Biomarkers for Predicting Clinical Outcomes in Heart Disease

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Cardiovascular disease is most frequently caused by the development and progression of atherosclerosis. When coronary arteries are afflicted, and the stenoses caused by atherosclerotic plaques are severe enough, the metabolic supply-and-offer balance is disturbed, leading to myocardial ischemia. If atherosclerotic plaques become unstable and local thrombosis develops, a myocardial infarction occurs. Sometimes, myocardial ischemia and infarction may result in significant and irreversible heart failure. To prevent severe complications, such as acute coronary syndromes and ischemia-related heart failure, extensive efforts have been made for developing biomarkers that would help identify patients at increased risk for cardiovascular events.

coronary artery disease | acute coronary syndrome | heart failure | biomarkers

1. Introduction

Cardiovascular disease (CVD) is very often caused by myocardial ischemia due to the development and progression of atherosclerosis. Coronary artery disease (CAD) includes acute coronary syndromes (ACS), such as myocardial infarction (MI) and unstable angina, and chronic coronary syndromes. Coronary artery disease may result in heart failure (HF) and is associated with poor clinical outcomes. In order to better assess the risk for poor cardiovascular (CV) outcomes, many humoral parameters have been investigated over the years as potential biomarkers for prognosis, with mixed results. Although progress has been made and some parameters proved to be sufficiently reliable for this purpose, the perfect biomarker has not been found.

2. Biomarkers for Predicting Clinical Outcomes in Heart Disease

2.1. Inflammatory Markers

2.1.1. Serum Amyloid A

Serum amyloid A (SAA) is an acute phase protein with persistently elevated levels in chronic inflammation, which seems to be linked to atherosclerosis development and may therefore play a part in CV risk prediction [1]. Zewinger et al. investigated the association between SAA and high-density lipoprotein cholesterol (HDL-C), relying on the premise that the interaction between SAA and anti-atherogenic HDLs (high-density lipoproteins) can lead to structural alterations associated with pro-atherosclerotic effects and overall worse CV outcomes [2]. In the study,

3310 patients undergoing coronary angiography were followed over a median of 9.9 years, and SAA was shown to have predictive value for CV mortality. In addition, a formula for calculating biologically effective HDL-C, while taking SAA concentrations into account, was elaborated, which might prove to be a feasible method of estimating the biological effectiveness of HDLs compared to more laborious techniques [2].

2.1.2. Obesity and Inflammation

Obesity is known to be associated with a systemic proinflammatory status by maintaining a chronic low-grade inflammation and thus contributing to atherogenesis [3]. Jia et al. explored the relationship between body weight, expressed by body mass index (BMI) and high-sensitivity C-reactive protein (hs-CRP) in an observational cohort study including 478 patients with unstable angina undergoing elective percutaneous coronary intervention (PCI) [4]. Patients meeting the composite endpoint of MACE (major adverse CV events, defined as CV death, heart failure, stroke, myocardial infarction, or repeated revascularization) had a significantly higher hs-CRP ($p = 0.033$).

2.1.3. Albumin

Systemic inflammation influences the levels of serum albumin by decreasing its rate of synthesis. Hypoalbuminemia is an expression of the inflammatory process and was previously studied for its prognostic role in patients with acute HF and/or cardiogenic shock [5][6].

2.1.4. Markers of Iron Metabolism

Iron deficiency is a frequent comorbidity in patients with chronic HF, leading to a decreased quality of life and worse overall clinical prognosis [7]. A cohort study investigated the prognostic relevance of biomarkers of iron status after an ACS by performing high-frequency blood sampling (a median of 17 determinations) in 844 patients over a one-year follow-up period [8]. The study revealed a higher incidence of the composite outcome of CV mortality and recurrent nonfatal ACS with decreasing log-iron, as well as with decreasing log-TSAT (transferrin saturation). However, no associations with the composite outcome were recorded for ferritin and transferrin [8].

