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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Biomarkers of apoptosis, inflammation, and cardiac extracellular matrix remodelling in the prognosis of heart failure

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INTRODUCTION

A biomarker is a biological parameter, which can be considered as an indicator of some physiological or pathological process.

In general, biomarkers can be divided in three groups: laboratory (biochemical, molecular), functional, and genetic biomarkers. This article examines laboratory biomarkers, i.e. those that are measured by laboratory test.

Clinically established biomarkers, such as troponins or B-type natriuretic peptide (BNP), are characterised by very high sensitivity, which is higher than standard functional tests. A concentration of 6 ng/L of troponin I, measured by recent high-sensi-

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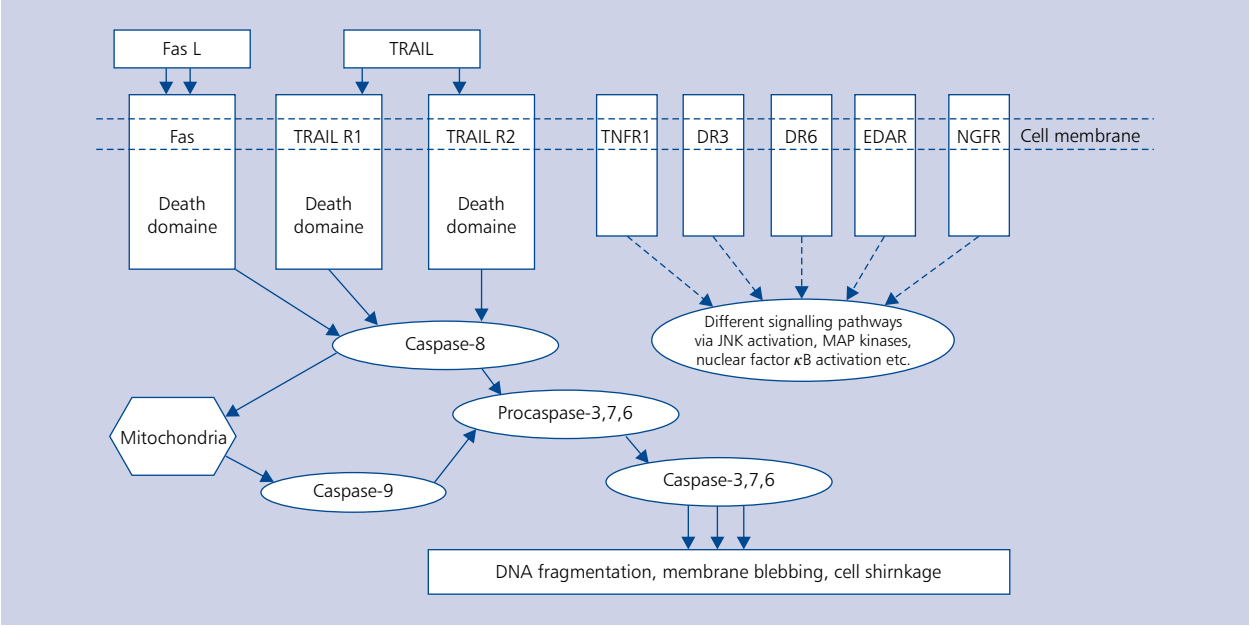

Figure 1. A schema showing the death receptor signalling, with a special focus on Fas and TRAIL receptor signalling pathway. Eight members of the death receptor family have been recognised. The activation of Fas (via Fas ligand) or TRAIL receptors (via TRAIL) leads to activation of caspase-8. Activated caspase-8 directly activates the downstream effector caspases and leads to apoptosis. Furthermore, an additional amplification loop through mitochondria exists, in which caspase-8 releases cytochrome-c from mitochondria, which results in activation of procaspase-9, which in turn cleaves the downstream effector caspases; Fas L — Fas ligand, TRAIL R1 — TRAIL receptor 1; TRAIL R2 — TRAIL receptor 2, TNFR1 — tumour necrosis factor receptor 1; DR3 — death receptor 3; DR 6 — death receptor 6; EDAR — ectodysplasin A receptor; NGFR — nerve growth factor receptor

tivity assays, corresponds to 1 mg of cardiac tissue damage and is detectable in most healthy persons. In patients with heart failure (HF), BNP is a better indicator of clinical severity than assessment of left ventricular (LV) systolic dysfunction using standard echocardiography. Measurements of laboratory biomarkers led to an improvement of diagnostic accuracy and therefore to earlier and better treatment of patients with coronary artery disease (CAD) and HF. However, many issues remain to be solved. More information is required for the prognosis assessment of HF patients. Moreover, the utility of the therapeutic implication of the concentration of laboratory biomarker is limited.

Biomarkers serve to make a diagnosis or prognosis of a disease. In an acute setting, the diagnosis making process can be especially difficult, assessing biomarkers, which are readily available (i.e. biomarkers are deliberate in the blood fast, the test which is used for the assessment of biomarkers is fast, ideally bed-site; in minutes) and have high specificity and sensitivity for the diagnosis (such as troponins, D-dimers).

