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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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INCIDENCE OF ADVERSE EVENTS RESULTING FROM BETA-BLOCKER TITRATION IN PATIENTS WITH HEART FAILURE

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Abstract.

Background and Objectives: Beta blockers are an essential part of the treatment and management of heart failure. Unfortunately, due to adverse events, it is not possible to titrate the medication to the recommended dose in all patients according to the guidelines. The role of adverse events in the treatment of bisoprolol, carvedilol, and metoprolol in the Georgian population when titration is not possible was studied.

Methods: A study was conducted to evaluate the side effects observed in low-dose and medium-dose beta blockers in Georgia. Initially 300 patients with reduced ejection fraction met the inclusion criteria, but only 223 developed side effects to beta blockers and were incorporated into the study. Patients were divided into 3 groups, depending on which beta blocker they were taking - bisoprolol, carvedilol, or metoprolol.

The data was evaluated using descriptive analysis and two-tailed independent t-tests.

Results: Out of the 223 patients that developed side-effects to beta blockers 64.1% had bradycardia, 54.2% had hypotension, 32.7% had dyspnea, 41.3% had fatigue, and 38.1% had dizziness. Episodes of bradycardia and hypotension prevailed in patients receiving bisoprolol, while the incidence of adverse events was more evenly distributed in the carvedilol and metoprolol groups. It is also worth noting that patients receiving bisoprolol more often experienced only 1 side effect compared to the carvedilol and metoprolol groups, where the simultaneous manifestation of multiple symptoms increased with increasing dose.

Summary: The inability to use beta-blockers at their maximum recommended dose is a major problem in Georgia. Only 25.7% of patients were able to take the recommended dose of the medication.

The study revealed the most frequently detected side effects that prevent medication titration, rarely occur alone, and in most cases the patient presents with a mixture of several side effects. Specific symptoms were noted to be associated with specific medications more often than with others, for example: patients on bisoprolol were noted to develop bradycardia more frequently than patients on carvedilol. Since titration to a higher dose of the medication is directly proportional to the increase in life-expectancy, it is preferable, if there is a choice, to prescribe treatment with the beta-blocker which the patient will be able to tolerate better and which has a lower risk of side effects.

Key words. Beta blockers, chronic heart failure, reduced ejection fraction, side effects, bisoprolol, carvedilol, metoprolol.

Introduction.

Heart failure is a clinical syndrome that develops when the heart is unable to provide an adequate blood supply to the body's metabolic needs. This change may be accompanied by structural and/or functional pathology manifested by a decrease in cardiac output and/or increased intracardial pressure. Heart failure is characterized by multiple symptoms that reduce a person's quality of life and reduce life-expectency: shortness of breath, ankle swelling, fatigue, pulmonary edema, ascites, hepatojugular reflux, etc. [1,2].

We can divide heart failure itself into three more classes. Heart failure with reduced ejection fraction (LVEF <40%), heart failure with moderately reduced ejection fraction (LVEF 40-49%), heart failure with preserved ejection fraction (LVEF ≥50%) [3].

Based on large-scale studies, it was determined that currently more than 64 million people in the world have heart failure, and the prevalence of any form of heart failure in developed countries is 12% [4,5]. The prognosis of the disease worsens with its progression; analysis of large-scale studies showed us (patients with any type of heart failure - 900,000 cases) that the probability of survival of patients with heart failure at 1, 5 and 10 years is 81.3%, 51.5% and 29.5%, respectively. The sharp decrease in life expectancy has emphasized the need for timely and adequate treatment tactics [6].

Despite many advances in medical devices, the treatment tactics recommended by the guidelines for heart failure are limited and include only drug treatment. Based on current guideline recommendations, beta-blockers represent one of the most dynamic parts of heart failure management. Since beta-blockers require titration, the medication needs frequent dose changes, which, in turn, present new challenges. In clinical practice, patients present with many comorbidities or develop side effects of drugs, it is impossible to titrate beta-blockers to the maximum recommended dose in all patients. Studies have shown that only 12% reach the optimal dose of beta-blockers [7]. The positive effect of beta-blockers in patients with heart failure is manifested by a decrease in sympathetic activity, catecholamine levels, and pulse. Beta-blockers promote left ventricular remodeling in young/middle-aged hypertensive patients and reduce the inflammatory background in heart failure [8].

Beta-blockers are most commonly used in the management and treatment of heart failure with reduced ejection fraction. In stable heart failure, it is recommended to start beta-blockers as early as possible and titrate them upwards [9]. Studies have shown that titration to a higher dose of beta-blocker was associated with longer survival in heart failure patients with reduced ejection fraction [10]. The most widely used beta-blockers in

heart failure are bisoprolol (a competitive inhibitor of beta1-adrenergic receptors), carvedilol (a competitive inhibitor of beta1, beta2 and alpha1 adrenergic receptors), and metoprolol (a competitive inhibitor of beta1-adrenergic receptors). Correct dosing and titration are of great importance when prescribing beta-blockers [11]. A study of 83,605 patients with heart failure with reduced ejection fraction found that the majority of patients were taking beta-blockers (81.4%), but only 49% were able to achieve ≥50% of the recommended dose in the guidelines [12]. The results highlight the problem of titration of beta-blockers. Another study, which included 72,336 patients, investigated the effect of beta-blockers on mortality. A meta-analysis of the studies found that beta-blocker therapy was associated with a 31% reduction in the risk of mortality. Another study, which looked at 11,558 patients over a period of 4 years, compared the effects of carvedilol, bisoprolol, and metoprolol in heart failure and chronic obstructive pulmonary disease. The results highlighted the superiority of bisoprolol in terms of increased survival and fewer side effects [13].

