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THE SCOPE OF ANTIARRHYTHMIC DRUGS AND THE PROSPECTS FOR THE USE OF HIGHLY EFFECTIVE ANTIARRHYTHMIC DRUGS

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ABOUT ARTICLE

Key words: Cardiac ion currents, proarrhythmic causes, antiarrhythmic drugs, antiarrhythmic tactics, and cardiac arrhythmias.

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Abstract: Cardiac arrhythmias remain a common cause of death and disability. Antiarrhythmic drugs (AADs) and antiarrhythmic agents remain a cornerstone of current cardiac arrhythmia management, despite moderate efficacy and the potential for significant adverse proarrhythmic effects. Due to conceptual, regulatory and financial considerations, the number of novel antiarrhythmic targets and agents in the development pipeline has decreased substantially during the last few decades. However, several promising candidates remain and there are exciting developments in repurposing and reformulating already existing drugs for indications related to cardiac arrhythmias. Due to the multifactorial intracardiac and extracardiac causes of Atrial fibrillation (AF) generation, current development of anti-AF agents is concentrated on modulation of ion channel activity as well as upstream therapies that reduce structural substrates. AF is a growing clinical problem associated with increased morbidity and mortality. While currently available antiarrhythmic drugs (AADs) are highly effective in acute cardioversion of paroxysmal AF, they are generally only moderately successful in maintaining sinus rhythm over the long-term maintenance. When taking into account both safety and efficacy, the existing

results suggest that multiple ion channel blockers that show strong suppression of peak INa with comparatively quick unbinding kinetics, as well as inhibition of late INa and IKr, may be better for the treatment of AF. This review highlights the potential for therapeutic repurposing, reviews new compounds and formulations now undergoing clinical development for rhythm management of atrial fibrillation, and addresses the important conceptual factors for the creation of new antiarrhythmic drugs. Lastly, prospective paths for AAD advancement are examined. These elements, when combined with a growing knowledge of the molecular mechanisms behind cardiac arrhythmias, provide a cautiously optimistic prognosis for better pharmacological therapy options for cardiac arrhythmia patients.

ANTIARTMIK DORI VOSITALARINING QO‘LLANISH SOHASI VA YUQORI SAMARALI ANTIARITMIK PREPARATLARNI QO‘LLASH ISTIQBOLLARI

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MAQOLA HAQIDA

Kalit so‘zlar: yurak ion toklari, proaritmik sabablar, antiaritmik dorilar, antiaritmik strategiyalar, yurak aritmiyalari.

Annotatsiya: Yurak aritmiyalari hanuzgacha o‘lim va nogironlikning keng tarqalgan sabablaridan biri bo‘lib qolmoqda. Antiari tmik dorilar (AAD) va antiaritmik vositalar o‘rtacha samaradorlikka ega bo‘lishiga va jiddiy proaritmik nojo‘ya ta’sirlar xavfiga qaramay, yurak aritmiyalarini davolashning asosiy ustunlaridan biri hisoblanadi. Konseptual, tartibga soluvchi va moliyaviy omillar tufayli so‘nggi bir necha o‘n yilliklar davomida yangi antiaritmik nishonlar va preparatlarning ishlab chiqilish jarayoni sezilarli darajada kamaydi. Shunga qaramay, bir qator istiqbolli nomzodlar saqlanib qolmoqda hamda mavjud dorilarni yurak aritmiyalari bilan bog‘liq ko‘rsatmalar uchun qayta qo‘llash va yangi shakllarda ishlab chiqish borasida muhim yutuqlar kuzatilmoqda. Bo‘lmachalar fibrillyatsiyasi (BF) rivojlanishining ko‘p omilli yurak ichki