2.2. Cytokines

2.2.1. Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine with pleiotropic effects, linked to atherosclerosis development and plaque vulnerability. The SOLID-TIMI 52 Trial evaluated serum IL-6 concentrations in 4939 patients with a recent ACS (≤30 days) over a median follow-up period of 2.5 years [9]. Serum IL-6 values in the highest quartile were associated with a higher risk of MACE. Furthermore, IL-6 was independently associated with an increased risk of MACE and CV death or HF after adjusting for established biomarkers [9]. On the other hand, an observational cohort study of patients with STEMI and primary PCI ($n = 989$, median follow-up of 4.6 years) [10] focusing on IL-6, CRP, and components of the IL-6 signaling pathway, such as soluble IL-6 receptor (sIL-6R) and soluble glycoprotein 130 (sgp130), found no significant relationship between IL-6 or sgp130 and adverse cardiac outcomes. However, sIL-6R concentration in the upper quartile (>47.7 ng/mL) was significantly associated with an increased risk of the

primary endpoint (a composite of all-cause mortality, MI, stroke, unplanned revascularization, or HF rehospitalization) [10].

2.2.2. Interleukin-34 (IL-34)

The pro-inflammatory cytokine IL-34, a multifunctional cytokine that participates in the differentiation and proliferation of mononuclear phagocytes, was advanced as a novel biomarker of impaired renal function and was recently studied in HF patients. An observational study of 510 patients with stable HF reported the significant associations between IL-34 levels and the primary endpoint (a composite of CV death and HF hospitalization), CV death alone, HF hospitalization alone, and all-cause mortality [11].

2.2.3. Interleukin-12 (IL-12) and Interleukin-18 (IL-18)

Opstad et al. investigated the proposed synergic effect of the inflammatory cytokines IL-18 and IL-12 on the prognosis of stable CAD patients in an observational study of 1001 patients [12]. Statistical analysis revealed no association between CV events (primary endpoint defined as fatal/nonfatal AMI, unstable angina, ischemic stroke, or death) and values of IL-18 or IL-12 alone when comparing upper tertiles of these parameters to the lower tertile [12]. However, the simultaneous analysis of IL-18 and IL-12 showed an increased risk of CV events when both biomarkers were in the upper tertile [12].

2.2.4. Soluble Suppression of Tumorigenesis-2 (sST2)

The suppression of tumorigenesis-2 (ST2) is a member of the IL-1 receptor family, which has two isoforms—a transmembrane form, which binds IL-33 and is involved in the immune response, and a soluble (sST2) form, which acts as a decoy receptor and may prevent exaggerated responses, while also preventing the beneficial effects of the ST2–IL 33 interaction [13]. Because sST2 is present in peripheral blood, it can be measured, and could be used as a marker of prognosis in patients with CVD [13].

2.2.5. Growth Differentiation Factor-15 (GDF-15)

Growth differentiation factor 15 (GDF-15) belongs to the transforming growth factor-β (TGF-β) superfamily, previously known as the macrophage-inhibiting cytokine, which increases as a consequence of inflammation and oxidative stress [14]. Because atherosclerosis is an inflammatory process, it has been hypothesized that GDF-15 may be used as a valid marker of prognosis in patients with atherosclerosis-related CVD. Recently, an observational cohort study evaluated the prognostic value of plasma GDF-15 in 3641 patients with CAD, who were followed up for 5.3–7.6 years [14]. Elevated GDF-15 levels > 1800 ng/L were independently associated with the primary endpoint (composite of all-cause mortality, ACS, or unplanned coronary revascularization) and all-cause mortality [14]. Moreover, GDF-15 provided incremental prognostic value to a model, including clinical data (age, sex, BMI, smoking, hypertension, diabetes mellitus, and hyperlipidemia) (AUC 0.628 vs. 0.583) [14].