Bisoprolol has a much higher selectivity for beta1 receptors than other beta-blockers. As a result of this property, bisoprolol is better tolerated in patients with chronic obstructive pulmonary disease and peripheral vascular disease [14,15]. Bisoprolol is also not characterized by metabolic disorders [16]. Thus Bisoprolol is preferred among beta-blockers in the treatment of heart failure. Most of the absorption of bisoprolol (90%) occurs through the enteric tract. 30% of it is bound to plasma proteins. 50% undergoes metabolism in the liver and 50% is excreted by the kidneys. The half-life of bisoprolol is 10-11 hours, and in renal disease this time increases to 17±5 hours [17]. The CIBIS and CIBIS-II studies played an important role in revealing the potential of bisoprolol. In the CIBIS study, patients (n=641) received no more than 5 mg of bisoprolol per day. Mortality did not change significantly, but the study demonstrated the tolerability of bisoprolol in patients with heart failure without serious adverse events. In the CIBIS-II study, patients (n=2647) received bisoprolol at a higher dose (all patients titrated to 10 mg per day). The researchers found a significant difference in mortality between the study and placebo groups - 8.8% mortality per year in the study group and 13.2% in the placebo group, and the number of sudden deaths in the placebo group was 45% higher than in the study group. There was also a 32% reduction in hospitalizations. The results of the CIBIS-II study were so positive that the study was stopped early to share the results with the rest of the world. These two studies helped popularize beta-blockers in patients with heart failure and made clear the benefits of titrating to higher doses [18,19]. The CIBIS study highlighted the effect of bisoprolol on heart rate variability as a predictor of survival; the more pronounced the change in heart rate during bisoprolol treatment, the higher the patients' survivability and quality of life [20]. The CIBIS-II study, on the other hand, demonstrated that the increase in survivbility was an independent phenomenon of heart rate variability and that this positive factor was due to the activity of bisoprolol and not directly to heart rate variability [21].

Other studies have also highlighted the effect of beta-blockers on survival. The OPTIMIZE-HF program was established to promote beta-blockers. The part of the patients registered in it, 17241 patients, was divided into 2 cohorts - patients with systolic dysfunction and with preserved systolic function. Analysis of these cohorts again highlighted the effectiveness of beta-blockers in increasing life expectancy in the setting of reduced ejection fraction. The study also highlighted the lesser effectiveness of beta-blockers in the presence of preserved systolic function [22].

Given the positive effects on life expectancy and quality of life, it is easy to see why the inability to titrate to a high dose of beta-blockers is a major problem in the management of patients with heart failure [23-25].

The Heart Failure Pilot Study conducted by the European Society of Cardiology showed that only a small proportion of the patients studied were able to reach the target dose of beta-blockers: carvedilol - 37%, bisoprolol - 21%, metoprolol - 37% [26]. In the CIBIS-ELD study, 25% of patients were able to achieve and maintain the target dose of bisoprolol or carvedilol recommended by the guidelines. The study included 41 centers and lasted 12 weeks [27]. In the study, which included 12,493 patients, only 17.8% achieved the recommended dose of beta-blockers [28]. Proper titration of beta-blockers requires starting at a low dose and increasing to the next dose after 2 weeks of stable administration [29].

One of the reasons for the inability to titrate medications to the target dose is the increased frequency and severity of side effects that occur with high doses of the drug. Possible side effects of beta-blockers include: bradycardia, hypotension, dizziness, and depression. Therefore, it is not possible to administer beta-blockers at the recommended dosage in patients with high NYHA class (NYHA IV), conduction problems/blocks, and hypotension [30,31]. Another reason for the inability to titrate to a higher dose of medication is the presence of many other diseases in patients with heart failure, which aggravate the patient's condition and complicate the treatment process.

Heart failure, as a syndrome, has a complex etiology and is often associated with multiple comorbidities - hypertension, ischemic heart disease, hyperlipidemia, diabetes, chronic kidney disease, atrial fibrillation, stroke, chronic obstructive pulmonary disease, anemia, some thyroid disease, sleep apnea [33]. According to the European Society of Cardiology, almost 75% of patients with heart failure have at least one comorbidity. A study that studied 122,630 patients over 65 years of age showed a 96% risk of having a comorbidity. We also know that patients with >5 comorbidities account for 81% of days spent in hospitals [34].

Consequently, a large proportion of patients are on the maximum tolerated dose of medications and do not receive optimal, recommended treatment. A study was planned to look at the frequency of common side effects of beta-blockers across Georgia.

Study description.

Intolerance to guideline recinmmended optimal drug treatments in patients with heart failure is a significant problem in today's medicine. One of the reasons for this intolerance is the side effects identified as a result of titration to a high dose of beta-blockers. A study was conducted to examine the frequency

of side effects in the Georgian population when administering beta-blockers at the maximum tolerated dose. The data was evaluated using descriptive analysis and two-tailed independent t-test.

The study included patients who had to be hospitalized due to heart failure decompensation from March 2023 to May 2024 and were taking bisoprolol, carvedilol or metoprolol before hospitalization. The medications were divided into three groups; low-dose, medium-dose and recommended dose groups (see Table 1).

Table 1. *Doses of bisoprolol, carvedilol and metoprolol.*

Medicine	Low dose(mg)	Medium dose (mg)	Target dose (mg) (recommended dose)
Bisoprolol	2.5	5	10
Carvedilol	6.25	12.5	25
Metoprolol	50	100	200

The moment of admission to the clinic was considered the starting point of the study. The patients were followed for 6 months. There was no intraclass substitution of medications during the study, and the beta-blocker active at the beginning of the study was continued for each patient until the end of the study.

The study included 300 patients, all of whom had congestive heart failure with reduced ejection fraction. 203 were male and 97 were female. 137 patients took bisoprolol, 106 took carvedilol, and 57 took metoprolol. The main end-point of the study: To determine the frequency of side effects in the Georgian population in patients who were unable to take the maximum recommended dose of beta-blockers and to determine the difference between medications based on their frequency for side effects.

The study design was reviewed and approved by the Ethical Committee of the Tbilisi Heart and Vascular Clinic. The study was conducted taking into account the concepts of good clinical practice. Each patient was included in the study by signing an informed consent form.

Results.

In 6 months out of the 300 enrolled patients 223 (74.3%) developed at least 1 side effect, and 77 (25.7%) patients were able to tolerate the guideline recommended, maximum recommended dose of beta-blockers and without developing any side effects and thus were not incorporated into the study (see Figure 2). From the 77 patients 27 took bisoprolol, 32 took carvedilol and 18 took metoprolol, which translates to 19.7% tolerability for bisoprolol, 30.2% tolerability to carvedilol and 31.6% tolerability to metoprolol. These align with the values presented to us by the Heart Failure Pilot Study conducted by the European Society of Cardiology (bisoprolol - 21%, carvedilol - 37%, metoprolol - 37%).

According to the results obtained at the end of the study, 28 patients in the bisoprolol group took the medication at a low dose (2.5 mg) and 82 took the medium dose (5 mg). In the carvedilol group, 33 patients took the medication at a low dose (6.25 mg) and 41 took the medication at a medium dose (12.5 mg). In the metoprolol group, 16 patients received the low dose (50 mg) and 23 received the medium dose (100 mg) (see Figure 3).

