

# Promising tools for future drug discovery and development in antiarrhythmic therapy

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## Running Title: Visualizing Future Antiarrhythmics

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46 **Abstract**

47 Arrhythmia refers to irregularities in the rate and rhythm of the heart, with symptoms spanning  
48 from mild palpitations to life-threatening arrhythmias and sudden cardiac death (SCD). The  
49 complex molecular nature of arrhythmias complicates the selection of appropriate treatment.  
50 Current therapies involve the use of antiarrhythmic drugs (class I-IV) with limited efficacy and  
51 dangerous side effects and implantable pacemakers and cardioverter-defibrillators with  
52 hardware-related complications and inappropriate shocks. The number of novel antiarrhythmic  
53 drugs in the development pipeline has decreased substantially during the last decade and  
54 underscores uncertainties regarding future developments in this field. Consequently, arrhythmia  
55 treatment poses significant challenges, prompting the need for alternative approaches.  
56 Remarkably, innovative drug discovery and development technologies show promise in helping  
57 advance antiarrhythmic therapies. Here, we review unique characteristics and the transformative  
58 potential of emerging technologies that offer unprecedented opportunities for transitioning from  
59 traditional antiarrhythmics to next-generation therapies. We assess stem cell technology,  
60 emphasizing the utility of innovative cell profiling using multi-omics, high-throughput screening,  
61 and advanced computational modeling in developing treatments tailored precisely to individual  
62 genetic and physiological profiles. We offer insights into gene therapy, peptide and peptibody  
63 approaches for drug delivery. We finally discuss potential strengths and weaknesses of such  
64 techniques in reducing adverse effects and enhancing overall treatment outcomes, leading to  
65 more effective, specific, and safer therapies. Altogether, this comprehensive overview introduces  
66 innovative avenues for personalized rhythm therapy, with particular emphasis on drug discovery,  
67 aiming to advance the arrhythmia treatment landscape and the prevention of SCD.

68 **Significance Statement**

69 Arrhythmias and sudden cardiac death account for 15–20% of deaths worldwide. However,  
70 current antiarrhythmic therapies are ineffective and with dangerous side effects. Here, we  
71 review the field of arrhythmia treatment underscoring the slow progress in advancing the cardiac  
72 rhythm therapy pipeline and the uncertainties regarding evolution of this field. We provide  
73 information on how emerging technological and experimental tools can help accelerate progress  
74 and address the limitations of antiarrhythmic drug discovery.

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89 **Abbreviations**

- 90 Acetylcholine activated inward rectifier potassium current ( $I_{KACh}$ )
- 91 Antiarrhythmic drugs (AADs)
- 92 Action potential (AP)
- 93 Action potential duration (APD)
- 94 Andersen-Tawil Syndrome Type 1 (ATS1)
- 95 Antisense oligonucleotides (ASOs)
- 96 Artificial Intelligence (AI)
- 97 Atrial fibrillation (AF)
- 98 Atrioventricular node (AVN)
- 99 Calcium or calmodulin-dependent protein kinase II (CaMKII)
- 100 Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- 101 Chromatin-immunoprecipitation sequencing (ChIP-seq)
- 102 Comprehensive in-vitro Proarrhythmia Assay (CiPA)
- 103 Delayed rectifier potassium current ( $I_{Kr}$ )
- 104 Docohexaenoic acid (DHA)
- 105 DNA methylation sequencing (Methyl-seq)
- 106 Duchenne muscular dystrophy (DMD)
- 107 Engineering heart tissues (EHTs)
- 108 Extracellular matrix (ECM)
- 109 Field potential duration (FPD)
- 110 Fragment crystallizable (Fc)
- 111 Heart rate (HR)

- 112 High-Throughput Screening (HTS)
- 113 Human ether-a-go-go-related gene (hERG)
- 114 Human induced Pluripotent Stem Cell (hiPSC)
- 115 hiPSC-derived cardiomyocytes (hiPSC-CMs)
- 116 Immunoglobulin G (IgG)
- 117 Implantable cardioverter-defibrillators (ICDs)
- 118 Inherited retinal disease (IRD)
- 119 Insulin-like growth factor-1 (IGF-1)
- 120 Inward rectifying potassium current ( $I_{KI}$ )
- 121 Lipoprotein lipase deficiency (LPLD)
- 122 Liquid chromatography and mass spectrometry (LC-MS)
- 123 Locked nucleic acid (LNA) antimiRs
- 124 Long noncoding-RNAs (lncRNAs)
- 125 Long QT syndrome (LQTS)
- 126 Mass spectrometry (MS)
- 127 Microelectrode array (MEA)
- 128 Myocardial Infarction (MI)
- 129 Next-generation sequencing (NGS)
- 130 Non-Invasive electrocardiographic imaging (ECGI)
- 131 Organ-on-a-chip (OoC)
- 132 Paroxysmal supraventricular tachycardia (PSVT)
- 133 Platelet-derived growth factor (PDGF)
- 134 Postoperative atrial fibrillation (POAF)

- 135 Quantitative Structure-Activity Relationship (QSAR)
- 136 Recombinant adeno-associated viruses (rAAVs)
- 137 RNA interference (RNAi)
- 138 RNA-sequencing (RNA-seq)
- 139 Ryanodine receptor 2 (RyR<sub>2</sub>),
- 140 Serum Glucocorticoid inducible Kinase 1 (SGK-1)
- 141 SNPs (single-nucleotide polymorphisms)
- 142 Sodium current ( $I_{Na}$ )
- 143 Spinal muscular atrophy (SMA)
- 144 STEM (science, technology, engineering and mathematics)
- 145 Sudden cardiac death (SCD)
- 146 TertiapinQ peptidotoxin (TP)
- 147 Torsade de Pointes (TdP)
- 148 Transcription activator-like effector nucleases (TALENs)
- 149 Tyrosine kinase inhibitors (TKI)
- 150 Variants of uncertain significance (VUSs)
- 151 Zinc-finger nucleases (ZFN)

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## 176 **1. Introduction**

177 Cardiac arrhythmias are abnormal heart rhythms that can lead to serious health problems,  
178 including heart failure and sudden cardiac death. Current antiarrhythmic treatments are empirical  
179 and subject to clinical judgment. They remain a weakness in contemporary cardiovascular  
180 medicine (Kingma et al., 2023; Schwartz et al., 2020). A broad pharmacological arsenal designed  
181 to modulate cardiac electrical activity exists aiming to restore the rhythm (Kingma et al., 2023).  
182 However, the complex nature of arrhythmias, coupled with limited effectiveness plus side effects  
183 associated with current therapeutic approaches, underscores the need for innovative strategies to  
184 propel the field forward. Fortunately, several emerging technologies are showing promise in the  
185 field of drug discovery and the development of antiarrhythmic therapies. Such technologies offer  
186 unprecedented opportunities to revolutionize drug discovery and development, marking the onset  
187 of a paradigm shift in the search for novel antiarrhythmic therapies. Transition from traditional  
188 antiarrhythmics to next-generation therapies may boost precision medicine, with treatments  
189 tailored to individual genetic, physiological and environmental profiles. Here, we explore for  
190 potential antiarrhythmic drug discovery and development tools by first delving briefly into the  
191 current landscape of antiarrhythmic therapy, critically evaluating the strengths and limitations of  
192 existing pharmaceutical agents (Saljic et al., 2023; Valderrábano, 2022). Subsequent sections  
193 describe the transformative potential of stem cell technology, multi-omics, advanced  
194 computational modeling, and high-throughput screening, all of which are gaining attention in  
195 drug discovery and development. We also look at the future potential of gene and peptide-based  
196 therapies in treating cardiac arrhythmias. Together with an ever-increasing understanding of the  
197 molecular mechanisms underlying cardiac arrhythmias, these technologies support an optimistic  
198 outlook toward improved pharmacological treatment opportunities for patients suffering from

199 cardiac arrhythmias. These auspicious tools also offer a better understanding of the intricacies of  
200 cardiac electrophysiology. They should help researchers develop new, more specific, safe, and  
201 effective therapies that are also tailored to the unique characteristics of each patient, promoting  
202 personalized medicine (Piccini et al., 2022). Therefore, this review aims to navigate the  
203 trajectories toward future alternatives in antiarrhythmic therapies, highlighting promises and  
204 challenges associated with them.

## 205 **2. The traditional Landscape of Antiarrhythmic Drug Therapy.**

206 Traditional antiarrhythmic drugs (AADs), categorized by their electrophysiological effects, are  
207 currently what is best for controlling the electrical activity of the heart and managing rhythm  
208 disturbances. Selecting the appropriate antiarrhythmic therapy depends on the specific type of  
209 arrhythmia, its underlying cause, and individual patient characteristics (Al-Khatib et al., 2018;  
210 Michowitz et al., 2021). Sodium channel blockers, or Class I AADs (quinidine, procainamide,  
211 disopyramide, lidocaine, flecainide, propafenone), inhibit sodium channels during  
212 depolarization, slowing the rate of rise of the action potential (AP), thus reducing cell excitability  
213 and conduction velocity (Lei et al., 2018). Class Ic AADs agents, such as flecainide and  
214 propafenone, also exert their antiarrhythmic effects by targeting the ryanodine receptor 2  
215 (RyR2), a critical calcium release channel in the heart (Hilliard et al., 2010; Kryshtal et al., 2021;  
216 Salvage et al., 2022; Watanabe et al., 2009). This action helps stabilize calcium handling and  
217 reduces the risk of arrhythmogenic events, making these drugs particularly effective in treating  
218 certain types of arrhythmias where calcium dysregulation plays a role (Bergeman et al., 2023;  
219 Kryshtal et al., 2021; Y. Li et al., 2022).  $\beta$ -adrenergic receptor blockers, or Class II AADs like  
220 propranolol, metoprolol and atenolol, reduce sympathetic stimulation and decrease heart rate  
221 (HR) and contractility (Wołowiec et al., 2022). Class III AADs are potassium channel blockers

222 (e.g., amiodarone, sotalol, dofetilide) that prolong the repolarization phase of the AP (Pannone et  
223 al., 2021; Roden, 2016). Similar to Class II, calcium channel blockers (Class IV AADs),  
224 including verapamil and diltiazem, decrease the HR and contractility by inhibiting the calcium  
225 influx during AP depolarization (Koldenhof et al., 2023; Meyer et al., 2023). There are other  
226 drugs not categorized within these 4 classes that exhibit antiarrhythmic actions. For example,  
227 digoxin, traditionally used in the most common clinical arrhythmia, atrial fibrillation (AF),  
228 increases the force of myocardial contraction and impairs conduction through the atrioventricular  
229 node (AVN) (Ziff & Kotecha, 2016). Adenosine, used to treat supraventricular tachycardias, also  
230 slows conduction through the AVN and interrupts reentry across accessory AVN pathways (Ziff  
231 & Kotecha, 2016; Gupta et al., 2021). Ranolazine is used in certain cases of angina and has also  
232 shown antiarrhythmic efficacy by inhibiting the late sodium current, reducing calcium overload  
233 (Frommeyer et al., 2016; Rouhana et al., 2021; Shenasa et al., 2016). Vernakalant, a relatively  
234 novel therapy for AF, also shows antiarrhythmics effects blocking multiple ion channels  
235 (Frommeyer et al., 2016, 2017; Hall & Mitchell, 2019). While these drugs have undoubtedly  
236 improved patient outcomes, their use must be carefully selected and monitored due to potential  
237 proarrhythmia (i.e., inducing new arrhythmias), limited efficacy, and adverse side effects. When  
238 pharmacologic therapy is not sufficient, non-pharmacological interventions such as catheter  
239 ablation and implantable devices are commonly used in the management of certain arrhythmias.  
240 Implantable cardioverter-defibrillators (ICDs) are implanted to detect and treat life-threatening  
241 ventricular arrhythmias by delivering an electric shock to restore normal rhythm. The use of  
242 pacemakers helps to coordinate contraction between the heart chambers (Arenal et al., 2022;  
243 Elsokkari & Sapp, 2021; Gopinathannair et al., 2019). However, it is extremely important to note

244 that patients treated with AADs or non-pharmacological interventions are not exempt from SCD  
245 risk (Mazzanti et al., 2020; Priori et al., 2015; Richards et al., 2015).