2.2.6. Leptin

Leptin is a protein with dual function, acting as a hormone to preserve energy homeostasis, and as a cytokine, eliciting inflammatory responses; due to its proven involvement in inflammation, it has been postulated that it may be used as a marker of prognosis in patients with CVD [15]. The most consistent data comes from a substudy of the ARTEMIS trial. According to Puurunen et al. [16], in a group of 1946 participants with stable CAD from the ARTEMIS trial, leptin had predictive value for the primary composite endpoint (MACE defined as CHF hospitalization or cardiac death) and the secondary endpoint (ACS or stroke) over a follow-up period of 2 years. Moreover, plasma leptin levels >14.1 ng/mL were independently associated with a significant increase in risk of MACE, while leptin levels > 9.9 ng/mL predicted a higher risk of ACS or stroke [16].

2.2.7. TNFSF14

TNFSF14 is a transmembrane protein belonging to the tumor necrosis factor (TNF) ligand family, which may have a pathogenic function in atherosclerosis. Recent data are limited.

2.3. Hematological Biomarkers

2.3.1. CBC Parameters

White blood cells (WBC) and WBC subsets may be associated with risk of HF. A LIPID substudy of 7101 patients who had an ACS 3–36 months before enrollment showed that a higher WBC count predicted the development of HF-related events over a period of follow-up of 5 years [17].

Some platelet and red blood cell parameters were also found to have predictive value for HF and mortality. A Polish retrospective observational study of 278 patients with a one-year follow-up after at least one stent implantation for ACS showed that platelet distribution width (PDW) was independently associated with both systolic HF and one-year mortality [18].

2.3.2. CBC-Derived Indices

A study of 1754 patients from the Utrecht Coronary Biobank aimed to analyze the association of baseline monocyte to lymphocyte ratio (MLR) with baseline characteristics of patients who underwent coronary angiography, as well as baseline MLR association with future HF hospitalization [19]. At baseline, univariate analysis showed that a 1-point increase in logMLR was associated with unstable angina vs. stable CAD, MI vs. stable CAD, and 1-category poorer EF [19]. In multivariate analysis, MLR was associated only with unstable angina vs. stable CAD. Moreover, high MLR predicted HF hospitalization over a follow-up period of 484 days [19]. A combined monocyte to HDL–cholesterol ratio (MHR) was also found to have predictive value in a study of 231 patients admitted with STEMI for the first time, who underwent primary PCI in the first 12 h [20]. MHR at the time of admission was higher in patients with adverse cardiac remodeling at the 6-month follow-up [20].

Platelet-related indices may also have predictive value in CHD patients. A study of 5886 patients admitted with STEMI [21] showed that, after a 81.6-month follow-up, adjusted all-cause mortality was higher in patients with a

higher platelet to lymphocyte ratio (PLR). In adjusted analysis, a higher PLR quartile (2nd to 4th) was also predictive for recurrent MI, HF, and ischemic stroke [21].

2.3.3. Blood Cell-Related Parameters Improve Existing Models

In acute HFpEF patients, the addition of both NLR on admission and absolute NLR trajectory (admission to discharge) improved the model combining GWTG-HF (Get With the Guidelines–Heart Failure) score and NT-proBNP as well as GWTG-HF score alone, enhancing its 1-year, 2-year, and 3-year predictive value for mortality [22]. MLR modestly, but significantly, improved risk prediction in patients undergoing coronary angiography when added to the full HF prediction model [19].

2.4. Parameters of the Carbohydrate Metabolism

In clinical settings, the investigation of the carbohydrate metabolism heavily relies on few parameters, namely plasma glucose (fasting, random, or after an oral glucose tolerance test—OGTT) and glycated hemoglobin (HbA1c). Impaired glucose metabolism is a well-established risk factor for CHD and patients with diabetes mellitus are at increased risk of CVD and mortality. Emerging evidence indicates that the parameters of the carbohydrate metabolism may be used to predict CV outcomes after ACS, both in healthy and diabetic patients.