At the end of the study, in 223 patients who were unable to titrate to the recommended dose of beta-blocker, the 5 most common adverse events were bradycardia, hypotension, dyspnea, fatigue, and dizziness. Overall, bradycardia occurred in 64.1% of patients, hypotension in 54.3%, dyspnea in 32.7%, fatigue in 41.3%, and dizziness in 38.1%. It is worth noting that the frequency of adverse events varied by drug and dose. In most cases, several adverse events were observed in each patient (see Table 2).

In 28 patients receiving low-dose Bisoprolol, bradycardia was seen in 71.4%, hypotension - 53.6%, dizziness - 28.6%, fatigue - 25% and dyspnea 17.9%. In the 82 patients receiving the medium dose of bisoprolol bradycardia was seen in 72%, hypotension - 62.2%, fatigue - 35.4%, dizziness - 31.7%, dyspnea 22% (see Figure 4).

In total in the 110 patients receiving bisoprolol, the most common side effect was bradycardia (71.8%), hypotension (60%), fatigue (32.7%), dizziness (30.9%), dyspnea (20.9%) (see Table 3).

In the 33 patients receiving the low dose carvedilol bradycardia was seen in 48.5%, fatigue -45.5), hypotension - 42.4%, dizziness - 42.4% and dyspnea - 39.4%. In the 41 patients receiving the medium dose of carvedilol dyspnea was seen in 61%, bradycardia - 58.5%, fatigue - 58.5%, dizziness - 53.7%, hypotension - 48.8% (see Figure 5).

In total, out of 74 patients receiving carvedilol, the most commonly seen side effect was bradycardia - 54.1%, followed by dizziness - 52.7%, fatigue - 51.4%, dyspnea - 48.6%, and hypotension - 45.9% (see Table 4).

In the 16 patients receiving the low dose metaprolol bradycardia was seen in 62.5%, hypotension - 56.3%, fatigue - 31.3%, dizziness - 31.3%, and dyspnea 25%. In the 23 patients receiving the medium dose of metoprolol bradycardia was seen in 60.9%, fatigue - 52.2%, hypotension - 52.2%, dizziness - 43.5%, dyspnea 34.8% (see Figure 6).

Of the 39 patients receiving metoprolol, bradycardia was the most common (61.5%), followed by hypotension (53.8%), fatigue (43.6%), dizziness (38.5%), dyspnea (30.8%) (see Table 5).

Discussion.

At the end of the study, 223 (74.3%) of the 300 patients developed some sort of side effect to taking beta blockers. It is also worth noting that the number and frequency of these adverse events in the study population varied depending on the medication and dose. The guidelines provide theoretically optimal doses of bisoprolol, carvedilol, and metoprolol for patients with reduced ejection fraction, while in reality, in clinical practice, it is not possible to administer beta-blockers at the recommended doses in all patients due to the occurrence of adverse events. The 5 most common adverse events identified during the study were bradycardia, hypotension, dyspnea, fatigue, and dizziness (see Table 6).

At the end of the study, bradycardia was the most common adverse event occurring in a total of 64.1% of patients. Most likely due to bisoprolols anti-adrenergic effect, bradycardia was most often detected in the bisoprolol group - 71.8% in

Table 2. *Number of patients with beta blockers by the number of side effects they experienced.*

Medicine	1 symptom	2 symptoms	3 symptoms	4 symptoms	5 symptoms
Bisoprolol 2.5 mg	10	11	5	2	0
Bisoprolol 5 mg	20	33	19	8	2
Carvedilol 6.25 mg	8	15	8	1	1
Carvedilol 12.5mg	3	11	19	7	1
Metoprolol 50 mg	6	6	2	1	1
Metoprolol 100 mg	2	12	6	3	0

Table 3. *Frequency of adverse events reported with bisoprolol divided by dose (%).*

Adverse events	Bisoprolol 2.5 mg (%)	Bisoprolol 5 mg (%)	Total (%)
bradycardia	71.4	72	71.8
hypotension	53.6	62.2	60
dyspnea	17.9	22	20.9
fatigue	25	35.4	32.7
dizziness	28.6	31.7	30.9

Table 4. *Frequency of adverse events reported with carvedilol divided by dose.*

Adverse Events	Carvedilol 6.25 mg (%)	Carvedilol 12.5 mg (%)	Total (%)
bradycardia	48.5	58.5	54.1
hypotension	42.4	48.8	45.9
dyspnea	39.4	61	51.4
fatigue	45.5	58.5	52.7
dizziness	42.4	53.7	48.6

Table 5. *Frequency of side effects reported with metoprolol divided by dose.*

Adverse Events	Metoprolol 50 mg (%)	Metoprolol 100 mg (%)	Total (%)
bradycardia	62.5	60.9	61.5
hypotension	56.3	52.2	53.8
dyspnea	25	34.8	30.8
fatigue	31.3	52.8	43.6
dizziness	31.3	43.5	38.8

Table 6. *Common side effects seen in patients taking beta-blockers.*

Adverse events	Number of patients	Frequency (%)
bradycardia	143	64.1
hypotension	121	54.3
dyspnea	73	32.7
fatigue	92	41.3
dizziness	85	38.1

Table 7. *The Frequency of developing various side effects when taking low doses of medication.*

Medicine	Frequency of 1 symptom occurrence (%)	Frequency of 2 symptom occurrence (%)	Frequency of 3 symptom occurrence (%)	Frequency of 4 symptom occurrence (%)	Frequency of 5 symptom occurrence (%)
Bisoprolol 2,5 mg	35.7	39.3	17.9	7.1	0
Carvedilol 6.25 mg	24.2	45.5	24.2	3.0	3.0
Metoprolol 50 mg	37.5	37.5	12.5	6.3	6.3

Table 8. *The frequency of developing a variety of side effects when taking an average dose of medication.*

Medicine	Frequency of 1 symptom occurrence (%)	Frequency of 2 symptom occurrence (%)	Frequency of 3 symptom occurrence (%)	Frequency of 4 symptom occurrence (%)	Frequency of 5 symptom occurrence (%)
Bisoprolol 5 mg	35.7	39.3	17.9	7.1	0
Carvedilol 12.5 mg	24.2	45.5	24.2	3.0	3.0
Metoprolol 100 mg	37.5	37.5	12.5	6.3	6.3