246 Importantly, the chronic use of Class I and Class II antiarrhythmic agents is associated with a  
247 significant risk of pro-arrhythmic effects and increased mortality, particularly in patients with  
248 underlying heart conditions (Freemantle et al., 1999; Zylla et al., 2024). The most notable  
249 evidence comes from the Cardiac Arrhythmia Suppression Trial (CAST), which found that the  
250 use of flecainide and encainide, class I antiarrhythmics, resulted in a higher mortality rate  
251 compared to placebo in post-myocardial infarction (MI) patients. Specifically, the trial revealed  
252 that these drugs could actually precipitate fatal arrhythmias, leading to the early termination of  
253 the study due to safety concerns (Cardiac Arrhythmia Suppression Trial (CAST) Investigators,  
254 1989). While the risks are lower for,  $\beta$ -adrenergic receptor blockers (class II antiarrhythmics),  
255 they must still also be used judiciously, particularly in patients with severe cardiac dysfunction.

256 In some cases, especially at high doses or in patients with severe heart failure,  $\beta$ -blockers can  
257 cause excessive bradycardia, hypotension, or heart block, potentially leading to adverse  
258 outcomes, including an increased risk of arrhythmias (Dondo et al., 2017; Freemantle et al.,  
259 1999; Waldo et al., 1996). Despite such risks,  $\beta$ -adrenergic receptor blockers are still widely used  
260 because their overall benefit in reducing SCD and improving survival in heart failure and post-  
261 MI patients, which often outweighs their risks (Yndigeñ et al., 2024). The above considerations  
262 highlight the need for careful patient selection and monitoring under antiarrhythmic therapy.

### 263 **3. Antiarrhythmic Therapy Development Pipeline, the last 10 years**

264 It has been estimated that the average cost of a traditional drug discovery pipeline is 2.6 billion  
265 USD, and a complete traditional workflow can take over 12 years (Mohs & Greig, 2017).  
266 Unfortunately, the number of novel antiarrhythmic targets and agents in the development

267 pipeline has decreased substantially during the last few decades due to conceptual, regulatory  
268 and financial considerations (Saljic et al., 2023). We have analyzed the AAD therapy  
269 development over the last 10 years using data extracted from [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) (**Figure**  
270 **1**). Alarming, the total number of interventional clinical trials encompassing preclinical, I, II,  
271 III and IV phases for the treatment of arrhythmias is significantly lower than in other areas of  
272 medicine. Specifically, only a total of 440 studies have been completed and/or are under  
273 development in the last decade (**Figure 1A**). This is striking because sudden cardiac death (SCD)  
274 and arrhythmia represent a major worldwide public health problem, accounting for 15–20 % of  
275 all deaths (Srinivasan & Schilling, 2018). About half of those 440 studies are in phase IV or  
276 pharmacovigilance stage looking for side effects caused over time after approval and marketing  
277 (**Figure 1B**). Studies in early stages such as preclinical, I and II show much lower percentages  
278 supporting the fact that there is limited innovation in the field of antiarrhythmic therapy. Within  
279 the different types of interventions, it can be observed that drug development, without other  
280 types of interventions, leads with about 74%, followed very far behind by device development  
281 (7.95%). While other areas like biologic medicine and gene therapy are growing rapidly, here  
282 they account for 1.14% and 0.45% respectively without combination with other types of  
283 interventions (**Figure 1C**). We also analyzed clinical trials focusing exclusively on  
284 pharmacological interventions (325 studies). As shown in **Figure 1D**, most of the studies  
285 (33.53%) are dedicated to clinical research and development of anticoagulant or antiplatelet  
286 therapy aiming to mitigate the risk of cerebrovascular accident (stroke), as frequently occurs in  
287 patients with AF. In addition to these strategies, 7.69% of clinical trials aim to explore  
288 improvements related to pharmacology during cardiac surgery, mainly to advance ablation  
289 techniques, improve cardiac device implantation (pacemaker, defibrillator, cardiac

290 resynchronizer and holters), and prevent or treat postoperative AF. For instance, 41% of all  
291 clinical trials are focused on palliating secondary effects of arrhythmias and avoid comorbidities  
292 after surgery. Other clinical trials (19%) aim to investigate whether traditional AADs or other  
293 known agents are more effective before or after electrical therapy or in combination with other  
294 AADs. Yet other trials are focused on different formulations, doses, routes of administration or  
295 small modifications in structure. As discussed in detail below, drug repurposing, also known as  
296 repositioning or reprofiling, has played a key role in the history of antiarrhythmic drugs. Drug  
297 repurposing still occupies an important place on anti-arrhythmic intervention, constituting almost  
298  $\approx 30\%$  of the clinical trials during the last 10 years as shown in Figure 1D. Many of these  
299 repurposing drugs are indicated for cardiovascular diseases (hypertension, diabetes,  
300 cardiomyopathies, angina...), which have been demonstrated to have an antiarrhythmic effect or  
301 to palliate the secondary arrhythmias induced by these diseases. It is impressive that all clinical  
302 trials reported in the last 10 years on anti-arrhythmic therapies are not disease-specific, are  
303 invasive or are only focused on palliating secondary effects or comorbidities. Critically, only  
304 8.61 % of all studies aimed at developing innovative molecules that specifically target each type  
305 of arrhythmia, highlighting those destined to AF, long QT syndrome (LQTS, catecholaminergic  
306 polymorphic ventricular tachycardia (CPVT), bradycardia and ventricular arrhythmia as listed in  
307 Figure 1D. Most of these innovative drugs are designed to modulate specific cardiac ion  
308 channels like voltage gated potassium, sodium and calcium channels, and sarcoplasmic release  
309 (RyR) channels, as listed in Figure 1D. Most are selective for modulating a single ion channel;  
310 for example, F373280, a new therapy based on docohexaenoic acid (DHA) delivery, for the  
311 maintenance of sinus rhythm after electrical cardioversion; BMS-919373, a highly functionalized  
312 quinazoline, and potent  $I_{Kur}$  blocker used to treat atrial fibrillation; eleclazine, an inhibitor of

313 the late cardiac sodium current, is being tested for ventricular tachycardia and LQTS, specifically  
314 LQTS type 3 (Bacic et al., 2017; El-Bizri et al., 2018); AP30663, a small conductance  $\text{Ca}^{2+}$ -  
315 activated  $\text{K}^+$  ( $\text{I}_{\text{KCa}}$ ) channel blocker shown to prolong the atrial effective refractory period and  
316 convert AF into normal sinus rhythm (Gal et al., 2020); nasal spray of etripamil (a calcium  
317 channel blocker) is being investigated for the acute reduction of rapid ventricular rate in patients  
318 with symptomatic AF or for the conversion of paroxysmal supraventricular tachycardia  
319 (Abuelazm et al., 2023; Camm et al., 2023; Stambler et al., 2022); ARM210 (also known  
320 S48168) is a potential disease-modifying therapy for CPVT as it repairs leaky RyR2 channels  
321 (Marks, n.d.). Some compounds have multichannel blocking effects, like the intravenous HBI-  
322 3000 studied for the conversion of recent onset AF (W. Chen et al., 2019; D. Guo et al., 2011).  
323 Other compounds do not directly target ion channels but do so through secondary mechanisms,  
324 including Oral LQT-1213 (Serum Glucocorticoid inducible Kinase 1) is indicated for congenital  
325 LQTS Type 1, 2 or 3; CRD-4730 ( $\text{Ca}^{2+}$  or calmodulin-dependent protein kinase II) evaluated in  
326 participants with CPVT or congenital heart defects, and OMT-28 (epoxyeicosanoid synthetic  
327 analog) tested in patients with persistent AF (Berlin et al., 2020; Giannetti et al., 2023; M. Kim et  
328 al., 2023). Yet other drugs such as OPC-108459 and HIP2001 and administered in patient with  
329 paroxysmal and persistent AF, and oral CARDIX 101 under development for the treatment of  
330 bradycardia, have unclear or unknown mechanisms or the mechanism has not been disclosed as  
331 in the case of HSY244 for the treatment of AF (Linz et al., 2024). Natural products (1.23 %)  
332 have also been tested as new drugs, such as Freeze-Dried California Table Grape, Wenxin  
333 Granules, DH001 (active monomer from traditional Chinese medicine); and Tongmai Yangxin  
334 Pill (TMYXP) (Dong et al., 2017; LIU et al., 2022; Shi et al., 2021). However, their molecular  
335 mechanisms are unclear and they are not disease-specific.

336

337 The findings extracted from Figure 1 unequivocally indicate that the pursuit for advances in  
338 antiarrhythmic therapies may be dwindling when juxtaposed with the progress observed in other  
339 realms of scientific research. The data underscore the limited impact of innovative drugs focused  
340 on the future antiarrhythmic pipeline and highlight the comparatively significant advances in the  
341 field of anticoagulation associated with arrhythmias and drug repurposing. These observations  
342 prompt a reevaluation of research priorities, urging a redirection of efforts towards areas that  
343 show more promise for discovery and development of novel antiarrhythmic drugs. Altogether,  
344 our compilation highlights the slow progress in advancing improved antiarrhythmic therapies  
345 and underscores uncertainties regarding future developments in this field. Consequently,  
346 developing new experimental and technological approaches is highly desirable and particularly  
347 urgent to help overcome limitations. In the following sections we discuss the limitations of  
348 antiarrhythmic drug discovery and how new tools can help accelerate progress.

#### 349 **4. Human induced Pluripotent Stem Cell Technology**

350 Human induced Pluripotent Stem Cell (hiPSC) technology may revolutionize the field of  
351 biomedical science allowing a “*clinical trial in a petri dish*” (Takahashi et al., 2007; Takahashi  
352 & Yamanaka, 2006; Yamanaka, 2020). In the case of human cardiac diseases, the use of stem  
353 cell technology in preclinical experimentation supposes a significant advance. Heart tissue from  
354 human donors is difficult to obtain and does not regenerate, which has limited the development  
355 and discovery of drugs. Although the use of murine models for human diseases is standardize in  
356 biomedical research, interspecies differences make the study of arrhythmias difficult to translate  
357 to the human (Doncheva et al., 2021). The heart rate of mice is ten times faster than human and  
358 the action potential characteristics are vastly different due to the lack of functional expression of



359 some human ion channels in the mouse (Edwards & Louch, 2017). On the other hand,  
360 heterologous cell lines (HEK, CHO, HL-1) lack the functional and structural characteristics of  
361 human cardiomyocytes and present aneuploidies (Baik & Lee, 2017; R. Li & Zhu, 2022). hiPSCs  
362 can be generated in nearly unlimited quantities- They can be cultured for long periods, and  
363 cryopreserved. In addition, they are readily available in the market, and can be differentiated into  
364 multiple cell lineages, including hiPSC-derived cardiomyocytes (hiPSC-CMs) (Shafa et al.,  
365 2018). In addition, they can model human diseases better than other platforms like immortalized  
366 human or transgenic cell lines and can be reprogrammed directly from patients' own cells. In  
367 addition, the ability to differentiate hiPSCs into hiPSC-CMs provides a unique platform to study  
368 cardiac diseases without cell limitation. Notably, hiPSC-CMs express a collection of ion  
369 channels that enable them to generate cardiac-like action potentials. This offers huge advantages  
370 over heterologous cell systems in which a single ion channel is tested (Cunningham et al., 2019;  
371 Rogers et al., 2016). Moreover, iPSC-CMs can form electrically coupled monolayers and  
372 engineered cardiac tissue constructs that can be used to quantify electrical impulse propagation  
373 and study mechanisms of re-entrant arrhythmias (Jimenez-Vazquez et al., 2022).

