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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.

GEORGIAN MEDICAL NEWS
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PROPORTION OF HEART FAILURE PATIENTS RECEIVING GUIDELINE RECOMMENDED DOSES OF BETA BLOCKERS IN GEORGIA: A STUDY ON TITRATION AND TOLERABILITY

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Abstract.

Background and Aims: Beta blockers are an essential part of the treatment and management of heart failure. Unfortunately, due to contraindications and side effects, it is impossible to titrate the medication to the recommended dose by available guidelines in all patients. The aim of this study was to determine the proportion of patients in Georgia receiving the maximum recommended dose of beta blockers and the proportion who could be titrated to a higher dose.

Methods: The conducted study focused on the proportion of patients in Georgia receiving the maximum recommended dose of beta blockers and the patient's receiving maximum tolerated dose of beta blockers. 300 patients with heart failure with reduced ejection fraction participated in the study. Patients were divided into 3 groups, depending on which beta blocker they were taking - bisoprolol, carvedilol or metoprolol. In patients who could not take the maximum recommended dose, an attempt was made to titrate to a higher dose.

Results: A total of 25.67% (n=77) of the 300 patients were able to reach the target dose and 223 patients were unable to reach the target dose of the medication due to various side effects. In the bisoprolol group, 19.7% reached the target dose, in the carvedilol group - 30.2% and in the metoprolol group - 31.6%. It was also noteworthy that 24.17% of patients (n=58) were able to titrate the prescribed medication to a higher dose. At the end of the study, of the 223 patients who were unable to titrate to the recommended dose of beta-blocker, 64.1% experienced bradycardia, 54.2% experienced hypotension, 32.7% experienced dyspnea, 41.3% experienced fatigue, and 38.1% experienced dizziness.

Conclusion: The inability to use beta-blockers, one of the most important medications for heart failure, is a major problem in Georgia, as only 25.67% of patients were able to take the recommended dose of the medication.

Since 24.17% of patients were able to titrate to a higher dose of beta blockers, we can conclude that with long-term and careful control of heart failure some patients may be able to titrate to a higher dose of beta blockers through adaptation to the medication and to the cardiac function. It is also possible that patients were not receiving optimal medication treatment at the time of medication initiation and the medication could actually have been titrated to a higher dose. This fact highlights the importance of attempting to titrate to a higher dose of beta blockers, as 24.17% of patients saw improvement in their prescribed medication over the course of the study.

Key words. Beta blockers, maximum recommended dose, titration, optimal medical treatment, Chronic heart failure.

Introduction.

Heart failure is a clinical syndrome characterized by typical symptoms (e.g., dyspnea, ankle swelling, and fatigue) and may be accompanied by certain signs caused by structural and/or functional cardiac pathology (e.g., increased jugular venous pressure, pulmonary edema, and peripheral edema), resulting in decreased cardiac output and/or increased intracardiac pressure at rest or during exercise [1]. More than 64 million people worldwide currently have heart failure [2]. Echocardiographic screening has shown that the prevalence of any type of heart failure in developed countries is 11.8% [3]. Studies have also shown that the lifetime risk of developing heart failure (from 45 to 95 years) was 30-42% in white men, 20-29% in black men, 23-39% in white women, and 24-46% in black women [4]. The prognosis of the disease worsens with its progression; a large-scale analysis of studies (patients with any type of heart failure - 1.5 million cases) showed that the probability of survival of patients with heart failure at 1, 2, 5, and 10 years is 87%, 73%, 57%, and 35%, respectively, and emphasized the need for timely and adequate treatment tactics [5]. Increased concentrations of proinflammatory biomarkers are common in both forms of heart failure and are associated with disease severity and mortality [6,7].

