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Frequency of use and Indications for Beta-Blockers in Heart Failure with Preserved Ejection Fraction

Aim	To evaluate trends in beta-blocker prescribing and incidence of possible reasons for beta-blocker administration, including arterial hypertension (AH), atrial fibrillation (AF), ischemic heart disease (IHD), and myocardial infarction, in participants of clinical studies enrolling patients with chronic heart failure with preserved ejection fraction (CHF-PEF).
Material and methods	A systematic literature search was performed in the PubMed and EMBASE databases. The study included RCSs of pharmacological therapies for patients with CHF-PEF conducted from 1993 through 2019. Studies of beta-blocker efficacy or those including a specific population (CHF-PEF+IHD or CHF-PEF+AH, etc.) were excluded from the analysis. Baseline characteristics of patients, incidence rate of beta-blocker prescribing, and prevalence of AH, AF, IHD, and MI were recorded. Trends in prevalence of concomitant diseases and the proportion of patients using beta-blockers by the year of enrollment to the study were analyzed with the Mann-Kendall test.
Results	14 RCSs of 718 selected publications completely met the inclusion and exclusion criteria. Beta-blocker prescribing significantly increased between 1993 and 2019 (tau=0.51; p=0.014) and reached 80% in recent studies. Furthermore, prevalence of IHD, MI, AH, and AF did not significantly change among the RCS participants (p>0.05 for all). However, while for AH and AF, a tendency toward an increasing prevalence (tau=0.4; p=0.055 and tau=0.043; p=0.063, respectively) could be considered and became statistically significant for AF when the ALDO-DHF study was excluded from the analysis (tau=0.5; p=0.042), the MI prevalence tended to decrease (tau= –0.73; p=0.06).
Conclusion	Beta-blocker prescribing to patients upon inclusion into RCSs for CHF-PEF has significantly increased for the recent 20 years while the incidence of formal reasons for beta-blocker administration (AF, AH, MI, IHD) did not significantly change.

Keywords	Beta-blockers; chronic heart failure with preserved ejection fraction; heart rate
For citation	Kokhan E.V., Kiyakbaev G.K., Kobalava Zh.D. Frequency of use and Indications for Beta-Blockers in Heart Failure With Preserved Ejection Fraction. Kardiologiia. 2020;60(6):30–40. [Russian: Кохан Е.В., Киякбаев Г.К., Кобалава Ж.Д. Частота и обоснованность назначения бета-адреноблокаторов у пациентов с хронической сердечной недостаточностью и сохраненной фракцией выброса: анализ динамики данных рандомизированных клинических исследований. Кардиология. 2020;60(6):30–40]
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Beta-blockers are the main group of drugs recommended to improve the prognosis in patients presenting with chronic heart failure (CHF) and reduced ejection fraction (HFrEF) [1, 2]. However, there is no conclusive evidence of the beneficial effect of beta-blockers on the prognosis in patients with CHF and preserved ejection fraction (HFpEF).

At the same time, beta-blockers are administered in patients with HFpEF under the current guidelines based on the need to control blood pressure (BP) and ventricular rate in concomitant atrial fibrillation (AF), and/or a diagnosis of coronary artery disease (CAD) [1, 3]. In the latter case, the use of beta-blockers seems to be the most reasonable, and are administered to improve the prognosis in patients with a recent (<1 year) myocardial infarction (MI) [4–6].

However, beta-blockers are relatively commonly administered in patients with HFpEF in clinical practice (70-80%), which is almost comparable with patients with HFrEF [7-10]. This is hypothetically due to both the high prevalence of the above diseases and perhaps an inertial approach of physicians projecting the treatment of HFrEF onto patients of this category regardless of a new attitude to the role of beta-blockers in the treatment of patients with hypertension and CAD, which has changed over the past decade.

The perspective of the pathogenesis of HFpEF is continuously evolving. This has not resulted in new proven treatments, yet has contributed to the development of new diagnostic algorithms (including the mandatory determination of the levels of natriuretic peptides) [1, 3, 11]

ISSN 0022-9040. Kardiologiia. 2020;60(6). DOI: 10.18087/cardio.2020.6.n1062

and slightly changed the perceptions of clinical and demographic profiles of such patients. For example, in the first trials, patients with HFpEF and HFrEF often differed only in the ejection fraction [12]. Now it is evident that there are differences between these two groups in the rates of other cardiovascular diseases, particularly CAD (e.g., MI) and hypertension, which is the most relevant in this context [7, 8, 13]. The role of CAD in the development of HFpEF appears to be relatively small. Hypertension is considered to be one of the leading causes of HFpEF [14]. It should be noted that according to the majority of current guidelines, beta-blockers are not the first-line of treatment of patients with hypertension [15–17]. This can mainly be attributed to the lack of efficacy in reducing central BP [18], the increased levels of which appear to be associated with the development of diastolic dysfunction and thus HFpEF [19].

Moreover, several recent retrospective trials have suggested that the use of beta-blockers in patients with documented HFpEF could be unfavorable from both hemodynamic and prognostic perspectives [20–22].

Thus, our objective was to assess the rate trend of using beta-blockers and the possible reasons for their administration (hypertension, AF, CAD, MI) in the subjects of randomized clinical trials (RCTs), including patients with HFpEF.

Material and methods

Literature search

A systematic search of the literature was carried out in the PubMed and EMBASE databases. The object of the search was the RCTs of drug therapy of HFpEF from December 1993 (publication of the MDC trial [23]) to November 2019. The following keywords were used: heart failure, preserved ejection fraction, normal ejection fraction, diastolic dysfunction, random*. The search field is shown in Figure 1. The abstracts and then the full-text versions of the publications were reviewed. One researcher retrieved the data.