va yurakdan tashqari sabablarini hisobga olgan holda, hozirgi vaqtda anti-BF preparatlarini ishlab chiqish ion kanallari faolligini modulyatsiya qilishga, shuningdek, strukturaviy substratlarni kamaytirishga qaratilgan yuqori bosqichli (upstream) terapiyalarga yo‘naltirilgan. Bo‘lmachalar fibrillyatsiyasi kasallanish va o‘lim ko‘rsatkichlarining oshishi bilan bog‘liq bo‘lgan tobora dolzarb klinik muammo hisoblanadi. Mavjud antiaritmik dorilar paroksizmal BF ni o‘tkir kardioversiya qilishda yuqori samaradorlikka ega bo‘lsa-da, sinus ritmini uzoq muddat davomida saqlab turishda, odatda, faqat o‘rtacha muvaffaqiyat ko‘rsatadi. Xavfsizlik va samaradorlikni birgalikda baholaganda, mavjud ma’lumotlar shuni ko‘rsatadiki, piki INa tokini kuchli bostiruvchi, nisbatan tez ajralish kinetikasiga ega bo‘lgan, shuningdek, kechki INa va IKr toklarini inhibitsiya qiluvchi ko‘p ion kanalli blokatorlar BF ni davolashda samaraliroq bo‘lishi mumkin. Ushbu sharhda terapevtik qayta yo‘naltirish imkoniyatlari yoritilib, hozirda bo‘lmachalar fibrillyatsiyasida ritmni boshqarish uchun klinik rivojlanish bosqichida bo‘lgan yangi birikmalar va dori shakllari ko‘rib chiqiladi hamda yangi antiaritmik preparatlarni yaratishdagi muhim konseptual omillar muhokama qilinadi. Yakunda antiaritmik dorilarni rivojlantirishning istiqbolli yo‘nalishlari tahlil qilinadi. Ushbu omillar yurak aritmiyalarining molekulyar mexanizmlari haqidagi bilimlarning kengayishi bilan birgalikda, yurak aritmiyalari bilan og‘rigan bemorlar uchun yanada samarali farmakologik davolash usullariga ehtiyotkorona optimistik prognoz berishga imkon yaratadi.

СФЕРА ПРИМЕНЕНИЯ АНТИАРИТМИЧЕСКИХ ПРЕПАРАТОВ И ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ ВЫСОКОЭФФЕКТИВНЫХ АНТИАРИТМИЧЕСКИХ СРЕДСТВ

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О СТАТЬЕ

Ключевые слова: ионные токи сердца, проаритмические причины, антиаритмические препараты, антиаритмические стратегии, сердечные аритмии.

Аннотация: Сердечные аритмии остаются одной из распространённых причин смертности и инвалидизации. Антиаритмические препараты (ААП) и антиаритмические средства продолжают играть ключевую роль в современной терапии сердечных аритмий, несмотря на их умеренную эффективность и потенциальный риск развития выраженных проаритмических побочных эффектов. В силу концептуальных, регуляторных и финансовых факторов за последние несколько десятилетий количество новых антиаритмических мишеней и препаратов, находящихся в стадии разработки, значительно сократилось. Тем не менее, ряд перспективных кандидатов сохраняется, а также наблюдаются значительные успехи в перепрофилировании и модификации уже существующих лекарственных средств для применения при сердечных аритмиях. Ввиду многофакторных внутрисердечных и внесердечных механизмов возникновения фибрилляции предсердий (ФП), современная разработка анти-ФП препаратов сосредоточена на модуляции активности ионных каналов, а также на так называемой «восходящей» терапии, направленной на уменьшение структурных субстратов. Фибрилляция предсердий представляет собой нарастающую клиническую проблему, связанную с повышенной заболеваемостью и смертностью. Несмотря на то что существующие антиаритмические препараты высокоэффективны при острой кардиоверсии пароксизмальной ФП, в долгосрочном поддержании синусового ритма они, как правило, демонстрируют лишь умеренную эффективность. С учётом показателей безопасности и эффективности, имеющиеся данные свидетельствуют о том, что многоканальные блокаторы ионных каналов, характеризующиеся выраженным подавлением пикового тока INa с относительно быстрой кинетикой диссоциации, а также ингибированием

