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Biomarkers in Heart Failure: Current and Future

Heart failure (HF) is the ending of practically all cardiovascular diseases and the reason for hospitalization of 49% of patients in a cardiological hospital. Available instrumental diagnostic methods and biomarkers not always allow verification of HF, particularly in patients with preserved left ventricular ejection fraction. Prediction of chronic HF in patients with risk factors faces great difficulties. Currently, natriuretic peptides (NUP) are widely used for the diagnosis, prognosis and management of patients with HF and are included in clinical guidelines for diagnosis and treatment of HF. Following multiple studies, the understanding of NUP significance has changed. This resulted in a need for new biomarkers to improve the insight into the process of HF and to personalize the treatment by better individual phenotyping. In addition, current technologies, such as transcriptomic, proteomic and metabolomic analyses, provide identification of new biomarkers and better understanding of features of the HF pathogenesis. The aim of this study was to discuss recent reports on NUP and novel, most promising biomarkers in respect of their possible use in clinical practice.

Keywords Heart failure; biomarkers; natriuretic peptides; sST2; galectin-3; microPRA; metabolomics

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Biomarkers are commonly used in clinical practice as a convenient and straightforward method for patient diagnosis and monitoring [1, 2]. Their main advantage consists in the possibility of early diagnosis, often before the appearance of clinical symptoms of severe or clinically significant structural changes in the internal organs.

This is of particular significance for early detection of heart failure (HF), since the first clinical manifestations of this condition are nonspecific, often resulting in late diagnosis, which contributes to a worse prognosis. "Biomonitoring" during treatment is another critical aspect of using biomarkers in patients with heart failure. The intermittent course of HF, involving remissions and progressions, requires continuous patient monitoring to adjust the treatment regimen. The risk of cardiovascular events (CVEs) can be significantly reduced by using biomarkers to assess the efficacy of therapy or identify symptomless free deterioration. Finally, biomarkers provide information about the complex pathophysiology that determines HF phenotype, helping to identify targets for nosotropic treatment. Thus, despite the apparently simple definition of the term "biomarker" proposed by the Food Drug Administration (FDA) – "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" – includes a wide range of indicators depending on their uses (Figure 1, adapted from [3]).

The classification of HF biomarkers based on HF pathogenesis originally proposed in 2008 is constantly being updated with new methods of diagnosis to significantly expand our understanding of the pathophysiological pathways of HF (Figure 2 adapted from [4]). Although there have been many recent studies in this area, their reliability and clinical significance remain unclear. In this paper, we discuss the current situation in the light of new data and provisions on the use of natriuretic peptides (NPs), the most well-studied novel biomarkers of HF, as well as promising modern directions of search of biomarkers, such as the assessment of the microRNA expression and metabolomics.

Figure 1. Functional types of biomarkers

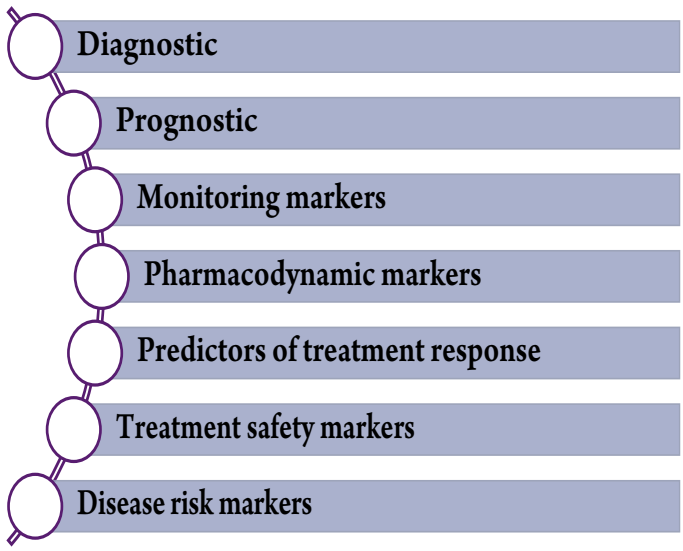

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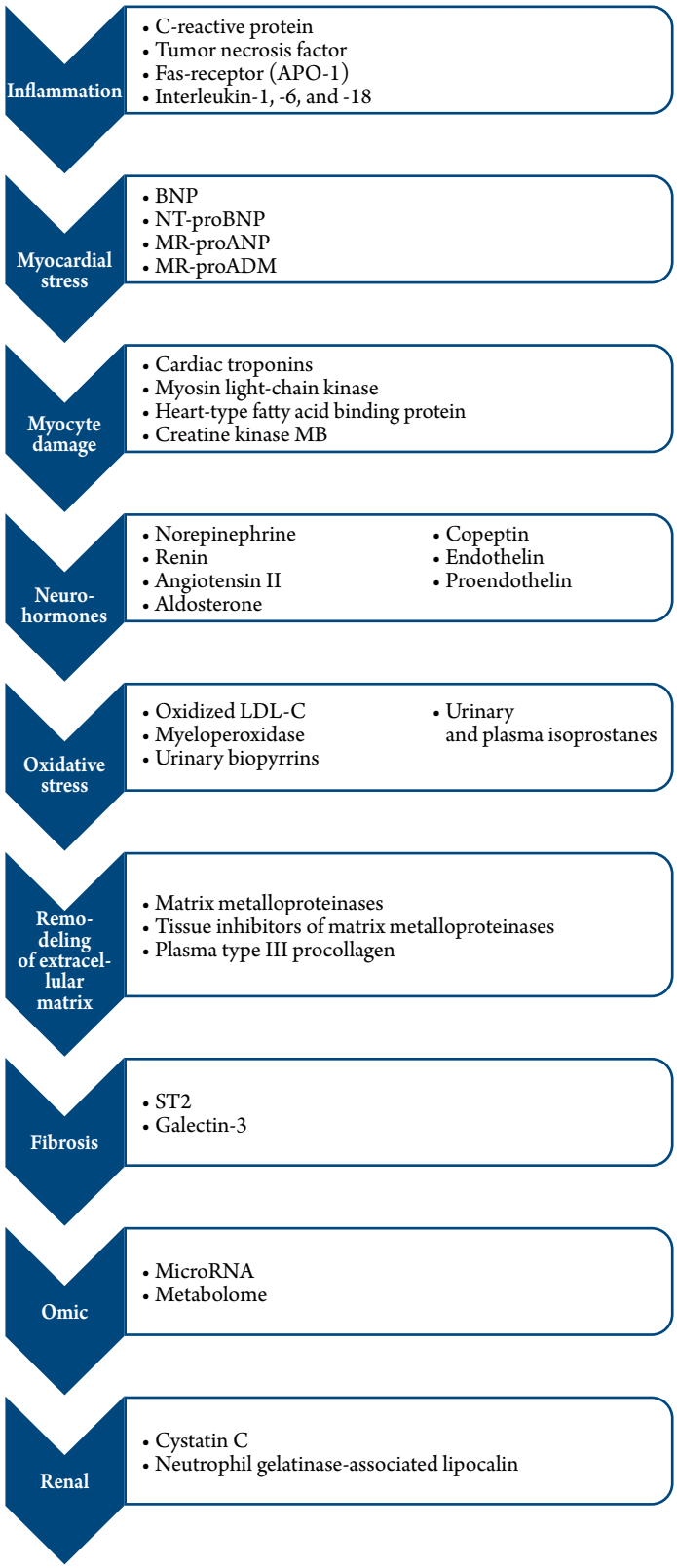
Figure 2. Cardiac biomarkers