In the outpatient (follow-up) setting, the diagnosis has already been determined, and the most important and difficult process is the assessment of patient prognosis. The speed of the assessment is no longer the most important feature. Additionally, the specificity requirements are no longer required because the patients serve as their own control, and biomarker levels can be compared to baseline levels for the patients The most important attribute for prognostic biomarkers are the ones associated with a positive and negative prognosis, i.e. to what extent do changes of the concentration of the biomarker reflect a prognosis. The best biomarkers are ones that offer a prognosis and can be used for titration and treatment.

The aim of the article is to review new biomarkers, especially biomarkers that reflect levels of apoptosis.

MARKERS OF CARDIAC NECROSIS AND INJURY

Markers of cardiac necrosis are the oldest used in cardiology. Creatine kinase (CK) was discovered as a marker of myocardial necrosis and was first used in the diagnosis of myocardial infarction (MI) in the 1960s. The more specific CK myocardial band (CK-MB) followed in 1972. The introduction of cardiac troponin (cTn) assays in 1989 was the next major step for very sensitive and specific molecular diagnosis of MI. The recent penetration of high-sensitivity assays has increased the sensitivity to the point of being able to detect 1 mg of necrotic tissue. Since the establishment of troponins as biomarkers, no new, more sensitive, or specific biomarkers of cardiac necrosis or injury have been developed, and troponins have become the gold standard for almost all new biomarkers tested.

MARKERS OF APOPTOSIS

A diagram showing the intracellular signalling pathway of death receptors Fas and TRAIL is shown in Figure 1.

TRAIL

Tumour necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the TNF ligand family, and is able to induce apoptosis *in vitro*. Studies using *in vitro* tumour cell lines have shown that TRAIL binding to TRAIL-receptor 1 or 2 leads to initiation of the caspase cascade that leads to apoptotic cell death [1]. Apoptosis is known to play an important role in LV remodelling. The extent of apoptosis differs from patient to patient and is associated with the level of LV remodelling following MI. Abbate et al. [2] showed that the degree of LV remodelling was directly associated with the extent of apoptosis in subjects who died shorty (10 days) after ST elevation MI. Moreover, *ex vivo* measured apoptotic activity in human sera is higher in patients shorty after an MI and can predict survival in patients with HF.

The effect of TRAIL can also be mediated by reducing pro-inflammatory activity, which is present during acute coronary syndromes (ACS) and is associated with a worse prognosis. In animal models, direct administration of recombinant TRAIL reduced the development of cardiomyopathy in a diabetic mouse model [3]. Matrix metalloproteinase-2 (MMP-2), the level of which is elevated in patients with ACS, can cleave TRAIL *in vitro*, which can be one of the explanations for decreased TRAIL concentrations in patients with acute MI.

TRAIL as a diagnostic marker of CAD

Although the exact molecular mechanism of TRAIL is not well understood, some recent cross-sectional and prospective studies suggest an inverse association between serum TRAIL levels and severity of CAD, development of HF (following acute MI), and with adverse outcomes in patients with HF. Mori et al. [4] measured serum TRAIL levels in 285 patients who underwent coronary angiography. Serum TRAIL levels were significantly lower in patients with CAD than in those without, and were inversely associated with the severity of CAD. Serum TRAIL levels were also significantly associated with the presence of CAD in multivariable logistic regression [4].

Serum levels of soluble TRAIL (but not Fas) are reduced significantly in patients with ACS compared to patients with stable atherosclerotic disease and healthy subjects. Secchierro et al. [5] found significantly lower concentrations of serum TRAIL in patients after MI (measured within 24 h after MI) compared to healthy subjects. Moreover, low TRAIL levels at patient discharge were associated with increased incidence of cardiac death and HF at the 12-month follow-up, even after adjustment for demographic and clinical risk parameters. Low TRAIL levels were associated with a high risk of developing HF following acute MI. Similar findings were recently reported by the lead author of this article, Osmancik et al. [6]. The serum TRAIL concentrations were examined in 295 patients with ACS over a six-month follow-up. Low serum TRAIL concentration was the strongest significant and independent predictor of the composite end-point of (1) death and (2) hospitalisation for HF with an odds ratio of 0.11 (95% confidence interval 0.03–0.45), $p = 0.002$ [6].

Volpato et al. [7] measured serum TRAIL in 1282 older adults; 321 had apparent cardiovascular disease, while the remaining appeared healthy. In the cohort of patients with apparent cardiovascular disease, baseline TRAIL levels were inversely related to all-cause mortality ($p = 0.008$) in a follow-up that lasted six years. As shown recently by Niessner et al. [8], low concentrations of soluble TRAIL (and high concentrations of soluble Fas) were predictors of poor prognosis in patients with chronic HF.

Despite the undetermined effect of TRAIL at the molecular level, in clinical practice its lower concentration seems to be associated with a poor prognosis. It is not known whether low concentrations of TRAIL in patients with worse prognosis reflect deficits of production or increased consumption. However, according to recent clinical trials, higher concentrations of sTRAIL seem to be protective and are associated with better prognosis.

TRAIL as a therapeutic target

No study has been done using TRAIL as a therapeutic target.

Fas

Fas (also known as CD95, DR2, or APO-1) are members of the death receptor family. The mechanisms of Fas-mediated apoptosis have been extensively reviewed in the literature. Briefly, upon ligand binding, there is aggregation of death receptors and their death domains (Fig. 1). This aggregation allows the recruitment and association of adaptor molecules, which have a caspase-binding domain (death effector domain). Caspases are synthesised as inactive procaspases and acquire catalytic activity after cleavage of their prodomain. The activation of Fas leads to cleavage and activation of caspases.