The analysis included RCTs carried out in several centers and included patients with HFpEF (ejection fraction ≥40%). Trials were excluded in which exercise-based treatment programs were tested using beta-blockers as comparators, and which lacked information about medication administered, and which included patients with HFpEF and additional criteria (e.g., hypertension, obesity, etc.). Patients with CAD and/or history of MI were also excluded. If a full-text English version was not available, the publication was not analyzed.

Data retrieved and analysis

The following data was extracted from each article: trial title if available/first author's name, enrollment period, number of patients included, average age, ejection fraction as an inclusion criterion, whether a certain level of NT-proBNP/BNP was used as an inclusion criterion, percentage of patients receiving beta-blockers and other drug treatments, patients with hypertension, AF, CAD, history of MI, and CHF of ischemic origin. If there was no required data in the main publication, an additional search of the trial-related publications was performed.

The Mann–Kendall test was used to estimate the rate trends for comorbidities and the percentage of patients receiving a specific drug treatment based on the inclusion years. The R statistical package was used. The results were considered statistically significant at $p < 0.05$.

Results

General characteristics of the trials

The search criteria were met by 718 abstracts. After reviewing titles and abstracts of the articles, 37 trials were selected, of which 14 publications (total number of patients n=18 077) fully met the inclusion and exclusion criteria and were included in the analysis (see Figure 1).

Figure 1. Flow-chart of the search and selection of trials included in the analysis

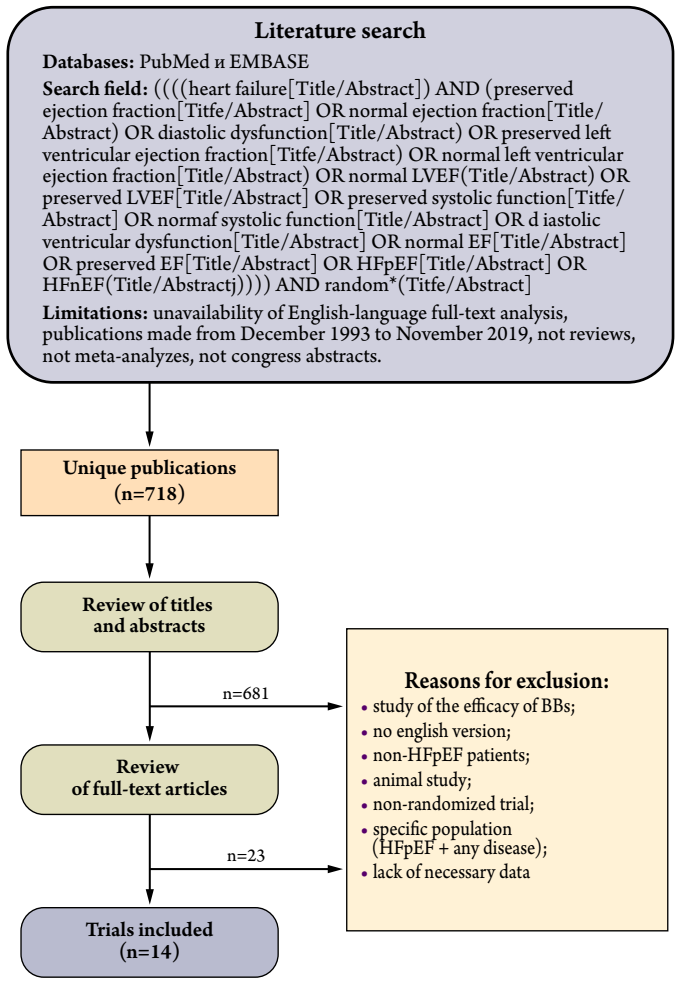


Table 1. Characteristics of trials included in the analysis

Title / first author	Period of inclusion	Number of subjects	EF for inclusion, %	Natriuretic peptides for inclusion	Comparison groups	Primary endpoint	Primary endpoint result
Zi et al. [24]	1997–1999	74	40	No	Quinapril vs. placebo	6MWD	Negative
CHARM-Preserved [25]	1999–2000	3023	40	No	Candesartan vs. placebo	Cardiovascular death + hospitalization for HF	Negative
PEP-CHF [26]	2000–2003	850	40 (40–50)*	No	Perindopril vs. placebo	All-cause death + hospitalization for HF	Negative
I-PRESERVE [27]	2002–2005	4128	45#	No	Irbesartan vs. placebo	All-cause death + hospitalization for cardiovascular diseases	Negative
TIME-CHF [28]	2003–2006	123	45	Yes	Correction of treatment according to NT-proBNP vs. a standard approach	18-month survival without hospitalization for HF	Negative
TOPCAT [29]	2006–2012	3445	45	Yes or hospitalization with HF	Spironolactone vs. placebo	Cardiovascular death + successful cardiac arrest resuscitation + hospitalization for HF	Negative
Aldo-DHF [30]	2007–2012	422	50#	No	Spironolactone vs. placebo	Change in E/E' and peak O_2 consumption at cardiopulmonary exercise test	E/E' positive and peak O_2 consumption negative
RELAX [31]	2008–2012	216	50	Yes or increase in LV filling pressure	Sildenafil vs. placebo	Change in peak O_2 consumption at cardiopulmonary exercise test	Negative
PARAMOUNT [32]	2009–2011	301	45	Yes	Sacubitril/valsartan vs. placebo	Change in NT-proBNP levels	Positive
EDIFY [33]	2013–2015	179	45§	Yes	Ivabradine vs. placebo	Change in E/E', 6MWD, and NT-proBNP	Negative
NEAT-HFpEF [34]	2014–2015	110	50	Yes or echo-cardiographic signs of LVDD	Isosorbide mononitrate vs. placebo	Daily activity (accelerometer measured)	Negative (the drug is inferior)
PARAGON-HF [35]	2014–2016	4,796	45#	Yes	Sacubitril/valsartan vs. placebo	Cardiovascular death + all hospitalizations for HF	Negative
INDIE-HFpEF [36]	2016–2017	105	50	Yes or echo-cardiographic signs of LVDD	Inorganic nitrite vs. placebo	Change in peak O_2 consumption at cardiopulmonary exercise test	Negative
Shah et al. [37]	2017–2018	305	45#	Yes	Neladenoson vs. placebo	6MWD	Negative