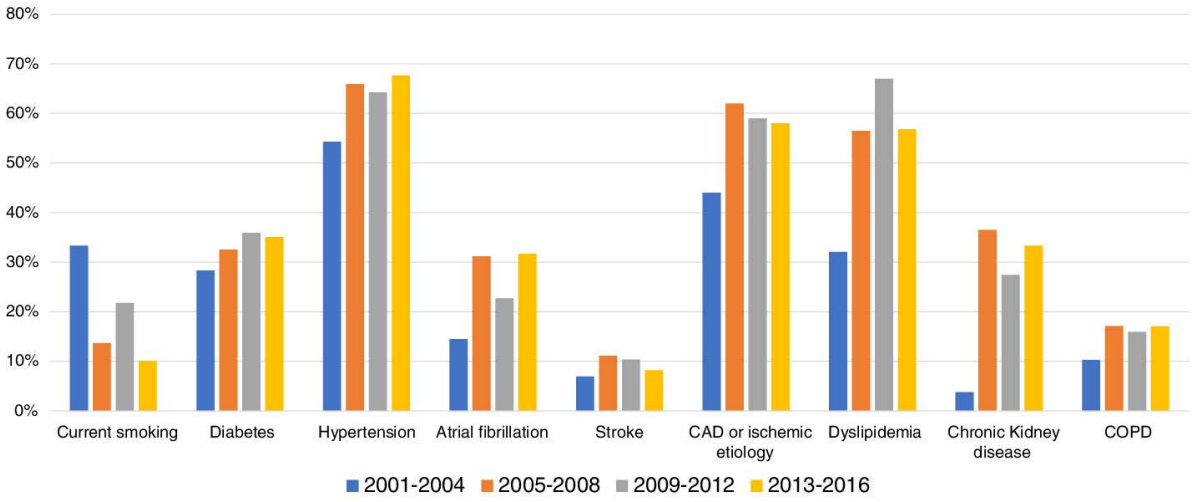

Figure 1. *Trends in major comorbidities across all heart failure clinical trials. Smoking prevalence decreased over time, while the prevalence of cardiometabolic comorbidities increased. CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease [32].*

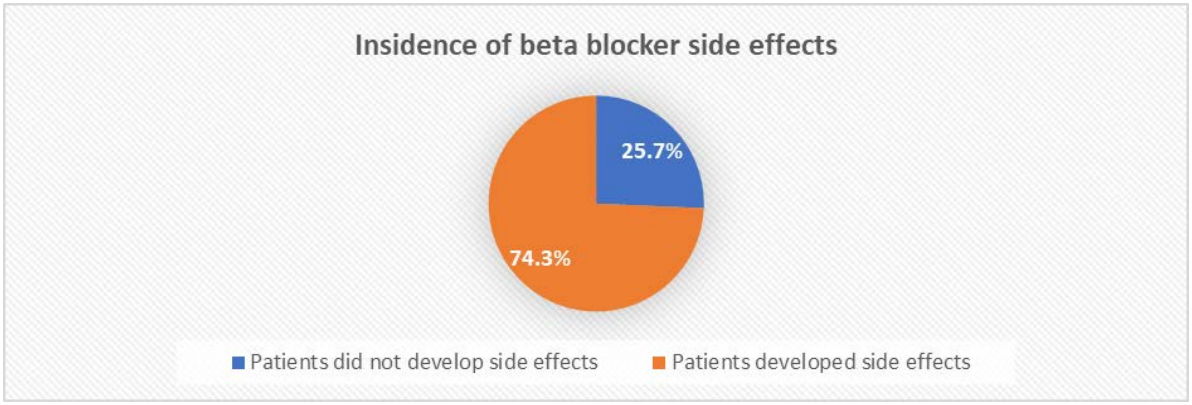

Figure 2. *Incidence of beta blocker side effects.*

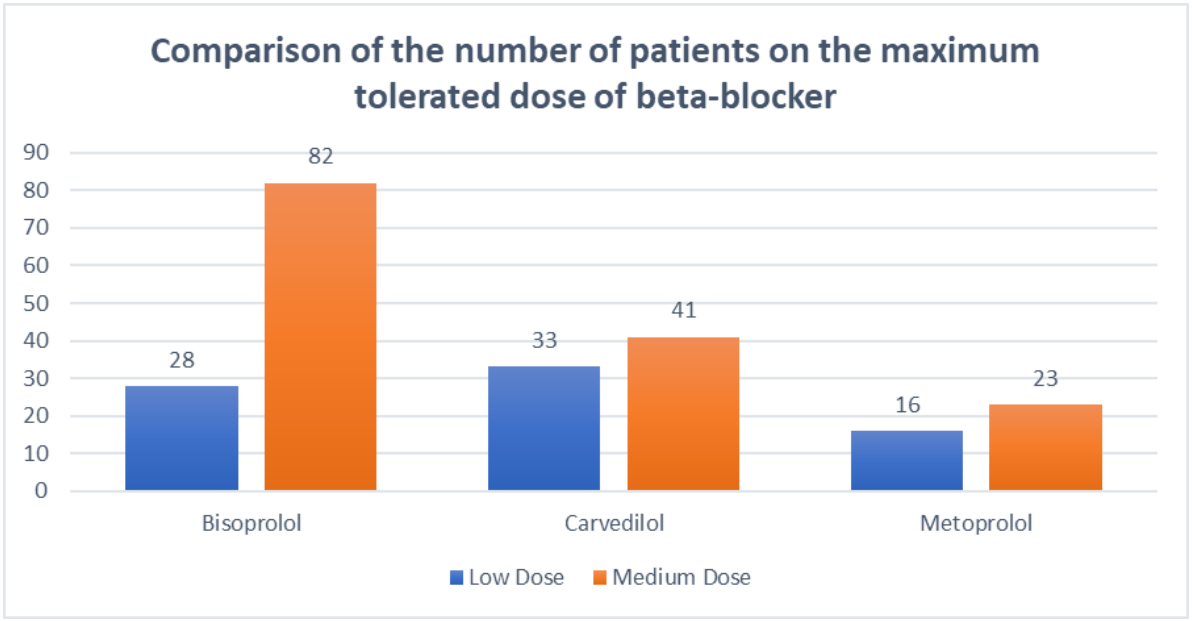

Figure 3. *Comparison of the number of patients on the maximum tolerated dose of beta-blocker.*