BNP – brain natriuretic peptide;
NT-proBNP – N-terminal prohormone of brain natriuretic peptide;
MR-proANP – mid-regional pro-atrial natriuretic peptide;
MR-proADM – mid-regional pro-adrenomedullin;
ST2 – suppression of tumorigenecity-2;
LDL – low-density lipoprotein.

Natriuretic peptides

NPs were discovered in 1963 when the secretory granules were first found in the atria of animal hearts [5]. Eighteen years later, it was experimentally established that injections of homogenized atrial tissue can be used to increase natriuresis [6]. The determination of the structure of atrial NP was followed by brain natriuretic peptide (BNP), which has a similar diuretic effect. The first studies assessing the role of NPs in the diagnosis of HF were published in the late 1990s. Research in this area carried out over the past two decades has confirmed the diagnostic value of NPs and the concomitant possibility of using these biomarkers in clinical practice. Determination of NP levels is included in all clinical guidelines of the diagnosis and treatment of patients with acute and chronic HF [1].

The release of NPs is stimulated by an increase in end-diastolic pressure and volume overload in the heart chambers. The resulting so-called myocardial stress can be caused by left ventricular (LV) dysfunction, pulmonary hypertension, myocardial ischemia, congenital and acquired myocardial diseases, valvular diseases or various arrhythmias. NPs are excreted by kidneys; reduced kidney function leads to increased levels of circulating proteins.

Levels of BNP and its N-terminal precursor (NT-proBNP) in obese patients are lower than those in people with a normal body mass index (BMI), both with and without CHF. The reason for this correlation is not well-understood, especially given the existence of the so-called «obesity paradox» in patients with CHF, wherein mild obesity is associated with better survival.

From a clinical point of view, it is necessary to consider the risk of lower NP levels in patients having a BMI≥30 kg/m^2. For the diagnosis of HF, it is useful in this category of patients to consider a decrease in the threshold levels to 50%. Thus, when interpreting the results of biomarker levels, factors that increase these levels, as well as factors that lower NP levels more than expected, should be taken into account.

Causes of elevated levels of natriuretic peptides:

1. Cardiac

- Heart failure
- Acute coronary syndrome
- Cardiomyopathy
- Pericarditis

- Valvular heart disease
- Atrial fibrillation
- Pulmonary hypertension
- Myocarditis
- Heart surgeries
- Heart valve birth defect
- Cardioversion, ablation

2. Noncardiac

- Advanced age
- Anemia
- Pulmonary embolism
- Sleep apnea
- Sepsis
- Burns
- Toxic and metabolic disorders
- Kidney failure

NT-proBNP and BNP thresholds were evaluated in several clinical trials. It was shown that their levels in acute heart failure (AHF) and CHF vary significantly, while the levels of NT-proBNP <300 pg/mL completely excluded the presence of AHF [7]. The use of NPs in clinical studies as inclusion-, exclusion-, treatment response- and endpoint criteria remains challenging. The use of BNP or NT-proBNP as inclusion criteria is based on the belief that this approach provides accurate verification of HF to recruit the required number of relevant patients and increase the frequency of events [8]. Despite the prevalence of this approach, there is an inconsistency in how the BNP or NT-proBNP test results are used in clinical trials [9]. The analysis of 3,446 clinical trials in HF, in 365 of which BNP or NT-proBNP was used as an inclusion criterion, showed that the thresholds used as inclusion criteria varied significantly. Thus, only 13 (10.3%) of 126 AHF trials and 48 (20.1%) of 239 CHF trials used different NP thresholds, which depended on the presence of factors that could influence the outcome, such as atrial fibrillation (AF), age, and BMI. Only in 6 (2.5%) CHF studies, were the thresholds adjusted for patients with heart failure with preserved ejection fraction (HFpEF) or with reduced ejection fraction (HFrEF). It should be noted that, when NPs were used as the inclusion criteria, the lack of recruitment was the most common cause of trial discontinuation. The lack of standard methods of using NPs in clinical trials makes it challenging to interpret the results and develop further practical guidelines. Thus, Ibrahim et al. offered recommendations on further use of NPs in clinical trials (Table 1, adapted from [9]).

Table 1. Recommendations for the estimation of NPs in clinical trials

If the objective is to exclude patients without heart failure
a. BNP <100 pg/mL or NT-proBNP <300 pg/mL to rule out AHF
b. BNP <35 pg/mL or NT-proBNP <125 pg/mL to rule out CHF
If the objective is to include patients with probable AHF in the emergency room, they should have dyspnea symptoms accompanied by the following thresholds
a. BNP > 100 pg/mL
b. NT-proBNP>450 pg/mL (<50 years); >900 pg/mL (50–75 years); > 1800 pg/mL (>75 years)
Risk assessment in patients with HFrEF and HFpEF
a. BNP ≥100 pg/mL or NT-proBNP ≥360 pg/mL in HFpEF
b. BNP ≥150 pg/mL or NT-proBNP ≥600 pg/mL in HFrEF
c. Consider the clinical manifestations, including the severity of symptoms, LVEF, and comorbidities, irrespective of the risk observed in patients with elevated BNP or NT-proBNP

NPs – natriuretic peptides; HF – heart failure; AHF – acute heart failure; CHF – chronic heart failure; HFrEF – heart failure with reduced ejection fraction; HFpEF – heart failure with preserved ejection fraction; LVEF – left ventricular ejection fraction; BNP – brain natriuretic peptide; NT-proBNP – N-terminal pro-brain natriuretic peptide