*, EF 40% was the exclusion criterion, one of the four echocardiographic inclusion criteria was EF 40–50%, explained by the authors by a common combination of systolic and diastolic dysfunction in HFpEF; #, EF <40% was the exclusion criterion; §, EF 50% was the initial inclusion criterion. EF, ejection fraction; 6MWD, 6-minute walk distance; CVD, cardiovascular disease; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; DD, diastolic dysfunction; LV, left ventricle; HFpEF, heart failure with preserved ejection fraction.

ISSN 0022-9040. Kardiologiia. 2020;60(6). DOI: 10.18087/cardio.2020.6.n1062

The characteristics of the included trials are detailed in Table 1. Several drugs were tested in each trial except for TIME-CHF. In these trials, both rigid (6 trials) and surrogate (8 trials) endpoints were outcomes. Fewer patients were expectedly included in the latter trials.

In earlier trials, EF 40% was used as the inclusion criterion – this was 45-50% in subsequent trials. Moreover, elevated NT-proBNP/BNP levels were not used as inclusion criteria in earlier trials. In later trials (since 2003), the elevated levels were used as either mandatory criteria or options to specific clinical and echocardiographic characteristics.

Characteristics of patients included in the trial

Table 2 provides the clinical and demographic characteristics of the subjects of each trial. In most trials, a little more than 50% of all subjects were female. The mean age of patients was 67–80 years old and in most trials was not higher than 75.

Several points should be emphasized in the characteristics of drug therapies. For example, although digoxin was administered in every third patient in the earlier RCTs, the number of patients taking digoxin in later trials either was not indicated or did not exceed 10-15%. The rate of angiotensin-converting enzyme (ACE) inhibitor/angiotensin II receptor blocker use is difficult to estimate since in the first RCTs they were the trial drugs. Thus, patients who had already been using them were almost not included in the trials. In later trials, the rate of their prescription at inclusion was 54-93%. It can also be noted that the rate of administration of mineralocorticoid receptor antagonists increased after the TOPCAT trial was complete.

The NEAT-HFpEF and INDIE-HFpEF trials were distinguished by the fact that patients much more rarely took ACE inhibitors, beta-blockers, and were more likely to have CAD. That was probably due to the fact that the trial drugs were nitrates, and the authors sought to select a population with the highest potential for using those agents.

The rate of beta-blocker use and indications for their use in the trial subjects

It should be noted that not all publications mentioned both a proposed etiological factor of CHF and the rate of such diseases as CAD and MI; this reduced the accuracy of subsequent analysis.

When the rate trends of beta-blocker use and patients with CAD, MI (Figure 2) was estimated, it was found that the percentage of patients taking beta-blockers increased statistically significantly over time (from earlier to later RCTs) (tau=0.51; p=0.014). The trend of the increase continued (tau=0.43; p=0.05) even when the earliest trial (ZI et al.), including only 14% of patients taking beta-blockers at enrollment, was excluded [24].

The rate of CHD and MI did not change statistically significantly (tau= –0.07; p=0.86 and tau= –0.73; p=0.06, respectively). However, it should be noted that only 6 of the 14 trials included data about the latter. In all of them, except for CHARM-Preserved, the rate of MI did not exceed 30% (see Table 2).

Table 2. Clinical and demographic characteristics of patients from the trials included in the analysis

Title / first author	Hyper-tension	CAD	MI	CHF of ischemic origin	AF	DM	Female	Age, years	HR, bpm	BB	ACE inhibitor / ARB	MCRA	Digoxin	CCB
Zi et al. [24]	30	57	–	–	35	15	65	78 ± 7		14	–	–	33	30
CHARM-Preserved [25]	64	–	44	56	29	28	40	67 ± 11	71 ± 12	56	Excl. (ACE inhibitor 19)	11	28	31
PEP-CHF [26]	79	–	27	–	21	21	56	75 [72; 79]	73 [66; 82]	55	Excl.	10	12	33
I-PRESERVE [27]	89	48	24	25	29	28	60	72 ± 7	72 ± 11	59	Excl. (ACE inhibitor 26)	15	14	40
TIME-CHF [28]	87	–	–	35	–	41	66	80 ± 7	75 ± 13	68	86	26	14	–
TOPCAT [29]	91	59	26	–	35	32	52	69 ± 10	68 ± 11	78	ACE inhibitors 65/ARB 20	Excl.	–	38
Aldo-DHF [30]	92	40	–	–	5	17	52	67 ± 8	65 ± 13	72	77	Excl.	–	25
RELAX [31]	85	39	–	–	51	43	48	69 [62; 77]	69 [61; 78]	76	70	11	–	31
PARAMOUNT [32]	93	–	21	–	42	38	57	71 ± 9	70 ± 13	79	93	21	–	
EDIFY [33]	91	53	–	–	Excl.	41	65	73 [67; 79]	75 [71; 79]	74	87	29	–	37

All data except for age and heart rate are given as percentage; empty cells — information is not available in the trial publications.
CAD, coronary artery disease; MI, myocardial infarction; CHF, chronic heart failure; AF, atrial fibrillation; DM, diabetes mellitus; BB, beta-blocker; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MCRA mineralocorticoid receptor antagonist; CCB, calcium channel blocker.