2.4.1. Admission Plasma Glucose (APG) in ACS

APG was shown to be associated with in-hospital outcomes. A study of 667 patients admitted with first STEMI reported that APG ≥11.1 mmol/L was the second-best predictor of in-hospital mortality after cardiac arrest [23]. Similarly, a study of 1168 Black Africans with ACS [24] reported that elevated APG was associated with in-hospital mortality at an even lower threshold (>7.8 mmol/L). However, subgroup analysis revealed that APG predicted in-hospital mortality only in patients without diabetes (n = 836) [24]. APG was also shown to be associated with clinical outcomes after patient discharge following ACS [24]. A large study of 5309 STEMI and NSTEMI patients treated with PCI investigated the association of APG with a medium-term composite CV outcome (first of mortality, MI, HF, stroke) within 180 days from admission [25]. In patients without known diabetes, grouped based on APG according to WHO criteria, the incidence of the composite outcome increased with increasing APG group [25]. Higher APG was also predictive for the composite outcome in patients with diabetes [25]. For longer-term prediction of outcomes, a study of 417 patients who were admitted with ACS and treated by PCI reported that APG >10 mmol/L was predictive for MACCEs over a 39-month period (cardiac death, recurrent ACS, revascularized angina, acute decompensated HF, or stroke) [26].

2.4.2. Glycemic Variability in ACS

The study of 417 patients mentioned above also investigated the predictive value of glycemic variability in ACS patients treated by PCI [26]. Using continuous glucose monitoring for at least 24 h, the study showed that the mean amplitude of glycemic excursion (MAGE) was correlated with MACCEs over a mean follow-up period of 39 months [26]. In a multivariate model, including high MAGE, glucose >10 mmol/L, and HbA1c, only MAGE remained

predictive for MACCEs. High MAGE remained significantly associated with MACCEs even after multivessel disease, HDL-C, BNP, and hs-CRP were added to the model [26].

2.4.3. Fasting Plasma Glucose (FPG), Impaired Glucose Tolerance (IGT), and HbA1c

Data from the literature are heterogeneous and contradictory regarding the predictive value of glycemic status in patients with CHD. A Japanese study of patients with CAD undergoing PCI investigated the 10-year association of IGT with a composite outcome of CV death, MI, stroke, repeat revascularization, and HF hospitalization [27]. IGT was shown to be a predictor of long-term CV risk, while previously known and newly diagnosed diabetes were not [27].

To further diversify the findings, a Swedish cohort study of 841 patients admitted with STEMI [28] and followed for a mean period of 4.8 years reported that glycemic status according to OGTT had no predictive value for the composite outcome (first of MI, HF, ischemic stroke, or mortality). However, glycemic status according to HbA1c was predictive for the composite outcome, but only in patients with prediabetes according to ADA criteria [28]. When comparing different cut-off values for glucose and HbA1c, only HbA1c ≥ 39 mmol/mol was predictive for the composite outcome [28].

2.4.4. Advanced Glycation End Products (AGEs)

A study of two age- and gender-matched cohorts of patients with either ACS or HF (n = 102 for each) investigated the 5-year predictive role of AGEs and their receptors (RAGE and sRAGE—soluble form) for cardiac death, non-fatal MI, or HF readmission [29]. ROC analysis revealed that fluorescent AGE (AUC 0.703 [0.597–0.809], p = 0.001), sRAGE (AUC 0.623 [0.512–0.734], p = 0.038) and endogenous secretory (es)RAGE (AUC 0.621 [0.510–0.713], p = 0.042), but not cleaved RAGE were predictive for cardiac death in the HF cohort [29].

2.4.5. Ketone Bodies (KBs)

Although KBs are more related to the lipid metabolism, they are discussed here due to their pathophysiological relevance in diabetes. Diabetes is the most frequent pathological cause of elevated KBs in blood. A study of 369 participants from GIPS-III trial, with early metformin therapy after STEMI [30], reported that circulating KBs were higher at presentation with STEMI and at 24 h after reperfusion, compared with levels at four-month follow-up (p < 0.001). More importantly, increased KBs concentrations at 24 h after reperfusion were independently associated with larger MI size and lower LVEF [30].