Currently, the management and treatment of heart failure is severely limited and mainly involves medications. 1) diuretics, 2) mineralocorticoid receptor antagonists, 3) sodium-glucose cotransporter 2 inhibitors, 4) beta-blockers, and 5) angiotensin-converting enzyme or angiotensin 2 receptor blockers or angiotensin receptor/neprilysin inhibitors. Modern medicine tells us that with the correct titration and dosage of these 5 different groups of drugs, it is possible to reduce cardiac workload and filling pressure - this means reducing heart failure symptoms, stabilizing the patient, improving quality of life and reducing the percentage of mortality, but in clinical practice, due to the presence of many comorbidities or drug side effects, it is impossible to titrate all patients to the maximum recommended dose of drugs. Only 22% of patients reach the recommended dose of angiotensin-converting enzyme and/or angiotensin 2 receptor blockers, and only 12% reach the optimal dose of beta-blockers [8].

The positive effect of beta-blockers in patients with heart failure is manifested by a decrease in sympathetic activity, catecholamine levels, and heart rate. Beta-blockers promote left ventricular remodeling in young/middle-aged hypertensive patients and reduce the inflammatory background present in heart failure [9].

Beta-blockers are most commonly used in practice for 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 [10]. 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 [11]. 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 important when prescribing beta-blockers [12]. Studies have also shown that correct dosing is still a major problem; 81.4% of the 83,605 heart failure patients with reduced ejection fraction studied were taking beta-blockers, and 49% of them were taking ≥50% of the target dose recommended by the guidelines [13]. A study was also published that examined data from 72,336 patients; it compared mortality in heart failure patients on high and low doses of beta-blockers. The study showed that high-dose beta-blockers were associated with better survival. Along with titrating beta-blockers to high doses, it is also important to remember that abrupt discontinuation of the medication can cause dangerous side effects (hypertension, tachycardia, myocardial infarction) and if withdrawal or dose reduction is necessary, it is necessary to titrate slowly to a lower dose [14].

Studies have shown the role of beta-blockers in cardiac remodeling; left ventricular dilatation and the risk of spheroidization have been reduced, mitral valve regurgitation has been reduced, and ejection fraction has been improved [15,16].

A study of 11,558 patients over a 4-year period showed that in the presence of comorbidities (e.g. chronic obstructive pulmonary disease), bisoprolol is associated with a more positive outcome compared to other beta-blockers [17]. Studies have also demonstrated bisoprolol's ability to protect against myocardial damage [18]. We also know that bisoprolol has a stronger anti-adrenergic effect than metoprolol and carvedilol, which is clinically reflected in improvements in important parameters such as: 6-minute walk test, quality of life, ejection fraction, NYHA class, and NT pro-BNP blood levels [19,20]. Possible side effects of beta-blockers include bradycardia, hypotension, dizziness, depression. Therefore, it is not possible to administer beta-blockers at the recommended dosage for a long time in patients with high NYHA class (NYHA IV), conduction problems/blocks, hypotension. Bisoprolol is also not characterized by metabolic disorders [21]. Accordingly, in the treatment of heart failure, preference is given to bisoprolol among beta-blockers.

Bisoprolol has a much higher selectivity for beta1 receptors than other beta-blockers. As a result of this property, this medication is better tolerated in the group of patients with chronic obstructive pulmonary disease and peripheral vascular disease [22,23].

Most of the bisoprolol (90%) is absorbed 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 [24]. 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. The mortality rate did not change significantly, but this study demonstrated the tolerability of bisoprolol in patients with heart failure without the occurrence of severe side effects. 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, while the number of sudden deaths in the placebo group was 45% higher than in the study group. The rate of hospitalizations was also reduced by 32%. The results of the CIBIS-II trial were so positive that the trial was stopped prematurely before the results could be shared. These two trials helped popularize beta-blockers in patients with heart failure and made the benefits of titrating to higher doses clear [25,26]. The CIBIS study highlighted the effect of bisoprolol on heart rate variability as a predictor of survival; the more pronounced the heart rate variability during bisoprolol treatment, the more viable the patient was [27]. The CIBIS-II studies, however, demonstrated that the increase in survival was an independent phenomenon from heart rate variability and that this positive effect was due to the activity of bisoprolol and not directly to heart rate variability [28].