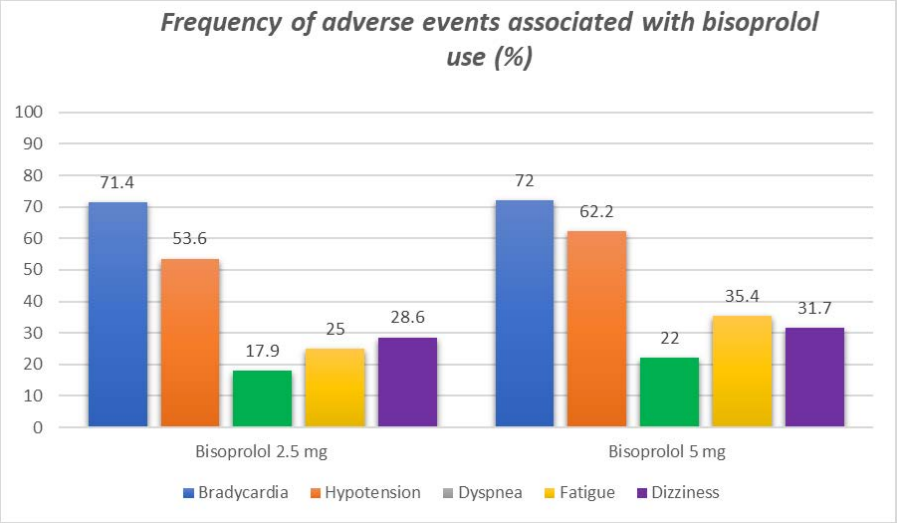

Figure 4. *Frequency of adverse events associated with bisoprolol use (%).*

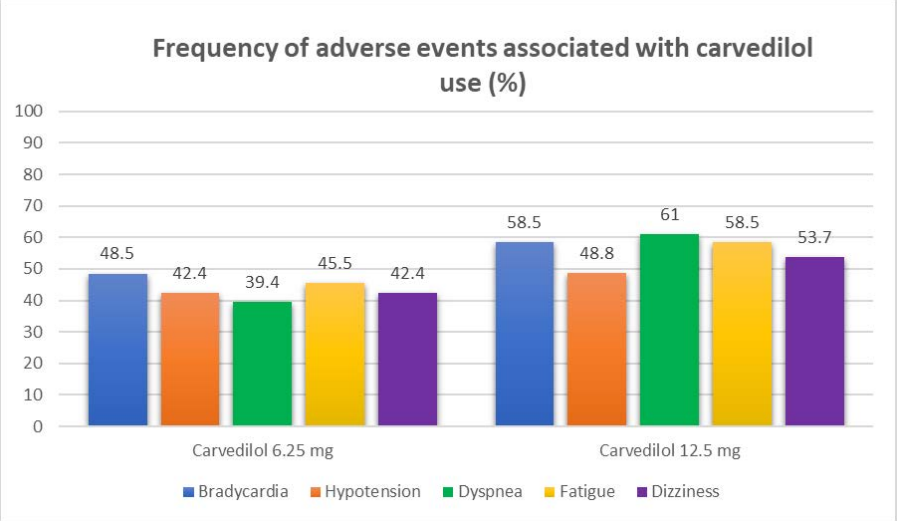

Figure 5. *Frequency of adverse events associated with carvedilol use (%).*

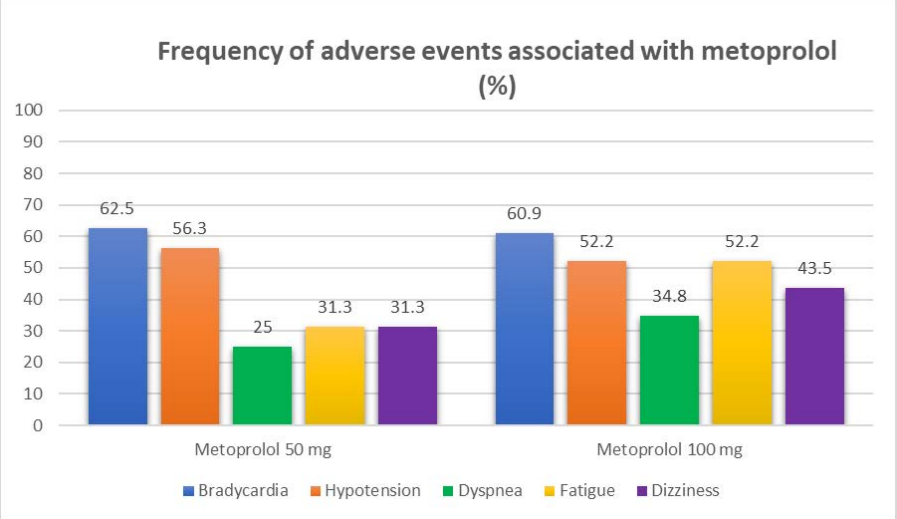

Figure 6. *Frequency of adverse events associated with metoprolol (%).*

