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in Cardiology

Flecainide How and When: A Practical Guide in Supraventricular Arrhythmias

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Editorial Office:
CCM Middle East S.A.R.L.
Rabieh, Bekfaya Road,opposite charcutier Aoun,
Postal Code: 2506 7901, 2nd floor, Beirut, Lebanon.
Tel.: (+961) 4 415222, Fax: (+961) 4 415223
Email: info@groupccm.com

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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are physicians in each specialty working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM will fill the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. ***Current Views in Cardiology*** was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Cardiology provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make ***Current Views in Cardiology*** a respected and useful tool for the daily practice of physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Am J Cardiol
Am J Hypertens.
Am J Med Sci.
Am J Physiol Renal Physiol.
Arch Neurol
Blood Press
BMC Cardiovasc Disord.
Cardiol J.
Circulation
Clin Pharmacol Drug Dev.
Clin Res Cardiol
Curr Med Res Opin.
Curr Opin Cardiol.
Front Cardiovasc Med.
Hypertension.
J Am Coll Cardiol.
J Clin Hypertens (Greenwich).
J Clin Invest.
J Hypertens.
JAMA
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Τηλ.: 210 7488821, **Φαξ:** 210 7488827, **E-mail:** info@winmedica.gr.

ΘΕΣ/ΝΙΚΗ:
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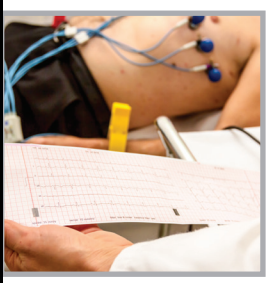

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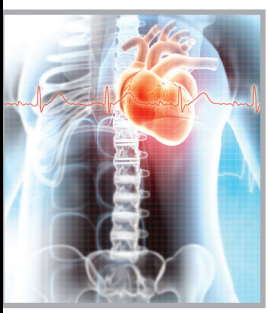

Arrhythmias

Hypertension

Heart Failure

Flecainide How and When: A Practical Guide in Supraventricular Arrhythmias

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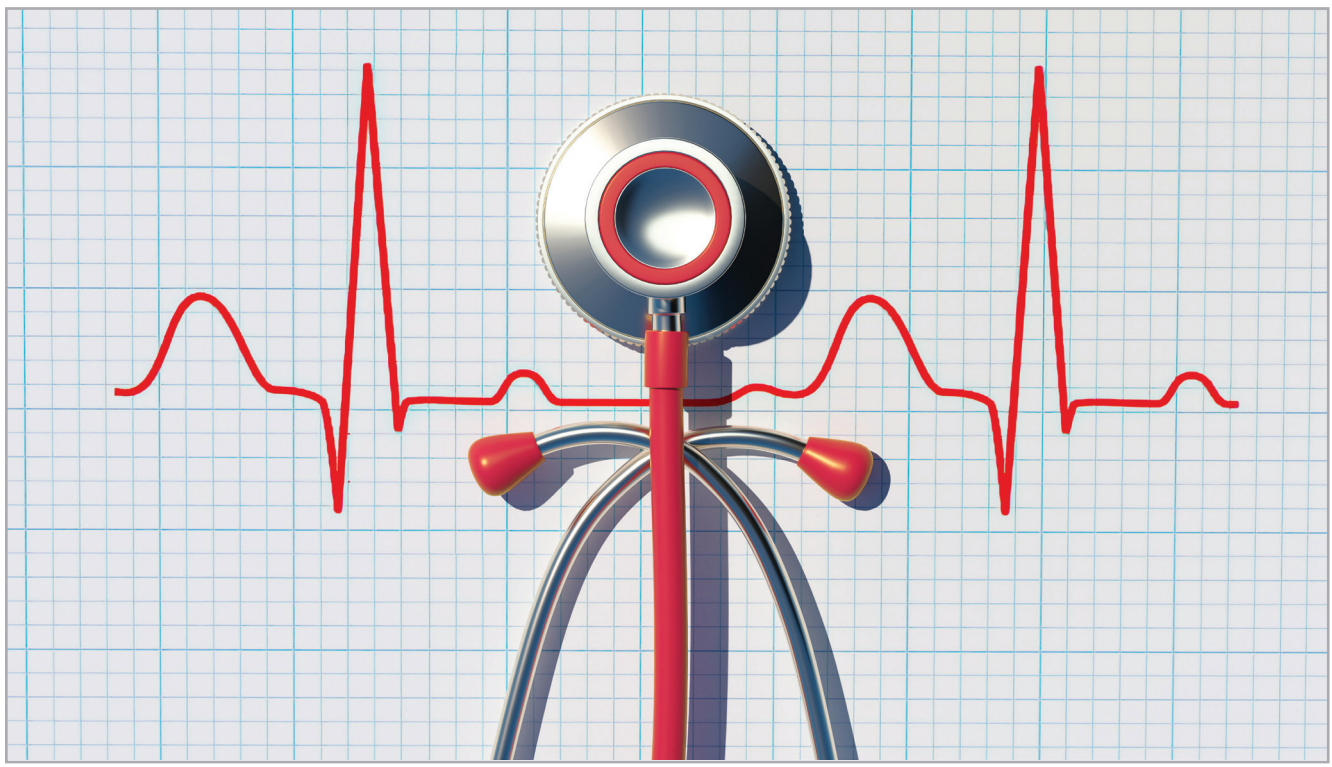

Introduction

In recent years several non-pharmacological therapies, in particular transcatheter ablation, have been increasingly and successfully used to treat symptomatic drug refractory patients affected by supraventricular arrhythmias (SVT), especially atrial fibrillation (AF). Nevertheless, antiarrhythmic drug treatment still plays a major role in patient management, alone or combined with non-pharmacological therapies.