Fas and CAD

In patients with acute MI, several studies failed to find a correlation between Fas levels and the infarct size, the extent of LV dysfunction, or prognosis. However, serum levels of soluble Fas (sFas) are higher in patients compared to healthy controls [9]. Fertin et al. [10] measured Fas concentration in 246 patients, one-month post-MI, and performed several echocardiographic measurements for up to one-year post-MI. LV end-diastolic and end-systolic volumes at three and 12 months post-MI did not differ according to sFas levels, and changes in LV volumes were not associated with sFas levels [10]. Similarly, Nilsson et al. [11] measured Fas concentrations prior to percutaneous coronary intervention (PCI) (for ST elevation MI) and 24 h after the procedure. Infarct size and LV dysfunction were measured five days and four months post-MI. Soluble Fas did not correlate with infarct size or the degree of LV dysfunction [11]. In our cohort of patients with ACS, Fas serum levels were not found to be associated with the prognosis [6].

Table 1. The effect of different cardiovascular diseases on matrix metaloproteinases (MMP) and tissue inhibitor of metaloproteinase (TIMP) activity

Cardiovascular diseases	Alternation of MMP
Heart failure with preserved ejection fraction	↑ CITP, PICP, PIIINP, MMP2, TIMP1
	↔ TIMP1, MMP1
Hypertensive heart failure with left ventricular hypertrophy	↑ TIMP1
	↔ PIIINP
Myocardial infarction	Differs in acute, subacute, and chronic phase.
	Acutely: ↑ MMP14, TIMP1, MMP2, ↓ MMP1
	Late phase: ↑ MMP2, MMP9, CITP, TIMP1, TIMP2, TIMP4, MMP3, MMP8
Ischaemic cardiomyopathy (in relation to prognosis)	↑ MMP9, TIMP1, MMP3, MMP2
	↓ TIMP3, TIMP4
	↔ TIMP2
Dilated cardiomyopathy	↓ TIMP1, MMP1
	↑ TIMP2, MMP2, MMP3, MMP9

CITP — carboxy-terminal telopeptide of collagen type I; PICP — procollagen type I carboxy-terminal propeptide; PIIINP — procollagen type III amino-terminal pro-peptide

Fas and heart failure

Very promising results have come from studies studying sFas levels in patients with chronic HF. Kawakami et al. [12] described higher concentrations of sFas in patients with chronic HF due to dilated cardiomyopathy compared to healthy controls. Niessner et al. [8] investigated the prognostic role of Fas in patients with decompensated HF. They measured Fas concentrations in 351 patients with advanced decompensated HF. During a 16-month follow-up, sFas concentrations were associated with significantly higher risk of death or readmission for decompensated HF [8]. Similarly, Tsutamoto et al. [13] measured sFas in 96 patients with chronic but compensated HF (most due to dilated cardiomyopathy) and followed them for three years. Higher baseline Fas concentration was an independent marker of mortality, which was independent of baseline concentration of BNP [13]. Thus, despite the disappointment in the usefulness of Fas in prognosis stratification of patients following MI, there are promising results in patients with chronic HF, especially HF caused by dilated cardiomyopathy.

MARKERS OF EXTRACELLULAR MATRIX MODELLING

The extracellular matrix of the heart plays an important role in the pathophysiology of HF progression. The extracellular matrix is subject to continuous reconstruction and involves collagen synthesis, and degradation of collagen and other matrix proteins by MMPs, which is regulated by tissue inhibitors of metalloproteinases (TIMPs). Myocardial remodelling, particularly changes in the structure and composition of the extracellular matrix, result in abnormal LV filling and a stiff, noncompliant LV, which increases diastolic pressure. Extracellular matrix remodelling is of great importance especially in the development of HF with preserved ejection fraction (EF), but also in the progression of systolic HF.

MMPs

There are many biomarkers that reflect changes in extracellular matrix homeostasis such as: (1) the rate of collagen synthesis (collagen I N-terminal propeptides [PINP] and collagen III N-terminal propeptide [PIIINP]), (2) processing and post-translational modification (osteopontin), and (3) degradation of MMPs and their tissue inhibitors (TIMPs). MMPs have been classified into four groups based on substrate specificity: i) gelatinases (MMP-2, MMP-9), ii) collagenases (MMP-1, MMP-8), iii) stromelysin (MMP-3), and iv) matrilysin (MMP-7). Changes in MMP and TIMP concentrations in several cardiovascular disorders are shown in Table 1.

The role of MMPs in the pathophysiology of the cardiac healing process

In patients with acute MI, remodelling of the infarct zone is a process in which collagen turnover plays an important role. In the early period after MI, MMPs play a role in both the healing process and the adverse remodelling of the infarcted ventricle [14, 15]. MMP levels increase early post-AMI in all MI patients. A number of different MMPs released from inflammatory cells and myofibroblast allow nascent scar formation. However, continuous and persistent release of MMPs beyond this initial healing process results in extracorporeal matrix instability, particularly in the infarct-viable border zone, and during remodelling of the extracellular matrix in remote healthy myocardium [16].