2.5. Urinary and Kidney-Related Parameters

2.5.1. Serum Creatinine and Blood Urea Nitrogen

The negative prognostic role of acute kidney injury in STEMI patients is undisputed; however, the relationship between subclinical increased serum creatinine levels and adverse cardiac outcomes in this category of patients is still uncertain. A retrospective analysis of 1897 STEMI patients who underwent primary PCI revealed that

subclinical acute kidney injury (delineated by increases in serum creatinine of ≥0.1 mg/dL, but <0.3 mg/dL) was independently associated with the composite endpoint (defined as HF, atrial fibrillation, need for mechanical ventilation, and in-hospital mortality) [31].

2.5.2. Cystatin-C

Cystatin-C is a marker of the renal function independent of age, sex, or muscle mass (contrary to serum creatinine), proposed in multiple recent studies for CV risk prediction. Serum cystatin-C was evaluated in relation to an outcome consisting of CV death or HF hospitalization in a substudy of the SOLID-TIMI 52 trial (*n* = 4965 patients with ACS ≤1 month, followed up for a median of 2.5 years) [32]. Increasing levels of cystatin-C were associated with a higher risk of the primary outcome, a higher risk of CV death alone, and a higher risk of HF hospitalization alone [32].

2.5.3. Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL), a small-size circulating protein first found in activated neutrophils, is a biomarker of renal dysfunction and has been investigated for its potential role in non-renal pathology, including CV disease [33].

2.5.4. Urinary Biomarkers

The measurement of biomarkers related to CVD outcomes from urine samples could help to better understand the correlations between renal function and the development of CVD. A report including a very large number of participants (*n* = 478,311) of the UK Biobank revealed an inverse association between the urine sodium–potassium ratio (UNa/UK) from random spot measurements and CAD [34]. A post hoc analysis of the ESPRIT study (*n* = 520 patients) showed that high sodium levels from measurements of spot urine (UNa ≥ 4 g/day) were associated with HF hospitalization, but not with other CV adverse outcomes [35].

2.6. Hormones and Mineral Metabolism Markers

2.6.1. Cortisol and Aldosterone

Aldosterone is known to contribute to the pathophysiology of HF, and many drugs for HF target the renin–angiotensin–aldosterone system [36]. Elevated cortisol is known to promote the development of risk factors for atherosclerosis, such as truncal obesity, hyperinsulinemia, hyperglycemia, insulin resistance, and dyslipidemia [37]. Despite their recognized involvement in CVD disease, these hormones are not routinely used as markers of prognosis.

2.6.2. Thyroid Hormones

The effects of thyroid hormones on the CV system are well known, as are the clinical changes that occur in hypo- or hyperthyroidism [38]. However, thyroid hormones are not currently considered mainstream biomarkers for CVD.

As for cortisol and aldosterone, data on the use of thyroid hormones as outcome predictors in patients with CVD are limited.

2.6.3. Copeptin

Although not a hormone per se, copeptin is a cleavage product of the preprohormone of arginine vasopressin (also known as the antidiuretic hormone) and a surrogate marker of arginine vasopressin. Recently, only small studies reported data on the use of copeptin as a prognostic marker in CVD.

In a long-term study comparing diabetics (*n* = 895) to non-diabetics (*n* = 4187), copeptin levels were associated with CV outcomes in diabetics only, over a mean follow-up of 14.4 years [39]. Copeptin was predictive for the composite outcome of CAD, death, or HF, as well as for each individual outcome. Copeptin maintained its predictive value for the composite outcome after adjustment for each of the following factors: diabetes medication, CRP, NT-proBNP, and glomerular filtration rate [39].