Flecainide is an IC antiarrhythmic drug approved in 1984 from the Food and Drug Administration for the suppression of sustained ventricular tachycardia (VT) and later for AF acute cardioversion and for sinus rhythm maintenance.

Currently, flecainide is mostly administered for sinus rhythm maintenance and, having regard to its effectiveness and safety profile, it may be considered underused.

Flecainide Pharmacology

Flecainide acts on the fast-inward Na+ ion channel and has a high affinity to activated or open Na+ channels. It prolongs the depolarization and increases refractoriness due to slow release from its binding site. It potently acts on the His-Purkinje system.

Controlled release flecainide allows a once-a-day administration. The pharmacokinetic profile is characterized by a reduced and delayed reaching maximum concentration and lower fluctuations of plasma concentrations during a dosing interval compared with an immediate-release form. Serum concentration peak is reached in 26 h, the steady state plasma level is reached after 4–5 days ranging from 0.27 to 0.33 mcg/mL far from the plasma level at risk of side effects. Controlled release form improves treatment compliance and reduces the risk of side effects and interactions with other drugs preserving clinical benefit.

What Does "Structural Heart Disease" Mean? A Critical View

Based on the findings of the CAST trial, it is reasonable to consider how flecainide exerts a proarrhythmic effect in patients with recent acute myocardial infarction (AMI) and/or LV disfunction. CAST patients were eligible for enrollment six days to two years after AMI if they had an average of six or more premature ventricular contraction per hour and a LV function < 55%. Unfortunately, the study was prematurely dismissed due to an increased proarrhythmic risk among patients treated with IC agents than patients treated with placebo. For this reason, the European Society of Cardiology in 2020 Guidelines for the management of AF contraindicated the use of flecainide in patients affected by structural heart disease. Despite this, a critical appraisal of the CAST trial is necessary; firstly, only in 17% of the enrolled patients a complete revascularization was performed, a clinical scenario now less and less frequent. Moreover, a CAST sub analysis showed that during the late post-myocardial infarction period, therapy with flecainide was associated with a steeper increase in death/cardiac arrest rate in the non-Q-AMI group than in the Q-AMI group. Lastly, 48% of CAST patients had severe left ventricular dysfunction. All these patients could have an augmented pro-arrhythmic risk, and therefore, it may be reasonable to perform a more detailed stratification of ischemic heart disease (Is the arrhythmia scar-related? Is there a critical coronary stenosis?).

Practice guidelines extended the findings of CAST to all IC agents and structural heart disease such as congenital heart disease, valvular or significant myocardial heart disease, although evidence is scarce. In recent years, some observational studies have shown promising results on the use of flecainide in patients with non-ischemic structural heart disease.

Flecainide can be useful in long QT syndrome type 3, an arrhythmogenic cardiomyopathy caused by gain-of-function mutations in the SCN5A-encoded Nav1.5 sodium channel involving a pathological increase in late sodium current and, consequently, prolonging QTc. Long-term flecainide therapy shortened QTc interval and is relatively safe and effective in patients affected by Long QT syndrome type 3; in particular, no cardiac events occurred among patients who were fully compliant with flecainide administration while in patients who discontinued therapy a cardiac event has been

Data available are still incomplete and further studies are recommended. In the meanwhile, the criteria listed in Figure 1 may drive the clinical choice in individual patients.

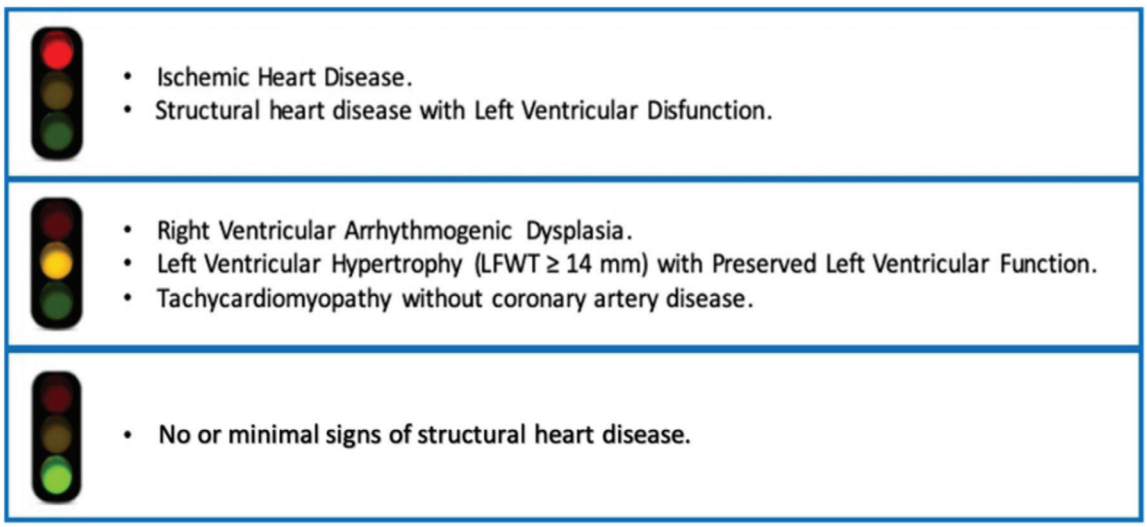

Figure 1: Current evidence on the use of flecainide. Structural heart disease is any abnormality, or defect, of the heart muscle or the heart valves.