The activation of MMPs during acute MI and following the healing process is very complex. MMPs are not a single

enzyme, but instead, a family of enzymes. Different MMPs play diverse roles relative to an MI, with a different spatial and temporal relevance, i.e. the role of different MMPs differs in the infarct area relative to remote healthy myocardium and at different time-points after MI, which complicates prognostic stratification based on concentrations of MMPs.

Several studies have looked at the spatiotemporal relevance of different MMPs. For example, MMP-1 is significantly reduced within the MI area, whereas others, such as MMP-14, increase in the early phase in all regions [14]. MMP-14 induction is elevated in both border and infarcted regions, and subsequent activation of soluble MMPs, such as MMP-2 and MMP-9, which were found elevated in the long-term phase post MI, could lead to continued instability in the extracorporeal matrix and expansion of the MI area and variable remodelling of remote myocardium [17]. Animal experimental studies, as well as clinical studies, have found that concentrations of different MMPs varied relative to the length of the post-MI interval. Eckart et al. [18] described the time-course of MMP-1, MMP-2, and MMP-9 in patients after PCI and compared the concentrations between patients with acute MI and those with stable CAD. The concentrations of those three markers showed different kinetics, and there were significant differences between patients with ACS and those without [18]. Results from the study confirmed the results of *in vitro* studies and indicated that MMP subtypes may play various roles in ACS as well as response to revascularisation.

MMPs as a prognostic marker in patients with CAD

Several markers for the MMP family have been tested as prognostic markers in patients with acute MI in the clinical setting. Soejima et al. [19] analysed the concentration of MMP-1 for up to four weeks post MI. MMP-1 concentrations were significantly higher seven days and two weeks post MI relative to admission; additionally, seven days and two weeks were also negatively correlated with the LV EF. The concentration of MMP-9 correlated with echocardiographic parameters of LV dysfunction and remodelling after acute MI.

Manhenke et al. [20] found that higher concentrations of MMP-1 and TIMP-1, measured three days post MI, were associated with higher one-year mortality. In a cohort of 382 acute MI patients, plasma concentration of MMP-3 at discharge correlated significantly with the degree of LV dysfunction and clinical prognosis. Dhillon et al. [21] analysed the concentration of MMP-2 in 1024 patients four days post-acute MI; the group was followed for more than one year. The concentrations of MMP-2 (but not of MMP-3 or MMP-9) represented an independent predictor of death during follow-up [21]. Although *in vitro* studies of MMP-14 have suggested that it plays an important role in myocardial expansion and remote remodelling, as of the date of this manuscript's writing, no human studies have been published regarding the prognostic importance of MMP-14 in patients with acute MI. In patients with acute MI, higher levels of TIMP-1 and MMP-9, measured during the index hospitalisation, correlated with changes in EF during follow-up and were associated with the clinical prognosis of the patients [22]. Plasma levels of MMP-2 determined within the days following MI were able to predict mortality during a two-year follow-up [21].

However, because of the complex interplay between single MMPs during scar development and ventricle remodelling, determining which MMP is the best marker for MI patient prognosis is impossible.

MMPs and dilated cardiomyopathy

Not only during the MI healing process, but also during dilated cardiomyopathy, MMPs seem to be of great importance. Serum concentration as well as tissue activity of MMP-9 was found to be higher in patients with dilated cardiomyopathy (DCMP) compared to controls [23]. Serum concentration of MMP-9, in patients with DCMP, was associated with poor survival [24].

The spectrum and particular forms of MMPs seem to be different in HF patients with ischaemic and non-ischaemic aetiology. Reinhardt et al. [23] found similar levels and tissue activities of MMP-9 in patients with ischaemic and non-ischaemic HF. On the other hand, Tziakas et al. [25] found that MMP-2 and MMP-3 levels were higher in patients with DCMP compared with ischaemic cardiomyopathy; serum TIMP-1 levels were lower in patients with DCMP than in those with ischaemic cardiomyopathy [25].

Most studies with MMPs have been positive in terms of confirmation of MMPs as predictors of poor survival. However, it is not known which MMP is the best marker for particular (ischaemic, non-ischaemic) patients. Moreover, most studies have not followed the recommendations of the multi-marker model with all old (clinical and laboratory) markers together with MMPs as a new marker. For example, few studies have included BNP or NT-proBNP biomarkers and calculated using the multi-marker model. Thus, often we do not know whether the prognostic information obtained from MMP levels is additive.

MARKERS OF INFLAMMATORY PROCESSES

The clinical syndrome of HF is characterised by a systemic inflammatory response that contributes to compromised circulation and heart damage, which can lead to worsening HF [26]. Therefore, markers of inflammation are often elevated in patients with decompensated HF and not surprisingly serve as useful prognostic markers (Fig. 2).