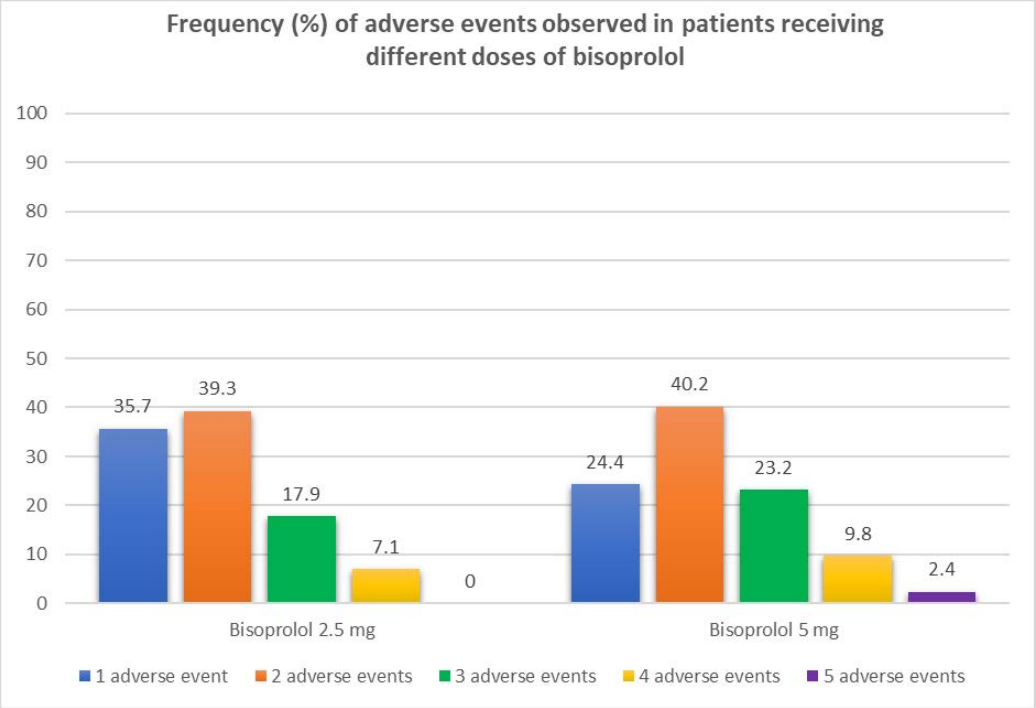

Figure 7. *Frequency (%) of adverse events observed in patients receiving different doses of bisoprolol.*

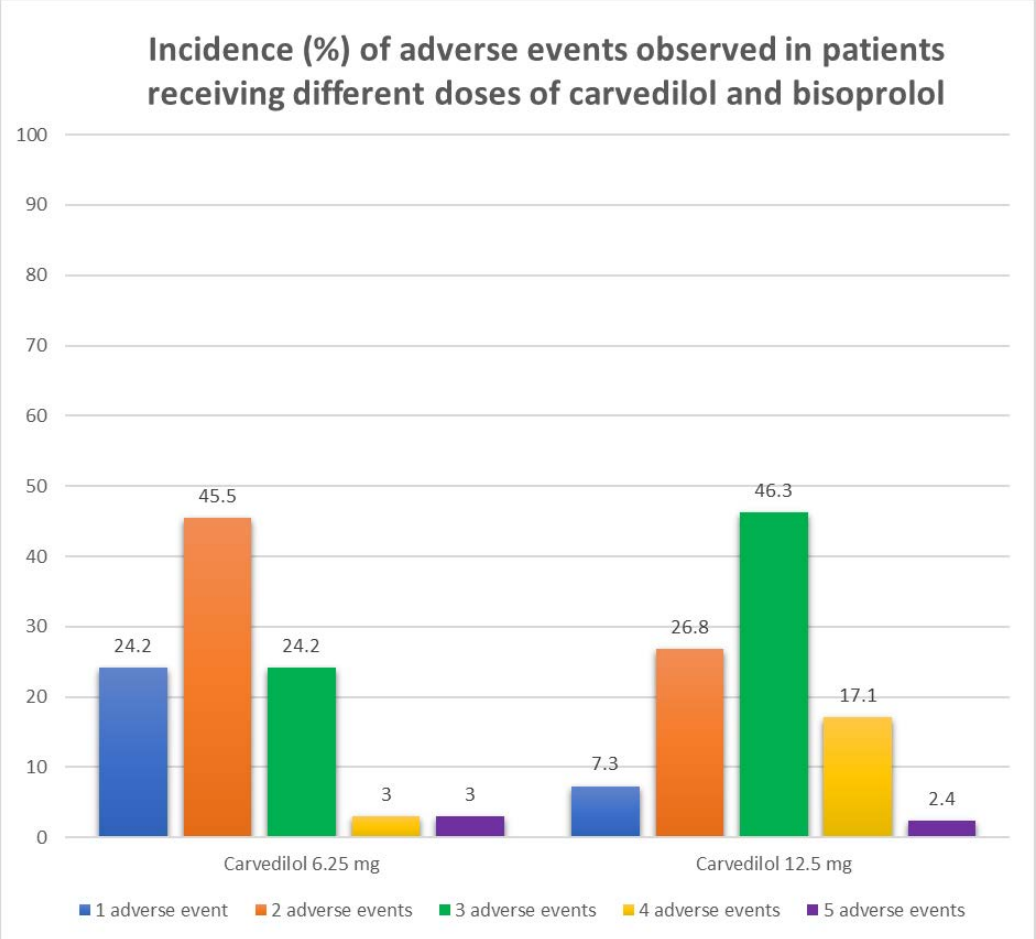

Figure 8. *Incidence (%) of adverse events observed in patients receiving different doses of carvedilol and bisoprolol.*