Prognostic value

The prognostic value of NPs has been estimated in several trials. For example, in 2014, Salah et al. [10] showed that cumulative 180-day mortality in patients with AHF admitted to the emergency room was 4.1% in patients with NT-proBNP <1,500 pg/mL. Mortality was twofold with NT-proBNP from 1,500 to 5,000 pg/mL, ir was 24% with NT-proBNP from 5,000 to 15,000 pg/mL, and reached 41% in patients with NT-proBNP more than 15,000 pg/mL [10]. Moreover, increased levels of NPs can be used as a prognostic marker in patients with documented HF to identify patients at higher risk even in the absence of HF symptoms. For example, in a large study of 30,487 patients, 62% of whom had no signs of HF, increased BNP levels were associated with twofold mortality comparable to patients with HF [11]. The possibility of using BNP for risk stratification and monitoring of patients with cardiovascular diseases (CVDs) was studied in the STOP-HF trial. The trial included 1,374 subjects who had risk factors for HF, such as arterial hypertension, dyslipidemia, obesity, coronary artery

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disease and manifested cardiac arrhythmias. The signs of systolic dysfunction confirmed by clinical investigations or clinical signs of heart failure were exclusion criteria. BNP levels were evaluated in all patients, but general practitioners could only access the test results of the main group. If BNP levels were >50 pg/mL, the patient was referred for cardiological consultation. Patients of the control group underwent annual examinations and received standard therapy. The follow-up period was 4 years. Monitoring the NP levels allowed the combined indicators of LV systolic dysfunction, LV diastolic dysfunction and HF, as well as the associated number of emergency admissions, to be reduced for severe CHF [12].

Treatment under NP monitoring

The diagnostic and prognostic roles of NPs in CHF have been well studied. However, the data used to determine patient management under NP monitoring are contradictory. The first studies in this area were promising. In the STARS-BNP study, Jourdain et al. [13] demonstrated a statistically significant decrease in HF mortality and hospitalization rates (24%) in the group of patients with CHF NYHA FC II-III and receiving therapy aimed at achieving BNP levels <100 pg/mL compared with patients treated without BNP monitoring (52%). However, only about one-third of patients in the treatment group reached the target BNP levels [13]. Similar results were obtained in the Pro-BNP study [14]. However, more recent and larger studies showed no superiority of treatment over BNP monitoring. GUIDE-IT was a randomized, multicenter trial including 1,100 patients with HFrEF, elevated BNP levels in the preceding 30 days, and a history of heart failure. Patients were randomized to the group of treatment under NT-proBNP monitoring aiming to achieve the target levels <1000 pg/mL or a group of conventional treatment according to the clinical guidelines. Cardiovascular death and time to the first hospitalization for CHF were used as the primary endpoints. The study included 894 patients who were followed up for an average of 15 months. The primary endpoint was achieved in 164 (37%) patients in the biomarker monitoring group and 164 (37%) patients in the conventional treatment group (adjusted odds ratio (OR) 0.98, 95% confidence interval (CI) 0.79–1.22; p=0.88). The incidence of the secondary endpoints or achievement of NT-proBNP target levels did not reduce. The study was terminated early due to the lack of effect of the chosen strategy. [15] Thus, if a patient receives adequate treatment following the clinical guidelines and under medical supervision, the management with the additional NP monitoring has no advantages.

The findings of the recent trials studying NPs are reflected in the 2019 European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations [16].

Main provisions of the practical guidance on the use of natriuretic peptide concentrations developed by the Heart Failure Association of the European Society of Cardiology

1. NPs should always be used in conjunction with all other clinical information.
2. NPs are reasonable surrogates for intracardiac volumes and filling pressures.
3. NPs should be measured in all patients presenting with symptoms suggestive of HF, such as dyspnoea and/or fatigue, as their use facilitates the early diagnosis and risk stratification of HF.
4. NPs have very high diagnostic accuracy in discriminating HF from other causes of dyspnoea: the higher the NP, the higher the likelihood that HF causes dyspnoea.
5. Optimal NP cut-off concentrations for the diagnosis of acute HF in patients presenting to the emergency department with acute dyspnoea are higher compared with those used in the diagnosis of chronic HF in patients with dyspnoea on exertion.
6. Obese patients have lower NP concentrations, mandating the use of lower cut-off concentrations (about 50% lower).
7. In stable HF patients, but also in patients with other cardiac disorders such as myocardial infarction, valvular heart disease, atrial fibrillation, or pulmonary embolism, NP concentrations have high prognostic accuracy for death and HF hospitalization.
8. Screening with NPs for the early detection of relevant cardiac disease, including left ventricular systolic dysfunction in patients with cardiovascular risk factors, may help to identify patients at increased risk, therefore allowing targeted preventive measures to prevent HF.
9. BNP, NT-proBNP, and MR-proANP have comparable diagnostic and prognostic accuracy.

10. In patients with shock, NPs cannot be used to identify the cause (e.g., cardiogenic vs. septic shock) but remain prognostic.
11. NPs cannot identify the underlying cause of HF and, therefore, if elevated, must always be used in conjunction with cardiac imaging.

The national clinical guidelines for chronic heart failure of 2020 are more categorical. "Brain natriuretic peptide and N-terminal pro-brain natriuretic peptide (NT-proBNP) should be estimated in all patients with suspected CHF". There is also a commentary: "Natriuretic peptides are biological markers of heart failure, which are also used to monitor treatment efficacy. Normal levels of NPs in treatment-naive patient virtually eliminate heart damage, i.e., CHF is unlikely. In the gradual (not acute) onset of symptoms, NT-proBNP and BNP levels lower than 125 pg/mL and 35 pg/mL, respectively, indicate the absence of heart failure)" [1].

Thus, in the light of experience gained over the past 20 years, which led to a new understanding of the interpretation of NP tests, it was necessary to find new, more specific, accurate and accessible biomarkers.

Stimulating growth factor sST2

Another very well-studied marker of HF is the growth stimulation expressed gene 2 (ST2). ST2 is a protein of the interleukin (IL)-1 receptor family, which is released under myocardial stress and has two isoforms: transmembrane ligand ST2L and soluble circulating component (sST2) [17]. Interleukin-33 (IL-33), comprising a member of the cytokines IL-1 superfamily expressed in epithelial and endothelial cells, is a ligand for ST2. IL-33 produces a cardioprotective effect by reducing apoptosis and suppressing fibrosis. Soluble component (sST2) acts, by contrast, as a decoy receptor for IL-33, prevents it from binding with the ST2 ligand, which causes the death of cardiomyocytes, fibrosis and ventricular remodeling. Several studies have showed that it is not only a marker of fibrosis, but also of inflammation. Given the involvement of sST2 in such pathogenetic aspects as the development of fibrosis, myocardial stress and inflammation, the use of this protein as a potential marker of heart failure is very promising.