Galectin-3

Galectin-3 (Gal-3) represents a link between fibrosis and inflammation. It is a member of the evolutionarily conserved lectin family, is a β-galactoside binding protein, and is involved

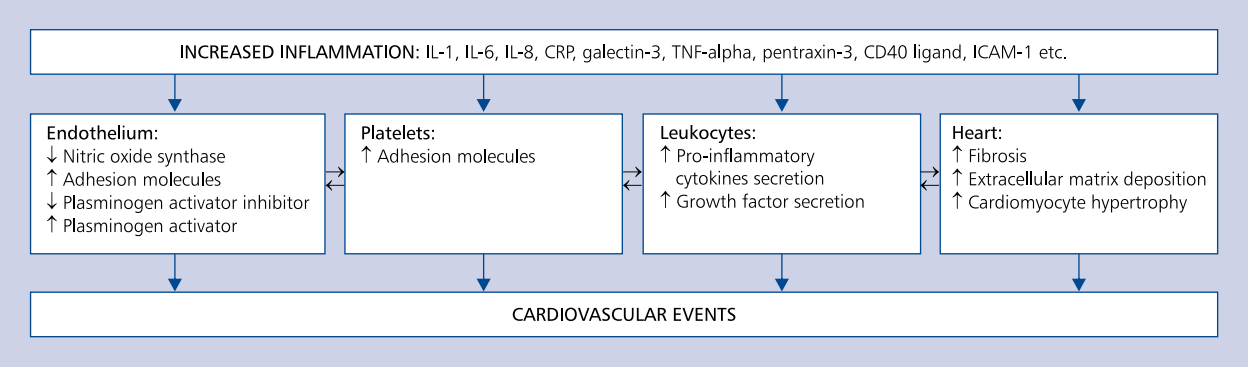

Figure 2. A vicious cycle of the effect of transforming growth factor-β1 (TGF-β1) in heart failure. Production of TGF-β1 is activated upon pressure overload, acute ischaemia, norepinephrine or angiotensin II stimulation. TGF-β1 is produced by cardiomyocytes and fibroblasts in the heart, and increased production of TGF-β1 leads to increased fibrosis and cardiomyocyte hypertrophy. This, in turn, worsens left ventricular function and worsens heart failure; IL — interleukin, CRP — C-reactive protein; TNF — tumour necrosis factor; ICAM — intercellular adhesion molecule

in several biological processes such as cell adhesion, cell activation, chemo-attraction, cell growth and differentiation, the cell cycle, and apoptosis. It is expressed in various locations (in the nucleus, cytoplasm, mitochondrion, cell surface, and extracellular space) and by various cells, mainly macrophages, eosinophils, and mast cells — these immune cells are recruited to the myocardium as part of the inflammatory response, and by activating fibroblasts and myofibroblasts they stimulate myofibroblast proliferation, fibrogenesis, tissue repair, and ventricular remodelling. In animal studies, pericardial infusion of Gal-3 in rats induced increased collagen expression and LV remodelling, and led to overt HF.

Gal-3 in a general population without overt HF

In the general population without overt HF, higher concentrations of Gal-3 have been associated with age, sex, diabetes, hypertension, hypercholesterolaemia, changes in body mass index, decreased renal function, and smoking [27]. Gal-3 as a prognostic marker, in a population without overt HF, was tested in two large observational studies: the Prevention of REnal and Vascular ENd-stage Disease (PREVEND) study and the Framingham Offspring Cohort study [27, 28]. In the PREVEND study, plasma Gal-3 was measured in 7968 subjects with a follow-up of 10 years. Plasma Gal-3 concentration was correlated, especially, with age and female gender. After correction for classical cardiovascular risk factors, plasma Gal-3 concentrations were independently associated with cardiovascular and all-cause mortality [27]. In the Framingham Offspring Cohort study, Gal-3 concentrations were measured in 3353 participants, and its association with new HF was assessed. Higher concentrations of Gal-3 were associated with higher risk of incident HF with a hazard ratio of 1.29 per 1 standard deviation increase and remained significant after adjustment for important clinical variables and BNP concentration. The Gal-3 concentration was also associated with all-cause mortality.

Gal-3 and HF diagnosis and prognosis

Galectin-3 concentration as a prognostic marker was tested in several studies with *de novo* HF patients and with patients with acute decompensation of chronic HF. An elevated level of Gal-3 was found to be significantly associated with higher risk of death in acute decompensated HF and chronic HF populations. In the PRIDE study, Gal-3 (and NT-proBNP) concentrations was measured in 599 patients with dyspnoea in the Emergency Department, of which 35% were diagnosed with HF. The concentration of NT-proBNP was better than Gal-3 for the diagnosis of acute HF. However, elevated levels of Gal-3 were better predictors of 60-day mortality than NT-proBNP in a multivariate regression. The combination of NT-proBNP and Gal3-3 had better predictive power than either of the biomarkers alone [29]. Similarly, Shah et al. [30] evaluated 115 patients with acute dyspnoea and found that patients in the upper quartile of Gal-3 concentration had 63% four-year mortality, compared with 37% mortality in the lowest quartile patients.