374 During the last decade, attempts have been made to standardize the use of hiPSC-CMs for drug  
375 discovery as well as the assessment of cardiotoxicity, which is a primary risk factor in cancer  
376 drug development (Gintant et al., 2019; Sharma et al., 2018). hiPSC-CMs are central to the  
377 Comprehensive in-vitro Proarrhythmia Assay (CiPA) consortium. CiPA was established in 2013,  
378 as a step to confirm the results of *in-vitro* and *in-silico* tests on drug effects on multiple cardiac  
379 ion channels and the cardiac AP. Such effects are focused on pro-arrhythmia and the potential to  
380 generate Torsade de Pointes (TdP), a polymorphic ventricular tachycardia that can lead to SCD  
381 (Sager et al., 2014; Strauss et al., 2019). It has the support of regulatory agencies, academic

382 laboratories and pharmaceutical companies (*Q&A ICH-Guideline E14/S7B Clinical and Non-*  
383 *Clinical Evaluation EMA Document, see reference section*). New technologies as artificial  
384 intelligence (AI) and deep learning are also helping to discern the risk of drug-induced  
385 arrhythmia by analyzing features of *in-vitro* AP recordings in hiPSC-CMs that correlate with  
386 clinical arrhythmia manifestations (Serrano et al., 2023). Ideally, some of the new candidate  
387 drugs would move to start the different phases of clinical trials directly after checking their  
388 effectiveness and toxicity in hiPSCs (Sharma et al., 2018). However, even the most common  
389 hiPSC-CMs *in vitro* assays have important limitations that limit their full acceptance by  
390 regulatory agencies, as well as scientific publications. Such limitations include the hiPSC-CMs'  
391 lack host immune components and their fetal/neonatal cardiomyocyte-like phenotypes, with  
392 paucity of important ion channels (e.g.,  $I_{K1}$ ) that make them unable to fully recapitulate drug  
393 effects on adult human cardiomyocytes (da Rocha et al., 2017; X. Yang et al., 2022).

394 Despite the above limitations, hiPSC-CMs are a promising tool for drug discovery. In addition,  
395 the use of this technology is not limited to testing new drugs, but also applies to disease  
396 modeling, disease phenotype anticipation, reengineering previous drugs with less side effects and  
397 personalized medicine (Correia et al., 2023). As reviewed recently by other authors (Matsa et al.,  
398 2016; Pourrier & Fedida, 2020) (Musunuru et al., 2018), advances in hiPSC-CM research have  
399 provided a platform to effectively study patient-specific heart disease *in vitro*. The use of patient-  
400 specific hiPSC-CMs may be useful for basic science investigations, as well as for patient-specific  
401 drug screening and personalized therapy. Several studies have focused on testing new anti-  
402 arrhythmic drugs in hiPSC-CMs with promising results. For example, Dago et al 2022, showed  
403 that the use of dapagliflozin and empagliflozin could be used as a new class of anti-arrhythmic in  
404 heart failure by increasing sodium ( $I_{Na}$ ) and inward rectifying potassium ( $I_{K1}$ ) currents (Dago et

405 al., 2022). Apart from testing new drugs, the use of hiPSC-CMs is helping in reengineering  
406 existing drugs with better therapeutic results and less side effects, as is the case of mexiletine in  
407 LQTS3 (McKeithan et al., 2020).

408 Human iPSC-CMs serve not only to study diseases in the patient's own cells. Gene editing tools  
409 like CRISPR/Cas 9 (Han et al., 2023), transcription activator-like effector nucleases (TALENs)  
410 and zinc-finger nucleases (ZFN) (Hockemeyer et al., 2011; H. L. Li et al., 2015; Y. Wang et al.,  
411 2014) are helping to develop new disease models and to generate isogenic hiPSC-CMs for  
412 experimental controls (F. Guo et al., 2019). Wang et al 2014 reproduce patient phenotype of  
413 LQTS by introducing dominant negative mutations in *KCNQ1* by ZFN (Y. Wang et al., 2014).  
414 Gene editing helps also in the discovery of new treatments for cardiac pathologies. Nowadays,  
415 variants of uncertain significance (VUSs) are emerging as an important challenge in clinical  
416 genetics, with enormous implications for precision medicine (Fatkin & Johnson, 2020). VUSs  
417 show no evidence of pathogenicity (Richards et al., 2015) but some health providers describe  
418 VUSs as likely related to monogenic cardiovascular disorders such as cardiomyopathies and  
419 rhythm disorders even though they do not meet clinical criteria (Muller et al., 2020). hiPSC-CMs  
420 are then a good platform to study such variants. Garg et al observed that a VUS in *KCNH2*  
421 (LQTS2) was pathogenic (Garg et al., 2018). The study of the molecular mechanisms of these  
422 pathogenic variants in the same or different genes, help scientists to observe common  
423 mechanisms to treat different diseases. Mutations in different genes or even different mutations  
424 in the same gene can have different consequences at the molecular level, but still have the same  
425 clinical outcome, e.g., cardiomyopathy (Spielmann et al., 2022). Patient-specific iPSCs offer the  
426 opportunity to dissect mechanisms directly relevant to the patients' mutations (Campbell et al.,  
427 2015; Ma et al., 2018). By virtue of having a perfectly matched genetic background, patient-

428 specific iPSCs can provide a model system that integrates all the genomic *loci* involved in the  
429 response to medication (Carcamo-Orive et al., 2017). This is crucial as antiarrhythmic therapy  
430 depends on the specific type of arrhythmia, its underlying cause, and individual patient  
431 characteristics. Another great advantage of using patient specific iPSC-CMs is that they are an  
432 unlimited resource to apply single cell omics assays, when it is almost impossible to obtain  
433 cardiac tissue from patients. This opens a new world of treatments and breaks out the traditional  
434 method of drug testing in the patient by trial and error. With patient-specific-iPSC-CMs, one can  
435 test the cell response to different types of drugs at wide ranges of drug concentration (Theodoris  
436 et al., 2021). Moreover, using omics one can identify new biomarkers and targets for disease  
437 treatment. The combination of any given patient's unique clinical, genomic, proteomic and *in-*  
438 *vitro* cellular characteristics obtained from hiPSC-CM experiments, may help the clinician in  
439 making decisions regarding diagnosis, treatment, and prevention of human diseases, providing a  
440 personalized treatment (Perry et al., 2021).

441 However, although the above approaches could lead to major advances, using iPSC-CM has  
442 potential limitations that must be considered. An immature phenotype is the principal concern.  
443 These cells are pro-arrhythmic due to their immature electrophysiological phenotype and cell  
444 structure (Goversen et al., 2018) . In addition, the level of hiPS-CMs maturation determines drug  
445 responsiveness in pre-clinical cardiotoxicity and pro-arrhythmia screening (da Rocha et al., 2017).  
446 Also, the time to reprogram cells and the mix of cell types after differentiation (ventricular, atrial  
447 and nodal cells) are a concern. In the past years, several methodologies have been developed to  
448 solve their fetal-like phenotype. Some methods include long term culture (Kamakura et al., 2013;  
449 Seibertz et al., 2023), addition of hormones (Parikh et al., 2017), and fatty acids to cell culture  
450 media (Feyen et al., 2020; X. Yang et al., 2019), cell co-culture, use of extracellular matrix

451 (ECM) or biomaterials, and mechanical or electrical stimulation (Ronaldson-Bouchard et al.,  
452 2018), and new platforms that try to recapitulate several of these methods are emerging. These  
453 new platforms also include co-culture of different cell types, interactions of cells with the  
454 microenvironment (cell-cell and cell-ECM interactions) and physiological cues, facilitating more  
455 translational studies due to their higher similarity to the adult heart (Beauchamp et al., 2020;  
456 Schmidt et al., 2023). hiPSC-CM monolayers are generally less mature than 3D constructs,  
457 however they do show some promise in enabling the study of action potential propagation and  
458 reentrant arrhythmias (da Rocha et al., 2017). On the other hand, it is expected that the new 3D  
459 platforms would solve problems seen with 2D constructs. Some engineering heart tissues (EHTs)  
460 are 3D scaffolds formed by hiPSC-CMs and extracellular matrix or biomaterials as hydrogels  
461 (Eder et al., 2016). An example is the commercialized Biowire, where EHTs are electrically  
462 stimulated, enabling cardiac maturation, with good results in cardiotoxicity testing (Feric et al.,  
463 2019; Nunes et al., 2013). Microtissues are 3D models containing hiPSC-CM co-cultured with  
464 fibroblasts and endothelial cells. Giacomelli et al have generated these cardiac microtissues with  
465 excellent results probing them in the study of arrhythmogenic cardiomyopathy and LQTS2  
466 (Giacomelli et al., 2020, 2021). However, microtissues cannot self-organize, they do not contain  
467 vasculature, and cannot recapitulate the developing heart. In contrast, organoids are small 3D  
468 self-organizing cellular aggregates containing multiple cell types that represent more structurally  
469 accurate models of the human myocardium. Some authors have used organoids for drug  
470 screening due to their similarity to an adult heart and as they contain cells from the 3 germ-layers  
471 (Mills et al., 2019). Beyond organoids are the assembloids, which can combine organoids with  
472 cells from diverse tissue lineages or from artificially assembling multiple organoids (Campostrini  
473 et al., 2021; Ng et al., 2022). Assembloids reproduce the interactions among multiple sub-regions

474 and cell types. In cardiovascular diseases, assembloids could advance targeted, tissue-specific  
475 drug treatment in scenarios where drugs differentially affect subsections of an organ or tissue, as  
476 for example the atria and the ventricle (Schmidt et al., 2023). However, the use of this platform  
477 has limitations as most organoid types resemble early stages of human heart during  
478 morphogenesis. Finally, nowadays the use of organ-on-a-chip (OoC) technology that allows the  
479 interaction of different cell types is taking relevance (M. B. Chen et al., 2013; D. Kim et al.,  
480 2014; Picollet-D'hahan et al., 2021). OoCs are designed for the growth of multiple organ-  
481 specific cell types in a fully integrated system, often with different cell types cultured in separate  
482 compartments that are interconnected via perforated membranes or juxtaposed microchannels.  
483 The approach allows co-culturing multiple cell lineages that underlie organ function and enables  
484 fluid flow, and in some cases, mimicking stretch to further simulate the *in-vivo* environment.  
485 This allows the administration of drugs to the “blood channel” of an OoC while observing the  
486 effects on an adjacent “tissue channel,” recapitulating the *in-vivo* environment and adding power  
487 to the model (Azizgolshani et al., 2021). However, OoCs are still under development and their  
488 primary focus resides on drug cardiotoxicity screening (Y. Zhao et al., 2020). An upgrade version  
489 of OoCs are the organoids in an OoC or body-on-a-chip. This revolutionary technique combines  
490 3D models of organoids with a fully integrated and connected system, where changes can be  
491 studied in a more complex microenvironment. A good example is the exposure to clomipramine  
492 (a tricyclic antidepressant) in an OoC, composed of a liver organoid chamber and heart  
493 organoids in the bottom chamber. Heart organoids presented impairments in cell viability,  
494 cardiac beating and calcium activities, suggesting the hepatic metabolism-dependent  
495 cardiotoxicity of clomipramine (Yin et al., 2021). This impressive multi-organoids-on-a-chip  
496 system can recapitulate the complex process of drug metabolism at the multi-organ level. Skardal

497 et al 2020 developed a 3-tissue organoid-on-a-chip platform to test a multipanel of FDA-recalled  
498 drugs, demonstrating that some of these drugs caused toxicity in liver and heart (Skardal et al.,  
499 2020). Moreover, they went a step further to develop a 6-tissue body-on-a-chip platform where  
500 they observed that capecitabine, an anticancer drug, must be metabolized in the liver to become  
501 active. This effect generated secondary effects in other organoids as cardiac and lung constructs.