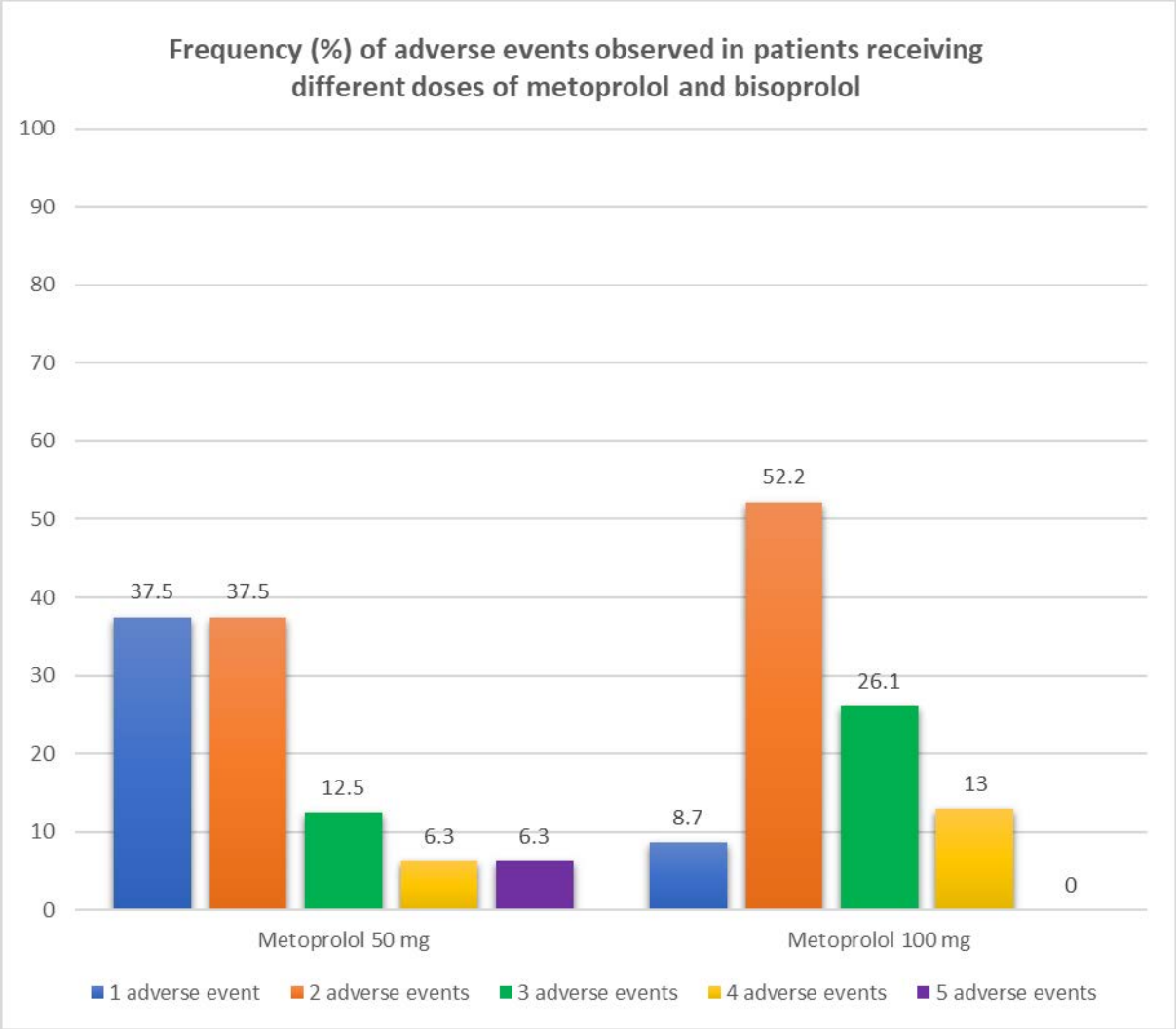

Figure 9. *Frequency (%) of adverse events observed in patients receiving different doses of metoprolol and bisoprolol.*

bisoprolol, 54.1% in carvedilol, and 61.5% in metoprolol. The difference in developing bradycardia between patients taking bisoprolol and carvedilol was significant ($p<0.05$), indicating that in situations where bradycardia is the main side effect prohibiting drug up titration switching to carvedilol may allow up titration and ultimately lead to a better treatment outcome. In regards to developing dyspnea, a clinically significant difference was noted between bisoprolol and carvedilol ($p<0.05$) and between carvedilol and metoprolol ($p<0.05$). Where 20.9% of patients taking bisoprolol and 30.8% patients taking metoprolol developed dyspnea, compared to 51.4% of patients taking carvedilol. Similarly, we can say that if the main issue in drug titration is dyspnea, then we can consider switching to either bisoprolol or metoprolol. In patients who developed fatigue a clinically significant difference was seen between bisoprolol and carvedilol. 32.7% of patients taking bisoprolol complained to fatigue compared to 52.7% of patients taking carvedilol ($p<0.05$), thus in patients taking carvedilol if the main side effect is fatigue, then switching to bisoprolol during drug titration should be considered. In patients that developed dizziness, the difference between patients taking bisoprolol and carvedilol showed clinically significant changes ($p<0.05$). 30.9% of patients taking bisoprolol and 48.6% of patients taking carvedilol developed dizziness. Thus, if the main barrier in drug titration is dizziness switching to bisoprolol may prove beneficial. Bisoprolol and to a lesser effect metoprolol seemed to juxtapose carvedilol in terms of side effects. Because bisoprolol has a strong anti-adrenergic effect compared to carvedilol and metoprolol bradycardia and, to a lesser extent, hypotenstion were more predominant in patients taking bisoprolol. While unlike bisoprolol and metoprolol, who only affect beta1-adrenergic receptors, carvedilol inhibits beta1, beta2 and alpha1 adrenergic receptors, which manifested in these patients as dyspnea dizziness and fatigue.

During the study, only 49 of 223 patients (22%) experienced only 1 adverse event, while 181 patients (78%) experienced some combination of the 5 studied adverse events. 88 patients (39.5%) experienced 2 adverse events; 59 patients (26.5%) experienced 3 adverse events; 22 patients (9.9%) experienced 4 adverse events and 5 patients (2.2%) experienced all 5 adverse events. The simultaneous occurrence of multiple adverse events highlights the difficulty of titrating beta-blockers to the recommended dose, where the challenge is not a single adverse event but a combination of symptoms.

The data also allow us to observe the frequency of adverse events across doses.

Patients on low doses are less likely to experience multiple adverse events simultaneously. As the dose of medication increases, the frequency of two, three, and four side effects increases (see Table 7 and Table 8).

In the case of bisoprolol, 35.7% of patients receiving the low dose experienced only 1 symptom, while this figure dropped to 24.4% of patients receiving the medium dose, and instead an increase in the frequency of 3 symptoms (from 17.9% to 23.2%) and 4 symptoms (from 0 to 2.4%) was observed (see Figure 6).

In the case of carvedilol, 24.2% of patients receiving a low dose of the drug experienced only 1 symptom, while among patients receiving a medium dose, this figure dropped to 7.3%, and instead, an increase in the frequency of 3 symptoms (from 24.2% to 46.3%) and 4 symptoms (from 3% to 17.1%) was observed (see Figure 7).

A similar trend was observed in patients receiving metoprolol; 37.5% of patients receiving a low dose developed only 1 symptom, while in the patients receiving the medium dose this figured decreased from 37.5% to 8.7%. The incidence of developing 3 symptoms (from 12.5% to 26.1%) and 4 symptoms (from 6.3% to 13%) also increased (see Figure 8).

Overall, among the three drugs, bisoprolol had the highest incidence of only one side effect (27.3%), followed by metoprolol (20.5%). Carvedilol had a lower incidence of 14.9%, suggesting that the patients taking carvedilol more frequently develop multiple side effects. It is also worth noting that the simultaneous occurrence of multiple adverse events is much less common with low doses of carvedilol and metoprolol than with medium doses of these drugs. Of the 33 patients receiving low doses of carvedilol, 24.2% experienced only one side effect, while in the 41 patients receiving the medium dose this figure dropped to 7.3% ($p<0.05$). When taking low doses of metoprolol, only 1 adverse event occurred in 37.5% of patients, while in patients taking medium doses this figure dropped to 8.7% ($p<0.05$). This means that when switching to high doses, the risk of developing 2 or more adverse events increased when taking carvedilol or metoprolol. Bisoprolol did not show a similar dynamic, as a result of which we can say that when taking medium doses of bisoprolol, the adverse event that occurred is more often limited to only 1 symptom than when taking medium doses of other beta-blockers.