Lok et al. [31] analysed the prognostic value of Gal-3 concentration in HF patients in the Deventer-Alkmaar HF (DEAL-HF) study. Baseline samples of Gal-3 were available in 232 patients, with a mean EF of 30%; 96% were in New York Heart Association (NYHA) class III, and the mean follow-up was four years. The baseline concentration of Gal-3 predicted a significantly worse prognosis and was associated with higher risk of a death event even after adjustment for all other known risk factors, including NT-proBNP. The Gal-3 concentration in patients with chronic HF diagnosis was evaluated in the HF-ACTION study [32]. The HF-ACTION study was a randomised study of exercise training in patients with chronic systolic HF; Gal-3 was assessed at baseline in a cohort of 895 participants. In an unadjusted analysis, there was a significant association between elevated Gal-3 levels and hospitalisation-free survival; however, in a multivariate model, and after inclusion of NT-proBNP, the prognostic impact of

Gal-3 was the same. Similarly, Gal-3 levels as a prognosis marker in HF was analysed in participants of a coordinated study evaluating outcomes of the Advising and Counselling in Heart Failure (COACH) trial [33]. Gal-3 concentrations were measured at baseline and at the six-month follow-up and were available for 592 study participants. In the univariate analysis, baseline Gal-3 concentrations were strongly associated with the risk of death or HF re-hospitalisation. The statistical significance of Gal-3 was maintained after adjusting for age, sex, and NT-proBNP; however, this statistical significance was lost after adjusting for EF. Different findings were found between patients with HF and preserved EF vs. decreased EF. Although absolute baseline levels of Gal-3 did not differ between the two subgroups, an increase in Gal-3 levels represented a strong significant incremental risk for death or HF in patients with HF with preserved EF vs. patients with HF and decreased EF [33]. The role of Gal-3 in patients with HF and preserved LV EF seems to be stronger than in patients with reduced LV EF. In a study by Carrasco-Sanchez et al. [34], Gal-3 was measured in 419 patients with HF and only slightly decreased EF (inclusion criterion: EF had to be more than 45%). During the follow-up, 219 patients underwent re-hospitalisation or died. Baseline Gal-3 was an independent risk factor for death or HF re-hospitalisation after adjustment for all other known risk factors including NT-proBNP, with a hazard ratio of 1.4.

Serial Gal-3 measurements seem to add incremental prognostic information and are better at predicting remodelling of LV. Serial Gal-3 concentrations were also assessed in the analysis of the Valsartan Heart Failure Trial (Val-HEFT) [35]. Gal-3 concentrations were measured at baseline and after four and 12 months, in 1650 study participants. Although in the univariate analysis baseline Gal-3 levels were associated with poor HF prognoses, this association was lost after including 23 other prognostic variables. However, when changes in Gal-3 over time were analysed, an increase in Gal-3 between baseline and four months were independently associated with all-cause mortality and hospitalisation for HF after correction for all known other risk factors. Treatment with valsartan was successful, especially in patients with lower Gal-3 values; patients with high values of Gal-3 had substantially lower responses to valsartan treatment.

Gal-3 and CAD

Recently, a prognostic role for Gal-3 in ACS and CAD was identified. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE IT-TIMI 22) study, patients with ACS were randomised to standard or intensive statin therapy arms [36]. In a nested case-control sub-analysis, 100 cases with hospitalisation for HF from the PROVE IT population were compared to cross-matched controls without HF hospitalisation. Patients who developed HF had a higher Gal-3 baseline concentration, and the association between Gal-3 and HF remained after adjustment for other clinical risk factors in the multivariate analysis [37]. Patients with Gal-3 baselines above the median were twice as likely to develop HF, and Gal-3 showed a graded relationship with regard to the risk of HF: those patients in the highest Gal-3 quartile had 3.6 times higher odds of developing HF. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study, the addition of statin was tested in a prospective, randomised manner in patients with chronic congestive ischaemic HF [38]. Compared to many previous trials, the goal population of the CORONA study was not patients with ACS or CAD at all, but with HF. Statin treatment was not associated with a better prognosis. However, when the population of the CORONA study was divided according to the concentration of Gal-3, patients with lower Gal-3 (below 19.0 ng/mL) and those assigned to rosuvastatin had a lower mortality and HF hospitalisation compared with placebo. High concentrations of Gal-3 indicated patients with severe, very advanced HF, probably with irreversible fibrosis.

Gal-3 as treatment target

Due to the established role of Gal-3 in LV remodelling and overt HF, Gal-3 could be considered a treatment target. Disruption of the Gal-3 gene was found to block fibroblast activation and procollagen expression *in vitro* and *in vivo*. Direct inhibition of Gal-3 is possible with N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP), a naturally occurring plasma tetrapeptide that prevents and reverses inflammation and collagen deposition in the heart [39].

Gal-3 — conclusions

Multiple studies have shown the prognostic value of Gal-3 in patients with HF. The value is incremental if NT-proBNP is added as part of a multiple logistic. The diagnostic value of Gal-3 for HF diagnosis is, however, less established. The production of Gal-3 represents an ongoing chronic pathophysiological process and, therefore, its levels are not affected by the current (compensated or decompensated) HF status. It is well established that Gal-3 levels are unaffected by short-term changes in clinical and haemodynamic status of patients with HF. However, there is an assumption that the inclusion of Gal-3 measurement in the evaluation of HF patients adds to the prognostic power of natriuretic peptides, so that the combined use appears superior to the measurement of either one by itself.