## 502 **5. Multi-Omics**

503 The use of OMICS has also contributed to revolutionize the field of drug discovery and drug  
504 testing (N. Nguyen et al., 2022). In recent years, genomics, transcriptomics, proteomics, and  
505 metabolomics platforms have been incorporated to the study of complex interactions in  
506 biological systems. Moreover, these new tools break away from the traditional concept of one  
507 drug, one target; i.e, a single molecular target with high selectivity to avoid other biological off-  
508 targets. The approach is useful in monogenic diseases, where traditionally one gene mutation has  
509 implied one phenotype. The majority of diseases are multifactorial or polygenic and need multi-  
510 target drugs to be treated (Bolognesi & Cavalli, 2016). Each of the different omics is focused on  
511 a regulatory process. Thus, genomics study DNA sequences and allelic variants in organisms by  
512 sequencing. Genomics also includes epigenomics, which studies how the genome is modified  
513 such that the DNA sequence does not change, but the organism's observable traits do  
514 (Westerman et al., 2020). Epigenomics can also show the functional interaction among  
515 regulatory genes and coding and non-coding regions. A step further, with an additive effect to  
516 these techniques, is the study of RNA by transcriptomics. Transcriptomics can give information  
517 about RNA structure, stability, variants, and alternative splicing (Litviňuková et al., 2020).  
518 Following the central molecular biology dogma: after RNA, translation occurs. A more complex  
519 omic is proteomics. Proteomics allows the study of changes in the levels and posttranslational

520 modifications of a protein in the organism (Alvarez-Franco et al., 2021; B. Liu et al., 2020).  
521 Finally, metabolomics, which is gaining relevance in recent years, studies complex interactions  
522 in the different cell compartments. Metabolites are the end-product of the cell and are involved in  
523 processes like degradation, enzyme kinetics, transport, and secretion (H. Zhang et al., 2022).  
524 However, although all omics are specialized in a part of a biological system, they are focused on  
525 the generation of complex networks of genes, transcripts, proteins, or metabolites to characterize  
526 cell types and also study normal and pathological conditions in a quantitative and qualitative  
527 manner.

528 All omics are based on new technical platforms as Next-generation sequencing (NGS), RNA-  
529 sequencing (RNA-seq), Chromatin-immunoprecipitation sequencing (ChIP-seq) and DNA  
530 methylation sequencing (Methyl-seq), single cell sequencing, liquid chromatography and mass  
531 spectrometry (LC-MS). All these new applied omics techniques generate large amounts of data  
532 that need to be process and registered in databases. Several articles have extensively reviewed  
533 the different types of databases (Matsa et al., 2016; Paananen & Fortino, 2020; Satam et al.,  
534 2023). Other omics that are emerging in recent years are lipidomics (full characterization of  
535 lipids); glycomics (study of glycans produced by cells under specified conditions), and  
536 glycoproteomics (study of glycoproteins, glycan structure, and protein identity and  
537 glycosilations). Nowadays, omics data help in pharmaceutical research. In the case of  
538 arrhythmogenic diseases, the combination of omics with stem cell technology has helped in  
539 diagnosis, drug discovery and treatment of diseases. As such, genomics helps in the  
540 identification of mutations responsible of genetic disorders or genetic polymorphisms and can  
541 predict prognosis, severity, and drug responsiveness (Wilson et al., 2015). Genomics also helps  
542 in understanding pathogenesis (e.g., GWAS databases), patient stratification, and discovery of



543 putative drug targets or assessing the efficacy and toxicity of drugs at the genetic level. For  
544 example, the identification by GWAS of new genes involved in AF (B et al., 2020). Another  
545 example is the use of genomics in Brugada Syndrome, which has helped in the development of a  
546 genetic risk score, due to the different *SCN5A* variants related to disease severity (Wijeyeratne et  
547 al., 2020). Transcriptomics also serves as a platform for drug discovery and drug evaluation, as  
548 well as to predict adverse drug target effects. Such is the case of the use of an agonist of PDGF  
549 (Platelet-derived growth factor) that decreased arrhythmia incidence in dilated cardiomyopathy  
550 caused by a Laminin A gene mutation (J. Lee et al., 2019). However, Transcriptomics goes a  
551 step further as it can decipher disease mechanisms and the mode of action of drugs (Alexander-  
552 Dann et al., 2018).

553 Although transcriptomic is the most readily used single-cell -omics level analysis, proteomics  
554 and metabolomics are gaining force in the discovery and toxicity evaluation of drugs, as well as  
555 identifying new biomarkers. Proteomics studies post-translational processes and the interactome,  
556 helping identify molecular pathways like the ProteomicsDB database that also helped in drug  
557 target identification (Samaras et al., 2020). Proteomics data also provide information for testing  
558 drug targeting efficacy and safety, as well as protein toxicology. Chemoproteomics is a new  
559 technology that combines mass spectrometry (MS) proteomics with chemical methods. In  
560 chemoproteomics small molecules bind to protein targets, indicating the amount of drug  
561 necessary for binding and what therapeutic effect it will produce. Moreover, the approach can  
562 assess off-target interactions by determining drug selectivity (Jones & Neubert, 2017). Finally,  
563 metabolomics has similar advantages as proteomics, but adding drug target discovery. An  
564 example of these omics applied to the arrhythmogenic field is the identification of proteomic and  
565 metabolite changes in Brugada patients with respect to control patients, identifying novel disease

566 biomarkers (Di Domenico et al., 2013). Although all omics are useful, focusing on a single omic  
567 technique cannot elucidate the entire biological response to drug treatment. Then, the  
568 combination of different omics in multi-omics or high-throughput technologies entails a better  
569 understanding of drug related mechanisms (N. Nguyen et al., 2022). The birth of AI and machine  
570 learning is also helping in processing the huge amounts of data obtained from omics. However,  
571 the results derived from the use of techniques should be complemented necessarily by functional  
572 studies to determine how individual genetic variants affect drug responses. Pharmacogenomics is  
573 then related to personalized medicine, as each patient is unique due to personal SNPs (single-  
574 nucleotide polymorphisms). These may induce patient variability in drug efficiency as described  
575 for the various degrees of severity of Brugada syndrome (Di Domenico et al., 2013; Wijeyeratne  
576 et al., 2020). Most AADs that target cardiac repolarization by blocking delayed rectifier  $K^+$   
577 current  $I_{Kr}$  (flecainide, amiodarone, dronedarone and sotalol) cause drug-induced TdP (Behr &  
578 Roden, 2013).

579 The risk of developing LQTS or TdP can be influenced by genetic factors, particularly SNPs that  
580 affect the function of cardiac ion channels. For example drug-induced LQTS due to  
581 sulfamethoxazole antibiotic medication. Sesti and colleagues reported that a SNP in the *KCNE2*  
582 gene encoding MiRP1 (T8A-MiRP1), a subunit of the hERG channels that has been associated  
583 previously with inherited LQTS, underlies genetic predisposition of sulfamethoxazole-induced  
584 LQTS (Sesti et al., 2000). Importantly,  $I_{Kr}$  in T8A-MiRP1 SNP patient was normal at baseline  
585 but at least 4-fold more sensitive to therapeutic levels of sulfamethoxazole than wild type  
586 channels (Sesti et al., 2000). Sulfamethoxazole speeded deactivation (closure) only of  $I_{Kr}$  formed  
587 with T8A-MiRP1 SNP (Sesti et al., 2000). Hence, patients carrying these genetic variants may be  
588 at a higher risk of developing drug-induced LQTS when exposed to sulfamethoxazole, as the

589 drug's effect on cardiac repolarization is amplified due to their underlying genetic predisposition.  
590 This illustrates the importance of pharmacogenomics in predicting adverse drug reactions and  
591 tailoring treatments to individual genetic profiles. For more examples, Dan et al 2012 provide a  
592 summarized table of the different drugs and genes involved in the pharmacogenomics of anti-  
593 arrhythmics (Dan et al., 2018).

## 594 **6. Computational Screening for Accurate Development of New Chemical Compounds**

595 Advancements in computational modeling in drug discovery have revolutionized the  
596 pharmaceutical industry, accelerating the identification and development of novel therapeutics.  
597 Traditional drug discovery methods are time-consuming and expensive, but computational  
598 modeling expedites the process by predicting molecular interactions, identifying potential drug  
599 targets, and optimizing compound structures (Sadybekov & Katritch, 2023; Sliwoski et al.,  
600 2014). The process involves algorithms, simulations, and databases to simulate molecular  
601 interactions, predict compound behaviors, and evaluate their efficacy and safety. This reduces  
602 considerably the need for extensive laboratory testing and significantly decreases the time and  
603 resources needed for drug discovery and basic science. Initially, researchers input structural data  
604 of target molecules or biological systems into computer models. Molecular docking predicts how  
605 small molecules (potential drugs) interact with target proteins, simulating their binding and  
606 affinity (Gioia et al., 2017; Kitchen et al., 2004; Kontoyianni, 2017). Using molecular docking  
607 software, the ligand's three-dimensional structure is virtually fitted into the binding site of the  
608 target molecule, exploring various orientations and conformations. The software evaluates and  
609 scores these ligand-protein interactions based on factors like binding energy, complementarity,  
610 and predicted stability of the complex. Docking studies help identify potential drug candidates by  
611 assessing their likelihood to bind to the target and modulate its activity. They guide medical

612 chemists by suggesting structural modifications to optimize binding affinity and specificity.  
613 However, docking models have limitations like considering only the static structure of proteins  
614 and simplifying the complexities of molecular interactions in living systems (Kolb et al., 2012).  
615 Nevertheless, the combination of new and feasible molecules by docking with molecular biology  
616 and STEM (science, technology, engineering and mathematics) technology will allow the  
617 discovery of new drugs. Further, molecular dynamics simulations allow researchers to  
618 understand the dynamic behavior of druggable molecules and their interactions with biological  
619 targets at a level of detail that was once unimaginable (Ahmed et al., 2023; De Vivo et al., 2016;  
620 Kuzmanic et al., 2020). This insight aids in designing more effective and specific drugs with  
621 fewer side effects. However, as before, integrating experimental proof is crucial to validate and  
622 enhance the reliability of the predictions generated through *in-silico* docking studies. For  
623 instance, research indicates that flecainide and propafenone increase  $I_{K1}$  by reducing polyamine  
624 blocking of the strong inward rectifier potassium channel Kir2.1 (Caballero et al., 2010; Gómez  
625 et al., 2014). Structural modeling combined with experimental validation has illustrated that both  
626 flecainide and propafenone bind to Kir2.1 through specific interactions with Cys311. Such an  
627 interaction has facilitated the identification of the pharmacophore associated with drugs that  
628 enhance Kir2.1 function (Caballero et al., 2010; Gómez et al., 2014). Similarly, investigations at  
629 the atomic scale have delved into the structure-based molecular mechanisms of AADs.  
630 Researchers employed Rosetta structural modeling, docking techniques, and molecular dynamics  
631 simulations to scrutinize the interactions of AADs like flecainide, lidocaine, and ranolazine, with  
632 the human voltage-gated sodium channel ( $Na_v1.5$ ) (Bender et al., 2016; Meiler & Baker, 2006).  
633 Those calculations unveiled pivotal drug binding sites within the pore lumen, capable of  
634 simultaneously accommodating up to two drug molecules. Interestingly, molecular dynamics

635 simulations further elucidated a hydrophilic access pathway through the intracellular gate and a  
636 hydrophobic access pathway via a fenestration situated between DIII and DIV of Na<sub>v</sub>1.5 (P. T.  
637 Nguyen et al., 2019). The assessment of AP within an *in-silico* modeling framework has also  
638 proven to be a potent tool for early detection of drug-induced proarrhythmic risk. This evaluation  
639 showcases its efficacy in discriminating torsadogenic compounds that impact the AP duration  
640 (APD) across isolated endocardial, midmyocardial, and epicardial cells, along with inducing QT  
641 prolongation in human ventricular action potential models (Romero et al., 2018).