This is important to consider when treating heart failure with reduced ejection fraction. Since titration to a higher dose of medication is directly proportional to the increase in survival, it is preferable, if there is a choice, to prescribe treatment with the beta-blocker to which the patient can better titrate to a higher dose and which has a lower risk of side effects.

REFERENCES

1. Kemp CD, Conte JV. The pathophysiology of heart failure. Cardiovascular Pathology. 2012;21:365-71.
2. Bozkurt B, Coats AJ, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the heart failure society of America, heart failure association of the European society of cardiology, Japanese heart failure society and writing committee of the universal definition of heart failure. Journal of Cardiac Failure. 2021;27:387-413.
3. Paulus WJ, Tschöpe C. A novel paradigm for heart failure with preserved ejection fraction: comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. Journal of the American College of Cardiology. 2013;62:263-271.
4. van Riet EE, Hoes AW, Wagenaar KP, et al. Epidemiology of heart failure: the prevalence of heart failure and ventricular dysfunction in older adults over time. A systematic review. European Journal of Heart Failure. 2016;18:242-252.
5. Loehr LR, Rosamond WD, Chang PP, et al. Heart failure incidence and survival (from the Atherosclerosis Risk in Communities study). The American Journal of Cardiology. 2008;101:1016-1022.
6. Jones NR, Roalfe AK, Adoki I, et al. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. European Journal of Heart Failure. 2019;21:1306-25.
7. Ouwerkerk W, Voors AA, Anker SD, et al. Determinants and clinical outcome of uptitration of ACE-inhibitors and beta-blockers in patients with heart failure: a prospective European study. European heart journal. 2017;38:1883-90.
8. Cruickshank JM. Beta-blockers and heart failure Dr. John M Cruickshank. Indian Heart J. 2010;62:101-10.
9. Chavey WE, Hogikyan RV, Van Harrison R, et al. Heart failure due to reduced ejection fraction: medical management. American Family Physician. 2017;95:13-20.
10. Komajda M, Cowie MR, Tavazzi L, et al. Physicians' guideline adherence is associated with better prognosis in outpatients with heart failure with reduced ejection fraction: the QUALIFY international registry. European Journal of Heart Failure. 2017;19:1414-23.
11. Authors/Task Force Members, McDonagh TA, Metra M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). With the special contribution of the Heart Failure Association (HFA) of the ESC. European Journal of Heart Failure. 2022;24:4-131.
12. Chin KL, Skiba M, Tonkin A, et al. The treatment gap in patients with chronic systolic heart failure: a systematic review of evidence-based prescribing in practice. Heart Failure Reviews. 2016;21:675-97.
13. Su VY, Chang YS, Hu YW, et al. Carvedilol, bisoprolol, and metoprolol use in patients with coexistent heart failure and chronic obstructive pulmonary disease. Medicine. 2016;95:e2427.
14. Sirak TE, Jelic S, Le Jemtel TH. Therapeutic update: non-selective beta-and alpha-adrenergic blockade in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. Journal of the American College of Cardiology. 2004;44:497-502.
15. Le Jemtel TH, Padeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. Journal of the American College of Cardiology. 2007;49:171-180.

16. Cruickshank JM. Are we misunderstanding beta-blockers. International Journal of Cardiology. 2007;120:10-27.
17. Metra M, Nodari S, Bordonali T, et al. Bisoprolol in the treatment of chronic heart failure: from pathophysiology to clinical pharmacology and trial results. Therapeutics and Clinical Risk Management. 2007;3:569-78.
18. CIBIs Investigators. A randomized trial of β-blockade in heart failure: the Cardiac Insufficiency Bisoprolol Study. Circulation. 1994;90:1765.
19. Investigators CI. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. The Lancet. 1999;353:9-13.
20. Lechat P, Escolano S, Golmard JL, et al. Prognostic value of bisoprolol-induced hemodynamic effects in heart failure during the Cardiac Insufficiency BIsoprolol Study (CIBIS). Circulation. 1997;96:2197-205.
21. Lechat P, Hulot JS, Escolano S, et al. Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in CIBIS II Trial. Circulation. 2001;103:1428-33.
22. Hernandez AF, Hammill BG, O'Connor CM, et al. Clinical effectiveness of beta-blockers in heart failure: findings from the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) Registry. Journal of the American College of Cardiology. 2009;53:184-192.
23. Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. New England Journal of Medicine. 2001;344:1651-8.
24. Investigators CI. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomised trial. The Lancet. 1999;353:9-13.
25. CR M. Effect of metoprolol CR/XL in chronic heart failure. Lancet. 1999;353:2001-7.
26. Maggioni AP, Anker SD, Dahlström U, et al. Are hospitalized or ambulatory patients with heart failure treated in accordance with European Society of Cardiology guidelines? Evidence from 12 440 patients of the ESC Heart Failure Long-Term Registry. European Journal of Heart Failure. 2013;15:1173-84.
27. Düngen HD, Apostolović S, Inkrot S, et al. Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial. European Journal of Heart Failure. 2011;13:670-680.
28. Komajda M, Follath F, Swedberg KO, et al. The EuroHeart Failure Survey programme—a survey on the quality of care among patients with heart failure in Europe: Part 2: treatment. European Heart Journal. 2003;24:464-74.
29. Basile JN. Titration of β-blockers in heart failure: How to maximize benefit while minimizing adverse events. Postgraduate Medicine. 2003;113:63-70.
30. Barron A.J, Zaman N, Cole G.D, et al. Systematic review of genuine versus spurious side-effects of beta-blockers in heart failure using placebo control: recommendations for patient information. International Journal of Cardiology. 2013;168:3572-3579.
31. Dahlöf C, Dimenäs E. Side effects of β-blocker treatments as related to the central nervous system. The American Journal of the Medical Sciences. 1990;299:236-44.
32. Khan MS, Samman Tahhan A, Vaduganathan M, et al. Trends in prevalence of comorbidities in heart failure clinical trials. European Journal of Heart Failure. 2020;22:1032-42.
33. van Deursen VM, Urso R, Laroche C, et al. Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. European Journal of Heart Failure. 2014;16:103-11.
34. Braunstein JB, Anderson GF, Gerstenblith G, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. Journal of the American College of Cardiology. 2003;42:1226-33.