Diagnosis and prognosis of HF

The first studies of the diagnostic significance of ST2 showed its increase in patients with AHF, but the diagnostic value of NP was higher than that of sST2 in the comparative analysis [18]. A series of trials and meta-analyzes have confirmed the advantage of ST2 as a prognostic marker. For example, a meta-analysis by Aimo et al. [19] of 7 studies with a total of 6,372 patients with CHF showed high predictive accuracy for the risk of all-cause death (OR 1.75, 95% CI 1.37–2.22) and cardiovascular death (OR 1.79, 95% CI 1.22–2.63; $p < 0.001$). The large-scale study PARAGON-HF provided further confirmation of the high prognostic value of ST2. Increased initial levels of sST2 were statistically significantly associated with the increased cardiovascular mortality and hospitalization for heart failure [20]. Skvortsov et al. [21] showed that levels of sST2 had the highest sensitivity to the development of a combined endpoint (cardiovascular death, repeated hospitalization due to HF, decompensated HF and clinical death with successful resuscitation) in patients hospitalized with decompensated CHF within a year. Changes in the sST2 levels during therapy were also prognostically valuable [21].

Treatment under sST2 monitoring

The studies demonstrated changes in sST2 levels occurring in response to treatment, which in combination with its high predictive value, makes it reasonable to use this biomarker for optimizing the treatment of patients with HF. A blind, randomized controlled trial STADE-HF recently performed to evaluate treatment efficacy under sST2 monitoring included 123 patients hospitalized for AHF. Patients were randomized to the conventional treatment group (unknown sST2 levels) or the treatment group under sST2 monitoring, which was estimated on Day 4 of hospitalization to determine the management. The primary endpoint was a frequency of repeated hospitalizations for any reason in 1 month. Although no significant differences in the endpoint were found between the groups, a greater than 18% decrease in the sST2 level was associated with a lower frequency of repeated hospitalization [22].

To sum up, it is clear that sST2 has a high prognostic value in predicting heart failure. It should be noted that this biomarker, which is unaffected by risk factors (sex, BMI reduced renal function), has an advantage over NP. Finally, the long-term outcomes of sST2 monitoring should be studied.

Galectin-3

Given the pathogenetic significance of fibrosis in the development of HF, it is of growing interest

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Супрозафен

ДВОЙНАЯ ЗАЩИТА
СЕРДЦА И СОСУДОВ
в 1 таблетке

ПЕРВАЯ И ЕДИНСТВЕННАЯ В РОССИИ ФИКСИРОВАННАЯ КОМБИНАЦИЯ РОЗУВАСТАТИНА И ФЕНОФИБРАТА[1,2]

НОРМАЛИЗАЦИЯ ЛИПИДНОГО СПЕКТРА[3,4]

СНИЖЕНИЕ РИСКА СЕРДЕЧНО-СОСУДИСТЫХ СОБЫТИЙ[5,6]