Safety Data

Considering the pharmacodynamic effects of flecainide, it is not surprising that it prolongs the PR (17–29%), the QT (4–11%) interval and the QRS complex (11–27%). It must be considered that most of the QT prolongation is due to the widening of the QRS complex, so that the JT interval and the rate-corrected QT interval remain unchanged or slightly increase (3–8%). An important proarrhythmic effect (3–5% of cases) is conversion of AF in atrial flutter with slow atrial rate (flutter IC) that may result in 1:1 atrioventricular (AV) conduction with high ventricular response and large QRS. Concomitant therapy with AV blockade (ß-blockers, verapamil, diltiazem, digoxin) could avoid this pro-arrhythmic effect. Moreover, QRS duration (>120 ms), advanced kidney failure (creatinine clearance < 30 mL/min/1.73 m^2), electrolyte abnormalities increase pro-arrhythmic effect of flecainide and should be carefully monitored.

Patients with Pacemaker and Implantable Cardioverter Defibrillator

In the last few years, use of implantable cardiac electronic devices has become increasingly common and at least 50% of these patients may develop AF requiring antiarrhythmic therapy. Early raised issue of negative effects of flecainide on pacing and defibrillation threshold are not a concern anymore due to progress in lead technology, automatic setting of pacemaker output and use of biphasic high energy shocks. On the other hand, antiarrhythmic drugs may enhance rhythm control in patients with pacemaker and AF in a hybrid approach. Boriani demonstrated that

use of flecainide was associated with lengthened atrial tachycardia cycles and consequently higher atrial anti-tachycardia pacing efficacies. This effect was probably correlated either to prolongation of atrial wavelength or widening of the temporal excitable gap during AF. Atrial anti-tachycardia pacing cannot terminate AF, but it can terminate atrial tachycardia episodes that are the first step in AF disease history. For these reasons, flecainide administration could increase atrial anti-tachycardia pacing efficacy that represented an independent predictor of permanent or persistent AF risk.

Patients with Sinus Bradycardia and/or AV-IV Conduction Disturbances

Administration of flecainide in patients affected by sinus node dysfunction or atrial conduction disorders depresses sinus activity and increases significantly the corrected sinus node recovery time. Due to dose-dependent prolongation of AV and IV conduction, unless a cardiac stimulator is available for emergency cardiac stimulation, flecainide should not be administered in patients with second degree or superior AV block, right or left bundle branch block.

Interaction between antiarrhythmic drugs and autonomic nervous system is very different; while flecainide exerts a mild vagolytic effect, other anti-arrhythmic drugs such as propafenone or amiodarone have anti-adrenergic effect. For this reason, flecainide could be the first drug therapy in the maintenance treatment of SVT in patients with physiological bradycardia.

Flecainide in Association with Other Antiarrhythmic Drugs

In some AF patients, a combined anti-arrhythmic strategy may be necessary to maintain sinus rhythm and reduce symptomatic AF recurrences. Flecainide in combination with amiodarone is interesting, not only because it may be effective when the efficacy of each is inadequate as a single-drug therapy, but also because it may allow a reduction in their respective dosages and side effects.

Flecainide in Pregnancy and in Pediatric Population

ESC guidelines recommend avoiding any antiarrhythmic drug during the first trimester of pregnancy [58]. Overall, there is no clear evidence of the teratogenic effect of flecainide. Therefore, it could be used for the treatment of fetal arrhythmias.

Vademecum for the Management of Flecainide

A 12-lead electrocardiogram is mandatory before starting the therapy; symptomatic bradycardia, second degree or superior AV block, QRS > 120 ms or Brugada syndrome contraindicate the flecainide prescription. It's reasonable to perform an echocardiogram to evaluate LV function and exercise stress testing in high-risk patients to exclude the possibility of coronary artery disease. It is strongly suggested to test the first dose under medical observation. The minimum effective plasma concentration of flecainide is about 200 ng/mL while optimal range is between 200 ng/mL and 400 ng/mL. This plasma concentration leads to a QRS prolongation of about 10 ms; a prolongation of 40 ms or more is associated to an increased probability of cardiovascular adverse effects.

A practical approach to flecainide dose ranging, in absence of kidney failure, is as follows (see also—Figure 2):

1. Exclude contraindications (structural heart disease, symptomatic bradycardia, second degree or superior AV block, QRS > 120 ms or Brugada syndrome).
2. Record an ECG with a paper speed of 50 mm/sec and calculate the QRS duration (1 mm = 20 ms).

