. Contrary to physiological formation of bones, cuspal calcific deposits in the heart are non-physiological and normally not found in healthy cardiovascular tissues [6, 8, 10–12]. Numerous clinical-pathological studies of calcified valves have demonstrated cuspal calcific deposits tightly associated with mineralisation of devitalised cells, indicating a cascade of (programmed?) molecular events leading to chronic degeneration of myocardial tissue [6]. Tissue homeostasis strictly depends on a balance between cell growth and death. These aspects have been investigated at the level of gene transcription as reported earlier [7]: Table 1 summarises the list of gene products, a corresponding function of which is suppressed specifically in calcified versus non-calcified aortic valves. Among them, 40 proteins essential for energy metabolism are suppressed by aortic calcification. Furthermore, an expression of cytoskeleton-formation as well as ECM-building and tissue remodelling proteins (altogether 23 proteins) is completely suppressed in calcified valvular tissue. The above given protein core is switched off specifically in the case when the balance between cell growth and death in tissue homeostasis is shifted towards cellular death.

Taking these data together, a well-coordinated programme of molecular events targeted in cellular death can be
Table 1 The data represent 63 gene products, the function of which is suppressed in calcified versus non-calcified degenerated aortic valves. There are following functional groups: energy metabolism, proteins responsible for cytoskeleton formation, matrix building, and tissue remodelling [7]

| GeneBank Accession / SwissProt Accession | Gene (protein) name / function                                                                 |
|-------------------------------------------|-----------------------------------------------------------------------------------------------|
| I. Energy metabolism proteins (40 genes)  |                                                                                               |
| S70154 Q16146                             | acetyl-Coenzyme A acetyltransferase 2 (acetoacetyl Coenzyme A thiolase)                       |
| D90228 P24752                             | acetyl-Coenzyme A acetyltransferase 1 (acetoacetyl Coenzyme A thiolase)                       |
| L07033 P35914                             | 3-hydroxymethyl-3-methylglutaryl-Coenzyme A lyase (hydroxymethylglutaricaciduria)             |
| X83618 P54868                             | 3-hydroxy-3-methylglutaryl-Coenzyme A synthase 2 (mitochondrial)                              |
| U62961 P55809                             | 3-oxoacid CoA transferase                                                                     |
| M93107 Q02338                             | 3-hydroxybutyrate dehydrogenase (heart, mitochondrial)                                        |
| X17025 Q13907                             | isopenentenyl-diphosphate delta isomerase                                                      |
| X69141 P37268                             | farnesyl-diphosphate farnesyltransferase                                                      |
| M88468 Q03426                             | mevalonate kinase (mevalonic aciduria)                                                         |
| U49260 P53602                             | mevalonate (diphospho) decarboxylase                                                           |
| D78130 Q14534                             | squalene epoxidase                                                                             |
| D63807 P48449                             | lanoster synthase (2,3-oxidosqualene-lanosterol cyclase)                                       |
| AF034544 O60492                           | 7-dehydrocholesterol reductase                                                                 |
| U60205 Q15800                             | sterol-C4-methyl oxidase-like                                                                  |
| M67466 P14060 Q14545                      | hydroxy-delta-5-steroid dehydrogenase, 3 beta- and steroid delta-isomerase 2                  |
| Y09501 P00387                             | diaphorase (NADH) (cytochrome b-5 reductase)                                                    |
| L21934 P35610                             | sterol O-acyltransferase (acyl-Coenzyme A: cholesterol acyltransferase) 1                      |
| R07932                                    | diacylglycerol O-acyltransferase homolog (mouse)                                                |
| M74047 P31213                             | steroid-5-alpha-reductase, alpha polypeptide 2 (3-oxo-5 alpha-sterol delta 4-dehydrogenase alpha 2) |
| L33179 Q13713 P40394                      | alcohol dehydrogenase 7 (class IV, mu or sigma polypeptide)                                   |
| M68895 P28332                             | alcohol dehydrogenase 6 (class V)                                                              |
| M69367 P30837                             | aldehyde dehydrogenase 1 family, member B1                                                     |
| X05409 P05091 Q03639                      | aldehyde dehydrogenase 2 family (mitochondrial)                                               |
| M73704 Q00169                             | phosphotidylinositol transfer protein                                                          |
| L34081 Q14032                             | bile acid Coenzyme A: amino acid N-acyltransferase (glycine N-choloyltransferase)              |
| U47105 Q15738                             | NAD(P) dependent steroid dehydrogenase-like; H105e3                                           |
| X05130 P30037 Q2079                       | procollagen-proline, 2-oxoglutaruate 4-dioxygenase (proline 4-hydroxylase), beta polypeptide   |
| X83368 P48736                             | phosphoinositide-3-kinase, catalytic, gamma polypeptide                                        |
| S67334 P24338                             | phosphoinositide-3-kinase, catalytic, beta polypeptide                                         |
| X66922 P29218                             | inositol(myo)-1(or 4)-monophosphatase 1                                                         |
| M74161 P32019                             | inositol polyphosphate-5-phosphatase, 75kD                                                    |
| L08488 P49441                             | inositol polyphosphate-1-phosphatase                                                           |
| D16481 P55084                             | hydroxyacyl-Coenzyme A dehydrogenase/3-ketoacyl-Coenzyme A thiolase/enoyl-Coenzyme A hydratase (trifunctional protein, beta subunit) |
postulated considering the pathomechanisms of aortic valve calcification. However, before the end-point is reached when valve tissue is calcified, a long-time chronic process of degeneration occurs in the valve tissue.