Супрозафен. Регистрационный номер: ЛП-006619. **Группировочное наименование:** розувастатин + фенофибрат. **Лекарственная форма:** таблетки, покрытые пленочной оболочкой, 5 мг +145 мг, 10 мг + 145 мг. **Показания к применению:** лекарственный препарат Супрозафен предназначен для применения у взрослых пациентов, которым показан одновременный прием розувастатина и фенофибрата в соответствующих дозах, при наличии следующих дислипидемий: – первичная гиперхолестеринемия (тип IIa по классификации Фредриксона) или смешанная гиперхолестеринемия (тип IIb по классификации Фредриксона) в качестве дополнения к диете, когда диета и другие немедикаментозные методы лечения (например, снижение массы тела, физические упражнения) оказываются недостаточными; – гипертриглицеридемия (тип IV по классификации Фредриксона) в качестве дополнения к диете. Лекарственный препарат Супрозафен не должен применяться для стартовой терапии у пациентов, ранее не получавших гиполипидемические лекарственные средства. **Противопоказания:** гиперчувствительность к розувастатину, фенофибрату или любому компоненту препарата; возраст до 18 лет (эффективность и безопасность не установлены); тяжелые нарушения функции печени: класс С по классификации Чайлд-Пью (10-15 баллов по шкале Чайлд-Пью), включая билиарный цирроз и персистирующее нарушение функции печени неясной этиологии; заболевания печени в активной фазе, включая стойкое повышение сывороточной активности трансаминаз и любое повышение активности трансаминаз в сыворотке крови (> 3 раза по сравнению с верхней границей нормы (ВГН)); тяжелое и умеренное нарушение функции почек (КК ниже 60 мл/мин); миопатия; предрасположенность к развитию миотоксических осложнений; миотоксичность на фоне применения ингибиторов ГМГ-КоА-редуктазы или фибратов в анамнезе; наличие в анамнезе фотосенсибилизации или фототоксичности при лечении фибратами или кетопрофеном; заболевания желчного пузыря в анамнезе; хронический или острый панкреатит, за исключением случаев острого панкреатита, обусловленного выраженной гипертриглицеридемией; одновременный прием лекарственного препарата Супрозафен и циклоспорина, других фибратов или других ингибиторов ГМГ-КоА-редуктазы (правастатин, аторвастатин, симвастатин и т.д.); у женщин: беременность, период грудного вскармливания, отсутствие адекватных методов контрацепции; врожденная галактоземия, непереносимость лактозы, недостаточность лактазы, нарушение всасывания глюкозы и галактозы (препарат содержит лактозу); врожденная фруктоземия, недостаточность сахаразы-изомальтазы, синдром глюкозо-галактозной мальабсорбции (препарат содержит сахарозу). **С осторожностью:** почечная недостаточность легкой степени тяжести, одновременный прием пероральных антикоагулянтов, возраст старше 65 лет, состояния, при которых отмечено повышение плазменной концентрации розувастатина, расовая принадлежность (азиатская раса), заболевания печени в анамнезе, сепсис, артериальная гипотензия, обширные хирургические вмешательства, травмы, тяжелые метаболические, эндокринные или электролитные нарушения или неконтролируемые судорожные припадки. **Применение при беременности и в период грудного вскармливания:** прием Супрозафена противопоказан при беременности и в период лактации. Фертильность: Клинические данные по влиянию препарата на фертильность у людей отсутствуют. Беременность: нет достаточных данных о применении фенофибрата у беременных. В случае возникновения беременности в процессе терапии, прием препарата Супрозафен должен быть прекращен немедленно. Период грудного вскармливания: Прием препарата Супрозафен в период грудного вскармливания противопоказан. При необходимости применения при лактации, грудное вскармливание необходимо прекратить. **Способ применения и дозы*:** внутрь, в любое время суток, независимо от времени приема пищи. Таблетку проглатывают целиком, не разжевывая и не измельчая, запивая водой. До начала терапии препаратом Супрозафен пациент должен начать соблюдать стандартную гипохолестеринемическую диету и продолжать соблюдать ее во время лечения. Препарат Супрозафен принимают по 1 таблетке один раз в сутки. Рекомендуемая начальная доза препарата Супрозафен составляет 5 мг + 145 мг 1 раз в сутки. В случае необходимости доза препарата может быть увеличена через 4 недели до максимальной дозы 10 мг +145 мг 1 раз в сутки. Пожилые пациенты. Коррекции дозы не требуется. Необходим мониторинг функции почек данной категории пациентов. Пациенты с нарушением функции почек. У пациентов с почечной недостаточностью легкой степени тяжести коррекция дозы не требуется. Препарат Супрозафен следует применять с осторожностью у пациентов с почечной недостаточностью легкой степени тяжести. У пациентов с умеренной и тяжелой почечной недостаточностью применение препарата Супрозафен противопоказано. Пациенты с нарушением функции печени. Препарат Супрозафен противопоказан пациентам с заболеваниями печени в активной фазе и с тяжелыми нарушениями функции печени. Этнические группы. При изучении фармакокинетических параметров розувастатина у пациентов разных этнических групп отмечено увеличение системной концентрации розувастатина у японцев и китайцев. Генетический полиморфизм. Для носителей генотипов с.521CC или с.421AA рекомендуемая максимальная доза розувастатина составляет 20 мг один раз в сутки. Сопутствующая терапия. При одновременном применении препарата Супрозафен с лекарственными препаратами, повышающими концентрацию розувастатина в плазме крови, может повышаться риск миопатии, включая рабдомиолиз. В таких случаях следует оценить возможность назначения альтернативной терапии или временного прекращения применения препарата Супрозафен. Дети. Препарат Супрозафен противопоказан к применению у детей в возрасте до 18 лет. **Побочное действие*:** со стороны эндокринной системы: сахарный диабет 2 типа; со стороны нервной системы: головная боль, головокружение; со стороны желудочно-кишечного тракта: боль в животе, рвота, диарея, метеоризм, тошнота, запор; со стороны печени и желчевыводящих путей: повышение активности сывороточных трансаминаз; со стороны скелетно-мышечной и соединительной ткани: миалгия; общие расстройства и нарушения в месте введения: астенический синдром; лабораторные и инструментальные данные: повышение уровня гомоцистеина крови. При приеме ингибиторов ГМГ-КоА-редуктазы сообщалось о побочных эффектах: депрессия, нарушения сна, включая бессонницу и «кошмарные» сновидения, сексуальная дисфункция, гипергликемия, повышение уровня гликированного гемоглобина. Описание отдельных нежелательных реакций при применении розувастатина: со стороны почек и мочевыводящей системы: протеинурия; со стороны скелетно-мышечной системы и соединительной ткани: миалгия, миопатия (включая миозит); лабораторные показатели: при приеме розувастатина отмечали изменения лабораторных показателей: повышение концентрации глюкозы, билирубина, активности гамма-глютамилтранспептидазы, щелочной фосфатазы, нарушения функции щитовидной железы. Перечень всех побочных действий представлен в инструкции по медицинскому применению. **Передозировка*:** Информация о передозировке для лекарственного препарата Супрозафен отсутствует. Розувастатин: при одновременном приеме нескольких суточных доз фармакокинетические параметры розувастатина не изменяются. Лечение: симптоматическое. Фенофибрат: есть единичные сообщения о передозировке, о симптомах не сообщалось. Лечение: симптоматическое. **Взаимодействие с другими лекарственными средствами*:** при приеме фенофибрата одновременно со статинами (правастатин, симвастатин, аторвастатин) или другими фибратами повышается риск серьезного токсического воздействия на мышцы. Дозу розувастатина корректируют при необходимости его совместного применения с лекарственными средствами, увеличивающими экспозицию к розувастатину. Требуется соблюдать особую осторожность при применении с антацидами, гемфиброзилом и другими гиполипидемическими средствами, ингибиторами транспортных белков, ингибиторами протеазы вируса иммунодефицита человека (ВИЧ), изоферментами цитохрома Р450, фузидовой кислотой, циклоспорином, эзетимибом, эритромицином, антагонистами витамина К, пероральными контрацептивами/гормон заместительной терапией, пероральными антикоагулянтами, производными тиазолидиндиона (глитазонами), секвестрантами желчных кислот, эстрогенами. **Особые указания*:** перед назначением препарата Супрозафен следует провести лечение для устранения причины вторичной гиперхолестеринемии. Розувастатин. Почечные эффекты: у пациентов, получавших высокие дозы розувастатина (в основном 40 мг), наблюдалась канальцевая протеинурия. Определение креатинфосфокиназы: терапия должна быть прекращена, если уровень КФК значительно увеличен (> 5 раз по сравнению с ВГН) или если симптомы со стороны мышц резко выражены и вызывают ежедневный дискомфорт. Печень: прием розувастатина прекратить или уменьшить дозу, если активность трансаминаз в сыворотке крови в 3 раза превышает ВГН. Ингибиторы протеаз: не рекомендуется совместное применение с ингибиторами протеаз. Интерстициальное заболевание легких: при подозрении на интерстициальное заболевание легких следует прекратить терапию препаратом Супрозафен. Сахарный диабет 2-го типа: при концентрации глюкозы от 5,6 до 6,9 ммоль/л терапия розувастатина ассоциировалась с повышенным риском развития СД 2-го типа. Фенофибрат. Функция печени: пациенты, у которых на фоне лечения повысилась активность «печеночных» трансаминаз, требуют внимания, и в случае повышения активности АЛТ и АСТ >3 раза по сравнению с ВГН прием препарата прекращают. При появлении симптомов гепатита (желтуха, кожный зуд) следует провести лабораторные исследования и, в случае подтверждения диагноза гепатит, отменить препарат. Панкреатит: описаны случаи развития панкреатита в период лечения фенофибратом. Мышцы: токсическое влияние на мышечную ткань может быть заподозрено на основании жалоб пациента на слабость, диффузную миалгию, миозит, мышечные спазмы и судороги и/или выраженного повышения активности КФК (более чем в 5 раз выше ВГН). В этих случаях лечение препаратом Супрозафен необходимо прекратить. Почечная функция: при повышении концентрации креатинина > 50 % выше ВГН лечение следует приостановить. Гематологические нарушения: после начала терапии фенофибратом наблюдалось легкое или умеренное снижение уровня гемоглобина, снижение гематокрита и уменьшение числа лейкоцитов. Сообщалось о возникновении тромбоцитопении и агранулоцитоза у отдельных пациентов, получавших фенофибрат. Гиперчувствительность немедленного типа: в случае, если наблюдаются признаки или симптомы гиперчувствительности немедленного типа, необходимо немедленно обратиться к врачу и прекратить применение препарата. Гиперчувствительность замедленного типа: при подозрении на серьезные нежелательные реакции со стороны кожи необходимо прекратить прием и проводить специфическое лечение. Парадоксальное снижение ЛВП: при выраженном снижении содержания ЛВП следует отменить препарат и контролировать содержание ЛВП до возвращения к исходным значениям. Вспомогательные вещества: препарат Супрозафен содержит лактозу и сахарозу, его не следует применять при лактазной недостаточности, непереносимости галактозы и глюкозо-галактозной мальабсорбции, врожденной фруктоземии, недостаточности сахаразы-изомальтазы, синдроме глюкозо-галактозной мальабсорбции. **Влияние на способность управлять транспортными средствами, механизмами:** следует соблюдать осторожность при управлении автотранспортом или работе, связанной с повышенной концентрацией внимания и психомоторной реакцией (риск развития головокружения). **Условия отпуска:** отпускают по рецепту. ***Полная информация представлена в инструкции по медицинскому применению.** СИП от 19.03.2021 на основании ИМП ЛП-006619 от 04.12.2020