642 Quantitative Structure-Activity Relationship (QSAR) models can be integrated in the workflow  
643 analysis of chemical and biological properties to forecast a compound's activity (Lipinski et al.,  
644 2001). Specially, QSAR models decipher the intricate relationship between a compound's  
645 structure and its biological activity through computational analysis. By scrutinizing various  
646 chemical descriptors—molecular size, shape, electronegativity, and more—alongside biological  
647 properties like receptor affinity or enzyme inhibition. QSAR models predict how structural  
648 modifications impact a compound's effectiveness or toxicity (Bradbury, 1995). These models  
649 employ statistical techniques to generate equations correlating the chemical structure's  
650 quantitative features with the observed biological activity, facilitating the prediction of untested  
651 compounds' behavior. *In silico* methods accelerate drug discovery by reducing the number of  
652 compounds requiring physical testing, optimizing lead compounds, and predicting potential side  
653 effects. However, they rely heavily on the quality of input data and model accuracy (Holzinger et  
654 al., 2019). Continuous advancements in computational power and algorithms enhance the  
655 precision and efficiency of these techniques, reshaping the landscape of pharmaceutical research  
656 and expediting the development of novel therapeutics. For example, QSAR plays a pivotal role  
657 in addressing drug-induced TdP risks (Broccatelli et al., 2012; Das et al., 2023; Frid &

658 Matthews, 2010). QSAR models utilize large datasets, such as those resulting from compulsory  
659 human ether-a-go-go-related gene channel (hERG) screening, to establish correlations between  
660 molecular structures and biological activities. QSAR aids in predicting IC50 values for hERG  
661 blockade, providing valuable insights into the potential cardiotoxic effects of drugs (Choi et al.,  
662 2020; Wacker & Noskov, 2018). However, the evolution beyond traditional QSAR techniques,  
663 with modern Machine Learning (ML) algorithms, particularly eXtreme Gradient Boosting  
664 (XGBoost), demonstrates superior accuracy in determining hERG blockade and paves the way  
665 for more advanced predictive models in drug development and safety assessment (Wacker &  
666 Noskov, 2018; X. Yang et al., 2023).

667 AI and machine learning have become pivotal in revolutionizing drug development in the future  
668 (Sarkar et al., 2023a). These are technologies based on vast datasets and advanced algorithms;  
669 they predict biological activities, and expedite drug discovery potentially reducing costs and  
670 timelines. Through pattern recognition and analysis, AI models can sift through massive amounts  
671 of biological, chemical, and clinical data to identify potential drug candidates, predict their  
672 efficacy, optimize molecular structures, and even anticipate adverse effects (Mullowney et al.,  
673 2023; X. Yang et al., 2023; Z. Zhu et al., 2022). These models learn from diverse data sources  
674 (e.g., omics information, protein structures, drug interactions, and patient data) to suggest  
675 promising compounds, assisting in virtual screening, and predicting a compound's potential  
676 activity against a target. For instance, AI and data mining helps in all omic data processing,  
677 contributing to the new field of pharmacogenomics and personalized medicine, as has been done  
678 in type 2 diabetes (Allesøe et al., 2023). Virtual screening, empowered by machine and deep  
679 learning, rapidly analyzes vast chemical libraries to identify potential candidates for further  
680 experimental validation processes to ensure the efficacy and safety of identified compounds. Its

681 integration into drug development pipelines has revolutionized early-stage screening, offering a  
682 more efficient pathway for identifying promising drug candidates (Chan et al., 2019; Sarkar et  
683 al., 2023a). Therefore, these technologies hold immense promise, despite facing challenges like  
684 data quality representation and ethical considerations, reshaping drug development and  
685 potentially expediting the delivery of safer and more effective treatments to patients worldwide  
686 (L. K. Vora et al., 2023). In summary, the integration of computational modeling techniques has  
687 greatly enhanced the efficiency and effectiveness of drug discovery, promising a future where  
688 the development of new therapies is not only faster but also more precise and tailored to  
689 individual patient needs. However, computational technologies are not understood alone. They  
690 need validation in biological samples that test functional outcomes like electrophysiology in the  
691 case of arrhythmogenic diseases and drug therapy.

## 692 **7. High-Throughput Screening Electrophysiological Platforms**

693 Drug discovery in the cardiovascular diseases field is constantly changing and has been evolving  
694 with emerging technologies and methodologies to meet challenges and needs. The recent  
695 evolution of High-Throughput Screening (HTS) is playing an essential role in drug discovery for  
696 antiarrhythmic therapy by contributing to increase success rates in the identification and  
697 development of effective and safe potential drug candidates (Bunch et al., 2023; Satam et al.,  
698 2023; Wilson et al., 2015). The use of HTS has revolutionized traditional drug development in  
699 cardiac diseases by expediting the efficient identification of lead compounds, optimizing their  
700 properties, and enhancing our understanding of the complex mechanisms underlying cardiac  
701 arrhythmias and potential drug interactions (Bruyneel et al., 2018; da Rocha et al., 2017). A good  
702 example is the study by Sharma *et al.*, where using hiPSC-CMs and applying various HTS  
703 assays they identified a signaling pathway by which different tyrosine kinase inhibitors (TKI),

704 used in oncology, produce cardiovascular side effects ranging from induced arrhythmias to heart  
705 failure. Increased cardioprotective signaling of this pathway identified with exogenous insulin or  
706 insulin-like growth factor-1 (IGF-1) enhanced the viability of hiPSC-CMs during co-treatment  
707 with cardiotoxic TKI. This approach provided the unexpected insight that cardiotoxicity and  
708 arrhythmias induced by certain anticancer drugs can be alleviated via cardioprotective  
709 insulin/IGF signaling (Sharma et al., 2017). HTS allows for the rapid and simultaneous screening  
710 of large compound libraries against multiple targets implicated in the complex mechanisms of  
711 arrhythmogenesis. Thus, HTS accelerates the identification of compounds with potential  
712 antiarrhythmic properties fostering innovation in drug discovery beyond traditional targets  
713 (Wells et al., 2019). HTS significantly reduces the time and resources required by automating the  
714 screening process in a short period. For example, Glazer and colleagues used a high-throughput  
715 automated patch-clamp system to study the function of the 83 variants in *SCN5A* gene associated  
716 with Brugada Syndrome. They reclassified the variants with functional data expressed in HEK  
717 cells (Glazer et al., 2020). This efficiency is particularly valuable in the context of arrhythmia  
718 stratification and antiarrhythmic therapy, where rapid intervention may be critical (Al-Khatib et  
719 al., 2018). For example, a study established a high-throughput drug testing system on 13  
720 different compounds using human iPSC derived atrial-like myocytes for drug discovery in AF  
721 (Honda et al., 2021). HTS assays facilitate the optimization of lead compounds, which can then  
722 be further investigated for enhanced doses, efficacy, and selectivity, improving the candidate's  
723 therapeutic profiles. These assays can also be employed to assess potential cardiotoxic effects  
724 early in the drug development process, helping to prioritize compounds with a lower risk of  
725 adverse cardiac effects (Krishna et al., 2021). HTS allows the use of patient-specific iPSC  
726 models, contributing to the development of personalized antiarrhythmic therapies that consider



727 individual variations in drug response, (del Álamo et al., 2016) as described in detail in previous  
728 sections. The complementary use of hiPSCs and HTS technologies offers great versatility and  
729 advantages for arrhythmia research; e.g., one can validate the targets involved in the  
730 development of arrhythmias identified by omics, as well as test new drugs designed against these  
731 specific targets designed by computational modeling as explained in previous sections.  
732 Evidently, not only has HTS benefited greatly from hiPSC technology, but many of these  
733 technologies have been designed specifically for application in hiPSC-CMs and not in animals or  
734 heterologous expression systems as previously shown. Priority is now being given to the HTS  
735 technologies using automated electrophysiological platforms. Automated patch-clamp systems  
736 can rapidly screen many genetic variants and/or compounds, and analyze their effects on  
737 multiple ion channels aiding in the identification of potential candidates (Obergrussberger et al.,  
738 2021; Walsh, 2015). For example, a study was able to test the effects of 26 drugs and 3 drug  
739 combinations on two iPSC-CM lines using high-throughput voltage-sensitive dye and  
740 microelectrode-array assays. Drugs were studied for the CiPA initiative and results were  
741 compared with clinical QT prolongation and TdP risk (Blinova et al., 2017). Automated systems  
742 often allow for parallel recordings from multiple cells or channels simultaneously. This enables  
743 researchers to study the effects of compounds on different cell types or ion channels more  
744 efficiently (Obergrussberger et al., 2021). Automated patch-clamp systems offer various  
745 advantages with respect to manual patch-clamp, such as much faster experimental rates,  
746 consistency, reproducibility, continuous recording, user-friendly interfaces, customization, and  
747 flexibility to design experiments (Obergrussberger et al., 2021). For example, a study validated  
748 state dependence and subtype selectivity of reference calcium channel modulators (nifedipine,  
749 BAY K8644, verapamil, mibefradil, and pimozone) on human Cav1.2, Cav2.1, Cav2.2, and

750 Cav3.2 channels using automated electrophysiology assays (Kuryshv et al., 2014). It is  
751 important to note that manual patch-clamp techniques still have their place, especially in  
752 situations where fine control, manual dexterity, or specific experimental conditions are crucial.  
753 Non-Invasive electrocardiographic imaging (ECGI), which allows the reconstruction of high-  
754 resolution cardiac electrical activity maps, enables the assessment of drug-induced changes in  
755 cardiac electrophysiology (Rudy, 2013). Experimental cardiac optical mapping is the gold  
756 standard for measuring complex electrophysiology in *ex-vivo* and *in-vitro* heart preparations.  
757 Optical mapping uses voltage-sensitive or calcium-sensitive fluorescent dyes to visualize and  
758 measure the dynamics and drug-induced changes in electrical wave propagation on both the  
759 surface of an animal heart (P. Lee et al., 2019) and hiPSC-CM monolayers (W. Liu et al., 2023).  
760 Microelectrode array (MEA) platforms can monitor the electrical activity. In 2D iPSC-CMs  
761 monolayers, recording the field potential duration (FPD), an electrical signal similar to the ECG.  
762 This technique also provides insights into drug-induced changes in cardiac rhythms (del Álamo  
763 et al., 2016; S. R. Zhao et al., 2022). In addition, techniques for the analysis of  
764 electrophysiological function in cardiac organoids, 3D culture systems, and organ-chips are  
765 being developed, which should provide more relevant insights compared to traditional cell  
766 culture models (X. Zhang et al., 2016). During the last decade, advanced automated microscopy  
767 techniques are being incorporated simultaneously to control and monitor the electrical activity  
768 and calcium handling of specific cardiac cell types for studying drug effects at a cellular and  
769 subcellular level (Dvinskikh et al., 2023; Huebsch et al., 2015). HTS generates large datasets that  
770 can be integrated with computational and bioinformatics approaches, providing a systems-level  
771 understanding of drug effects on cardiac electrophysiology. The integration of all such  
772 electrophysiological data sets with multi-omics and bioinformatics approaches (machine learning

773 algorithms and AI) can help identify potential antiarrhythmic therapies (Galappaththige et al.,  
774 2022; Sarkar et al., 2023b; Trayanova et al., 2021). These emerging HTS electrophysiological  
775 technologies offer more precise, relevant, and efficient ways to evaluate the antiarrhythmic  
776 potential of new drugs, ultimately enhancing drug safety assessments and reducing the risk of  
777 adverse cardiac events during drug development and clinical use.