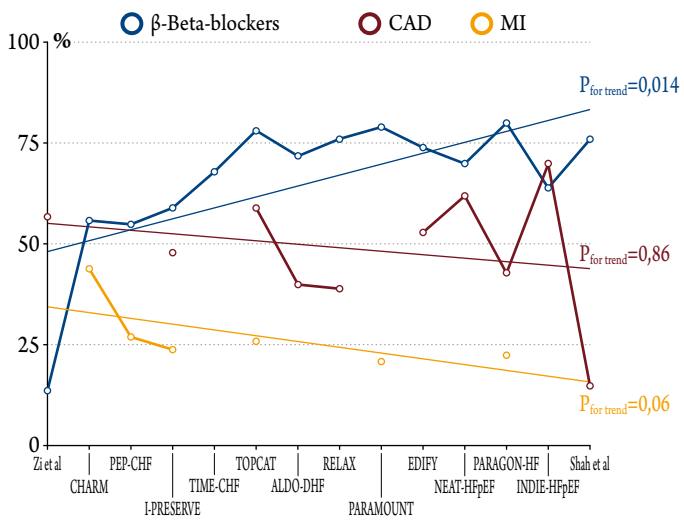
From a statistical point of view, the percentage of patients with hypertension and AF (Figure 3) in the RCT subjects also did not change significantly over time (tau=0.4; p=0.055 and tau=0.43; p=0.063, respectively). However, there was a clear trend towards statistical significance in both cases. At the same time, it is obvious that most of the hypertension curve is almost parallel to that of beta-blockers. As for AF, when the ALDO-DHF trial with a minimal number of patients with AF was excluded from the analysis since the primary endpoint was a change in E/E' (which is most informative in sinus rhythm), the increase in the rate of AF, reached statistical significance as the trials continued (tau=0.5; p=0.042).

Discussion

Several RCTs assessed the efficacy of beta-blockers in patients with HFpEF. The first trial was SWEDIC which demonstrated improved diastolic function versus placebo in the form of an increased E/A after six-month therapy using carvedilol [38]. However, the assessment of predictive value in the J-DHF trial did not show that carvedilol had a significant effect on the composite endpoint, which included cardiovascular death and unscheduled hospitalizations for CHF. It should be noted that the J-DHF trial was conducted only in the Japanese population. The achieved median dose of carvedilol was only 7.5 mg/day, which could be insufficient to detect its positive effects. An unplanned analysis to assess the dose-dependent effects of carvedilol established that patients who took more than 7.5 mg/day of carvedilol were at lower risk of experiencing the primary endpoint than those in the placebo subgroup (odds ratio [OR] 0.54; 95% confidence interval [CI] 0.30–0.96; p=0.036) [39].

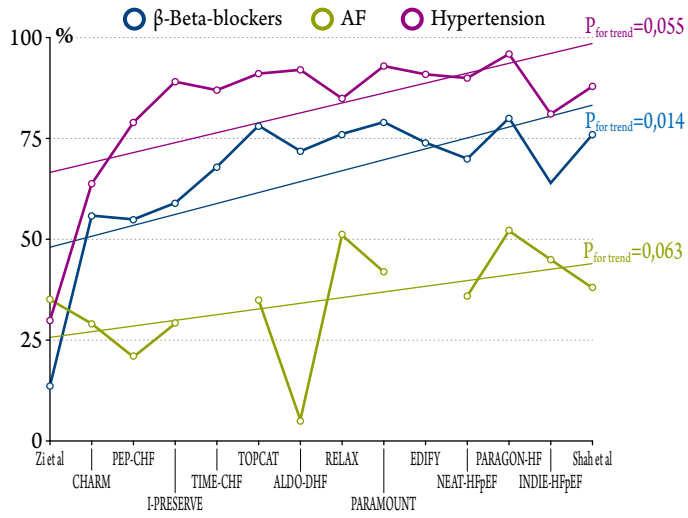
The efficacy of nebivolol was estimated in patients with CHF in the SENIORS trial which found that from a statistical point of view the drug significantly reduced the risk of the primary endpoint, which included all-cause death and hospitalization for cardiovascular disease exacerbation (OR 0.86; 95% CI 0.74–0.99; p=0.039) [40]. At the same time, based on the fact that every third subject had preserved EF (>35%), it was suggested that this data could be extrapolated to patients with HFpEF. This was confirmed by the results of a pre-designed subanalysis. This analysis found that the efficacy of nebivolol was comparable in the subgroups with reduced (<35%) and conditionally preserved (≥35%) EF (p=0.72) [41]. However, it should be emphasized that mean EV in the preserved EF subgroup was only 49%. According to the current classification of CHF, this would have put most patients into the mid-range EF subgroup [42]. These patients were more likely to be more comparable to patients with CHF not only in terms of clinical and demographic characteristics but also the responses to various therapies [8, 42–45]. Prospective randomized clinical trial ELANDD showed no increase in the 6 -minute walk distance after six-month therapy with nebivolol in patients with HFpEF (EF >45%) [46].

Figure 2. The rate trends of beta-blockers and representation of patients with CAD and MI



The interruption of the MI and CAD curves is due to the lack of information relating to their presence in the subjects of the corresponding trials. The Y-axis is the percentage of patients taking beta-blockers or having CAD or MI in a corresponding trial. The X-axis presents trials in order of time. CAD, coronary artery disease; MI, myocardial infarction.

Figure 3. The rate trends of beta-blockers and the percentage of patients with hypertension and AF



The interruption of the AF curve is due to the absence of information on its presence in subjects of the TIME-CHF trial and the exclusion of patients with AF from the EDIFY trial. The Y-axis is the percentage of patients taking beta-blockers or having CAD or MI in a corresponding trial. The X-axis presents trials in order of time. AF, atrial fibrillation.