позднего тока INa и тока IKr, могут быть более предпочтительными для лечения ФП. В данном обзоре подчёркивается потенциал терапевтического перепрофилирования, анализируются новые соединения и лекарственные формы, находящиеся в настоящее время на стадии клинической разработки для контроля ритма при фибрилляции предсердий, а также рассматриваются ключевые концептуальные факторы, определяющие создание новых антиаритмических препаратов. В заключение анализируются перспективные направления развития антиаритмической фармакотерапии. Совокупность этих факторов, наряду с углубляющимися знаниями молекулярных механизмов сердечных аритмий, позволяет с осторожным оптимизмом оценивать перспективы улучшения фармакологического лечения пациентов с сердечными аритмиями.

Introduction. Cardiac arrhythmias significantly impact global health. A definitive cure by invasive procedures has been pursued in the last decades. However, despite advances in invasive management by catheter ablation, challenges remain, such as anatomical limitations, procedural risks, and complex arrhythmias. In addition, the prevalence of some arrhythmic disorders limits the generalizability of invasive arrhythmia management. For example, atrial fibrillation (AF), the most common sustained arrhythmia, affects 1–2% of the population. Presently, the demand for its invasive treatment commonly surpasses healthcare system capacity. In developed countries, only about 1% of AF patients currently receive ablation, with projections of it reaching only 10% in the foreseeable future due to limited resources and personnel. Furthermore, pharmaceutical therapy is still essential for some patients, either as part of peri-procedural care or because of ablation failure. After index ablation, around 50% of patients continue to take anti-arrhythmic medications (AADs), one in six have repeat ablation, and the majority continue to receive concurrent AAD therapy [1-5]. These results demonstrate that rhythm regulation frequently depends on a combination strategy combining catheter ablation and AADs in modern clinical practice. Additionally, AADs are crucial in preventing recurrent arrhythmias in patients with cardiac implantable electronic devices (CIEDs). AADs are also required for conditions like channelopathies, which are frequently inappropriate for ablative therapy. The critical significance of these drugs is further highlighted by the acute treatment of arrhythmias in emergency situations. An estimated 2.3 million persons in the US alone suffer from atrial fibrillation (AF), the most

prevalent persistent arrhythmia. One of the main risk factors for AF is getting older, and as the population ages, the condition's incidence is alarmingly increasing. Rate control, which regulates ventricular rate as the atria continue to fibrillate, is seen to be inferior to rhythm control, which seeks to reestablish and maintain sinus rhythm. However, there are significant drawbacks to the rhythm control methods currently in use, which are covered below. In many situations, rate control is better, especially for older patients who have comparatively little AF symptoms [6-11]. Electrical cardioversion, catheter ablation, and antiarrhythmic medications (AADs) can all be used to modulate the rhythm of AF. After cardioversion or catheter ablation, AADs are frequently effective in preserving sinus rhythm. Long-term pharmacologic rhythm management in AF patients is difficult since the majority of AADs currently on the market have poor safety profiles and insufficient long-term efficacy. According to the findings of several multicenter, randomized, and prospective clinical trials, such as AFFIRM and the AF-CHF, RACE, and PIAF studies, the rhythm control approach with AADs may be linked to a higher hospitalization rate and is not better than rate control in terms of survival. The poor efficacy of AADs to maintain sinus rhythm is anticipated to be offset by adverse effects such ventricular proarrhythmia and extracardiac toxicity. Patients who were kept in sinus rhythm had a higher survival rate than those whose AF persisted, according to the post-hoc analysis of the AFFIRM data. There is growing evidence that catheter ablation is better than currently available AADs for long-term sinus rhythm maintenance in some AF instances, especially in relatively young (<65 years of age) symptomatic patients [12-17]. However, AADs continue to be the first-line treatment for AF rhythm management and are anticipated to stay so for some time to come, despite advancements in catheter ablation technologies and increases in the effectiveness of these methods. A number of intracardiac and extracardiac conditions, such as heart failure, hypertension, coronary artery disease, myocardial infarction, and valvular heart defects, are frequently linked to AF in addition to atrial electrical and structural abnormalities. These conditions can arise independently of AF but may be exacerbated by it. The safety and anti-AF effectiveness of AAD therapy may be affected by each of these AF-associated abnormalities and diseases, as well as the many mediating elements of these disorders, which can also be pharmaceutical targets for AF treatment. Therefore, ion channel activity modulation and upstream therapies that target these intracardiac and extracardiac elements that trigger or enhance structural remodeling are now the main focus of anti-AF drug development. Additional preclinical studies focus on intracellular calcium activity and gap junction pharmacological manipulation. We address both new and existing pharmaceutical strategies for rhythm regulation in AF patients in this review [18-24].