Other studies have also highlighted the effect of beta-blockers on survival. The OPTIMIZE-HF program was established to promote beta-blockers. Part of the patients enrolled in it, 17,241 patients, were divided into 2 cohorts - patients with systolic dysfunction and patients with preserved systolic function. Analysis of these cohorts again highlighted the effectiveness of beta-blockers in increasing survival in the setting of reduced ejection fraction. The study also highlighted the lesser effectiveness of beta-blockers in preserved systolic function [29].

Given the positive effects on life expectancy and quality of life, it is easy to see why the inability to titrate beta-blockers to a higher dose is a major problem in the management of patients with heart failure [30-32].

A pilot study of heart failure by the European Society of Cardiology showed that only a small proportion of the patients studied were able to achieve the target dose of beta-blockers: carvedilol - 37%, bisoprolol - 21%, metoprolol - 37% [33]. In the CIBIS-ELD trial, 25% of patients were able to achieve and maintain the target dose of bisoprolol or carvedilol recommended by the guidelines. The trial included 41 centers and lasted 12 weeks [34]. In a study involving 12,493 patients, only 17.8% reached the recommended dose of beta-blockers (see Table 1) [35].

Table 1. *Target doses and total daily doses of beta blockers.*

Medicine	Target dose (mg)	Total Daily dose (mg)
Bisoprolol	10	10
Carvedilol	25-50 – twice a day	50-100
Metoprolol	200	200

Proper titration of a beta-blocker requires starting at a low dose and increasing to the next dose after 2 weeks of stable use (see Table 2) [36].

Table 2. *Recommended beta blocker titration schedule.*

Medicine	Starting dose (mg)	Low dose (mg) (first titration)	Medium dose (mg) (second titration)	Target dose (mg) (recommended dose)
Bisoprolol	1.25	2.5	5	10
Carvedilol	3.125 – twice a day	6.25 – twice a day	12.5 – twice a day	25 – twice a day
Metoprolol	25	50	100	200

One reason for the inability to titrate medications to the target dose is the increased frequency and severity of side effects associated with higher doses of the medication

The second reason for the inability to titrate medications to a higher dose is the many other diseases present in patients with heart failure, which aggravate the patient's condition and complicate the treatment process (Figure 1).

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 [38]. According to the European Society of Cardiology, almost 75% of patients with heart failure have at least one comorbidity. A study that examined 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 [39].

Consequently, a large proportion of patients are on the maximum tolerated dose of medications and are not receiving optimal, recommended treatment. To correlate these data with Georgian data, a study was planned to study patients receiving suboptimal doses of beta-blockers and discuss the issue of optimizing beta-blockers in these patients.

Study description.

Guideline recommended optimal medication treatment intolerance in patients with heart failure is a significant problem in medicine. One of the reasons for this is the inability to titrate to a higher dose of beta-blockers. A study was conducted to investigate the number of patients in the Georgian population who were taking beta-blockers at the maximum recommended dose and if the patient was taking a beta-blocker at a low dose, then whether it was possible to titrate to a higher dose. To see the number of patients receiving a suboptimal dose of beta-blockers, an active attempt was made to titrate the medication to a higher dose for 6 months. The data was evaluated by descriptive analysis and paired t-test, right-tailed.

The study included 300 patients, all of whom had congestive heart failure with reduced ejection fraction. Of the patients, 203 were male and 97 were female. Of the patients, 137 were taking bisoprolol, 106 were taking carvedilol, and 57 were taking metoprolol. The main endpoint of the study: to identify the contingent of patients in whom treatment optimization is possible. Secondary endpoint: to estimate what proportion of patients in the Georgian population is optimally treated with beta-blockers.

The study design was reviewed and approved by the Ethics Committee of the Tbilisi Heart and Vascular Clinic. The study was conducted in accordance with the concepts of good clinical practice. Each patient that participated in the study signed an informed consent form.