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to study galectin-3, which is a lectin product of macrophages, which is involved in a fibrosis cascade. The role of galectin-3 in myocardial remodeling was first described in 2006 by van Kimmenade et al. [23].

Diagnosis and prognosis of HF

The diagnostic value of galectin-3 has been extensively studied in patients with AHF and CHF. The controlled and randomized HF-ACTION study showed a significant increase in the galectin-3 levels in patients with CHF. However, this biomarker is considered to be inferior to NP as a predictor of adverse outcomes [24]. Given the role of fibrosis in the pathogenesis of HFpEF, the data obtained by Dubolazova & Drapkina [25] are of interest; according to these data, there was a significant increase in the serum levels of galectin-3 in patients with HFpEF compared to patients HFrEF. The possibility of using this biomarker in the diagnosis of HFpEF was confirmed by Kanukurti et al. [26], who showed that serum galectin-3 within 10.1 ng/mL has 77.78% sensitivity and 95% specificity with an area under the curve (AUC) of 0.93, which exceeds the diagnostic sensitivity of NT-proBNP in patients of this group.

The prognostic value of galectin-3 remains unclear. In the study assessing the efficacy of valsartan therapy (Val-HeFT), initial levels of galectin-3 were not associated with the risk of all-cause death or hospitalization due to heart failure. However, an increase in the galectin-3 levels per 1 ng/mL was associated with increased risks of death at 2.9%, achieving primary endpoint at 2.1% and hospitalization for heart failure at 2.2% [27]. When comparing the prognostic significance of biomarkers of interest, the superiority of sST2 in assessing risks of achieving endpoints should be noted [28].

To sum up, galectin-3 appears to be an attractive candidate for the diagnosis of HFpEF. However, its application as a prognostic marker and a method of HF treatment monitoring is still relatively unknown.

Omics-based biomarkers

Omics-based biomarkers include four levels: genomics (a study of genes and their functions), transcriptomics (a study of all RNA molecules, including non-coding RNA), proteomics (a study of proteins) and metabolomics (an analysis of molecules involved in metabolism). The rapid development of postgenomic researches in the past decade caused a stir in all areas of medicine, including cardiology, giving hope for the development of new biomarkers. A postgenomic research is a study of mechanisms that can effect changes in gene expression, or, in other words, changes in protein synthesis without altering the DNA sequence. Experimental studies allowed to correlate the presence of risk factors and epigenetic modifications. It is currently believed that at least three mechanisms are responsible for initiating and maintaining epigenetic changes: DNA methylation, histone modification and non-coding RNA (ncRNA). Combined with data on the stability of these molecules, the detection of ncRNA, such as microRNA, long non-coding RNA (lncRNA) and annular RNA circulating in the blood and other biological fluids, makes them potentially interesting and promising biomarkers for the diagnosis and monitoring of various diseases.

MicroRNAs that control gene expression through the transcript degradation or the translation suppression when bounding to the three prime untranslated regions (3' – UTR) of the target mRNA are among the best studied. Fundamental and clinical trials demonstrated the significance of microRNAs in the regulation of cell differentiation, growth, proliferation, apoptosis, oxidative stress and inflammation. In other words, microRNAs are involved in the regulation of basic pathogenetic links of the development and progression of HF [29–32] (Figure 3). Since the range of circulating microRNAs may vary considerably in different phenotypes of HF, HF patients are likely to have reduced levels of circulating microRNA. However, the origin and functions of circulating microRNAs are still unclear. One of the controversial issues is whether the levels of circulating microRNAs reflect the tissue levels of microRNA? In attempting to answer this question, Akat et al. [33] showed that differences in tissue microRNA expression in patients with severe HF compared to healthy individuals usually do not affect the levels of circulating microRNAs. Moreover, microRNA expressed by hematopoietic and endothelial cells prevailed among the circulating ncRNAs, with only 0.1% expressed by cardiac microRNA. However, the expression of these microRNAs correlates with changes in the expression of tissue microRNAs. Although the detection of microRNA may be hindered by low blood levels, they still represent highly specific markers [33]. Tijsen et al. [34] revealed increased levels of circulating miR-423-5p in patients with HF and similar tissue expression in a pathological study in patients with dilated cardiomyopathy. It should also be noted that microRNAs circulating in HF may be due to system