Molecular attributes characteristic for the process of valvular degeneration

Altogether 99 genes have been reported earlier with the expression well detectable in calcified aortic valves (Table 2, [7]). Thereby, an expression level of 42 genes remains unaffected by the grade (calcified versus non-calcified) of degeneration severity such as albumin, specific receptors of oxidised low-density lipoprotein, advanced glycosylation end-products and natriuretic-peptide, potassium inwardly-rectifying channel-5, gap-junction proteins, particular integrins, tropins and cadherins [7]. However, the majority (57 proteins) detected was highly affected as a function of the degeneration grade: these are potassium voltage-gated channel-1, cardiotrophin, cardiac myosins, metalloproteinases, endothelins, neuropilins, caveolins, progesterone-, vasopressin-, tumour-necrosis-factor- and adrenergic-receptors. Moreover, whereas well-expressed hepatic lipase has been demonstrated in calcified valves, no traces of its expression could be detected in non-calcified tissue. Those gene products should be taken into account as the stage-specific targets in the cascade of cellular and molecular events that accompany chronic aortic degeneration for a predictive diagnosis and considering individualised therapeutic approaches.
Table 2 Among 99 gene reported to be expressed at the transcriptional level in human calcified degenerated aortic valves, there are 57 gene products listed below the expression level of which is specifically altered as compared to non-calcified valves [7]

| GeneBank Accession / SwissProt Accession | Gene (protein) name / function |
|------------------------------------------|-------------------------------|
| **Increased**                            |                               |
| M65199                                   | P20800 endothelin 2           |
| L25615                                   | P37288 arginine vasopressin receptor 1A |
| Z11687                                   | P30518 arginine vasopressin receptor 2 (nephrogenic diabetes insipidus) |
| D31833                                   | P47901 arginine vasopressin receptor 1B |
| L02911                                   | Q04771 activin A receptor, type I |
| AF015257                                 | Q99527 G protein-coupled receptor 30 |
|                                          | Q99981                         |
|                                          | Q00143                         |
|                                          | Q13631                         |
| L35545                                   | Q14218 protein C receptor, endothelial (EPCR) |
| AJ002962                                 | Q01540 fatty acid binding protein 7, brain |
|                                          | O14951                         |
| M86917                                   | P22059 oxysterol binding protein |
| L06133                                   | Q04656 ATPase, Cu++ transporting, alpha polypeptide (Menkes syndrome) |
| U057043                                  | P54710 FXYD domain-containing ion transport regulator 2 |
| U89364                                   | P51787 potassium voltage-gated channel, KQT-like subfamily, member 1 |
|                                          | Q92960                         |
| M93718                                   | P29474 nitric oxide synthase 3 (endothelial cell) |
| U05291                                   | Q06828 fibromodulin            |
|                                          | Q15333                         |
| S73813                                   | P49961 ectonucleoside triphosphate diphosphohydrolase 1 |
| M90657                                   | P30408 transmembrane 4 superfamily member 1 |
| D26512                                   | P50281 matrix metalloproteinase 14 (membrane-inserted) |
| S39329                                   | P20151 kallikrein 2, prostatic |
| M13143                                   | P03952 kallikrein B, plasma (Fletcher factor) 1 |
| J05262                                   | P14324 farnesyl diphosphate synthase (farnesyl pyrophosphate synthetase, dimethylallyltransferase) |
| X68505                                   | Q02078 MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A) |
|                                          | Q14223                         |
|                                          | Q14224                         |
| X07228                                   | P78529 lipase, hepatic         |
|                                          | P11150                         |
| **Decreased**                            |                               |
| M21121                                   | P13501 small inducible cytokine A5 (RANTES) |
|                                          | O43646                         |
| M31210                                   | P21453 endothelial differentiation, sphingolipid G-protein-coupled receptor, 1 |
| U03865                                   | P35368 adrenergic, alpha-1B-, receptor |
| AF016098                                 | O60462 neuropilin 2            |
| AF016050                                 | O14786 neuropilin 1            |
|                                          | O60461                         |
| U41070                                   | Q15722 leukotriene b4 receptor (chemokine receptor-like 1) |
|                                          | Q13305                         |
|                                          | Q92641                         |
| U01839                                   | Q16570 Duffy blood group       |
|                                          | Q16300                         |
| Y12711                                   | O00264 progesterone receptor membrane component 1 |
| L49399                                   | Q13772 nuclear receptor coactivator 4 |
| J04739                                   | P17213 bactericidal/permeability-increasing protein |
| L27213                                   | P48751 solute carrier family 4, anion exchanger, member 3 |
A functional link between cell cycle-control and calcification of aortic valves: potential diagnostic and prognostic targets