Results.

Of the 300 patients studied, 60 were seen at baseline to be taking beta-blockers at the optimal recommended dose. 240 patients were on suboptimal, maximally tolerated doses. At the start of the study, 106 patients were taking carvedilol, of whom 24 were taking the optimal recommended daily dose (25 mg), 35 were taking the halved daily dose (12.5 mg), and 47 were taking the lower daily dose (6.25 mg) (see Table 3).

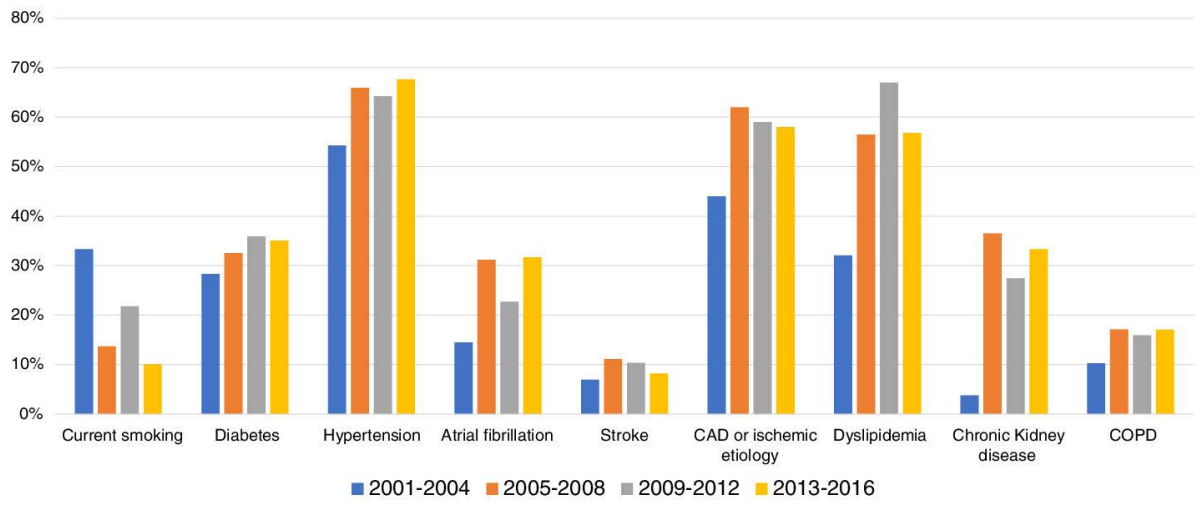


Figure 1. *Trends in major comorbidities across all heart failure clinical trials. Smoking prevalence decreased over time, while the prevalence of cardiometabolic comorbidities increased. CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease [37].*

Table 3. *Number of patients receiving different doses of carvedilol at the start of the study.*

Carvedilol daily dose (mg)	Number of patients	Patient percentage (%)
6.25	47	44.3
12.5	35	33
25	24	22.6

At baseline, 137 patients were taking bisoprolol, of whom 22 were taking the optimal recommended daily dose (10 mg), 63 were taking the halved daily dose (5 mg), and 52 were taking the low daily dose (2.5 mg) (see Table 4).

Table 4. *Number of patients receiving different doses bisoprolol at the start of the study.*

Bisoprolol daily dose (mg)	Number of patients	Patient percentage (%)
2.5	52	38
5	63	46
10	22	16.1

At baseline, 57 patients were taking metoprolol, of whom 14 were taking the optimal recommended daily dose (200 mg), 17 were taking the halved daily dose (100 mg), and 26 were taking the low daily dose (50 mg) (see Table 3).