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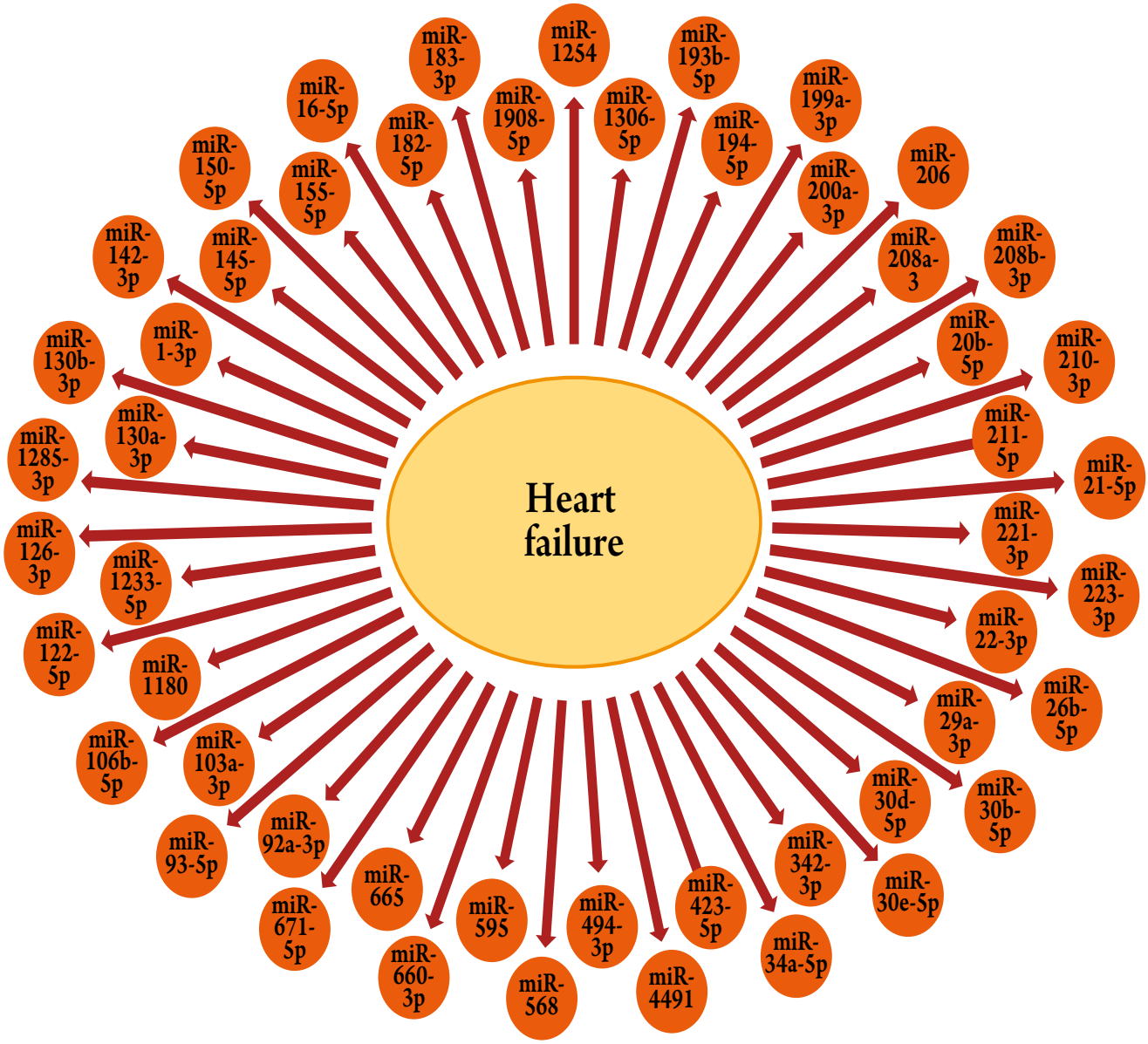
Figure 3. MicroRNAs associated with heart failure



disorders caused by volume overload and impaired organ perfusion, which in turn may be of interest in terms of searching for possible biomarkers.

HF diagnosis

The first studies aimed at assessing the diagnostic value of microRNAs in AHF and CHF appeared about 10 years ago. A study in a small sample of patients showed the most interesting results for miR-21 associated with fibrosis, myocardial hypertrophy and apoptosis; miR-23 related to the regulation of angiogenesis and apoptosis, while miR-423-5p demonstrated value as a diagnostic and prognostic marker of HF in several clinical trials [29]. The study carried out by Seronde et al. [29], which included 294 patients with AHF, 58 with noncardiac dyspnea and 44 with CHF, seem interesting. It shows a significant decrease in the expression of miR-126 and miR-423-5p in the groups of patients with dyspnea compared to the group of patients with CHF. Here, the levels of miR-21 and miR-23 did not differ between the groups. The same study assessed the prognostic value of miR-423-5p in the main group and in the validation group (n=711) [29]. The results of a study evaluating the expression of 132 microRNAs in 1,700 patients have been published recently. The analysis identified a panel of 8 microRNAs with high specificity and sensitivity comparable to NP. The total score of NP and the microRNA panel increased the specificity to 99%.

Studying microRNA as a marker differentiating HFrEF and HFpEF was another objective of the trial. However, both sensitivity and specificity were significantly lower in this case [31].

Prognosis for HF

The prognostic value of microRNA concerning the development HF is also of interest. Besides small researches, there are new works studying larger cohorts using standardized measurement methods. A study of the predictive value of 12 circulating microRNAs in two independent cohorts with a total of 2,203 subjects carried out by Bayés-Genis et al. [35] demonstrated a statistically significant correlation of miR-1254 and miR-1306-5p along with the development of the endpoints such as all-cause death and hospitalization due to HF.

Treatment under the microRNA monitoring

Assessment of the microRNA levels as a marker of treatment response can be very promising since microRNAs regulate various mechanisms of myocardial remodeling and are expressed in different ways depending on the degree of structural and functional heart disorders. In a recent study, the expression of 84 microRNAs was analyzed before and after the implantation of a cardiac resynchronization device. A total of 24 circulating microRNAs associated with HF and 5 microRNAs (26b-5p, 145-5p, 92a-3p, 30e-5p, 29a-3p) were found, whose levels were directly correlated with left ventricular ejection fraction (LVEF) and inversely correlated with the levels of NT-proBNP. CRT-induced reverse LV myocardial remodeling and improvement of the systolic function of the heart were associated with increased expression of 19 microRNAs. The absence of positive effects after the device implantation was accompanied by a modified expression of only 6 microRNAs [32].

The results of the microRNA analysis in patients with severe CHF and heart transplant recipients in early and late post-transplantation periods have been published recently. It has been shown that patients with end-stage HF had a statistically significant increase in the expression of microRNA-101, -27, -339 and -424 in the blood plasma. The levels of expression of miR-101 and -27 decreased in the early post-transplantation period [36].