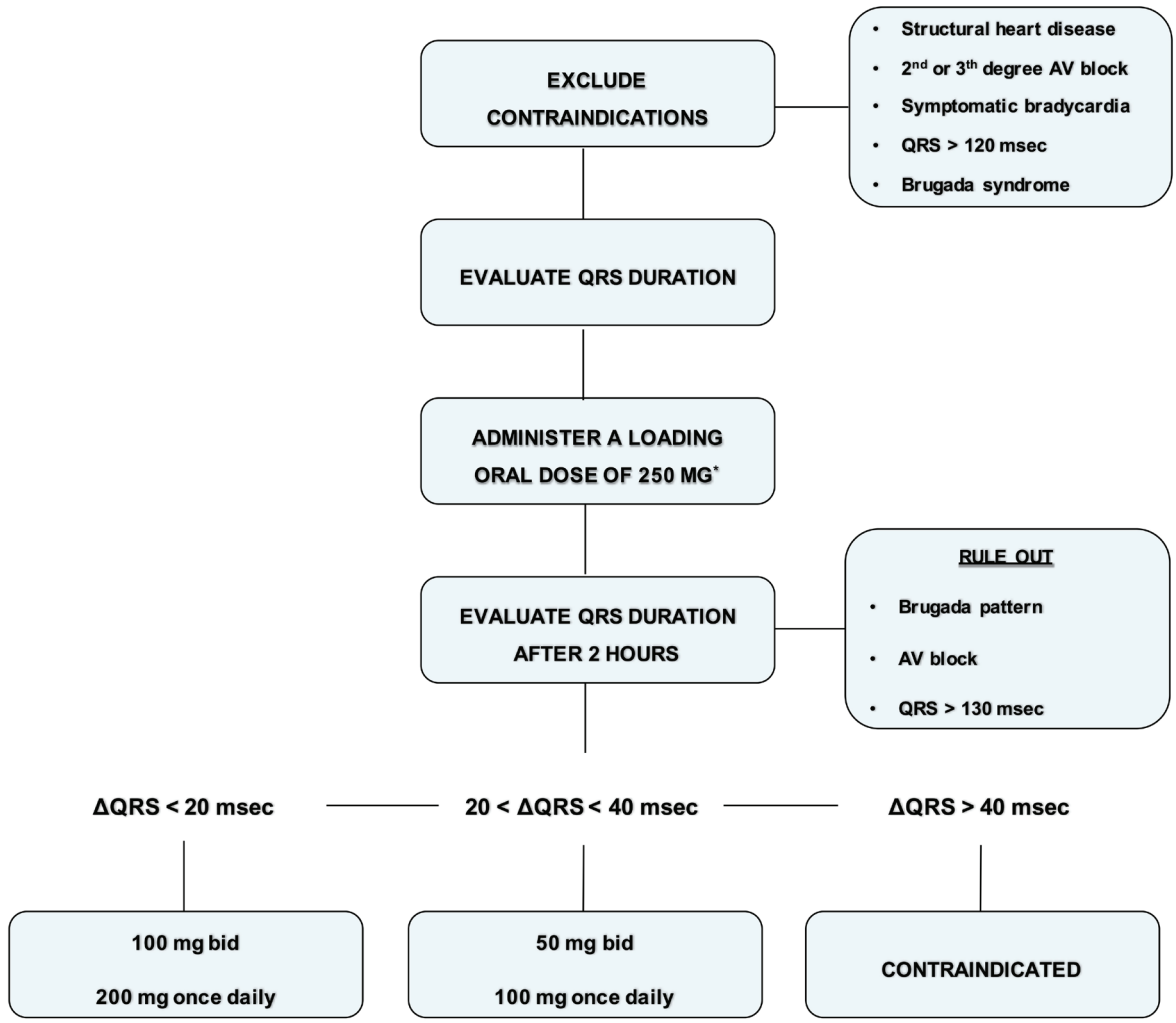

*Figure 2: Flowchart for administration of flecainide. * Loading oral dose of 200 mg is recommended if the weight is lower than 70 kg.*

3. Administer a loading oral dose of 250 mg (200 mg if the weight is lower than 70 kg).
4. At plasma concentration peak, after 90–120 min, evaluate blood pressure and record an ECG with a paper speed of 50 mm/s and calculate the QRS duration.
5. Rule out Brugada ECG pattern and AV block.
   a. If the QRS duration is increased within 20 ms, prescribe 100 mg twice daily or 200 mg once daily. Check again the ECG after one week.

b. If the QRS duration is increased between 20 and 40 ms or is wider than 120 ms, prescribe 50 mg twice daily or 100 mg once daily. Check again the ECG after 5 days.

c. If the QRS duration is increased more than 40 ms or is wider than 130 ms, or a Brugada pattern is detected, consider flecainide contraindicated in that patient.

The proarrhythmic risk and other serious adverse effects can be minimized by keeping strict adherence to treatment, limiting the number of drugs prescribed, starting the treatment at low doses that will be increased on the basis of the patient's response and comorbidities. The recommended dose of flecainide in SVTs are reported in Table 1.

Table 1. Recommended dose of flecainide in supraventricular arrhythmias (SVT).