2.6.4. Fibroblast Growth Factor 23 (FGF-23) and Klotho

Fibroblast growth factor 23 (FGF-23) is a bone-derived hormone involved in the suppression of phosphate reabsorption and the downregulation of 1,25-dihydroxyvitamin D hormone synthesis in the kidney [40]. In order to exert its renal effects and contribute to the development of the cardiorenal syndrome, FGF-23 needs to bind to certain receptors in the presence of a co-factor called Klotho, promoting phosphaturia. FGF-23 may also have direct effects on the heart, in a Klotho-independent interaction [41]. Experimental studies suggested that, in the heart, FGF-23 may contribute to myocardial hypertrophy, endothelial dysfunction and atherosclerosis, and, therefore, may be used as a biomarker of CV disease [40].

2.6.5. Osteonectin and Serum Phosphate

Osteonectin is a matrix cellular protein which is involved in collagen processing after synthesis in the HF myocardium and in modulating cell adhesion, growth factor activity, and cell cycle [42]. Phosphate is a main structural component of nucleic acids, adenosine triphosphate, and the cell membrane and is also involved in cellular signaling and mineral metabolism. Excess phosphate can have deleterious effects on the CV system, promoting endothelial dysfunction, vascular calcification, and myocardial hypertrophy [43]. In clinical settings, data from two Swedish registries, namely the SWEDEHEART registry and the SCREAM project, suggest the unfavorable effect of hyperphosphatemia on CV outcomes [43]. Xu H. et al. identified 2547 patients from the two registries who were admitted with a suspicion of ACS and reported that higher serum phosphate during hospitalization was associated with in-hospital CV outcomes [43]. Patients with serum phosphate ≥ 1.3 mmol/L (75th percentile) exhibited a higher risk of in-hospital mortality, while patients with serum phosphate ≥ 2.1 mmol/L (95th percentile) had an increased risk for in-hospital events (composite of MI reinfarction, cardiogenic shock, resuscitated cardiac arrest, atrial fibrillation, or atrioventricular block) and in-hospital mortality. Elevated serum phosphate was also predictive for 1-year post-discharge CVD events and mortality [43].

2.7. Omics

2.7.1. Transcriptomics

A study of 2763 participants in the Framingham Heart Study investigated possible associations between HF incidence and 398 circulating extracellular RNAs (ex-RNA) from plasma over a median follow-up of 7.7 years [44]. A total of 12 ex-RNAs were associated with LV mass and at least one other echocardiographic phenotype (left atrial size or LV end-diastolic volume), of which three miRs were associated with lower risk of incident HF (about 15% risk reduction/2-fold increase) after adjustment for clinical variables: miR-20a-5p (HR 0.86 [0.73–1.00], $p = 0.047$), miR-17–5p (HR 0.84 [0.72–0.99], $p = 0.03$), and miR-106b-5p (HR 0.85 [0.73–0.99], $p = 0.04$) [44].

2.7.2. Proteomics

A matched case–control study evaluated the association of proteomic biomarkers with CV outcomes in 455 controls and 485 cases with CAD and HFrEF after an episode of worsening HF [45]. A total of 276 plasma proteins were analyzed, resulting in 49 proteins significantly associated with clinical outcomes. Seven of these proteins had an adjusted false discovery rate < 0.001: BNP, NT-proBNP, FGF23, growth differentiation factor 15 (GDF15), T-cell immunoglobulin, and mucin domain containing 4 (TIMD4), spondin 1 (SPON1), and pulmonary surfactant-associated protein D (PSP-D). Neither of these proteins were associated with individual clinical events (HF hospitalization, sudden cardiac death, and combined MI or stroke) [45]. Therefore, these proteins were considered strong but indiscriminate predictors of diverse CV events. The addition of these biomarkers to a clinical model significantly improved its predictive value [45].