In total, only 60 patients (20%) were receiving the optimal recommended dose of the medication. Preliminary results of the study showed that patients had different tolerances to the different medications. At baseline, from the patients taking bisoprolol 22 patients (16.1%) were on the maximum recommended dose, while 115 patients (83.9%) were on the maximum tolerated dose. Of the patients receiving metoprolol, 14 (24.6%) were on the maximum recommended dose, and 43 (75.4%) were on the maximum tolerated dose. Of the patients receiving carvedilol, 24 (22.6%) were on the maximum recommended dose, and 82 (77.4%) were on the maximum tolerated dose (see Figure 3 and Figure 4). The tolerability of metoprolol and carvedilol was similar across the number of patients. They differed by about 3%; 3% at the low dose, 1.7% at the medium dose, and 1.4% at the optimal dose.

Dose adjustments were made over a 6-month period in patients who were not receiving the optimal recommended dose of beta-blockers. Of the initial 300 patients, 77 (25.67%) remained on optimal medication and 223 patients failed to fully titrate. At the end of the study, the number of patients receiving carvedilol who were receiving the optimal recommended daily dose (25 mg) was 32, 41 patients were receiving a halved daily dose (12.5 mg), and 33 patients were receiving a lower daily dose (6.25 mg) (see Table 6).

At the end of the study, 27 of the patients receiving bisoprolol were receiving the optimal recommended daily dose (10 mg), 82 were receiving the halved daily dose (5 mg), and 28 were receiving the lower daily dose (2.5 mg) (see Table 7).

At the end of the study, 18 of the patients receiving metoprolol were receiving the optimal recommended daily dose (200 mg), 23 were receiving the halved daily dose (100 mg), and 16 were receiving the low daily dose (50 mg) (see Table 8).

The study showed a trend toward patients being able to switch to higher doses, as the number of patients on low doses decreased for all three medications and the number of patients on the optimal recommended doses and the average doses of the medication increased (see Figure 5 and Figure 6).

Table 5. *Number of patients receiving different doses metoprolol at the start of the study.*

Daily dose of metoprolol (mg)	Number of patients	Patient percentage (%)
50	26	45.6
100	17	29.8
200	14	24.6

Table 6. *Number of patients receiving different doses of carvedilol at the end of the study.*

Carvedilol daily dose (mg)	Number of patients	Patient percentage (%)
6.25	33	31.1
12.5	41	38.7
25	32	30.2

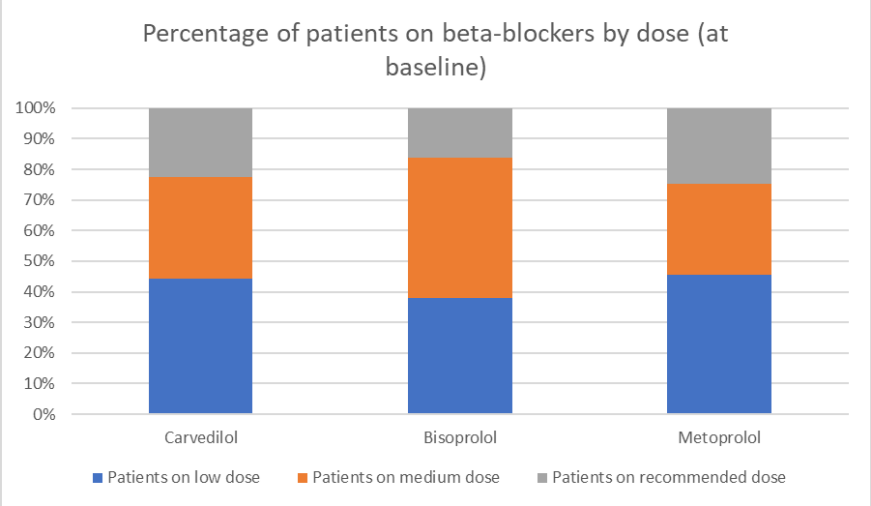
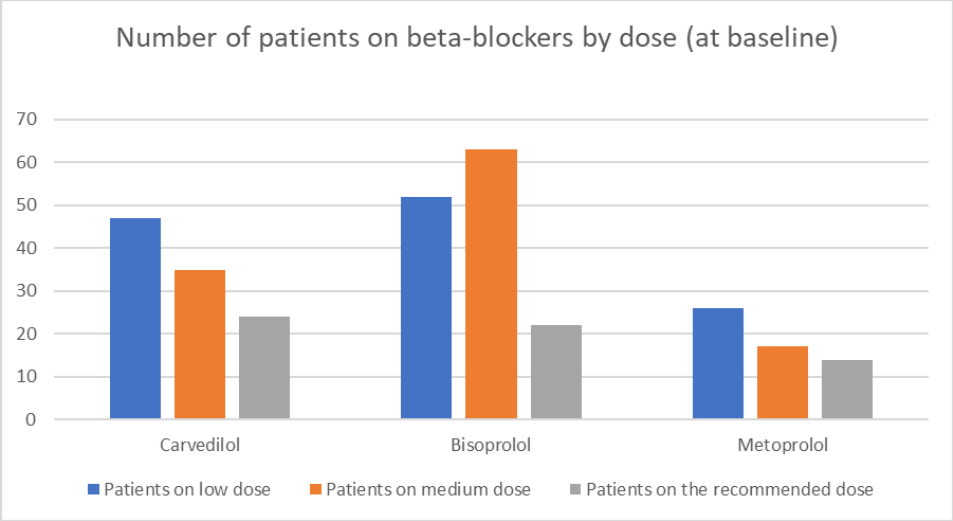