ISSN 0022-9040. Kardiologiia. 2020;60(6). DOI: 10.18087/cardio.2020.6.n1062

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Повышенная чувствительность к ивабрадину, метопрололу (и другим препаратам группы бета-адреноблокаторов ввиду возможной перекрестной чувствительности), а также к вспомогательным веществам; выраженная или симптоматическая брадикардия; кардиогенный шок; острый инфаркт миокарда (ОИМ) или подозрение на ОИМ, осложненный выраженной брадикардией, атриовентрикулярной блокадой I степени, артериальной гипотензией (АГ) (систолическое артериальное давление (АД) менее 100 мм рт.ст.) и/или тяжелой сердечной недостаточностью; синдром слабости синусового узла (включая синоатриальную блокаду); атриовентрикулярная блокада (AV) II и III степени; тяжелая артериальная гипотензия (АД менее 90/50 мм рт.ст.) или симптоматическая артериальная гипотензия; нестабильная или острая сердечная недостаточность; у пациентов, периодически получающих кратковременное лечение бета-адреномиметиками; пациенты, зависимые от кардиостимулятора (у которых сердечный ритм обеспечивается только постоянной кардиостимуляцией); нестабильная стенокардия; тяжелое заболевание периферических сосудов; нелеченая феохромоцитома; тяжелая печеночная недостаточность; метаболический ацидоз; одновременное применение с мощными ингибиторами изоферментов CYP3A4, такими как противогрибковые средства группы азолов (кетоконазол, итраконазол), антибиотики группы макролидов (кларитромицин, эритромицин для приема внутрь, джозамицин, телитромицин), ингибиторы ВИЧ-протеазы (нелфинавир, ритонавир) и нефазодон; одновременное применение с верапамилом или дилтиазеом; беременность, грудное вскармливание и применение женщинами с сохраненным детородным потенциалом, не использующими надежные методы контрацепции; возраст до 18 лет (эффективность и безопасность применения в данной возрастной группе не изучалась). ОСОБЫЕ УКАЗАНИЯ*. Пациенты с умеренно выраженной печеночной недостаточностью (менее 9 баллов по шкале Чайлд-Пью): с осторожностью. Недостаточность положительного эффекта в отношении клинических исходов у пациентов с симптоматической стабильной стенокардией: в качестве симптоматической терапии стабильной стенокардии, поскольку ивабрадин не оказывает положительного эффекта на частоту сердечно-сосудистых событий (например, инфаркт миокарда или смерть вследствие сердечно-сосудистых причин) у таких пациентов. Контроль ЧСС: определение ЧСС в покое у пациентов, принимающих ивабрадин, при принятии решения о коррекции дозы должно быть выполнено одним из указанных способов: серийное измерение ЧСС, ЭКГ или 24-часовое амбулаторное мониторирование ЭКГ. Нарушения сердечного ритма: Импликор® не рекомендуется пациентам с фибрилляцией предсердий или другими типами аритмий, связанными с функцией синусового узла. Повышен риск развития фибрилляции предсердий. Необходимо регулярное клиническое наблюдение за пациентами для своевременного выявления фибрилляции предсердий. Если в период лечения возникла фибрилляция предсердий, соотношение ожидаемой пользы к возможному риску при дальнейшем применении ивабрадина должно быть еще раз тщательным образом проанализировано. Пациенты с хронической сердечной недостаточностью (ХСН) и нарушениями внутрижелудочковой проводимости (блокада левой или правой ножки пучка Гиса) и желудочковой диссинхронией должны находиться под пристальным контролем. Применение у пациентов с низкой ЧСС: противопоказан, если до начала терапии ЧСС в покое составляет менее 70 уд. Если на фоне терапии наблюдается стойкое снижение ЧСС в покое менее 50 уд/мин или у пациента возникают симптомы, связанные с брадикардией, необходимо уменьшить дозу препарата, перейдя на прием препаратов на основе монокомпонентов, до достижения оптимальной дозы метопролола или отменить лечение. Комбинированное применение с блокаторами «медленных» кальциевых каналов (БМКК): противопоказано. ХСН: у пациентов с ХСН IV ФК по классификации NYHA применять с осторожностью. Инсульт: не рекомендуется назначать препарат сразу после перенесенного инсульта. AV I степени: с осторожностью. Тяжелые нарушения функции почек (клиренс креатинина менее 15 мл/мин): с осторожностью. Функции зрительного восприятия: применять с осторожностью у пациентов с пигментной дегенерацией сетчатки. Отмена терапии: нельзя резко отменять бета-адреноблокаторы. Прекращение приема должно сопровождаться одновременным приемом метопролола в виде монокомпонентного препарата в оптимальной для пациента дозе. Если необходимо, применение ивабрадина можно прекратить резко. Дозу метопролола следует снижать постепенно, желательно в течение не менее 2 недель, одновременно начиная заместительную терапию, если необходимо. В случае появления у пациента любых симптомов отмены снижение дозы должно быть более постепенным. Артериальная гипотензия: с осторожностью, при тяжелой артериальной гипотензии (АД менее 90/50 мм рт.ст.) применение противопоказано. Фибрилляция предсердий – сердечные аритмии: плановую электрическую кардиоверсию следует проводить не ранее чем через 24 часа после приема последней дозы ивабрадина. Применение у пациентов с врожденным синдромом удлиненного интервала QT или у пациентов, принимающих препараты, удлиняющие интервал QT: не следует назначать. Применение у пациентов с артериальной гипертензией, которым требуется изменение антигипертензивной терапии: терапия должна сопровождаться регулярным контролем АД. Применение у пациентов с бронхиальной астмой и ХОБЛ: с осторожностью и при необходимости назначать бронходилатирующие средства. Тяжелые поражения периферических сосудов: следует отменить препарат и подобрать индивидуальные дозы монокомпонентных препаратов. Феохромоцитома: при подтвержденном или предполагаемом диагнозе «феохромоцитома» применять бета-адреноблокаторы следует в комбинации с альфа-адреноблокаторами. Пациенты с сахарным диабетом: следует применять с осторожностью (бета-адреноблокаторы