These results are not only of interest for the development of predictors of drug and implant response, but also suggest that microRNA-based pharmaceuticals could improve the outcomes in patients with HF.

Given the complexity of HFpEF diagnosis, the active search for microRNAs differentiating HFrEF and HFpEF continues. The first papers described the microRNA panels, which are significantly different in patients with HFrEF and HFpEF [37–39]. In 2019, Chen et al. [40] highlighted the potential of two microRNAs characteristic of HFpEF – miR-3135b and miR-3908 – as markers differentiating HFrEF and HFpEF. However, it should be noted that these studies were based on small patient samples. Each study provided a unique set of microRNAs, whose conflicting results were possibly due to different inclusion criteria and heterogeneous comorbidities.

There is still a long way to study the biological role, pathogenetic features, and diagnostic possibilities of circulating microRNA in HF. First of all, there are several technical issues to solve, and the methodology should be standardized to achieve better reproducibility. Only then would it be possible to implement protocols for using microRNA in clinical practice. However, it is now possible to talk about the great potential of assessing microRNA as a biomarker with higher diagnostic and prognostic value than conventional indicators [41].

Metabolomics

Another promising area to search for HF biomarkers is metabolomics, a comprehensive assessment of endogenous metabolites. Recent advances in this area showed the crucial role of previously unknown metabolites or metabolic pathways in the development of cardiovascular diseases. Given the high energy needs of the myocardium, systemic and myocardial metabolic disorders may directly initiate a vicious cycle causing HF and promoting its progression [42]. More papers are becoming available in the literature that analyze the association of metabolites with the parameters of myocardial remodeling and the HF course. For example, a retrospective study of metabolomic profiles of 2,336 subjects of the Framingham trial followed up for an average of 15.8 years showed a clear correlation between three metabolites and LV remodeling: kynurenine, diacylglycerol and leucine with left ventricular end-diastolic dimension [43]. In another study of 74 patients with coronary artery disease, a negative correlation was found between the levels of sphingosine-1 phosphate and sphingomyelin with LVEF [44]. Our study showed a significant association of the circulating

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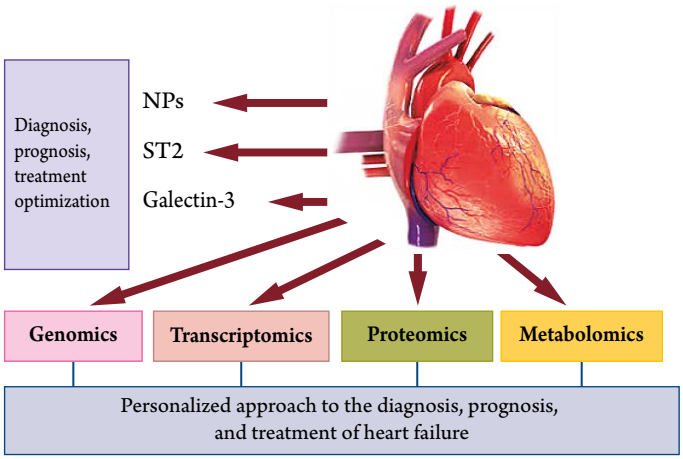
Figure 4. Potential heart failure biomarkers



acylcarnitine levels with the degree of myocardial hypertrophy and parameters of diastolic dysfunction [45].

Diagnosis and prognosis of HF

The diagnostic value of plasma metabolomic profiling was shown in a study by Cheng et al. [46]. The most valuable metabolites for CHF diagnosis were histidine, phenylalanine, spermidine and phosphatidylcholine C34:4. Statistically significant differences in groups of patients with CHF at various stages were identified by the levels of histidine, phenylalanine, ornithine, spermine, spermidine, phosphatidylcholines and taurine [47]. Metabolomic profiling allows identifying biomarkers in blood plasma and urine. Kang et al. [47] detected decreased levels of 1 methylnicotinamide, pyruvate and 2 oxoglutarate in urine samples of HF patients. Very few papers on the prognostic value of metabolomic profile in CHF patients were published. Analyzing metabolomic profiles of 5,341 patients from the PROSPER trial and 7,330 patients from the FINRISK trial, among whom 182 and 133 patients, respectively, had been hospitalized for decompensated CHF within the previous 3–5 years, Delles et al. [48] found a direct association of phenylalamine levels and negative association of acetate levels with the risk of developing CHF. Despite the large scale, the study had several limitations. Since the nuclear magnetic resonance spectroscopy was performed on 20-year old samples, some of the metabolic compounds may have been affected by degradation. Moreover, the results could have been distorted by a failure to distinguish the origin and course of CHF among patients. Lanfear et al. [49] also demonstrated the prognostic significance of the metabolomic profile in 1,032 patients with HF and LVEF <50%. The results show the presence of a combination of amino acids and acylcarnitines (metabolomic profile), whose significant variation depending on the severity and type of CHF was shown to function as predictors of death in this group of patients.

Thus, these studies suggest that the profile of plasma metabolites may be a useful tool to understand the phenotype subgroups in HF and a possible substrate for the identification of novel biomarkers (Figure 4). However, additional large randomized clinical trials should be carried out. There is no doubt that metabolomics will enormously improve the understanding of HF pathophysiology.

Conclusion

The study of biomarkers in terms of their pathophysiological role and changes in their levels under the effect of various treatment options leads to insights into the pathogenetic features of the course of heart failure, providing a basis for the development of new drug therapies. While the evaluation of the levels of brain natriuretic peptide and its N-terminal precursor remains the gold standard for the diagnosis and prognosis of heart failure, limitations associated with the influence of various factors on the levels of natriuretic peptides, as well as threshold ambiguity and low informative value in heart failure with preserved ejection fraction, stimulate the continuing search for highly sensitive and specific biomarkers.

Novel biomarkers, such as ST2 and galectin-3, were gradually finding their way into clinical practice and were included in the Guideline for the Management of Heart Failure of the American College of Cardiology [50]. The development and rapid progress in the improvement of modern technologies opened the door to the identification of novel biomarkers. Multiomic profiling is likely to be the next logical step. Of course, this will require the development of bioinformatic technologies necessary for the analysis of large data. Omics technologies are just starting to develop, and many more reproducible clinical observations are needed to move from experimental studies to clinical application. However, this area is of great potential in searching for novel biomarkers and a possible breakthrough in the treatment of heart failure.

No conflict of interest is reported.

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