SVT	Recommended Dose	Administration Route
Atrial Fibrillation (Restoration of sinus rhythm)	200–300 mg 2 mg/kg	Oral Intravenous
Atrial Fibrillation (Maintenance of sinus rhythm)	100–200 mg bid 200 mg once daily	Oral
AVNRT/AVRT	50–150 mg bid	Oral
Focal Atrial Tachycardia	50–150 mg bid	Oral

AVNRT: atrioventricular nodal reentrant tachycardia; AVRT: atrioventricular reentrant tachycardia.

ECG monitoring is suggested in case of drug adjustments or concomitant therapy with other antiarrhythmic drugs, particularly in the elderly and in patients with hepatic and/or renal dysfunction. For appropriately selected patients who have received an initial oral loading dose under monitored conditions, a "pill in the pocket" strategy could be suggested for patient self-administration at the onset of recurrent AF. A practical guide on the management of adverse events due to flecainide is provided in Table 2.

Table 2: Management of adverse events due to flecainide.

Adverse Event	Incidence	Indication
Drug induced Brugada	<1%	Discontinue
QRS increased more than 40 ms or wider than 130 ms	<1%	Discontinue
QRS increased more than 20 ms	1–2%	Reduce Dosage
Bradyarrhythmia, sinus pause, AV block	1–2%	Discontinue
Hypotension	3–5% (mostly with IV)	Reduce Dosage
1:1 atrial flutter	3–5%	Discontinue and consider ablate CTI dependent-flutter
Worsening heart failure	<1%	Discontinue
Extracardiac effects (dizziness, tremor, nausea)	1–2%	Reduce Dosage

AV: atrioventricular; CTI: cavotricuspid isthmus; IV: intravenous.

Table 3: Reversion rate of recent-onset atrial fibrillation to sinus rhythm.

Study	Population in Flecainide Arm	AF Duration	Flecainide	Reversion Rate	Adverse Event
Martínez-Marcos et al. [65]	50	≤2 d	Intravenous (2 mg/kg followed by 1 mg/kg at 8 h if not in sinus rhythm)	1 h → 58% 8 h → 82% 12 h → 90%	Transient junctional rhythm: 4% Atrial flutter: 2% Symptomatic hypotension:2% Paresthesia: 4% Total: 12%
Capucci et al. [67]	58	≤7 d	Single oral dose (300 mg)	3 h → 59% 8 h → 78%	Transient junctional rhythm:1.7% Atrial flutter: 3.4%
Crijns et al. [68]	13	≤24 h	Intravenous (2 mg/kg up to 150 mg)	3 h → 77%	-
Boriani et al. [69]	69	≤7 d	Single oral dose (300 mg)	1 h → 13% 3 h → 57% 8 h → 75%	-
Capucci et al. [70]	22	≤7 d	Single oral dose (300 mg)	8 h → 91% 24 h → 95%	no
Romano et al. [71]	138	≤3 d	Intravenous	1 h → 73% 3 h → 80% 6 h → 86% 24 h → 90%	-

Flecainide in Atrial Fibrillation

Flecainide in Converting Recent Onset of Atrial Fibrillation

In the acute setting, flecainide is very effective in restoring sinus rhythm with high percentages of success, greater than both propafenone and amiodarone as well as with shorter cardioversion (Table 3).

Flecainide is also effective when administered orally; an Italian multicenter study evaluated the efficacy and safety of "pill in the pocket" therapy with flecainide or propafenone in 210 of 268 hospitalized patients for AF onset by less than 48 h who were effectively treated in hospital setting. The pill in the pocket strategy was effective in 94% of patients with an average resolution time of 113 min; adverse events were 7% and in only one case was a high ventricular response atrial flutter. The "pill in the pocket" strategy is currently indicated as a therapeutic strategy in selected patients, with recent onset of AF without significant structural or ischemic heart disease or pro-arrhythmic conditions as Brugada syndrome and able to self-diagnose AF in which could be avoided the emergency room admission.

Table 4: Flecainide for maintenance of sinus rhythm.

Author	*n.* Patient	Type of AF	Compared Treatment	Endpoint of AF Recurrence	Results
Chimienti et al. [82]	200	Paroxysmal	Flecainide vs. Propafenone	Palpitation recurrence on days 15, 30, 90, 180, 270, 360	No difference between flecainide and propafenone
Gulizia et al. [83]	176 with PMK	Paroxysmal	Ic AAD vs. Amiodarone	Time to first occurrence of death, atrial cardioversion, cardiovascular hospitalization or change of AAD	IC AAD non-inferior to Amiodarone. Similar AT recurrences
Naccarelli et al] . [95]	239	Paroxysmal	Flecainide vs. Quinidine	AF recurrence at 12 months	Flecainide similar efficacy to quinidine but better tolerated
Allot et al. [94]	97	Paroxysmal	Flecainide vs. Propafenone	AF recurrence at 12 months	Flecainide similar efficacy to propafenone
Carunchio et al. [96]	66	Paroxysmal	Flecainide vs. Sotalolo vs. Placebo	AF recurrence at 1, 3, 6 and 12 months	Flecainide similar efficacy to sotalol and superior to placebo
van Wijk et al. [97]	26	Paroxysmal	Flecainide vs. Quinidine	AF recurrence during 3-months follow-up period	Flecainide superior to quinidine

AAD: antiarrhythmic drug, AF: atrial fibrillation; AT: atrial tachycardia; PMK: pacemaker.