могут маскировать некоторые симптомы гипогликемии, в том числе тахикардию). Стенокардия Принцметала: применение бета-адреноблокаторов может увеличить продолжительность и частоту приступов стенокардии Принцметала. Применение кардиоселективных бета1-адреноблокаторов возможно в случае минимальных и ассоциированных форм заболевания и только в сочетании с вазодилататорами. Псориаз: можно применять только после тщательной оценки соотношения пользы и риска. Тиреотоксикоз: симптомы тиреотоксикоза могут маскироваться при приеме бета-адреноблокаторов. Общая анестезия: необходимо предупредить врача-анестезиолога о проводимом лечении. Если необходима отмена бета-блокатора, применение препарата прекращают постепенно. Полностью прием препарата должен быть прекращен за 48 часов до общей анестезии. Пациенты пожилого возраста: необходимо тщательно контролировать клиническое состояние пожилых пациентов, поскольку чрезмерное снижение АД или ЧСС может привести к недостаточному кровоснабжению жизненно важных органов. Аллергические реакции: с осторожностью, так как метопролол может повышать чувствительность к аллергенам и усиливать тяжесть анафилактических реакций. У спортсменов: следует принимать во внимание возможность получения положительных результатов допинг-теста. ВЗАИМОДЕЙСТВИЕ С ДРУГИМИ ЛЕКАРСТВЕННЫМИ СРЕДСТВАМИ*. Противопоказанные сочетания: мощные ингибиторы изофермента CYP3A4; умеренные ингибиторы изофермента CYP3A4 (дилтиазем или верапамил), бета-адреномиметики. Нежелательные сочетания: лекарственные средства, удлиняющие интервал QT, грейпфрутовый сок, барбитураты, гипотензивные лекарственные препараты центрального действия, антиаритмические препараты I класса. Сопутствующее применение с осторожностью: калийнесберегающие диуретики (тиазидные и «петлевые» диуретики), другие умеренные ингибиторы изофермента CYP3A4, индукторы изофермента CYP3A4, индукторы изофермента CYP2D6, ингибиторы изофермента CYP2D6, лидокаин, ингаляционные анастетики, нитраты, сердечные гликозиды, бета-адреноблокаторы и ингибиторы моноаминооксидазы, адреналин, парасимпатомиметики, нестероидные противовоспалительные препараты, инсулин и пероральные сахароснижающие препараты. Комбинации, которые нужно принимать во внимание: трициклические антидепрессанты, нейролептики, мефлохин, дипиридамол (в/в), альфа-адреноблокаторы, применяемые в урологии, эрготамин, курареподобные миорелаксанты, флоктафенин, антациды. БЕРЕМЕННОСТЬ И ПЕРИОД ЛАКТАЦИИ*. Противопоказан. ВЛИЯНИЕ НА СПОСОБНОСТЬ УПРАВЛЯТЬ ТРАНСПОРТНЫМИ СРЕДСТВАМИ И ВЫПОЛНЯТЬ РАБОТЫ, ТРЕБУЮЩИЕ ВЫСОКОЙ СКОРОСТИ ПСИХОМОТОРНЫХ РЕАКЦИЙ*. Пациентов следует предупредить о возможных нежелательных симптомах (таких как головная боль, головокружение, повышенная утомляемость), которые могут усиливаться на фоне приема алкоголя или изменения терапии. ПОБОЧНОЕ ДЕЙСТВИЕ*. Очень часто: изменения световосприятия (фосфены), повышенная утомляемость. Часто: ночные кошмары, патологические сновидения, головная боль, бессонница, сонливость, головокружение, нечеткость зрения, брадикардия, AV-блокада I степени (удлинение интервала PQ на ЭКГ); желудочковая экстрасистолия, ощущение сердцебиения, неконтролируемое АД, фибрилляция предсердий, ощущение похолодания конечностей, болезнь Рейно, ортостатическая гипотензия, одышка при физической нагрузке, тошнота, запор, диарея, боли в животе, рвота, нарушение либидо. Нечасто: эозинофилия, обострение псориаза, гиперурикемия, гипогликемия, депрессия, спутанность сознания, галлюцинации, замедление скорости психических и двигательных реакций, понимания, эпизоды потери сознания, паркостезии, ступор, нарушение зрения, синдром «сухого» глаза, раздражение конъюнктивы, диплопия, вертиго, атриовентрикулярная блокада I степени, ощущение сердцебиения, суправентрикулярные экстрасистолы, сердечная недостаточность, кардиогенный шок, боль в грудной клетке, артериальная гипотензия, перемежающаяся хромота, снижение АД, одышка, бронхоспазм, ангионевротический отек, кожная сыпь, дистрофические изменения кожи, крапивница, гипергидроз, псориаз, мышечные судороги, мышечные спазмы, астения, отеки, увеличение массы тела, повышение концентрации кратинина в плазме крови, удлинение интервала QT на ЭКГ. Редко: тромбоцитопения, повышенная возбудимость, тревога, снижение продукции слезы, конъюнктивит, шум в ушах, нарушения ритма сердца, нарушение проводимости миокарда, ринит, сухость слизистой оболочки полости рта, дисгевзия, отклонения показателей функции печени, нарушения функции печени, эритема, кожный зуд, алопеция, мышечная слабость, недомогание, повышение активности «печеночных» трансаминаз, половая дисфункция/импотенция. Очень редко: лейкопения, деперсонализация, амнезия, ксерофтальмия, нарушение слуха, снижение слуха, глухота, AV блокада II и III степени, синдром слабости синусового узла, учащение и утяжеление приступов у пациентов со стенокардией, сухая гангрена, ретроперитонеальный фиброз, гепатит, реакции фотосенсибилизации, артралгия, болезнь Пейрони. ПЕРЕДОЗИРОВКА*. ФАРМАКОЛОГИЧЕСКОЕ ДЕЙСТВИЕ*. Ивабрадин – препарат, замедляющий ритм сердца, механизм действия которого заключается в селективном и специфическом ингибировании I_f каналов синусового узла, контролирующих спонтанную диастолическую деполяризацию в синусовом узле и регулирующих ЧСС. Ивабрадин дозозависимо снижает ЧСС. Метопролол – кардиоселективный блокатор, блокирующий β_1-адренорецепторы (расположенные преимущественно в сердце) в дозах значительно меньших, чем дозы, требующиеся для блокирования β_2-адренорецепторов (локализованные главным образом в периферических сосудах и бронхах). Метопролол не обладает мембраностабилизирующей и внутренней симпатомиметической активностью. ФОРМА ВЫПУСКА*: Таблетки, покрытые пленочной оболочкой, 5 мг + 25 мг, 7,5 мг + 25 мг, 5 мг + 50 мг, 7,5 мг + 50 мг. По 14 таблеток в блистер (ПВХ/Ал). По 1, 2, 4 и 6 блистеров с инструкцией по медицинскому применению в пачку картонную.