## 778 **8. Exploring Drug Repurposing for Arrhythmia Treatment**

779 Developing a new drug from scratch is a time-consuming and expensive process (Kale et al.,  
780 2022). To move forward, researchers have to consider and explore other approaches like drug  
781 repurposing. Drug repurposing involves identifying novel therapeutic uses for existing drugs  
782 outside their originally intended scope (Abdelsayed et al., 2022; Choudhury et al., 2022; Gelosa  
783 et al., 2020). The strategy offers a cost-effective alternative and leverages the extensive  
784 knowledge available about a drug's safety profile, pharmacokinetics, and mechanisms of action,  
785 potentially expediting the development process (Kale et al., 2022). Known safety profiles of  
786 repurposed drugs can mitigate the risk of unexpected adverse effects. This advantage is  
787 particularly crucial in cardiac care, where the consequences of adverse reactions can be severe  
788 (Abdelsayed et al., 2022; Gelosa et al., 2020; Saljic et al., 2023). Moreover, repurposed drugs  
789 often possess mechanisms of action that can address multiple pathways involved in  
790 arrhythmogenesis. This multifaceted approach may enhance therapeutic efficacy compared with  
791 traditional single-target drugs (Wasim et al., 2023). In addition, HTS technology can also be used  
792 to screen existing drug libraries to identify compounds with unforeseen antiarrhythmic  
793 properties, facilitating drug repurposing strategies (Abdelsayed et al., 2022). There are several  
794 interesting examples of repurposed drugs for arrhythmias. For example, originally amiodarone  
795 was developed as an antianginal agent owing to its vasodilating effect; however, amiodarone was

796 repurposed as an antiarrhythmic drug due to its potent effect on various ion channels  
797 (Tavolinejad et al., 2019). It is now widely used to treat life-threatening ventricular arrhythmias.  
798 A derivative of amiodarone, dronedarone, was developed to reduce amiodarone's side effects  
799 while retaining its antiarrhythmic properties and is used in the management of AF (Pannone et  
800 al., 2021; Vamos & Hohnloser, 2016). Other examples are verapamil and diltiazem, calcium  
801 channel blockers, initially designed for hypertension and angina treatment. These drugs have  
802 shown efficacy in certain supraventricular arrhythmias by modulating calcium currents in the  
803 heart (Godfraind, 2017). A more recent example is ranolazine which was developed initially as a  
804 metabolic modulator and approved as an antianginal agent; however, it was also identified as an  
805 inhibitor of the cardiac late  $\text{Na}^+$  and hERG currents. The latter actions underlie ranolazine's  
806 antiarrhythmic effects on both supraventricular and ventricular arrhythmias. However, despite  
807 initial enthusiasm, ranolazine is only authorized as a second-line treatment in patients with  
808 chronic angina pectoris, notwithstanding its antiarrhythmic properties (Frommeyer et al., 2016;  
809 Rouhana et al., 2021; Shenasa et al., 2016). In summary, while drug repurposing holds great  
810 promise for arrhythmia treatment, challenges persist. Rigorous clinical trials are essential to  
811 establish the safety and efficacy of repurposed drugs in specific arrhythmia subtypes.  
812 Additionally, identifying suitable candidates for repurposing and understanding the precise  
813 mechanisms of action remain ongoing challenges.

## 814 **9. Gene Therapy Approaches**

815 Recombinant adeno-associated (rAAV) viruses have been successfully used as the selected  
816 vehicle for viral gene delivery in a wide range of clinical applications in multiple diseases  
817 (Mendell et al., 2021). In the last decades, AAV-gene delivery progressed to FDA-approved  
818 clinical trials with a good safety profile and promising results in the treatment of genetic diseases

819 such as hemophilia, lipoprotein lipase deficiency (LPLD), inherited retinal disease (IRD) and  
820 spinal muscular atrophy (SMA) (Gaudet et al., 2013; Mingozzi & High, 2011; Nathwani et al.,  
821 2011). However, the use of AAV-gene therapy has limited success to prevent and treat cardiac  
822 disorder (Bass-Stringer et al., 2018a; Ishikawa et al., 2018a). Intracoronary infusion of AAV1  
823 encoding SerCA2a (a phase iib) failed to demonstrate beneficial results of AAVs-based gene  
824 therapy in patients with heart failure (Greenberg et al., 2016). There are still numerous  
825 challenges that need to be resolved, such as the inability of rAAVs to effectively target specific  
826 tissues, preexisting neutralizing antibodies in human populations, the wrong molecular targets or  
827 inadequate doses administered (Shen et al., 2022). However, the interest for clinical rAAV-gene  
828 transfer approaches to treat various disorders in other tissues has propelled growing interest and  
829 progress in utilizing rAAVs for cardiac disorders. Gene therapy has the potential to correct the  
830 underlying genetic defects that contribute to the development of arrhythmias rather than simply  
831 alleviating symptoms, offering long-term, precise, and targeted treatment (Bass-Stringer et al.,  
832 2018b). However, gene therapy for cardiac arrhythmias is still in a research-and-development  
833 phase, and there are significant challenges to overcome before it can become a standard  
834 treatment. As described above, AAVs are one of the most widely used gene delivery systems;  
835 however, it presents specific limitations for cardiac gene therapy (Ishikawa et al., 2018b; Shen et  
836 al., 2022). AAVs DNA capacity is limited to < 4.8 kb for efficient packaging, which means that  
837 they can only carry and deliver genes of relatively small size. This is a major limitation for the  
838 treatment of arrhythmias since cardiac ion channel encoding genes are usually very large.  
839 Furthermore, achieving uniform, efficient, and specific transduction in cardiac cells can be  
840 challenging and AAVs tend to accumulate in other tissues, especially liver, leading to adverse  
841 effects. CRISPR technology is therefore considered for gene therapy in certain instances,

842 although it has its own limitations. Despite such limitations, AAVs remain a valuable option in  
843 cardiac gene therapy, especially in preclinical research and early clinical trials.

844

845 Similarly, RNA-based therapies have emerged as a promising avenue in drug development for  
846 cardiac diseases. Specifically, approaches like RNA interference (RNAi) and antisense  
847 oligonucleotides (ASOs) offer potential treatments in cardiovascular disease (Crooke et al.,  
848 2021). Many microRNAs or long noncoding-RNAs (lncRNAs) have been suggested to  
849 potentially enhance cardiac activity in acute myocardial infarction, fibrosis, hypertrophy or heart  
850 failure among others (Lucas et al., 2018; Lucas & Dimmeler, 2016). A further successful concept  
851 of cardiovascular cell delivery using AAV was achieved using two proliferative miRNAs miR-  
852 500 and miR-199a to promote cardiomyocyte regeneration and recover cardiac function after  
853 myocardial infarction in mice (Eulalio et al., 2012). Similarly, miR-1 expression demonstrated a  
854 potential novel therapeutic strategy to reverse pressure-induced cardiac hypertrophy and prevent  
855 maladaptive cardiac remodeling (Karakikes et al., 2013; Luo et al., 2018). Over the past decade,  
856 numerous oligonucleotide-based therapies have been developed utilizing LNA-modified  
857 chemistries to modulate cardiac miRNAs. AntagomiRs and locked nucleic acid (LNA) antimiRs  
858 stand out as prominent examples in the category of miRNA inhibitors (Krützfeldt et al., 2005).  
859 Dysregulated miRNAs can contribute to the development or progression of cardiovascular  
860 pathological conditions by promoting harmful processes and antimiRs are therapeutic molecules  
861 designed to inhibit the function of specific miRNAs (Rupaimoole & Slack, 2017). LNA antimiRs  
862 are an advanced form, chemically modified for greater stability and stronger binding to target  
863 miRNAs (Samolovac & Hinkel, 2022). By blocking miRNA function, LNA antimiRs offer a  
864 promising approach to treating cardiovascular diseases by potentially reversing damage caused

865 by abnormal miRNA activity (Samolovac & Hinkel, 2022). For instance, the therapeutic  
866 potential of miR-15 as a target for manipulating cardiac remodeling and function in ischemic  
867 injury has been validated (Hullinger et al., 2012). Additionally, therapeutic inhibition through  
868 LNA-based antimiRs targeting miR-208a has shown improvements in cardiac function and  
869 increased survival during heart failure (Montgomery et al., 2011). Another observation is that  
870 inhibiting the entire miR-34 family reduces cell death and fibrosis following myocardial  
871 infarction (Bernardo et al., 2012; Y. Yang et al., 2015). These advancements underscore the  
872 growing significance of LNA-modified chemistries and antimiRs in the development of  
873 oligonucleotide-based therapies, particularly in the context of cardiac miRNA modulation.  
874 Altogether, these RNA-based therapies hold promise due to their specificity and potential for  
875 personalized medicine. By targeting specific genes or molecular pathways implicated in cardiac  
876 diseases, they offer a tailored approach to treatment. Ongoing research aims to refine these  
877 therapies to enhance their efficacy, reduce off-target effects, and bring forth safer and more  
878 efficient treatments for multitude of cardiac disorders (Cornu et al., 2017; Dhakne et al., 2023;  
879 Mann et al., 2002; Sasso et al., 2022).

880  
881 In proof-of-concept studies, Nelson et al., and Tabebordbar et al. used AAV9 to deliver the  
882 CRISPR/Cas9 gene-editing system to young mice with a mutation in the gene coding for  
883 dystrophin deficiency in patients with Duchenne muscular dystrophy (DMD) (Nelson et al.,  
884 2019; Tabebordbar et al., 2021). Gene editing partially restored dystrophin protein expression in  
885 skeletal and cardiac muscle and improved skeletal muscle function. rAAV-delivery of  
886 CRISPR/Cas9 or other enzymes to perform genome editing in mouse cardiomyocytes or hiPSC-  
887 CMs (as previously discussed) is a powerful tool in both gene therapy and generating new

888 models. Novel Myo-AAV capsid has been used to achieve gene expression of CRISPR-based  
889 gene therapy treating dilated cardiomyopathy (Grosch et al., 2023). Thus, gene-editing systems  
890 elude any complication derived from vector size and can theoretically be applied to edit any gene  
891 across diverse genetic backgrounds. This technology could offer a suitable platform in treating  
892 cardiac diseases whose pharmacological spectrum fails in reducing arrhythmias.

### 893 **10. Peptide-based treatment, new antiarrhythmic modality**

894 Sudden cardiac death in children and young adults is a relatively rare but tragic event whose  
895 molecular pathophysiology is unknown and treatment is inadequate (Mazzanti et al., 2020;  
896 Moreno-Manuel et al., 2023). The identification of the interaction at the molecular level of the  
897 main sodium channel ( $\text{Na}_v1.5$ ) with the strong inward rectifying potassium channel (Kir2.1) in  
898 the control of cardiac excitability and impulse conduction (Milstein et al., 2012) has opened a  
899 new paradigm for drug discovery and treatment of arrhythmias and SCD. Kir2.1 and  $\text{Na}_v1.5$   
900 form "channelosomes" that are anchored together at their eventual membrane microdomains by  
901 physically interacting via specific PDZ binding domains in their respective COOH terminal with  
902 scaffolding proteins like SAP97 and  $\alpha1$ -syntrophin (Gillet et al., 2015; Milstein et al., 2012;  
903 Petitprez et al., 2011). Certain loss-of-function Kir2.1 mutations can also reduce  $\text{Na}_v1.5$  function  
904 in Andersen-Tawil Syndrome Type 1 (ATS1), a rare but potentially lethal inheritable cardiac ion  
905 channel disease (Cruz et al., 2023; Macías et al., 2022; Moreno-Manuel et al., 2023). For  
906 example, arrhythmias associated with a trafficking deficient mutation ( $\Delta314-315$ ) in Kir2.1 alters  
907 both  $I_{K1}$  and  $I_{\text{Na}}$  (Macías et al., 2022). Similarly, another loss of function Kir2.1(C122Y)  
908 mutation that enables channel trafficking to the membrane but alters channel structure and  
909 biophysics also reduces both  $I_{K1}$  and  $I_{\text{Na}}$  leading to slow ventricular conduction and arrhythmias  
910 in ATS1 (Cruz et al., 2023). In many of these patients, the treatment provided by clinical



911 guidelines is based on combinations of  $\beta$ -blockers and traditional class 1C AADs like  
912 flecainide. . Such treatments are empirical, subject to trial and error and may even be  
913 proarrhythmic, likely because they impair sodium channel function (Kukla et al., 2014; Mazzanti  
914 et al., 2020; Tristani-Firouzi & Etheridge, 2010). Therefore, the development of advanced and  
915 targeted drug therapies based on small peptides that combine the elements necessary to transport  
916 and anchor Kir2.1 and  $\text{Na}_v1.5$  to the cell membrane could have an impact in treating cardiac  
917 diseases related to ion channel remodeling. Patients with cardiomyopathy of DMD are at risk of  
918 developing life-threatening arrhythmias because of ion channel remodeling that reducing both  $I_{\text{Na}}$   
919 and  $I_{\text{K1}}$  (Jimenez-Vazquez et al., 2022). Interestingly, transfecting just one component of the  
920 dystrophin protein complex ( $\alpha1$ -syntrophin) restored channelosome function, increasing  $I_{\text{Na}}$  and  
921  $I_{\text{K1}}$  densities in hemizygous iPSC-CMs from a DMD patient (Jimenez-Vazquez et al., 2022).  
922 Thus, reimagining antiarrhythmic pharmacotherapy by developing bold, and tailored peptidic  
923 solutions that restore channelosome dysfunction may have a powerful impact in treating a whole  
924 spectrum of cardiac arrhythmias, from the molecule to the bedside. The approach could offer  
925 improved efficacy and safety compared to conventional AADs, and may target neurological  
926 disorders, cardiovascular diseases or even certain types of cancer.