The main purpose of the presented review manuscript is a brief analysis of the extent of the use of antiarrhythmic drugs and the prospects for the use of highly active antiarrhythmic drugs based on the results of reputable scientific research.

Conceptual Aspects of the Development of Antiarrhythmic Drugs (AAD). Drug combinations and multi-target effects. An ideal AAD must fulfill a number of requirements before it can be used in clinical settings. Safety is the main criterion. When developing AADs, cardiac pro-arrhythmic effects and extracardiac side effects pose serious obstacles that must be carefully considered. To lower the risk of ventricular pro-arrhythmia, considerable efforts have been made to target ion channels that are specifically expressed in the atria. Few channels are actually atrial selective, though, and the regional expression of AAD targets can be differently impacted by disease-related remodeling. Both therapeutic efficacy (if the primary therapeutic target is down-regulated in the atria, reducing the drug's antiarrhythmic effect) and safety (if the ventricles are up-regulated, increasing the risk of pro-arrhythmia) may be adversely affected by this ionic remodeling. Targeting several channels at once may also increase drug persistence and compliance by limiting polypharmacy and improving therapeutic efficacy [1-6]. For instance, the HARMONY trial demonstrated that the combination of lower doses of dronedarone with medium dosages of oral ranolazine was well tolerated and synergistically reduced the AF burden in individuals with paroxysmal AF. The effectiveness of a polypill-based treatment approach was also examined in the recent global randomized controlled Secondary Prevention of Cardiovascular Disease in the Elderly (SECURE) experiment. A polypill consisting of aspirin, ramipril (an angiotensin-converting enzyme [ACE] inhibitor), and atorvastatin (a statin) was compared to standard treatment in the SECURE research, which included patients who had experienced a myocardial infarction during the preceding six months [9-13].

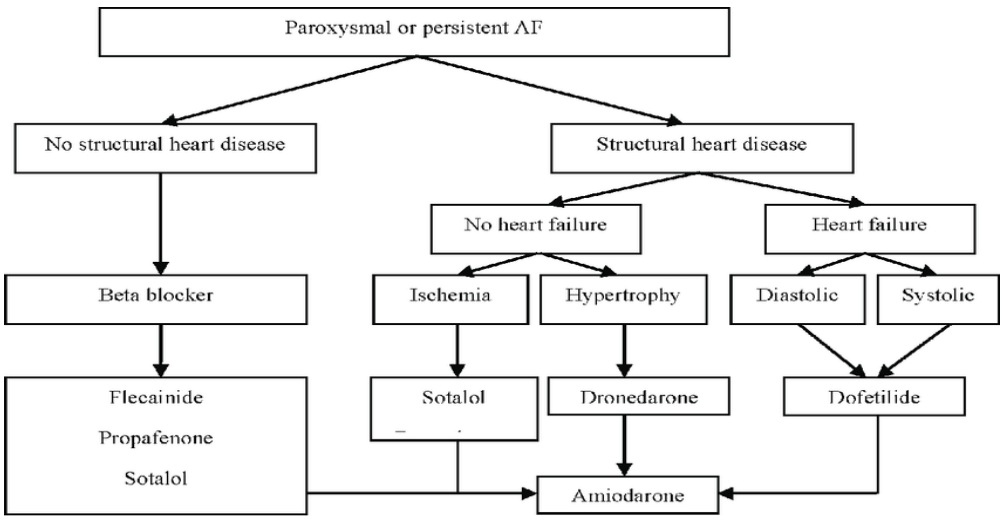

Figure 1. The best antiarrhythmic medication selection in various clinical contexts.