Pre-Treatment with Flecainide in Patients Undergoing Electrical Cardioversion

There is strong evidence supporting the use of flecainide prior cardioversion: in a prospective, randomized, double-blinded study 54 patients with persistent AF scheduled to electrical cardioversion were enrolled. Patients that received flecainide before cardioversion had a more successful first shock in comparison to placebo (65% vs. 30% respectively, $p = 0.04$).

Flecainide in Long Term Rhythm Control

The maintenance of the sinus rhythm is more advantageous than rate-control both in terms of survival and quality of life. According the 2020 ESC Guidelines, catheter ablation is indicated after one failed/intolerant treatment with class I or III drug or to improve symptoms of AF recurrences in patients with paroxysmal and persistent AF. A rhythm control strategy based on drug administration could be preferable when catheter ablation was hazardous. In this scenario, amiodarone could be considered the most effective in the maintenance of sinus rhythm, but for the high adverse effect rate, a lot of patients withdraw prematurely the treatment. Otherwise, several studies showed as flecainide was effective in reducing the recurrences of paroxysmal AF and safer when compared to

other antiarrhythmic drugs, including amiodarone (Table 4). To reduce adverse event rate a flecainide short-term treatment should be considered for patients with AF who are at increased risk for complications and amiodarone is contraindicated [94]. Indeed, the randomized Flec-SL blinded trial compare flecainide (200–300 mg per day) for four weeks (short-term treatment) with flecainide for six months (long-term treatment) in patients with persistent AF after an effective cardioversion; short-term treatment after cardioversion is less effective than long-term treatment, but in any case, it can prevent most recurrences of AF.

Flecainide in Other Supraventricular Arrhythmias

Although procainamide is the drug of choice in patients with atrio-ventricular reentrant tachycardia, flecainide is effective and safe by directly slowing or blocking conduction over the Na+ dependent fast accessory pathway. Flecainide is efficient in approximately 85% to 90% of patients, with 30% reporting an absence of tachycardia. Flecainide is also successful in terminating pre-excited AF in hemodynamically stable patients with high-ventricular response and should be considered in the prevention of SVT in pregnant patients with the Wolff–Parkinson–White syndrome. However, the gold standard for patients with symptomatic recurrences remains catheter ablation and pharmacological therapy would be reserved for cases where ablation is not desired or feasible.

Atrial premature beats and atrial tachycardia are a common finding in older individuals and frequent atrial premature beats are considered a marker of atrial electrical vulnerability and predictors of incident AF. The use of flecainide is effective in addition to optimization of medical therapy when catheter ablation was not feasible. Data to support the recommendation for flecainide for maintenance of sinus rhythm in patients with atrial flutter is derived from trials that pooled patients with AF and atrial flutter. It is no longer recommended for acute cardioversion of macro-re-entrant atrial arrhythmias and no longer mentioned for chronic therapy of typical atrial flutter. Recommended dose of flecainide in SVTs is reported in Table 1.

Conclusions

Flecainide is highly effective for the acute termination and for the chronic suppression of AF. An excellent safety profile is described in patients with minimal or no signs of structural heart disease while mounting promising evidence will be available in patients with cardiomyopathy. The “pill in the pocket” approach reduces the need for emergency care and should be more widely employed in patients to achieve rhythm control without long term antiarrhythmic drug exposure and to avoid the necessity for electrical conversion. A 12-lead ECG is required before starting therapy while ECG monitoring is suggested in case of drug adjustments or concomitant therapy with other antiarrhythmic drugs, particularly in the elderly and in patients with hepatic and/or renal dysfunction.

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Arrhythmias

Beneficial Effect of Flecainide Controlled Release on the Quality of Life of Patients with Atrial Fibrillation-the REFLEC-CR Study[1]

Tzeis S, Tsiachris D, Asvestas D, Kourouklis S, Patsourakos F, Karlis D, Kouskos G, Papadimitriou G, Gavriilidou M, Vatkalis N, Kapetanios K, Koufaki P, Taxiarchou E, Giannakoulas G; REFLEC-CR study investigators. Beneficial Effect of Flecainide Controlled Release on the Quality of Life of Patients with Atrial Fibrillation-the REFLEC-CR Study. Cardiovasc Drugs Ther. 2020 Jun;34(3):383-389.

Atrial fibrillation (AF) is the most common cardiac arrhythmia with a considerable impact on patients' quality of life (QoL).The authors aimed to assess the effect of flecainide CR on the QoL of AF patients in a prospectively selected cohort of patients with symptomatic, paroxysmal or persistent AF.

This was a prospective, multicenter, observational study aimed to evaluate the effect of oral treatment with controlled-release (CR) flecainide on AF patients' QoL and treatment compliance during a 12-week period. A total of 70 sites enrolled consecutive patients with paroxysmal (PAF) or persistent AF (PerAF), treated with flecainide CR in the context of a rhythm control strategy. The effect on QoL was assessed by the Canadian Cardiovascular Society Severity of Atrial Fibrillation scale (CCS-SAF). This score is analogous to the NYHA heart failure functional class and the CCS angina severity class.