A proper control over cell-cycle progression seems to be a crucial step in the maintenance of a physiological cell population. Although cardiac cells undergo terminal differentiation soon after birth, irreversibly withdrawing from the cell-cycle, growth stimulation induces cell hypertrophy, the first visible step of a developing imbalance in the maintenance of the cardiac cell population. The hypertrophic growth has been shown to be associated with the re-activation of the fetal gene programme in cardiac cells – the key event is the positive regulation of a cell-cycle progression [13–15]. This switch in the programme seems to be crucial for myocardial cell regulation. Such growth stimulation is responsible for the up-regulated activity of cyclin-dependent kinases, CDKs, that consist of a kinase-core and an associated cyclin-subunit acting as the positive regulator [16]. In the matter, different CDK inhibitors keep a negative control over CDK activities. CDK inhibitors are classified on the basis of their sequence homology and substrate specificity. A cardiac helicase CHAMP was described as inhibiting cell proliferation and cardiac hypertrophy [13]. The CHAMP-dependent inhibition of cardiac hypertrophy is accompanied by the strictly programmed up-regulation of the cyclin-dependent protein-kinase inhibitor P21WAF1/CIP1, a 21-kDa protein and member of the CIP/KIP family [16]. Furthermore, the targeted over-expression of P21WAF1/CIP1 prevents cell enlargement and suppresses a specific gene expression of cardiac hypertrophy markers in the cell population in vitro [17] indicating the key role of p21WAF1/CIP1 in the regulation of the hypertrophic response.

The physiological expression of p21WAF1/CIP1 shows a gradual increase during development in both rat and man, becoming maximal in adulthood [18]. A direct link between the Bel-2 dependent down-regulation of p21WAF1/CIP1 and an increased myocyte density in the left ventricle has been shown in experimental work with transgenic mice [19]. These findings are in agreement with those achieved by

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Table 2 (continued)

| GeneBank Accession / SwissProt Accession | Gene (protein) name / function |
|----------------------------------------|--------------------------------|
| M20747 P14672                          | solute carrier family 2 (facilitated glucose transporter), member 4 |
| X52882 P17987 Q15556                   | t-complex 1 |
| Z18951 Q03135                          | caveolin 1, caveola protein, 22kD |
| AF035752 P51636                        | caveolin 2 |
| AF043101 P56539                        | caveolin 3 |
| X60592 P25942                          | tumor necrosis factor receptor superfamily, member 5 |
| AB000895 O15098                        | protocadherin 16 dachsous-like (Drosophila) |
| AF047826 O60574                        | cadherin 19, type 2 |
| AF016272 P75309                        | cadherin 16, KSP-cadherin |
| AB006757 O60247                        | BH-protocadherin (brain-heart) |
| L34954 P36382                          | gap junction protein, alpha 5, 40kD (connexin 40) |
| X87241 Q14517                          | FAT tumor suppressor homolog 1 (Drosophila) |
| M14993 P11171                          | erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked) |
| U49837 P50461                          | cysteine and glycine-rich protein 3 (cardiac LIM protein) |
| U43030 Q16619                          | cardiotrophin 1 |
| M94547 Q01449                          | myosin light chain 2a |
| X84075 Q14896                          | myosin binding protein C, cardiac |
| D00943 P13533 Q13943 Q14906            | myosin, heavy polypeptide 6, cardiac muscle, alpha (cardiomyopathy, hypertrophic 1) |
| M86406 P35609                          | actin, alpha 2 |
| U02031 Q12772                          | sterol regulatory element binding transcription factor 2 |
| L10413 P49354                          | farnesyltransferase, CAAX box, alpha |
| Y08200 Q92696                          | Rab geranylgeranyltransferase, alpha subunit |
| Y12856 O00286                          | protein kinase, AMP-activated, alpha 1 catalytic subunit |
| U16660 Q13011                          | enoyl Coenzyme A hydratase 1, peroxisomal |