Patients using the polypill had a considerably lower risk of serious adverse cardiovascular events, such as cardiovascular death, nonfatal ischemic stroke, or urgent revascularization, according to the study. Higher patient compliance was another outcome of the polypill strategy, underscoring the potential to combine already available treatments to lower polypharmacy, boost compliance, and hopefully improve efficacy. Nevertheless, the combination of AADs to enhance long-term rhythm control has not been thoroughly assessed outside of the HARMONY trial. Lastly, it should be mentioned that patients with AF frequently experience negative drug-drug interactions with various pharmacological therapy [20-24].

Drug Formulation and Administration Method. The chemical drug design, drug formulation, and method of administration are further crucial factors that must be taken into account while developing AADs. Since many cardiac ion channels are also expressed in the brain, where they are essential for controlling the central nervous system, new antiarrhythmic drugs must be created in a way that keeps them from crossing the blood-brain barrier to prevent major neurological side effects. Oral medication formulations are generally favored over other kinds of formulations. Oral formulations are more easily converted to large-scale production because they are more cost-effective for the pharmaceutical industry, and patient compliance is higher with oral formulations than with other routes of administration since they are more convenient for patients. However, because pharmacokinetics are determined by changes in physiochemical and metabolic processes, oral bioavailability can vary greatly. The first-pass hepatic metabolism, intestinal metabolism, and reverse transport in the gut are significant barriers that significantly affect the bioavailability of medications taken orally. Additionally, in order to achieve better treatment outcomes and fewer side effects, more targeted organ medication delivery employing various routes of administration must be taken into consideration [5-12].

The vulnerable electrophysiological substrate can be modulated directly or indirectly. Targeting important nodal signaling pathways implicated in proarrhythmic cardiac remodeling and direct modulators of cardiac electrophysiology (usually inhibitors of cardiac ion channels) should be conceptually distinguished. Effective risk factor and lifestyle control has been demonstrated to have antiarrhythmic potential, particularly in AF. Examples of conditions that can be effectively controlled to enhance the management of AF include obesity, diabetes mellitus, sleep apnea, and hypertension. According to the PREVEntion and RegReSsive Effect of weight-loss and risk factor modification on Atrial Fibrillation (REVERSE-AF) study, losing at least 10% of one's body weight can both stop AF from getting worse and turn persistent AF into paroxysmal AF or no arrhythmia [7-13]. By pharmacologically addressing processes similar to those impacted by effective lifestyle and risk-factor management, such as hypertrophy, fibrosis, and inflammation, upstream therapy similarly seeks to stop or reverse the progression of cardiac remodeling to avoid arrhythmia

recurrence. The true efficacy of traditional "upstream therapy," which involves systemic inhibition of major receptor systems and pathways to prevent the development of a vulnerable substrate, can only be assessed with long-term follow-up and is probably limited when a substrate is already present. This presents difficulties for both clinical trial design and practical application. In fact, standard upstream therapy has been shown to be only modestly effective for primary prevention of AF and significantly less successful for subsequent prevention, given that AF is frequently discovered rather late in many individuals. On the other hand, specific molecular targeting of important signaling molecules and nodal points may be a viable alternative to attain both respectable efficacy and a sufficient decrease of symptoms, leading to an improvement in quality of life. Although addressing modifiable risk factors may potentially help achieve this, we will concentrate on possible pharmaceutical strategies below [20-26].