* Для получения полной информации, пожалуйста, обратитесь к инструкции по медицинскому применению лекарственного препарата.

1. Divchev D. et al. Cardiol Ther. 2017;6: 239-249. Дивчев Д. и соавт. Кардиология и терапия. 2017; 6: 239-249

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Реклама.

Thus, RCTs carried out at different times did not demonstrate any evidence supporting the use of beta-blockers in patients with HFpEF. However, when we analyzed the rates of administration of beta-blockers in patients with HFpEF with the inclusion in RCTs (1997–2018), we found that it increased to 75-80% in the most recent trials.

This trend could be due, inter alia, to an increase in the rates of such factors of HFpEF as hypertension, AF, CAD, MI which serve as an independent indication for the administration of beta-blockers. For this reason, we evaluated the rate trends of these diseases in the selected trials. However, it should be noted that there was a limitation related to the fact that some of those trials lacked information about the presence of CAD, MI, and AF. Thus, it was difficult to judge the validity of our findings. Given the general trends in the understanding of origin and pathogenesis of HFpEF [47], it can be assumed that the rate of CAD and MI in subjects of the RCTs at least did not increase, whereas there was a certain trend towards a decrease in the rate of MI. This is important since it is MI, especially within a year after the accident, which serves an indication for the administration of beta-blockers to improve the prognosis [4–6]. Thus, the most reasonable indication for the use of beta-blockers (i.e., history of MI) is hardly sufficient to explain the increased rate of their administration by the RCT subjects.

According to our findings, the rate of hypertension and AF in the RCT subjects are most likely to increase. The analysis did not provide a clear explanation of the causal relationship between this trend and the increased rate of beta-blocker use, since it did not take into account the individual characteristics of patients. However, the parallel curves of the rate trends for beta-blockers and the presence of hypertension indicate that this relationship is possible and that hypertension could often be the reason for the administration of beta-blockers. The latter allows for a cautious suggestion that the increased rate of hypertension in the subjects could explain the increased rate of beta-blocker use. This is also important since, as mentioned above, beta-blockers are recommended in hypertension only in specific clinical situations (AF, CAD, MI) [15–17]. The recommendations were provided mainly after the meta-analysis published by Bangalore et al. in 2008 showing that a decrease in the heart rate during the use of beta-blockers in patients with hypertension increased the risk of adverse cardiovascular events [48]. The increased risk is most often explained from a pathophysiological point of view by an insufficient decrease or even an increase in central BP when beta-blockers are used [18, 49, 50]. However, despite considerable discussions of this phenomenon, the rate of beta-blocker use in the RCTs analyzed appeared to be highest after 2008. Therefore, it is relevant to assess the changes in the percentage of patients with AF, since there are no signs of an increase in the percentage of patients with CAD and MI in the HFpEF trials. During the trial period, the number of such patients, as well as the percentage of patients with hypertension, was most likely to show a trend towards an increase. From a statistical point of view, this became significant when the ALDO-DHF trial (with the selection at inclusion based on AF) was excluded from the analysis.

At the same time, if we consider AF as the basis for using beta-blockers in patients with HFpEF in our analysis, we should pay attention to the EDIFY trial from which patients with AF were excluded, and a heart rate of more than 70 bpm was an inclusion criterion. Even in that case, the rate of beta-blocker use was relatively high (74%) and comparable to that in other trials conducted in this period. Moreover, the rate of AF in later trials did not exceed 35-45%, while almost 80% of subjects took beta-blockers. Thus, we suggest that the contribution of the increased rate of AF to an increase in the rate of beta-blocker use in the HFpEF trials could hardly be considered critical.

In the context of the relevance of using beta-blockers to control the ventricular rate in AF and HFpEF, there is as yet no evidence of the predictive efficacy of beta-blockers in AF. Moreover, the presence of AF in patients with HFrEF undermines the positive effects of beta-blockers [43, 51, 52]. Ulimoen et al. have demonstrated that metoprolol or carvedilol reduced exercise tolerance and increased the NT-proBNP levels in patients with permanent AF and no CHF, while diltiazem or verapamil, on the contrary, increased exercise tolerance and decreased the NT-proBNP levels [53]. Therefore, the control of the ventricular rate with beta-blockers is likely not to be the best tool in the case of preserved EF.