927 A new class of peptidic agents, known as peptibodies is emerging. Peptibodies are chimeras  
928 generated as fusion proteins of the fragment crystallizable (Fc) domain of the human  
929 immunoglobulin G (IgG) with a bioactive “warhead” peptide (Cavaco et al., 2017; Shimamoto et  
930 al., 2012). Peptibodies combine the biologic/therapeutic activity of a given peptide, with the  
931 stability of monoclonal antibodies. They are stable and safe molecules that are developed as  
932 viable clinical therapeutics. For instance, the first peptibody in clinical use is Romiplostim,  
933 which is approved for the treatment of immune thrombocytopenic purpura (Hubulashvili &

934 Marzella, 2009). Romiplostim is composed of thrombopoietin mimetic peptides fused to the C  
935 terminus of the Fc region of human IgG (McElroy et al., 2015; Molineux, 2011; Molineux &  
936 Newland, 2010; Nichol, 2006; B. Wang et al., 2004). New studies have proposed the peptibody  
937 technology to selectively design peptides that bind to and modulate the function of specific ion  
938 channels involved in arrhythmogenesis (Calvo et al., 2018; Chidipi et al., 2022; Ehrlich et al.,  
939 2008; Heijman et al., 2018). Specially, in persistent AF, the acetylcholine activated inward  
940 rectifier potassium current ( $I_{K_{ACh}}$ ) is constitutively active, behaves as a background potassium  
941 inward rectifier channel, and can thus contribute to the initiation and maintenance of the  
942 arrhythmia (Dobrev et al., 2005; Heijman et al., 2018). Since  $I_{K_{ACh}}$  is mainly expressed in the  
943 atria and is largely absent from the working ventricular myocardium, it has been proposed that  
944 blocking  $I_{K_{ACh}}$  can be an atrial-selective rhythm control pharmacotherapy (Calvo et al., 2018;  
945 Ehrlich et al., 2008; Heijman et al., 2018). An  $I_{K_{ACh}}$  blocking peptibody (Fc-TP) was engineered  
946 as a fusion protein between the Fc fragment of the human IgG1 and a tertiapinQ peptidotoxin  
947 (TP) originally isolated from the venom of the European honey bee (Drici et al., 2000)). Patch-  
948 clamping experiments showed that Fc-TP was ~300-fold more potent than TP alone, which could  
949 be due to an increased stabilization between the peptibody and  $I_{K_{ACh}}$ . Interestingly, the peptibody  
950 blocked carbachol-activated  $I_{K_{ACh}}$  in atrial tissue reducing inducibility of AF in aged mice while  
951 minimizing off-target effects (Chidipi et al., 2022), but it did not affect the potassium current in  
952 ventricular myocytes. Therefore, the advancement in designing peptibodies to target and  
953 modulate ion channels implicated in arrhythmias represents a step forward in the development of  
954 next-generation antiarrhythmic modalities with enhanced specificity and reduced adverse effects  
955 for a variety of diseases.

## 11. Advancements in Drug Delivery

956  
957 Traditional systemic drug administration can result in low drug concentrations at the heart and  
958 potential side effects in non-cardiac tissues. Ensuring effective delivery of AADs to cardiac  
959 tissue remains a critical challenge (Nadimi et al., 2018). Recent advancements in drug delivery  
960 technologies are revolutionizing the landscape, offering new hope for improved therapeutic  
961 outcomes. Targeted drug delivery systems aim to overcome these limitations by selectively  
962 delivering medications to the affected cardiac tissue (Omidian et al., 2023). Development of  
963 nanoscale drug delivery systems offers unique advantages. Nanoparticles Metal-, lipid-, and  
964 polymer-based nanoparticles represent ideal materials for use in cardiovascular therapeutics  
965 allowing enhanced drug stability, controlled release, and improved bioavailability (Qian et al.,  
966 2023). Nanoparticles can be engineered to allow encapsulated antiarrhythmic drugs navigate  
967 through the circulatory system and reach specific heart tissues (Nadimi et al., 2018; Z. Wang et  
968 al., 2022; F. Yang et al., 2022) . For example, a study demonstrated that liposomal amiodarone  
969 augments antiarrhythmic effects and reduces hemodynamic adverse effects in an  
970 ischemia/reperfusion rat model (Takahama et al., 2013). Many studies have reported the  
971 application of different nano-drug delivery systems charged with botulinum toxin, CaCl<sub>2</sub>; L-  
972 glutamate, budesonide, carvedilol, and N-isopropyl acrylamide monomer (Z. Wang et al., 2022)  
973 in the treatment of AF. Such precision minimizes off-target effects and enhances therapeutic  
974 efficacy. Moreover, surface modifications can enable nanoparticles to actively target areas such  
975 as inflammation or fibrosis within the heart (Omidian et al., 2023). Implantable devices, such as  
976 drug-eluting stents and patches, provide a localized and sustained release of antiarrhythmic  
977 medications (Adhami et al., 2023; Fayzullin et al., 2021). These devices can be strategically  
978 placed in or around the heart, ensuring continuous drug delivery to the affected area. For

979 instance, drug-eluting stents, have been designed to release medications directly into the  
980 coronary arteries, reducing the risk of reoccurrence of arrhythmias following interventions like  
981 catheter ablation (Adhami et al., 2023). The use of drug-eluting stents, among myocardial  
982 infarction patients with AF has increased over time (A. N. Vora et al., 2023). In addition,  
983 innovations in electro-responsive drug delivery systems involve the incorporation of smart  
984 materials that respond to changes in the electrical environment of the heart. These systems can  
985 release drugs in response to specific cardiac conditions, offering a real time and on-demand  
986 therapeutic approach (Y. Zhao et al., 2016). For example, several hydrogels with conductive  
987 properties have been designed to restore the electrical impulses to the heart, preventing further  
988 remodeling and ventricular dysfunction after myocardial infarction (Tapeinos et al., 2022).

989  
990 3D printing has emerged as a customized transformative technology allowing for the creation of  
991 intricately designed structures and personalized medications. 3D printing enables the fabrication  
992 of intricate drug formulations with precise control over drug release kinetics. Antiarrhythmic  
993 medications can be embedded within biocompatible materials, such as polymers, in a controlled  
994 and layered fashion (Vaz & Kumar, 2021). This design allows for sustained and targeted drug  
995 release, ensuring optimal therapeutic concentrations in the affected cardiac tissue. For example,  
996 the production of 3D-printed preparations of high-quality filaments containing amiodarone and  
997 dronedarone have been described in the literature (Matijašić et al., 2019; Roulon et al., 2021). A  
998 recent study also prepared propranolol hydrochloride gummy chewable tablets tailored for  
999 children by semisolid extrusion 3D printing technology to meet personalized medicine needs in  
1000 pediatrics (C. Zhu et al., 2022). 3D printing also facilitates the incorporation of multiple  
1001 medications into a single, complex structure. This capability is particularly valuable in

1002 antiarrhythmic therapy, where combination drug regimens may be more effective (Lu et al.,  
1003 2023). The versatility of 3D printing extends to the creation of implantable devices specifically  
1004 designed for antiarrhythmic drug delivery. Implantable patches, stents, or microstructures can be  
1005 customized to fit the unique anatomy of the heart, offering localized and sustained release of  
1006 medications (Domsta & Seidlitz, 2021, 2021; Lu et al., 2023). These devices can be strategically  
1007 placed to deliver drugs directly to the affected areas, improving the precision of treatment and  
1008 reducing the risk of adverse effects. There are challenges related to 3D printing, which include  
1009 ensuring the biocompatibility of printed materials, refining printing techniques for  
1010 pharmaceutical applications, and navigating regulatory pathways. While these new drug delivery  
1011 technologies hold immense promise, several challenges must be addressed to bring this  
1012 technology to widespread clinical use. Optimizing biocompatibility, long-term stability, and  
1013 scalability of these technologies remains a focus of ongoing research.

## 1014 **12. Concluding Remarks**

1015 Current antiarrhythmic therapies have limited efficacy and are frequently associated with adverse  
1016 effects. Alarmingly, while the number of new therapies under investigation in other fields is  
1017 growing exponentially, the number of novel antiarrhythmic targets and agents in the  
1018 development pipeline has decreased substantially during the last few decades due to conceptual,  
1019 regulatory and financial considerations (Saljic et al., 2023). Catheter ablation significantly  
1020 contributes to the management AF, particularly in patients who are refractory or intolerant to  
1021 antiarrhythmic drugs (Chugh et al., 2014; Parameswaran et al., 2021). The CABANA (Catheter  
1022 Ablation vs Anti-arrhythmic Drug Therapy for Atrial Fibrillation Trial [CABANA];  
1023 NCT00911508) trial's findings are particularly notable, demonstrating the effectiveness of  
1024 catheter ablation in reducing the recurrence of AF and symptomatic episodes compared to drug

1025 therapy over a five-year follow-up period (Poole et al., 2020). It is crucial to consider not only  
1026 the physical outcomes but also the impact of interventions such as catheter ablation on mental  
1027 health in patients with AF. ANZCTR trial data (ACTRN12618000062224) suggest that catheter  
1028 ablation may lead to greater improvements in markers of psychological distress, specifically  
1029 symptoms of anxiety and depression, compared to medical therapy alone in individuals with  
1030 symptomatic AF (Al-Kaisey et al., 2023). Nevertheless, it is not a universally applicable solution  
1031 and the proposition of subjecting over 46 million AF patients to one or more ablation procedures  
1032 would be exceedingly unreasonable. Consequently, arrhythmia treatment poses a significant  
1033 challenge in the realm of cardiovascular health, prompting the need for alternative approaches.  
1034 This has a point of complexity given that the heart is difficult to access, donors are limited, and  
1035 data from rodent models are hard to extrapolate because the cardiac electrophysiological  
1036 characteristics of small animals are significantly different from humans. This forces the use of  
1037 large animals such as sheep, dogs, or pigs that have major cost and ethical limitations. Yet,  
1038 disparities between animals and humans can confound results and likely contribute to the failure  
1039 of promising therapeutics when advancing to later stage clinical trials. Fortunately, new  
1040 technologies and computational models are now available to solve these problems. Last year, the  
1041 FDA Modernization Act 2.0 paved the way for alternative methods to bolster the preclinical data  
1042 pipeline, aiming to reduce the dependence on animal models that have frequently resulted in  
1043 therapeutic dead ends. The FDA Modernization Act 2.0 reinforced the transitioning beyond  
1044 animal models with human cells, organoids, and AI/ML-based approaches (Zushin et al., 2024).  
1045 Despite all the advantages that hiPSC-CMs can hold to the discovery and development of anti-  
1046 arrhythmic drugs, it is necessary to keep in mind all the current technical, economic and time  
1047 limitations that need to be addressed, mainly in terms of electrophysiology. The