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examination of human tissue: the coordinated down-regulation of both G1 and G2 checkpoint genes p21WAF1/CIP1 and 14-3-3-sigma, respectively, correlates well with increasing cardiac cell density and the calcification appearance of aortic valve tissue [20]. The coordinated suppression of checkpoint genes in calcified aortic valves at both transcription (A) and translation (B) levels is represented in Fig. 3 [21]. Both cellularity and number of macrophages are significantly increased in calcified tissue (see Fig. 3c, d, respectively) [21]. According to the monitored CD68 positive signals, macrophages are localised predominantly in the sub-endothelial layer of the valvular fibrosa, whereas 14-3-3-sigma and p21WAF1/CIP1 can be observed in both sub-endothelial layer and valvular interstitium of non-calcified tissue, being mainly co-localised with alpha-actin in the valvular spongiosa and pointing to the target expression in myofibroblasts. There is a growing body of evidence that in response to stimulus/injury the heart valves undergo tissue remodelling including phenotypic modulation and transformation of fibroblast-like into myofibroblast-like cells [22]. Therefore, the target protein expression of 14-3-3-sigma and p21WAF1/CIP1 observed in degenerated valvular tissue, can originate predominantly from myofibroblasts.

Moreover, both the increased cell density and coordinated down-regulation of p21WAF1/CIP1 and 14-3-3-sigma gene expression were found to be characteristic for calcification, in contrast to non-calcified valvular tissue [23]. Therefore, the double-control via both check-point proteins over DNA quality and cell proliferation in valvular cells might be efficient only in non-calcified tissue, whereas in the calcifying one this function is getting suppressed at both G1 and G2 phases of cell-cycle. These findings give further evidence that the efficiency of cell-cycle control in human non-calcified valvular tissue depends not only on the positive/negative CDK regulation in the G1 phase but also on the coordinated regulation of both G1 and G2 dependent checkpoints. Further in vitro experiments on rat cardiac fibroblasts showed that a target up-regulation of inhibitors for G1 dependent CDKs effectively suppresses the DNA synthesis and may decrease a potential risk of cardiovascular diseases [23].

The dissociation of P21WAF1/CIP1 from the CDK complexes correlates well with the activation of CDK2, CDK4, CDK6, and the release from cell-cycle arrest, whereby the number of cardiac cells in S phase rises considerably [24]. Further, in contrast to P16 (a specific inhibitor of CDK4/6), the “universal” CDK inhibitor P21WAF1/CIP1 was shown to be able to block completely an E2F-1-induced G1 exit [25]. However, E1A binding activity to target protein complexes has effects on the cell-cycle progression beyond those produced by E2F-1 alone and can drive S-phase entry that is resistant to P21WAF1/CIP1 [24]. These facts explain the necessity of the coordinated regulation of both G1 and G2 dependent checkpoints, in order to keep the control over the cell population maintenance in cardiac tissue.

Pronounced up-regulation of both genes in non-calcified in contrast to their down-regulation in calcified degenerated valvular tissue indicates the central regulatory role of checkpoint genes in keeping functional the valvular cells.
Blockade of cell-cycle progression results in a prolonged resistance to macrophage invasion and foam cell deposition [26]. Therefore, it is likely that reduced cell-cycle control in valvular tissue leads to the increased macrophage invasion that, in turn, can contribute to non-physiological calcification by both triggered unspecific inflammation and NO-toxicity [27–31]. Taken together, the coordinated activation of both G1 and G2 dependent checkpoint genes may be an attribute of the valvular tissue resistance against the calcification processes. These data should be taken into consideration to design novel therapeutic approaches targeted at pro-calcification mechanisms in the heart.

Risk assessment: factors involved in degenerative valve disease

Recent studies demonstrate an association between atherosclerosis and AS. Traditional cardiovascular risk factors such as lipid disorders, diabetes, arterial hypertension, smoking and male gender [32, 33] are reported to increase also the incidence of AS. At least one of these factors or, more frequently, even the combination of them is usually observed in this cohort of patients [20]. Although advanced age is the main risk factor, worldwide statistics indicate that degenerative aortic valve disease (DAVD) cannot be explained by ageing alone. No longer considered as a natural consequence of ageing, DAVD is the result of actively driven pathological processes including programmed (de)regulation of target genes, metabolic alterations, inflammatory cell infiltration, subcellular disruption, and consequent tissue degeneration, calcification and remodelling [20]. Due to extremely high morbidity and mortality caused by DAVD particularly in Western world, the central question has to be answered: Is an individual predisposition to the disease predictable? From this viewpoint a clear definition of disease specific risk factors is of particular interest.