Finally, another reason for the increased rate of beta-blocker use due to the time of RCTs may be a better awareness of the corresponding evidence obtained for HFrEF at the turn of the centuries [54]. These were extrapolated to populations with preserved EF and partially confirmed by the current guidelines. The rate of beta-blocker use in patients with HFpEF and HFrEF was often almost comparable and varied by no more than 10-15% in various registers [7-9]. This approach seems to be not entirely justified and may even be unsafe [50, 55]. For example, in addition to the absence of data that beta-blockers are able to improve the prognosis of life in patients with HFpEF, there is also a need to stress the results of several retrospective analyzes, according to which the use of these drugs in patients with HFpEF may increase the number of hospitalizations for CHF [20–22]. For example, in the most recent TOPCAT trial using the fit index paired design, the use of beta-blockers in patients with EF ≥50%

ISSN 0022-9040. Kardiologiia. 2020;60(6). DOI: 10.18087/cardio.2020.6.n1062

increased the risk of hospitalization for CHF by 74% (OR 1.74, 95% CI 1.28–2.37). It should be noted that prior to comparingpatients based on various characteristics, the rates of AF in subgroups of patients taking and not taking beta-blockers were almost the same, 42.6 and 40.7%, respectively [22]. It also implicitly confirms our suggestion that AF has no significant influence on the increasing rate of beta-blocker use in patients with HFpEF.

The reasons for the lack of efficacy and perhaps partially the safety of beta-blockers in HFpEF are unclear. The effects of beta-blockers are known to be inversely associated with the heart rate in HFrEF [56]. Elevated levels ofe heart rate (>70 bpm) are common in patients with both HFrEF and HFpEF. However, in the latter case, the association between an increase in the heart rate and risk of adverse outcomes was not identified in all trials [57]. Otherwise, the lower heart rate appeared to be associated with better outcomes, regardless of beta-blocker use [58–60]. This poses the question whether a decrease in the heart rate is a more important target than the use of beta-blockers.

In connection with using of a decrease in the heart rate as a tool to improve the course of HFpEF, the EDIFY trial should be mentioned. In this the isolated decrease in the heart rate by 13 (– 18; – 6) bpm during the use of ivabradine with the baseline level of 75 (72–78) bpm did not improve echocardiographic (E/E'), clinical (6-minute walk distance), and laboratory (NT-proBNP) values in patients with HFrEF. Moreover, a decrease in the heart rate appears to have some adverse hemodynamic effects in HFpEF; mainly when beta-blockers are used. For example, a possible increase after stres, associated with the increased pressure in the aorta, was discussed. Besides, the increased duration of diastole with limited relaxation capacity of the left ventricle accompanying the decrease in the heart rate leads to an increase in the end-diastolic pressure in the left ventricle (which explains the increased NT-proBNP levels during the use of beta-blockers in patients with HFpEF [38, 46, 61]). This causes difficulties in its filling and may eventually be accompanied by a decrease in stroke volume and, thus, cardiac index [50, 55]. One of the main factors limiting the functional reserve of patients with HFpEF is a failure to increase stroke volume and cardiac index under stress. This is obviously aggravated when drugs slowing down the heart rate are used [62]. Thus, we acknowledge that a high heart rate in HFpEF is an adverse factor. However, it is unclear what level of the heart rate is subject to pharmacological correction. The use of beta-blockers for this purpose may not be reasonable.

Despite the lack of convincing evidence of clinical predictive efficacy and safety of beta-blockers in HFpEF, the rate of their use in the patient population at inclusion in randomized clinical trials has increased over the past 20 years. Our analysis showed that this phenomenon is likely to be explained by a cumulative effect: a more significant number of patients with formal indications for beta-blockers (mainly AF and hypertension) on the one hand, and the extrapolation of the RCT findings on the use of beta-blockers in patients with HFrEF to the treatment of patients with preserved EF on the other. Of particular concern are the similar trends in the use of beta-blockers and the increase in the percentage of patients with hypertension, in which beta-blockers have less prognostic efficacy than other hypotensive agents. This indirectly indicates the presence of therapeutic inertness and may partly explain the failure of RCTs in HFpEF.

Thus, planned and current RCTs assessing the effects of beta-blocker withdrawal in patients with HFpEF are of interest [63, 64]. For example, the preliminary results of one of the trials showed that the withdrawal of beta-blockers is accompanied by a decrease in NT-proBNP in patients with HFpEF [64].

Study limitations

The results of our analysis do not reflect real-world clinical practice since it included the subjects of RCTs. This was due to our desire to assess the rate of beta-blocker use in patients with HFpEF over time by the critical stages of the evolution of knowledge of this disease. In some trials, the years of patient inclusion coincided, making it difficult to arrange them in order of time.

Moreover, given the nature of the data analyzed, we did not have the opportunity to determine the reason for the use of beta-blockers in each individual case. In most of the trials analyzed, a history of low EF was not an exclusion criterion, meaning that it could also be a reason for the use of beta-blockers in some patients. It is also not inconceivable that beta-blockers could be administered not for CVDs (migraine, etc.).

Next, as was stated earlier, some trials lacked data on the rate of analyzed diseases (AF, CAD, MI) reducing the accuracy of findings.

Finally, the judgments about the contribution of projecting the results of HFrEF randomized clinical trials onto the real-world treatment of patients with HFpEF are based only on the absence of a statistically significant association between the trends studied and are purely evaluative (assumption).

Conclusion

The rate of beta-blocker use in the patient population at inclusion in randomized clinical trials due to chronic heart failure and preserved ejection fraction statistically significantly has increased over the past 20 years. In contrast, the rate of formal causes for their administration (atrial

fibrillation, hypertension, myocardial infarction, coronary artery disease) has not significantly changed. At the same time, there has been a trend towards including more patients with hypertension and atrial fibrillation in these trials. However, the rate of patients with myocardial infarction, the only listed disease in which beta-blockers are administered to improve prognosis, was likely to decrease.

No conflict of interest is reported.

The article was received on 12/02/20

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