Figure 2. *Percentage of patients on beta-blockers by dose (at baseline).*



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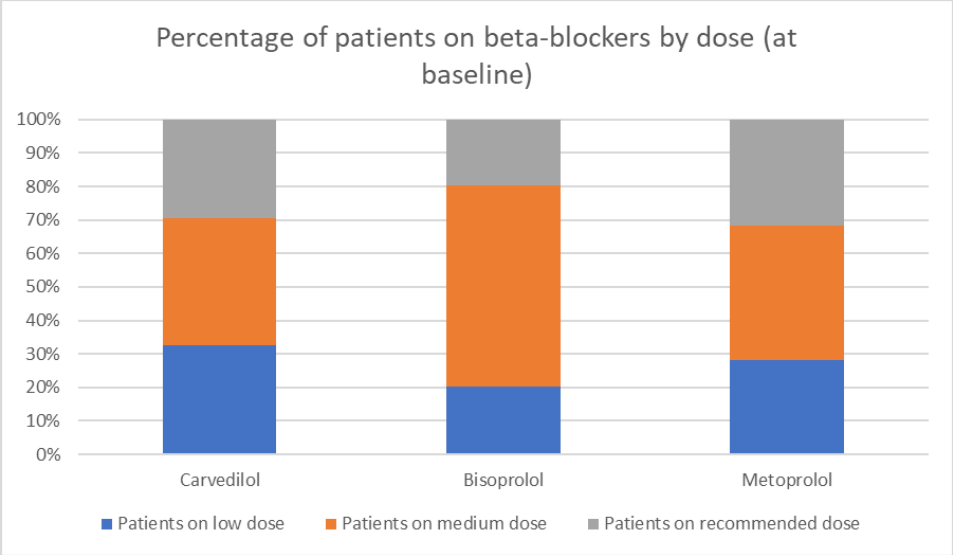

Figure 4. *Percentage of patients on beta blockers by dose (after 6 months), p<0.05.*