Although the causal mechanisms are still largely unclear, all molecular as well as cellular processes attributed to DAVD are generally triggered secondarily to a central metabolic failure (diabetes, hypercholesterolemia, hypercalcaemia, leanness), hormonal deregulation (hyperparathyroidism), hypertension, and extreme stress conditions such as tobacco use and environmental stress factors [34–37]. Thus, an inverse relationship was demonstrated between body mass index and DAVD incidence: calcific changes were more frequently observed in lean people even independently of the risk factor of age, and, therefore, cannot be explained by leanness frequently observed in patients with highly advanced age. These facts indicate, further, an association of DAVD with metabolic disorders causing weight loss such as osteoporosis [36].

In diabetes, an increased production of highly aggressive reactive oxygen species (ROS) under hyperglycaemic conditions is considered as the main trigger for severe, chronic complications such as DAVD. Moreover, using advanced biomedical technologies such as clinical proteomics, individual stress reactions and resulting complications can be quite precisely predicted; disease specific molecular markers are already close to their clinical application specifically for the diabetic complication [38]. Similarly to diabetic patients, smokers also suffer from highly increased ROS production leading to enhanced incidence of DAVD, although specific pathomechanisms deserve further clarification. Deregulation of angiotensin-II metabolism and activity of angiotensin-specific receptors is considered to be the key molecule in the pathomechanisms that underlie DAVD in hypertension [37, 39, 40].

Individualised treatment of aortic stenosis and prognosis

A large body of evidence indicates that aortic stenosis is an active process with a distinctive histological appearance, associated clinical factors, and, variable disease progression proposing that this disease may be amenable in terms of the variety of risk factors but also successful treatments by individualised therapeutic approaches to prevent or at least slow down the disease progression [41, 42]. Indeed, several retrospective studies have consistently demonstrated that statin-based treatments are associated with notably lower haemodynamic progression of aortic stenosis [43–46]; however, statins failed in the prospective SALTIRE trial. It was suggested that the beneficial effects by statin are independent of lowering cholesterol impacts [43, 44]. Interestingly, both CRP expression at the valvular tissue level and serum CRP levels were found to be significantly lower under statin-based treatments [47] suggesting its pleiotropic and/or anti-inflammatory properties. As demonstrated by several independent studies (SALTIRE, SEAS, ASTRONOMER) lowering LDL-cholesterol levels do not halt the progression of aortic stenosis in patients with mild to moderate aortic-valve disease [48, 49]. The fact that angiotensin converting enzyme (ACE) and angiotensin II can be found in sclerotic but not in normal aortic valves indicates an important role of the renin-angiotensin system (RAS) in the pathogenesis of AS [50]. Further, the RAS has already been shown to play an important role in atherosclerosis. Consequently, ACE inhibitors slow down the calcium accumulation in aortic valves [43]. However, studies evaluating the effects of ACE inhibitors [46] and angiotensin II type 1 receptor blockers [51] did not find any difference in haemodynamic progression of AS in untreated patients versus patients who were taking these drugs.

In conclusion, it is too early for recommendations in terms of prevention of AS progression by currently applied treatments: further studies are highly desired. The recommended approach to treat the symptomatic, advanced AS remains the prosthetic valve replacement. Moreover, there
is a clear consensus that urgent valve replacement is required for symptomatic AS, while the management of asymptomatic patients with severe AS is still controversially discussed. In the matter, inhibitors of angiotensin-converting enzyme are currently under extensive consideration for their therapeutic application to effectively prevent both hypertension and DAVD [37, 39, 43, 52]. Independently from individual risk factors, the crucial role of metalloproteinases in the central pathomechanisms of the progressive tissue remodelling during the chronic development of DAVD is well recognised [20, 53]. Novel therapeutic interventions consider, therefore, metalloproteinases as the preferred target to delay or even prevent the progression of DAVD [37].

Aortic valve replacement: risk factors, geometry remodelling, complications

Dysfunction and bioactivity of implanted bioprostheses

Twenty percent to thirty percent of implanted bioprostheses show dysfunction after about 10 years post-implantation. Recent reports predict that a greater than 50% incidence of failure will be seen in bioprostheses at 12–15 years [54]. In addition, risk factors of atherosclerosis as well as chronic renal disease and parathyroid tumours might play a substantial role in the degeneration of bioprostheses. In order to improve the quality of life after cardiac valvular surgery, innovative procedures and new generations of prostheses have been developed in the past decade. The most frequently used porcine bioprostheses have been demonstrated to be bioactive in the human organism. DNA and RNA analysis of non-implanted bioprostheses before aortic valve replacement (AVR) has revealed sequences able to hybridise to as many as 112 human genes/transcripts relevant to cardiovascular pathologies [7]. Among those genes there are several overlapping sequences, the expression of which strictly depends on the grade of degeneration: endothelins, sodium / calcium exchangers, potassium voltage-gated channel-1, metalloproteinases, vasopressin- and adrenergic-receptors. Altogether, there are 74 genes found to be specifically altered by expression in human calcified degenerated aortic valves as summarised in Table 3.