2.7.3. Metabolomics

A post hoc analysis of the CorLipid trial on 316 patients with CAD and diabetes mellitus after coronary intervention for chronic or acute coronary syndrome aimed to identify metabolomic predictors for various CV outcomes over a median follow-up of 2 years [46]. The primary outcome was defined as a composite of MACCE, repeat revascularization, and CV hospitalizations. The study reported that acylcarnitine ratio C4/C18:2 (adjusted HR 1.89 [1.09–3.29], $p < 0.01$) and apolipoprotein B (adjusted HR 1.02 [1.01–1.04], $p = 0.01$) were independent predictors of the primary outcome [46]. Higher levels of acylcarnitine ratio C4/C18:2 (adjusted β 3.02 [0.09–6.06], $p = 0.04$) and ceramide ratio C24:1/C24:0 (adjusted β 7.36 [5.74–20.47], $p = 0.02$) independently predicted a higher complexity of CAD [46].

2.8. Other Emerging and Candidate Biomarkers

2.8.1. Endothelial Function

Baseline and 1-month changes in big endothelin-1 levels were shown to be associated with combined CV death and hospitalization for worsening HF in patients with LV dysfunction after recent MI [47]. Mid-regional pro-adrenomedullin (MR-proADM) is involved in vascular permeability and microcirculation stabilization by regulating the endothelial barrier [48]. MR-proADM was shown to be associated with long-term mortality and HF in patients admitted with STEMI [49] and could be a potentially useful biomarker for discriminating type 1 from type 2 MI on admission [50]. YKL-40 is a mammalian chitinase-like protein considered a marker of endothelial dysfunction and

inflammation [51]. Elevated levels of serum YKL-40 were shown to predict long-term MACE in both STEMI patients treated by primary PCI [52] and hypertensive patients [53].

2.8.2. Oxidative Stress and Antioxidant Potential

Superoxide dismutase (SOD), nitrite/nitrate ratio, neopterin, and ferric-reducing ability of plasma were reported as prognostic factors for all-cause mortality and HF hospitalization in patients with STEMI treated by primary PCI [54]. Moreover, SOD and nitrite/nitrate markers added predictive value to the GRACE risk score [54]. Additionally, SOD, nitric oxide (NO), and neopterin were reported to be predictors of acute kidney injury in patients admitted with STEMI and treated with PCI [55]. A decreased level of biological antioxidant potential at 6 months after a PCI-treated STEMI, was shown to be an independent predictor of long-term CV events [56]. The serial monitoring of antioxidant capacity may serve as a predictor of CV outcomes in STEMI patients.

2.8.3. Enzymes and Other Proteins

Serum-activated aspartic lysosomal endopeptidase cathepsin D (Cathepsin D) levels after primary PCI for STEMI were decreased in patients with post-STEMI new-onset cardiac dysfunction [57]. Lower levels of cathepsin D were associated with MACE at the 6-month follow-up post-STEMI [57]. Patients with higher levels of nardilysin (*n*-arginine dibasic convertase, a type of metalloendopeptidase) at admission for STEMI were shown to be at increased risk for future all-cause mortality [58]. Higher neprilysin (also known as CD10 or common acute lymphoblastic leukemia antigen—CALLA) levels were associated with stunned myocardium early after STEMI, with better improvement of LVEF at follow-up [59]. Serum matrix metalloproteinase 9 (MMP-9) is a candidate biomarker for the early discrimination of MI from unstable angina and a predictor of poor clinical outcomes in patients with ACS [60].

2.8.4. Coagulation Proteins and Other Molecules

D-dimer was shown to be associated with an increased incidence of HF after an ACS [17] and its addition to the GRACE score along with NT-proBNP and fibrinogen, significantly improved the predictive value of GRACE for MACE [61]. An ARIC substudy reported that γ' fibrinogen is unlikely to influence CVD-related events via its prothrombotic properties [62]. Although a modest predictor of CVD death, γ' fibrinogen added little information to CVD prediction beyond hs-CRP and/or total fibrinogen [62].

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