Prospective paths. Improving patient morbidity (and, consequently, quality of life) and lowering mortality are the ultimate goals of pharmaceutical therapy for AF. Large-scale, randomized, placebo-controlled clinical trials assessing anti-AF AADs' potential to reduce all-cause mortality have, at most, produced neutral results. However, using AADs can greatly improve the morbidity (and quality of life) of AF patients. The findings of ATHENA, which showed notable decreases in cardiovascular-related morbidity and mortality in dronedarone-treated AF patients, may promote a shift in the focus of AF management away from electrocardiographically derived metrics, such as rhythm control and rate control, and toward more general end points, such as morbidity and mortality. This new paradigm relates to the fact that, despite dronedarone's relatively low capacity to maintain sinus rhythm, positive results can be obtained. In the combined study of EURIDIS and ADONIS, 64% of patients randomly assigned to dronedarone experienced an AF recurrence after a year of follow-up, compared to 75% of those receiving a placebo. Future research must address a number of important issues with the pharmacological treatment of AF patients. Future research must ascertain whether dronedarone is better than the other AADs in extending survival free of cardiovascular hospitalization because the major end outcome of ATHENA was distinct (time to first cardiovascular hospitalization or death) [4-9]. Furthermore, in patients with myocardial infarction (LV ejection fraction ≤40%), amiodarone significantly decreased arrhythmic death when compared to placebo; however, it did not improve all-cause mortality in EMIAT and CAMIAT. In order to achieve safe and efficient rhythm regulation, atrial-selective sodium-channel blockage for the treatment of AF needs to be further investigated and developed. Studies now available indicate that while novel medicines exhibiting anti-AF efficacy are multiple ion channel blockers, most, if not all, of them are atrial-selective INa blockers and potently inhibit early INa (e.g., vernakalant, dronedarone, AZD7009, ranolazine). We have previously discussed this topic. Combining mostly inactivated-state and

activated-state INa blockers has been shown to provide a special synergistic effect. In isolated canine atria, the combination of long-term therapy with amiodarone and acute administration of ranolazine—both atrial-selective ion channel blockers—produced a significant atrial-selective use-dependent inhibition of INa and depression of INa-dependent parameters, resulting in a powerful effect of the drug combination for the prevention of AF (figure 2) [20-25].