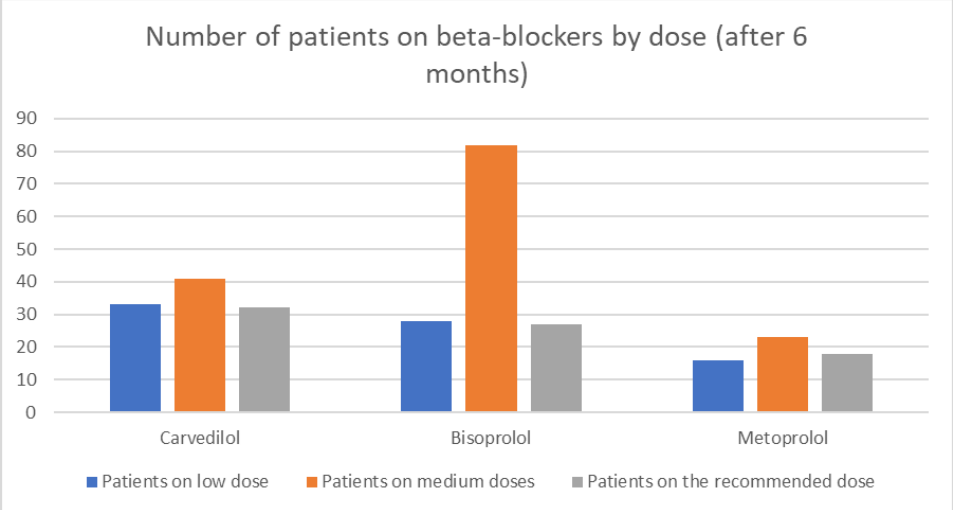

Figure 5. *Number of patients on beta-blockers by dose (after 6 months), p<0.05.*

Table 7. *Number of patients receiving different doses bisoprolol at the start of the study.*

Bisoprolol daily dose (mg)	Number of patients	Patient percentage (%)
2.5	28	20.4
5	82	59.9
10	27	19.7

Table 8. *Number of patients receiving different doses metoprolol at the start of the study.*

Metoprolol daily dose (mg)	Number of patients	Patient percentage (%)
50	16	28.1
100	23	40.4
200	18	31.6

Significant changes were also observed in the number of patients changing medication doses.

Of the patients receiving carvedilol, 18 patients had their dose increased. Of these, 10 patients were switched from a low dose to a medium dose, 4 patients were switched from a low dose to a recommended dose, and 4 patients were switched from a medium dose to a recommended dose.

Of the patients receiving bisoprolol, 27 patients were switched from a low dose to a medium dose, 2 patients were switched from a low dose to a recommended dose, and 3 patients were switched from a medium dose to a recommended dose.

Of the patients receiving metoprolol, 13 patients were switched from a low dose to a medium dose, 1 patient was switched from a low dose to a recommended dose, and 3 patients were switched from a medium dose to a recommended dose.

At the end of the study, 58 of the 240 patients (24.17%) receiving suboptimal doses of beta-blockers were able to increase their dose. Of these, 41 patients increased from the low dose to the medium dose ($p<0.05$) and 18 patients increased to the recommended dose ($p<0.05$). It is also noteworthy that 7 patients were able to titrate from the low dose to the recommended dose ($p<0.05$). 182 patients were unable to titrate to a higher dose.

The most common adverse events that prevented titration to higher doses were bradycardia, hypotension, dyspnea, fatigue, and dizziness.

110 patients receiving bisoprolol were unable to reach the recommended dose (see Table 9).

Table 9. *Common adverse effects seen in patients taking bisoprolol.*

Adverse effects	Number of patients	Frequency %
Bradycardia	79	71.8
Hypotension	66	60
Dyspnea	23	20.9
Tiredness	36	32.7
Dizziness	34	30.9

74 patients receiving carvedilol were unable to reach the recommended dose (see Table 10).

39 patients receiving metoprolol were unable to reach the recommended dose (see Table 11).