Currently, poor information is available concerning the bioactivity of prosthetic material when they are implanted in human valves. In vivo-hybridisation to human nucleic acids might be one feasible reason for several well-known complications triggered by implantation. Thus, worldwide statistics indicate that each kind of AVR is not rarely followed by different metabolic impairments and physiological complications such as progressively abnormal lipid profiles, a non-specific inflammation, blood trauma, haemorheologic changes or severe congestive heart failure and even death during individually long postoperative time [55–61]. After AVR, the wall thickness becomes significantly greater than normal for patients with aortic stenosis, and after 5 years of follow-up the remodelling of the left ventricular geometry is usually observed after AVR [62].

Tissue remodelling of replaced valves: matrix metalloproteinases as biomarkers and potential therapeutic targets

Matrix metalloproteinases (MMPs) play the key role in tissue remodelling under both physiological and pathological conditions. MMPs are produced as zymogens (pro-MMPs) that require proteolytic activation through the elimination of the N-terminal propeptide via membrane type-matrix metalloproteinase (MT-MMPs) activity. Tissue inhibitors of metalloproteinases (TIMPs) act to inhibit metalloproteinase activity by forming a non-covalent irreversible complex with MMPs. A shifted balance in resulting MMPs / TIMPs activity is well documented under stress conditions [58].

However, less is known about a regulation of ECM degrading enzymes in native degenerating aortic valves and in valvular tissue after replacement. Aortic valves tissue is characterised by considerable heterogeneity of the cellular population: endocardial, interstitial, smooth muscle cells as well as fibroblasts and myofibroblasts have been identified in highly sophisticated dynamic structures of cardiac valves [63]. The ECM is thought to be an integral component of this coordinated dynamism [64]. The cores of activated ECM degrading genes differ both qualitatively and quantitatively at each stage of valvular degeneration; after AVR it is regulated in a different manner [36]. The activation grade of the MMP cores is found to be specific for each stages of the valve degeneration: whereas MMP-9 activation differs quantitatively, an activation of MMP-2 was observed solely at the earliest stages of degenerative process [53, 65]. In contrast, the stage of progressive calcification is characterised by dropping of the ECM-degradation potential. Therefore, the highly activated ECM-degradation potential might be considered as an early marker for the triggered degeneration of valvular tissue. Consequently, ex vivo evaluation of the dynamic in the ECM-degradation potential, e.g. measured by comparative zymography in blood samples, seems to be of great prognostic value [66].

This is of note that the set-up of ECM-degrading enzymatic-core changes dramatically after AVR: in contrast to the expression rates well-detectable in native valvular tissue, neither MMP-2 expression nor this of MMP-9 was detected in the replaced tissue. In addition, TIMP-1 was shown to be activated in the valves after replacement. TIMP-1 represents the very last step in the negative
Table 3: DNA and RNA analysis of porcine bioprosthetic material before the aortic valve replacement revealed sequences able to hybridise to 74 human genes/transcripts, the expression of which is altered in human calcified degenerative aortic valves [7]