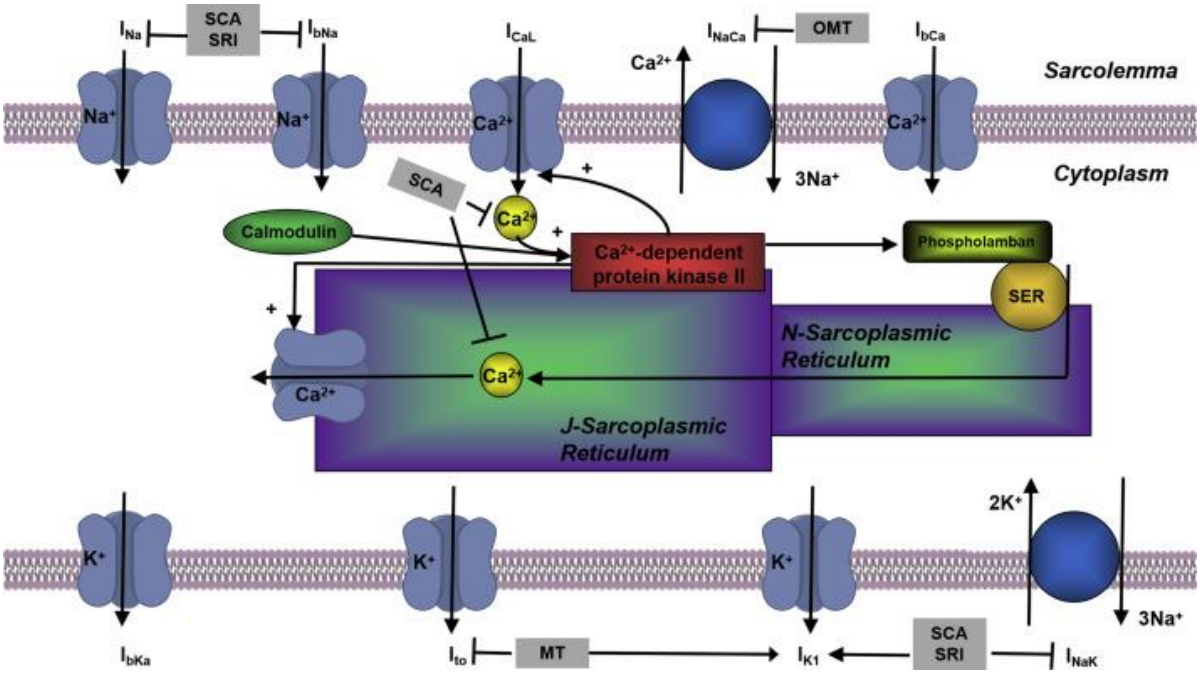

Figure 2. Cellular mechanism of antiarrhythmic agents [26].

To better understand the foundation for pharmacological agents' atrial selectivity and create ever-more-selective medications, studies of the molecular distinctions between atrial and ventricular sodium channels are required. Studies especially intended to assess the possible therapeutic function of atrial-selective sodium-channel blockers, such as ranolazine and amiodarone, as antiarrhythmics are warranted, according to experimental observations [3-19].

Discussion. A number of new AADs have advanced to Phase II or Phase III pre-approval trials following a pause in recent years, and one or more may become accessible in the coming years. Only a small percentage of the new compounds with anti-arrhythmic potential are like this. In the near future, pre-clinical development may produce more of these. The only new drug with a radically different mode of action is the histone deacetylase 6 (HDAC6) inhibitor (see below). It is worth mentioning seven new medications or formulations. Two take advantage of novel drug delivery techniques to enable patient self-administration in an out-of-hospital environment. Two of these medications primarily block ion channels, which were not previously thought to be AAD targets. Many of these medications are multiple ion channel blockers, but the PK/PD characteristics of the formulations or the balance of ion channel inhibition change enough to present novel therapeutic possibilities [3-8]. The continued development of novel and promising

AADs, in spite of the strict regulations that lead to a lengthy, complex, and expensive development process, emphasizes this importance even more. New or infrequently utilized therapeutic techniques, like individual self-administration for arrhythmia termination, may be prompted by these advancements. Proper selection requires an understanding of how these medications function, but it is also necessary to take into account any potentially dangerous interactions with other medications or patient circumstances. Over the past few decades, there has been a decrease in the development of new antiarrhythmic drugs. However, despite the advancements in ablation therapy, there is still a need for arrhythmia control, and recent big clinical trials have shown that antiarrhythmic medications are safe and effective enough. Even though there aren't many new medications under development, their preliminary findings seem encouraging, and some may even reach the clinical stage. Crucially, new avenues for the development of innovative antiarrhythmic therapies that could help lower the morbidity and mortality associated with cardiac arrhythmias and enhance the quality of life for millions of patients are provided by the repurposing and reformulation of previously approved medications to novel therapeutic indications and new, ideally atrial-selective delivery methods [9-17].

Conclusions. The continually high prevalence of cardiac arrhythmias, the synergistic effects of AADs in conjunction with other treatments, and their indispensability in treating acute episodes all highlight the enduring significance of AADs in the face of diminishing attention owing to the emergence of alternative therapies. When it comes to managing cardiac arrhythmias, AADs continue to fulfill the ABC strategy, which stands for appropriate therapy, backup therapy, and complementary therapy.

Improving patient quality of life and lowering mortality are the ultimate goals of AF therapy. Targeting both AF-related electrical and nonelectrical (intracardiac and extracardiac) problems, ongoing research aims to create new pharmaceutical techniques for the management of AF. The discovery of atrial-selective drugs and targets, along with the creation of upstream therapies, show promise for the creation of efficient and secure novel treatments, despite the limited success to yet.

This valuable guide provides a thorough overview of the information required to prescribe these medicines, which are powerful and helpful but also have the potential for serious side effects. For medical experts looking to maximize the treatment of cardiac arrhythmias, striking this equilibrium is crucial.

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