ST2

ST2 is a member of the Zoll-like/interleukin 1 (IL-1) receptor superfamily. It is expressed by the haematopoietic organs, T-helper 2, and mast cells, and exists in two isoforms: (i) a soluble form (referred to as sST2); and (ii) a transmembrane form (referred to as ST2 ligand or ST2L) [40]. Several experimental and clinical studies have demonstrated that sST2 is a biomarker associated with mechanical stress, with a pivotal role

in myocardial fibrosis. IL-33 was recently identified as a ligand. IL-33/ST2 ligand signalling protects the myocardium under mechanical strain and acts in ways similar to the biomechanically activated fibroblast-cardiomyocyte paracrine system to prevent cardiac hypertrophy and fibrosis. sST2 might interfere with this adaptive response by binding IL-33 and preventing signalling via the ST2 ligand. ST2L mediates the effects of IL-33, whereas sST2 limits the activity of IL-33 by competitive binding with its receptors. The derangement of sST2 signalling leads to a phenotype consistent with myocardial remodelling. Weir et al. [41] showed a connection between sST2 levels and cardiac remodelling parameters, including the LV EF and the LV end-diastolic volume. The concentration of sST2 appears to predict a clinical phenotype that is vulnerable to remodelling and prognostically meaningful in the context of acutely decompensated HF.

sST2 and HF diagnosis and prognosis

Concentrations of sST2 are higher in patients with HF than in patients with non-cardiac causes of dyspnoea [42]. However, in many studies comparing sST2 and BNP for HF diagnosis, sST2 was less accurate diagnostically than NT-proBNP. On the other hand, patients with elevated BNP, higher sST2 values were associated with a higher probability of an acute HF diagnosis and worse symptoms. The importance of sST2 values has been effectively shown, especially in the prognosis stratification of HF patients. Manzano-Fernandez et al. [43] demonstrated that the determination of sST2 concentration measured in patients with decompensated HF improved risk prediction compared to BNP alone. sST2 concentrations were lower in patients with HF with preserved EF; however, sST2 remained an independent predictor of mortality, regardless of LV EF. Boisot et al. [44] measured sST2 in acutely decompensated HF, initially at admission to hospital and then five more times prior to discharge. From admission to discharge, the percentage change in sST2 was strongly predictive of 90-day mortality. Patients with sST2 values that decreased by 15.5% or more during the study period had a 7% chance of death, whereas patients whose sST2 levels failed to decrease over the same time interval had a 33% chance of dying.

The additive value of combined sST2 and natriuretic peptide measurement with regard to risk stratification was also confirmed by a study by Rehman et al. [45]; five different biomarkers (sST2, NT-proBNP, C-reactive protein, haemoglobin, and blood urea nitrogen) were used to assess one-year mortality risk. sST2 achieved the highest area-under-the curve, and the combination of all these biomarkers offered the greatest predictive value for mortality prediction.

sST2 and CAD

sST2 has been shown to have some prognostic value in patients with ACS. sST2 levels were measured in serum from 810 patients in the Thrombolysis In Myocardial Infarction (TIMI) 14 study (362 patients) and the TIMI-23 study (448 patients); both compared different anticoagulation strategies in patients after acute MI with ST segment elevation [46]. Baseline levels of sST2 were significantly higher in patients who died or developed congestive HF within 30 days. In a logistic regression analysis adjusted for clinically important variables, increased sST2 levels remained significantly associated with higher risk of death. Similarly, Aldous et al. [47] measured sST2 in 995 patients who attended the Emergency Department with a complaint of chest pain. Elevated sST2 values had a sensitivity of 73% and specificity of 79% relative to a HF diagnosis, which was more specific than BNP. Moreover, elevated sST2 levels were independently associated with death or HF, with an odds ratio of 1.9 at 18 months.

The myocardial expression of ST2 is not elevated for humans with HF. Although the heart endothelium and leukocytes express components of the ST2/ST2L/IL-33 pathway, the source of circulating sT2 is extra-myocardial. Thus, in patients with ACS, sST2 does not reflect the severity of cardiac ischaemia (or MI size); however, the level of the systemic response to MI and can serve as marker for future development of HF.

Transforming growth factor-β1

Transforming growth factor-β (TGF-β) is a multifunctional peptide growth factor that has an important role in the regulation of cell growth, differentiation, and repair in a variety of tissues. In humans, the cytokine has three isoforms: TGF-β1, TGF-β2, and TGF-β3. Almost all tissues produce all three isoforms of TGF-β1 [48]. The TGF-β1 gene has been mapped on chromosome 19q13.1-q13.3.

In the heart, TGF-β1 is induced by MI, pressure overload, angiotensin II infusion, norepinephrine infusion, and inhibition of nitric oxide [49]. In the myocardium, TGF-β1 is produced by both cardiofibroblasts and cardiomyocytes and plays a key role in the development of tissue fibrosis. The role of TGF-β1 in HF is shown in Figure 3. *In vitro*, TGF-β1 markedly enhances collagen type I and III synthesis. It acts on cells to induce the deposition of extracellular matrix by simultaneously stimulating cells to increase several fold the synthesis of matrix proteins; it also decreases production of matrix degrading proteolytic enzymes and increases production of inhibitors of these proteases. As a result, TGF-β1 is increasingly recognised as an important growth factor in mediating myocardial fibrosis.

TGF-β1 and HF and prognosis

Agarwal et al. [50] measured the concentration of TGF-β1 in 1371 older subjects, who were then followed for 14 years. TGF-β1 was not associated with cardiovascular outcomes in the full cohort; however, among individuals with C-reactive protein above the median of the cohort, higher concentrations of TGF-β1 were associated with higher incidences of HF and with total cardiovascular outcomes.