| GeneBank Accession | SwissProt Accession | Gene (protein) name / function |
|--------------------|---------------------|------------------------------|
| M65199             | P20800              | endothelin 2                 |
| M18185             | P09681              | gastric inhibitory polypeptide |
| AB010710           | P78380              | oxidised low density lipoprotein (lectin-like) receptor 1 |
| L25615             | P37288              | arginine vasopressin receptor 1A |
| Z11687             | P30518              | arginine vasopressin receptor 2 (nephrogenic diabetes insipidus) |
| D31833             | P47901              | arginine vasopressin receptor 1B |
| M31210             | P21453              | endothelial differentiation, sphingolipid G-protein-coupled receptor, 1 |
| U03865             | P35368              | adrenergic, alpha-1B-, receptor |
| L13436             | P20594              | natriuretic peptide receptor B/guanylate cyclase B (atrionatriuretic peptide receptor B) |
| X52282             | P17342              | natriuretic peptide receptor C/guanylate cyclase C (atrionatriuretic peptide receptor C) |
| L02911             | Q04771              | activin A receptor, type I |
| AF015257           | Q99527              | G protein-coupled receptor 30 |
|                    | Q99981              |                              |
|                    | O00143              |                              |
|                    | Q13631              |                              |
| Y10659             | P78552              | interleukin 13 receptor, alpha 1 |
|                    | Q99656              |                              |
| M91211             | Q15109              | advanced glycosylation end product-specific receptor |
|                   | Q15279              |                              |
| L35545             | Q14218              | protein C receptor, endothelial (EPCR) |
| AF016050           | O14786              | neuropilin 1 |
|                   | O06461              |                              |
| U41070             | Q15722              | leukotriene b4 receptor (chemokine receptor-like 1) |
|                   | Q13305              |                              |
|                   | Q92641              |                              |
| AJ002962           | O15540              | fatty acid binding protein 7, brain |
|                   | O14951              |                              |
| M86917             | P22059              | oxysterol binding protein |
| S73197             | P41181              | aquaporin 2 (collecting duct) |
| L27213             | P48751              | solute carrier family 4, anion exchanger, member 3 |
| U89364             | P51787              | potassium voltage-gated channel, KQT-like subfamily, member 1 |
| M20747             | P14672              | solute carrier family 2 (facilitated glucose transporter), member 4 |
| U39195             | P48544              | potassium inwardly-rectifying channel, subfamily J, member 5 |
|                   | Q92807              |                              |
| M91368             | P32418              | solute carrier family 8 (sodium/calcium exchanger), member 1 |
| M23234             | P21439              | ATP-binding cassette, sub-family B (MDR/TAP), member 4 |
| J04456             | P09382              | lectin, galactoside-binding, soluble, 1 (gaelctin 1) |
| M93718             | P29474              | nitric oxide synthase 3 (endothelial cell) |
| X52882             | P17987              | t-complex 1 |
|                   | Q15556              |                              |
| X65784             | Q04762              | cell matrix adhesion regulator |
| U05291             | Q06828              | fibromodulin |
|                   | Q15331              |                              |
| M58664             | P25063              | CD24 antigen (small cell lung carcinoma cluster 4 antigen) |
| S57235             | P34810              | CD68 antigen |
| U85611             | Q99828              | calcium and integrin binding 1 (calmyrin) |
| Z34974             | Q15152              | plakophilin 1 (ectodermal dysplasia/skin fragility syndrome) |
|                   | O00645              |                              |
| GeneBank Accession | SwissProt Accession | Gene (protein) name / function |
|-------------------|---------------------|-----------------------------|
| U49240            | Q92797              | symplekin; Huntingtin interactin protein 1 |
|                   | O00733              |                             |
|                   | O00689              |                             |
| U49240            | O00733              | protocadherin gamma subfamily A, 12 |
| AB000897          | O15100              | cadherin 19, type 2         |
| AF047826          | O00689              | cadherin 17, LI cadherin (liver-intestine) |
| U07969            | Q12864              | cadherin 18, type 2         |
| X52947            | P17302              | gap junction protein, alpha 1, 43kD (connexin 43) |
| M96789            | P35212              | gap junction protein, alpha 4, 37kD (connexin 37) |
| L34954            | P36382              | gap junction protein, alpha 5, 40kD (connexin 40) |
| U03493            | P36383              | gap junction protein, alpha 7, 45kD (connexin 45) |
| U34802            | P48165              | gap junction protein, alpha 8, 50kD (connexin 50) |
| X04325            | P08034              | gap junction protein, beta 1, 32kD (connexin 32, Charcot-Marie-Tooth neuropathy, X-linked) |
| M86849            | P29033              | gap junction protein, beta 2, 26kD (connexin 26) |
| X53416            | P21333              | filamin A, alpha (actin binding protein 280) |
| S73813            | P49961              | ecatonucleoside triphosphate diphosphohydrolase 1 |
| M90657            | P30408              | transmembrane 4 superfamily member 1 |
| X82157            | Q14515              | SPARC-like 1 (mast9, hevin) |
| X87241            | Q14517              | FAT tumor suppressor homolog 1 (Drosophila) |
| Y00796            | P20701              | integrin, alpha L (antigen CD11A (p180), lymphocyte function-associated antigen 1; alpha polypeptide) |
| U81984            | Q99814              | endothelial PAS domain protein 1 |
|                   | Q99630              |                             |
| X07897            | P02590 P04463       | troponin C, slow |
| S64668            | P45379              | troponin T2, cardiac |
|                   | Q99596              |                             |
| M14993            | P11171              | erythrocyte membrane protein band 4.1 (elliptocytosis 1, RH-linked) |
| M95627            | Q13685              | angio-associated, migratory cell protein |
| U49837            | P50461              | cysteine and glycine-rich protein 3 (cardiac LIM protein) |
| U43030            | Q16619              | cardiotoxin 1 |
| M86406            | P35609              | actinin, alpha 2 |
| D26512            | P50281              | matrix metalloproteinase 14 (membrane-inserted) |
| S39329            | P20151              | kallikrein 2, prostatic |
| M13143            | P03952              | kallikrein B, plasma (Fletcher factor) 1 |
| L19684            | P29622              | serine (or cysteine) proteinase inhibitor, clade A (alpha-1 antiproteinase, antitrypsin), member 4 |
| X14329            | P15169              | carboxypeptidase N, polypeptide 1, 50kD |
| M32313            | P18405              | steroid-5-alpha-reductase, alpha polypeptide 1 (3-oxo-5 alpha-steroid delta 4-dehydrogenase alpha 1) |
| U16660            | Q13011              | enoyl Coenzyme A hydratase 1, peroxisomal |
| X07228            | P78529              | lipase, hepatic |
| X22662            | Q13133              | nuclear receptor subfamily 1, group H, member 3 |
| X02750            | Q16001              | protein C (inactivator of coagulation factors Va and VIIa) |
|                   | Q15190              |                             |
|                   | Q15189              |                             |
|                   | P04070              |                             |
| M11723            | P00748              | coagulation factor XII (Hageman factor) |
| X68505            | Q02078              | MADS box transcription enhancer factor 2, polypeptide A (myocyte enhancer factor 2A) |
|                   | Q14223              |                             |
|                   | Q14224              |                             |
regulation of collagenases, stromelysinases, and gelatinases [67, 68] and has been found to be highly expressed in actively resorbing tissue [69]. Also, the key-role is considered for MT1-MMP as a matrix degrading protease, specifically in geometry remodelling after AVR, and opens good perspectives for new targeted therapy approaches, in order to avoid the most common metabolic impairments and clinical complications well-known to be frequently developed by the patients after AVR [53].