1048 electrophysiological maturation state of hiPSC-CMs can determine drugs responsiveness (da  
1049 Rocha et al., 2017). As discussed throughout this review, the advent of new and emerging tools  
1050 that combine biological systems like stem-cells with cell profiling platforms (multi-omics), new  
1051 technologies for data processing, computational modelling, and functional HTS techniques have  
1052 made drug discovery and design much more sophisticated and technology-driven. This will  
1053 improve the quality, safety, and efficacy of future anti-arrhythmic therapies by enhancing  
1054 precision and personalized medicine. In this review we have especially highlighted the promising  
1055 therapeutic potential of alternatives like gene therapy and the use of peptide-based therapies in  
1056 the treatment of arrhythmias. It is important to note that both technologies are dynamic and  
1057 subject to ongoing research and development. As we previously highlighted, gene therapy has  
1058 the potential to treat arrhythmias by correcting or compensating for the genetic defects that cause  
1059 abnormal heart rhythms, potentially providing a long-term solution. However, limitations include  
1060 difficulties in delivering genes safely into heart tissue and ensuring precise and long-lasting  
1061 effects without unintended consequences. The other alternative, peptibodies, designed and  
1062 engineered to target specific proteins or receptors, offer several potential advantages in treating  
1063 arrhythmias like reduced side effects, modularity and customization and biological compatibility  
1064 (Chidipi et al., 2022). While peptibodies hold promise in the treatment of various conditions,  
1065 including arrhythmias, there are certain limitations and challenges associated with their use.  
1066 Those are delivery and stability, immunogenicity, short half-life, development costs, lack of  
1067 long-term safety, regulatory approval hurdles, and patient variability. However, ongoing research  
1068 and technological advancements may address some of these limitations over time. In summary,  
1069 the use of hiPSCs, together with new emerging technologies and computational integration,  
1070 offers the unprecedented possibility of improving the discovery of arrhythmia targets,

1071 biomarkers and drugs. New alternatives such as gene therapy and peptide-based therapy open a  
1072 new path for the development of a new and promising next-generation antiarrhythmic therapy  
1073 with great clinical translation potential.

#### 1074 **Figure Legend**

1075 **Figure 1. Interventional Clinical Trials in the last 10 years.** *A.* Total number of interventional  
1076 clinical trial studies in different clinical phases over the last 10 years, extracted from  
1077 ClinicalTrials.gov. *B.* Total number of interventional clinical trial studies for arrhythmia  
1078 treatment. *C.* Different types of interventions for all clinical trial phases from *B.* *D.*  
1079 Pharmacological interventional clinical studies for arrhythmia treatment. AAD, antiarrhythmic  
1080 drugs; AF, atrial fibrillation; CPVT, catecholaminergic polymorphic ventricular tachycardia;  
1081 LQTS, long QT syndrome; POAF, postoperative atrial fibrillation. PSVT, paroxysmal  
1082 supraventricular tachycardia. SGK-1, Serum Glucocorticoid inducible Kinase 1. CaMKII, Ca<sup>2+</sup>  
1083 or calmodulin-dependent protein kinase II.

#### 1084 **Data Availability Statement**

1085 The authors declare that all the data supporting the findings of this study are contained within the  
1086 paper.

1087

#### 1088 **Author Contributions**

1089 All authors co-wrote the manuscript and conceived the review. G.M.P. performed the analysis of  
1090 interventional antiarrhythmic clinical trials and provided writing of iHigh-Throughput Screening,  
1091 Drug Repurposing and Advancements in Drug Delivery. P.S.P. wrote hiPSC and OMICS



1092 technology sections. F.M.C. was in charge of writing Computational screening, Peptide-based  
1093 treatment, and gene therapy approaches sections. Dr. José Jalife provided writing, supervision,  
1094 funding and revision. All authors have read, discussed and agreed to the published version of the  
1095 manuscript.

## 1096 **Conflicts of Interest**

1097 Declare conflicts of interest or state “The authors declare no conflict of interest.”

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2216

## 2217 **Footnotes**

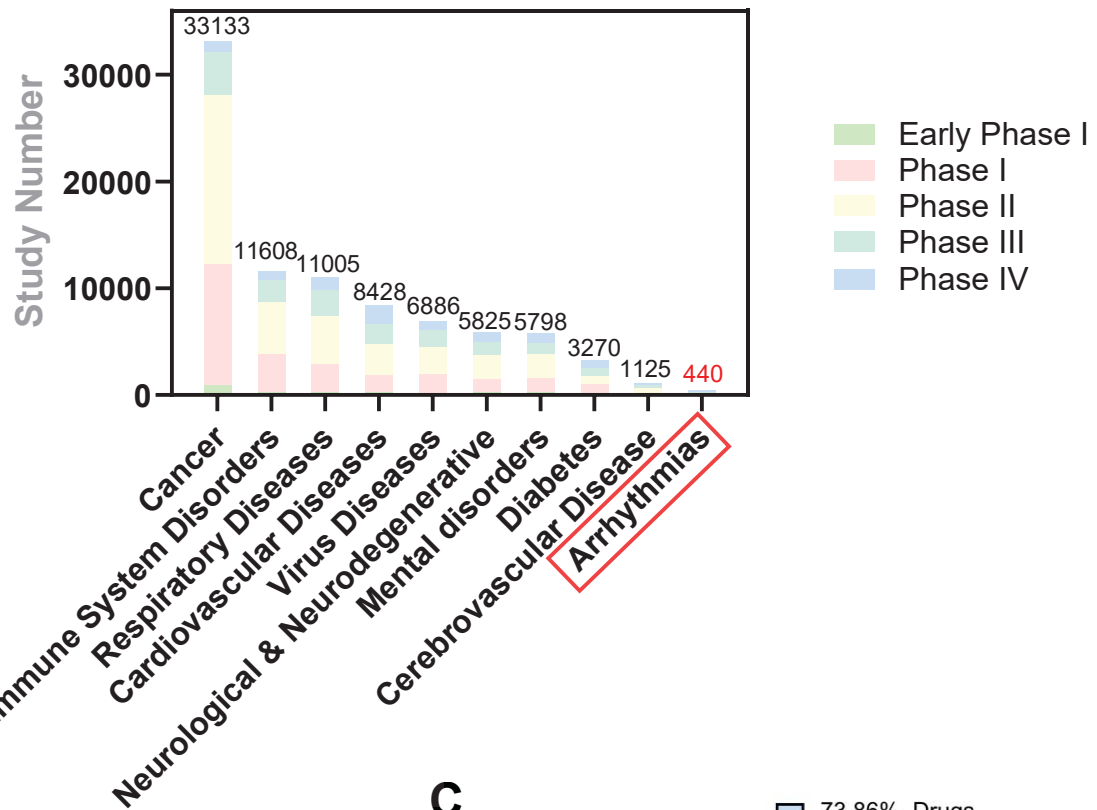
2218 This work was supported by National Institutes of Health R01 HL163943; La Caixa Banking  
2219 Foundation [project code638LCF/PR/HR19/52160013]; grant PI20/01220 of the public call  
2220 “Proyectos de Investigación en Salud 2020” [PI-FIS-2020] funded by Instituto de Salud Carlos  
2221 III (ISCIII); MCIU grant BFU2016-75144-R and PID2020-116935RB-I00, and co-founded by  
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2228 (ISCIII), the Ministerio de Ciencia e Innovación (MCIN) and the Pro CNIC Foundation, and is a

2229 Severo Ochoa Center of Excellence [grant CEX2020-001041-S649 funded by  
2230 MICIN/AEI/10.13039/501100011033].

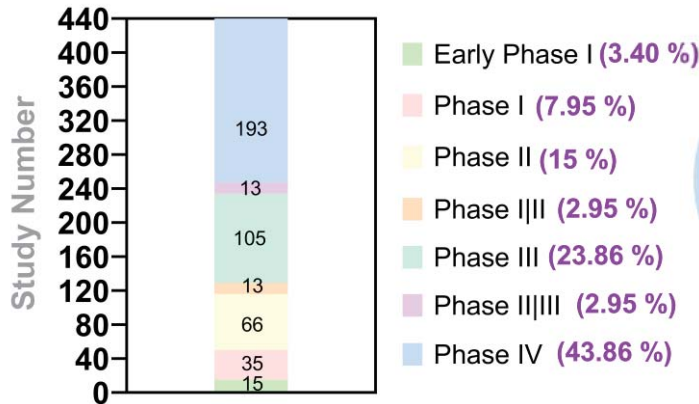
**A**

# Interventional Clinical Trial Studies Last 10 Years

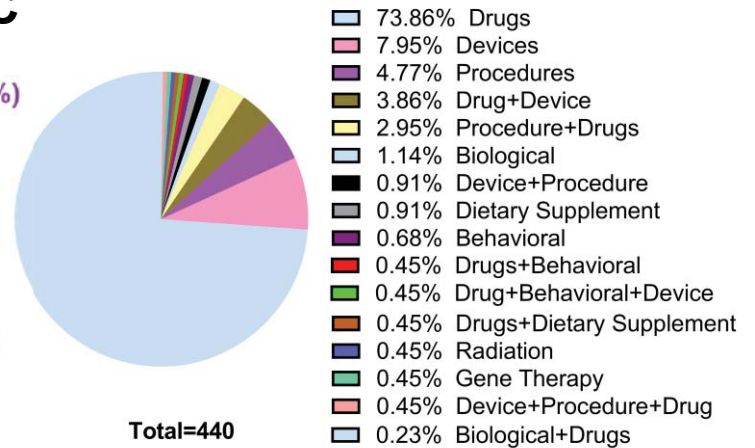
(Data extracted from *ClinicalTrials.gov*)



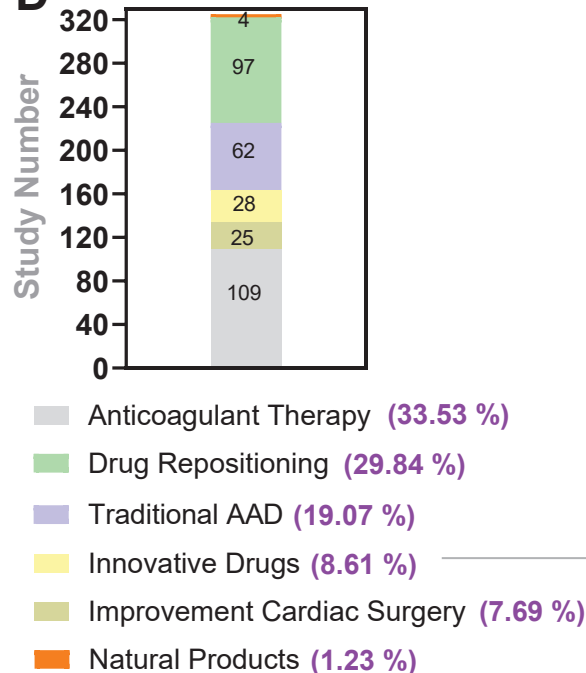
**B**



**C**



**D**



- Etripamil (PSVT|AF) (ICaL)
- F373280 (AF) (IKur)
- BMS-919373 (AF|Paroxysmal AF) (IKur)
- Eleclazine (Ventricular Arrhythmia|LQTS|LQTS2-3) (INa)
- AP30663 (AF) (IKCa)
- S48168 or ARM210 (CPVT1) (RyR channel)
- HSY244 (AF) (Undisclosed mechanism)
- HBI-3000 (AF) (Multichannel)
- GS-6615 (LQTS) (INa,weak IK)
- OPC-108459 (AF) (Unknown)
- LQT-1213 (LQTS) (SGK-1 inhibitor)
- CARDIX-101 (Bradycardia) (Unknown)
- CRD-4730 (CPVT1|Heart Defects) (CaMKII inhibitor)
- HIP2001 (AF) (Unknown)
- OMT-28 (AF) (synthetic analog of epoxyeicosanoids)

**Figure 1**