In patients with DCMP, gene expression of collagen type I and III correlates with gene expression of TGF-β1 in myocar-

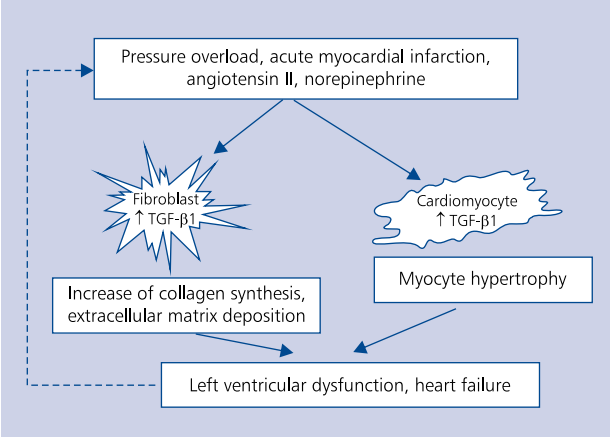

Figure 3. Diagram showing multiple effects of increased inflammation on the cardiovascular system; TGF-β1 — transforming growth factor-β1

dial biopsy specimens. Plasma concentrations of TGF-β1 were found to be elevated in patients with HF, which was correlated with LV remodelling, determined by echocardiography. Treatment with angiotensin converting enzyme inhibitors or AT1 receptor blockers significantly decreases tissue TGF-β1 levels in hypertrophied or infarcted hearts [51], and the degree of decrease is linked to the degree of LV positive remodelling.

Concentrations of TGF-β1 were higher in patients with chronic HF compared to healthy matched controls, and correlated with NYHA class [52]. In patients with end-stage HF undergoing cardiac transplant, TGF-β1 bioactivity measured in cardiac tissue was substantially higher in diseased heart tissue compared to tissue samples of healthy donor hearts. In human cardiac resynchronisation therapy (CRT) recipients, the concentration of TGF-β1 decreases in CRT responders, compared to non-responders [53]. It was shown in a small study with 18 patients that the concentration of osteopontin, a matrix glycoprotein required for fibroblast activation in response to TGF-β1 stimulation, decreased in CRT responders while remaining unchanged in non-responders [54]. In that study, pre-implant concentrations of TGF-β1 were higher in CRT recipients compared to healthy subjects, and there was also a trend towards decreased TGF-β1 in responders compared to non-responders [54]. CRT yields an early and sustained reduction in BNP, which is a well-known plasma marker of HF. However, while BNP is a sensitive marker of short-term cardiac function and overload, indexes from the TGF-β family (as markers of extracellular matrix turnover) might provide additional and better information regarding LV remodelling and long-term prognosis. Not surprisingly, higher pre-implantation values, in CRT recipients, were independently associated with a poor prognosis in CRT patients [53]. Extracellular matrix gene expression was also studied in patients with advanced DCMP being treated with an LV assist device. In the subgroup who developed sustained myocardial recovery, pre-implantation values of TGF-β1 were lower compared to the non-recovery group [55].

TGF-β1 and CAD

Different findings of TGF-β1 have been described in patients with stable CAD. Some authors found lower TGF-β1 concentrations in patients with chronic CAD compared to healthy controls without coronary atherosclerosis, and, surprisingly, the lowest concentrations of TGF-β1 were associated with poorer prognoses in patients with stable CAD [56]. Based on these finding, there is speculation about some type of positive atherosclerosis plaque stabilisation effect associated with TGF-β1 in chronic CAD. Conversely, other authors have found a positive correlation between TGF-β1 concentration and the severity of CAD [57]. In patients with acute MI, the concentration of TGF-β1 increases to a peak within 72 h after the MI. The peak levels have been negatively correlated with LV function [58]. Presently, there is a shortage of suitable studies addressing the predictive value of TGF-β1 on mortality.

The role of BNP, which is a very reliable, sensitive marker of short-term cardiac function and overload, has been well established. On the other hand, indexes of the TGF-β family, as markers of extracellular matrix turnover, may be able to provide additional and perhaps superior information regarding LV remodelling and long-term prognosis. However, its prognostic potential has not yet be evaluated in a large HF population, and a large observational study is badly needed.

TGF-β1 as a therapeutic target

In HF patients, the interplay between angiotensin II and TGF-β1 might enhance cardiac remodelling and fibrosis, and therefore worsen HF [59]. Blockade of the renin–angiotensin system, not surprisingly, leads to a decrease in some fibrotic markers. Recently, new antagonists of TGF-β1 may play an important role in preventing progression of cardiac remodelling in HF. A number of therapeutic approaches for decreasing the action of TGF-β1 have been suggested; these include tranilast, anti-TGF-β1 neutralising antibody, soluble TGF-β type II receptor, TGF-β antisense oligonucleotide, and pirfenidone [59]. Pinto et al. [60] reported the effect of tranilast on reduction of TGF-β1 mRNA in an animal model; however, reduction in TGF-β1 expression did not prevent impairment of LV function. A study of anti-TGF-β1 antibody was found to prevent myocardial fibrosis and diastolic dysfunction in pressure-overloaded rats [61]. Whether any of these new agents will lead to the development of an effective antifibrotic drug is unknown. To further obfuscate matters, TGF-β1 signalling involves extensive cross-talk with other signalling pathways, and the complexity of these interactions is not known in detail. However, understanding TGF-β1 as a key factor in myocardial fibrosis may yield an important target for new HF therapies.

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