Table 10. *Common adverse effects are seen in patients taking Carvedilol.*

Adverse effects	Number of patients	Frequency %
Bradycardia	40	54.1
Hypotension	34	45.9
Dyspnea	38	51.4
Tiredness	39	52.7
dizziness	36	48.6

Table 11. *Common adverse effects seen in patients taking Metoprolol.*

Adverse effects	Number of patients	Frequency %
Bradycardia	24	61.5
Hypotension	21	53.8
Dyspnea	12	30.8
Tiredness	17	43.6
dizziness	15	38.5

Table 12. *Common adverse effects seen in patients taking beta-blockers.*

Adverse effects	Number of patients	Frequency %
Bradycardia	143	64.1
Hypotension	121	54.3
Dyspnea	73	32.7
Tiredness	92	41.3
dizziness	85	38.1

At the end of the study, of the 223 patients who were unable to titrate to the recommended dose of beta-blocker, 64.1% experienced bradycardia, 54.2% experienced hypotension, 32.7% experienced dyspnea, 41.3% experienced fatigue, and 38.1% experienced dizziness.

Discussion.

Of the 240 patients who were on suboptimal beta-blocker doses at baseline, 58 (24.17%) experienced some increase in their dose of medication. At the end of the study, bisoprolol tolerability at the recommended dose increased from 16.1% to 19.7% ($p<0.05$), carvedilol tolerability increased from 22.6% to 30.2% ($p<0.05$), and metoprolol tolerability increased from 24.6% to 31.6% ($p<0.05$). These were clinically significant changes that underscored the need for attempting titration.

The final results of the study showed that a total of 77 patients received optimal medication treatment, and 223 patients did not reach the target dose of the medication due to various side effects. According to the data, bisoprolol was the most frequently used medication and also the most difficult to tolerate medication at high doses, since only 19.7% of 137 patients ($p<0.05$) were able to take the medication at the recommended dose. However, it is also worth noting that a large number of patients were able to switch from the low dose to the medium dose, and the number of patients receiving the medium dose of the medication ultimately exceeded the sum of the number of patients receiving the low dose and the number receiving the recommended dose.

The above trend highlights the problem of beta-blocker intolerance in the study population. The guidelines provide theoretically optimal doses of bisoprolol, carvedilol, and metoprolol for patients with reduced ejection fraction, while in

clinical practice, it is not possible to use beta-blockers at the recommended doses in every patient due to the occurrence of side effects. The study identified the 5 most common reasons for not optimizing drug doses: bradycardia, hypotension, dyspnea, fatigue, and dizziness (see Table 12). Bradycardia was the most common cause of patient non-adherence, occurring in 64.1% of patients receiving suboptimal doses at the end of the study. And according to individual medications, it was most often detected in the bisoprolol group - 71.8% in bisoprolol, 54.1% in carvedilol, and 61.5% in metoprolol.

Factors that may prompt future dose adjustments include improvements in cardiac function, changes in concomitant medications that affect hemodynamics, improved volume status, resolution of temporary contraindications, and patient adaptation to side effects over time. Ongoing reassessment of patient tolerance is recommended, as some patients may develop improved tolerance to beta-blockers with cardiac remodelling and improved ejection fraction.

At this stage, it is necessary to pay more attention to titration to a higher dose of beta-blockers. Since the number of patients receiving the average and recommended doses of the drug increased at the end of the study, we can assume that, against the background of stabilization of patients with heart failure, patients had more resources freed up to tolerate the negative effects of beta-blockers and, accordingly, it became possible to titrate to a higher dose of the drug. This is certainly not a result that can be achieved in a few days and is the result of positive remodelling and adaptation to the drugs that occurs over many months or possibly years of treatment. It is also possible that adequate drug treatment was not initiated and/or the correct titration to a higher dose of the drug was not performed when beta-blockers were initially prescribed.

Conclusion.

This result emphasizes the need to first try to optimize drug treatment and try to titrate beta blockers when managing patients. It is possible that a patient may not tolerate the titration of the drug at the initial stage of taking beta blockers, but with continued treatment and monitoring, they may be able to titrate the drug to a higher dose. Despite the problem of tolerability of beta blockers, where only 20% of 300 patients were taking the drug at the recommended dose at the beginning of the study, with proper titration it was possible to improve this data to 25.67%, which is clinically significant ($p<0.05$).

The study was conducted in Tbilisi Heart and Vascular Clinic.

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