Acute aortic insufficiency is a frequent complication after AVR: risk assessment

Besides cases with an acute injury, e.g. aortic dissection and thoracic injury, the main aetiologies of the progressive insufficiency are bioprostesis degeneration and infectious endocarditis [70, 71]. In order to forestall a dysfunction of degenerating bioprostheses, patients without diagnosed risk factors undergo, on average, a re-operation 9–10 years after AVR. Against this, the period of time can be more than halved for patients demonstrating at least two of following risk factors: smoking, Diabetes mellitus, risk by gender (females), high cholesterol level [72]. Furthermore, these risk factors have a higher impact in bioprostheses degeneration for younger patients than for the elderly. Therefore, targeted preventive measures such as proper (pre)diabetes care would be highly beneficial, in particular for subpopulations of young female diabetes-predisposed AVR-patients.

1. patients with DM are at highly increased risk of infections
2. most patients with infectious endocarditis have a history of pre-existing heart valve lesions, which DM patients are significantly predisposed to [73, 76].

Although, both causes are considered as independent risk factors for infectious endocarditis prevalence in DM [75], the synergistic effects can lead to a “vicious circle” in further progression of infectious endocarditis, heart valve lesions/ degeneration and vulnerability of DM patients for infections (see Fig. 4) [21]. Due to a high symptomatic heterogeneity of the diabetic population, the better defined “metabolic syndrome” as a cluster of atherogenic, inflammatory, and atherothrombotic abnormalities linked to abdominal obesity and insulin resistance has been demonstrated to be a

*Fig. 4* Various factors, burden and pathologic processes, contributing to cardiac complications in metabolic syndrome [20]. The crucial role of environmental factors as increasing the overall risk is discussed in our previous reviews [7, 15, 21-38]
particularly strong independent predictor for poor prognosis in both degenerative valve disease and accelerated degeneration of bioprosthetic valves [73, 77]. The pro-atherogenic and pro-inflammatory pathomechanisms have been proposed to underlie the degenerative valvular processes, since statins-based treatment approaches are known to slow down the progression of valvular degeneration [73, 74, 78]. Identification of metabolic syndrome characteristic factors responsible for structural failure of a bioprosthesis is necessary for a development of individualised target-specific therapy approaches avoiding the need for re-operation after AVR. Improved (pre)Diabetes care is currently discussed as being one of the highest priorities of desirable healthcare worldwide [79–82].

Concluding remarks and Outlook

There is a long period of time during which patients predisposed to valvular degeneration remain asymptomatic. In this period a pathology progression can and must be detected followed by targeted therapeutic measures. Molecular attributes characteristic for early stages of valvular degeneration represent reliable predictive biomarkers and – at the same time – the targets for more effective individualised treatment approaches before the pathology is clinically manifested. Risk factors should be considered individually. The characteristic molecular signature is one of them.

Besides several kinds of acute injury (aortic dissection, thoracic injury) the main aetiology of the aortic insufficiency in patients after AVR is a bioprosthesis dysfunction and infectious endocarditis. On average, patients without diagnosed risk factors undergo a re-operation 9–10 years after AVR. Against this, the period of time can be more than halved for patients demonstrating at least two of following risk factors: smoking, Diabetes mellitus, risk by gender (females), high cholesterol levels. Therefore, individualised targeted measures would be highly effective in prevention of AVD and re-operation after AVR. Pathology and stage-specific molecular patterns should be taken into consideration for the reliable prediction, individualised treatment algorithms and correct prognosis.

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