In total, 679 patients (53.2% females, 66 ± 11.7 years, 86.9% PAF) were included. Prior antiarrhythmic medication had been administered in 43.8% of patients. A daily dose of 200 mg was administered to 66.4% of patients by the end of study. Flecainide CR resulted in a significant reduction in the CCS-

SAF score (mean (SD)) at the end of the study as compared with baseline (1.32 (0.57) vs 1.64 (0.73), $p < 0.0001$).

The main study finding is that flecainide CR significantly improves AF patients' QoL.

The treatment effect remains significant in both paroxysmal as well as persistent AF patient subgroups. However, the magnitude of QoL improvement seems larger among paroxysmal as compared with persistent AF patients.

Flecainide CR significantly reduced the CCS-SAF score both in PAF (1.27 (0.52) vs 1.61 (0.72), $p < 0.0001$) as well as in PerAF (1.63(0.77) vs 1.84(0.81), $p = 0.017$). Overall, 4 (0.6%) patients experienced a total of 6 adverse events during the study period. The compliance to flecainide CR treatment was very high with 93.6% of patients responding that they had not missed any dose during the study period.

In conclusion, this prospective, multicenter, observational study demonstrated that treatment with flecainide CR significantly improves QoL in both paroxysmal and persistent AF patients, with an excellent safety profile and associated patient compliance.

Use of Flecainide for the Treatment of Atrial Fibrillation[2]

Echt DS, Ruskin JN. Use of Flecainide for the Treatment of Atrial Fibrillation. Am J Cardiol. 2020 Apr 1;125(7):1123-1133.

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with substantial morbidity and impairment of quality of life. Restoration and maintenance of normal sinus rhythm is a desirable goal for many patients with AF; however, this strategy is limited by the relatively small number of antiarrhythmic drugs (AADs) available for AF rhythm control. Although it is recommended in current medical guidelines as first-line therapy for patients without structural heart disease, the use of flecainide has been curtailed since the completion of the Cardiac Arrhythmia Suppression Trial. In clinical trials and real-world use, flecainide has proven to be more effective than other AADs for the acute termination of recent onset AF. Flecainide is also moderately effective and, with the exception of amiodarone, equivalent to other AADs for the chronic suppression of paroxysmal and persistent AF.

In patients without structural heart disease, flecainide has been demonstrated to be safe and well tolerated relative to other AADs. Despite this favorable profile, flecainide is underutilized, likely due to a perceived risk of ventricular proarrhythmia, a concern that has not been borne out in patients without underlying structural heart disease.

Flecainide acetate is highly effective for the acute termination of recent onset AF and is moderately effective for the chronic suppression of AF. The drug has an excellent safety profile when administered to patients with minimal or no structural heart disease. Flecainide is more effective and safer than other AADs for the acute conversion of patients in AF. Despite its favorable safety and efficacy profile in patients with no or minimal structural heart disease, flecainide is underutilized due to misconceptions about the risk for ventricular proarrhythmia, a safety concern that has not been observed. Pharmacologic conversion of episodic AF with flecainide should be considered in eligible patients to accomplish rhythm control without chronic drug exposure and to avoid the necessity for electrical conversion.

The ideal pharmacologic approach is one that appropriately selects patients that can self-administer to terminate AF rapidly and safely. The PiP approach avoids the need for these patients to seek emergency care. With the recent availability of wearable, handheld, and implanted ECG monitors with accurate automated AF detection, the PiP approach with its inherent advantages has the potential to be more widely employed in clinical practice.

JCS/JHRS 2019 Guideline on Non Pharmacotherapy of Cardiac Arrhythmias[3]

Nogami A, Kurita T, Abe H, et al. JCS/JHRS 2019 guideline on non-pharmacotherapy of cardiac arrhythmias. J Arrhythm. 2021;37(4):709-870.

Advances in non-pharmacological treatment of arrhythmia have accelerated, with the succeeding emergence of new functions, usefulness, and evidence. Against the background of these remarkable developments, the guidelines needed to undergo many changes and revisions. Therefore, the format has been revised to include cardiac implantable electronic devices and catheter ablation therapies.

Since 2011, there has been a succession of innovative devices and treatment methods, such as:

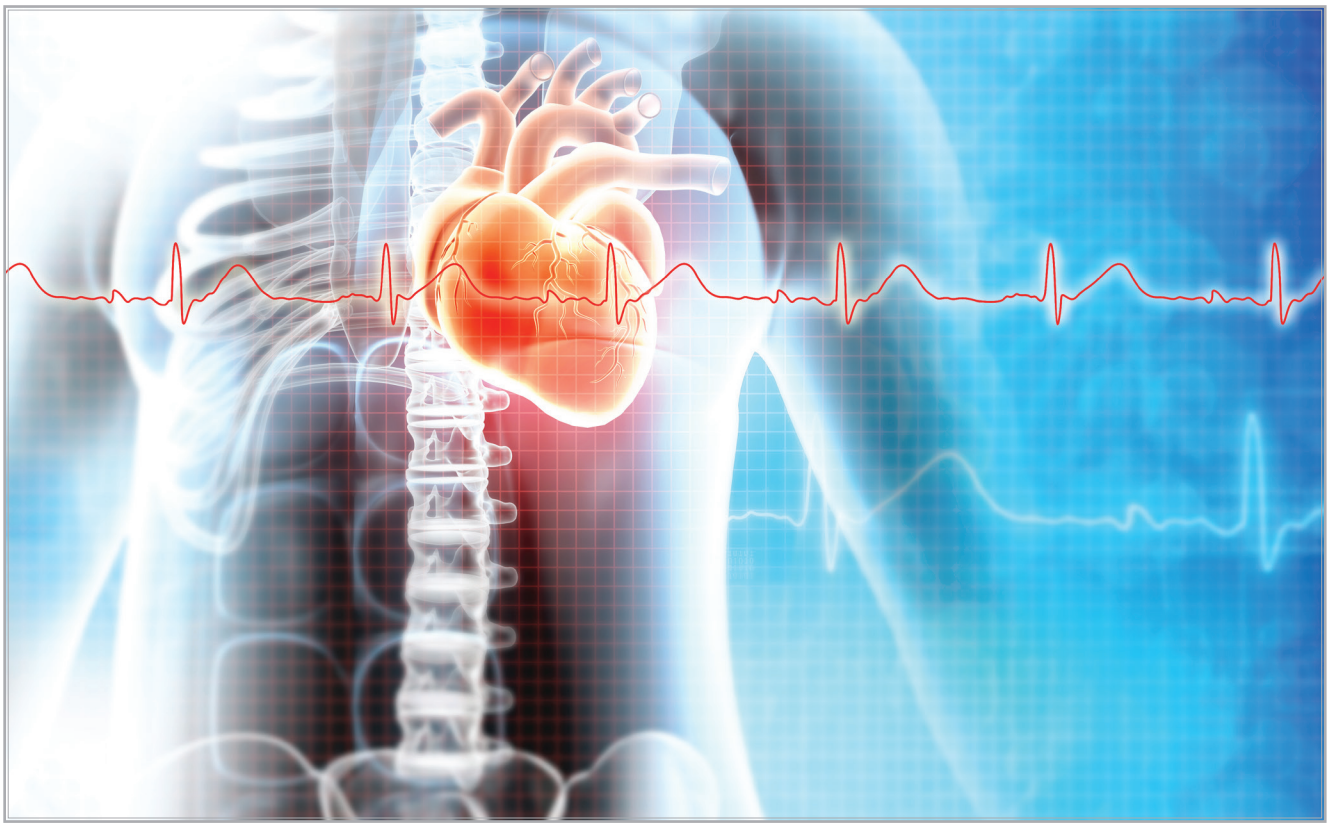
1. implantable cardiac monitoring,
2. subcutaneous implantable cardioverter-defibrillators,
3. wearable cardioverter-defibrillators,
4. remote monitoring,
5. magnetic resonance imaging-compatible devices,
6. leadless pacemakers,
7. balloon technology for pulmonary vein isolation,
8. percutaneous lead extraction, and
9. left atrial appendage closure devices.

Non-pharmacotherapy in the broad sense includes external cardioversion for atrial fibrillation and sustained ventricular tachyarrhythmias, temporary intravenous pacing, and percutaneous pacing.

This guideline recommends indications for non-pharmacotherapy of arrhythmia based on the latest findings and evidence. There is an increasing variety of non-pharmacotherapies, and extensive progress is being made in this field. This guideline contains information on conventional cardiac implantable electronic devices (CIEDs), such as pacemakers, ICDs, and ICDs with biventricular pacing function, as well as new information on remote monitoring, magnetic resonance imaging-conditional CIEDs, leadless pacemakers, percutaneous lead extraction, implantable monitors, S-ICDs, and WCDs. Information on catheter ablation includes radiation exposure, new 3D mapping systems, balloon ablation for AF, bipolar ablation, and chemical ablation. In addition, this guideline discusses the LAAC device for the first time, which is not a treatment for arrhythmia itself but for preventing thromboembolism – a serious problem associated with AF.

Non-pharmacotherapy of arrhythmia is expected to increase in the future, so there is a need to standardize all non-pharmacotherapy processes, including not only treatment indications but also their theoretical background, recommended procedures, necessary equipment and implementation system, and precautions that have to be taken before and after the procedure.

The indications of non-pharmacological treatments of tachyarrhythmia in children differ from those in adults, so there are many cautionary points to note. Therefore, CIEDs and catheter ablation for children are described under independent chapters, as in previous guidelines. The information on surgical treatment for arrhythmia mainly focuses on surgical treatment for AF and VT. Surgery for supraventricular tachycardia has been omitted from this guideline because the number of surgical procedures has dramatically decreased in recent



years. Nevertheless, surgery is still indicated for some patients with supraventricular tachycardias, including those with unsuccessful ablation.

The aim of this guideline is to clarify the indications, results, and complications of non-pharmacological treatments for arrhythmias such as bradyarrhythmia, supraventricular tachycardia, AF, premature ventricular contractions, VT, and ventricular fibrillation, as well as treatment for the associated heart failure and thromboembolism. The authors strived for standardized treatment by explicitly describing the procedures. Specific information on the procedures is also included, such as the knowledge, equipment, and doctor/facility conditions required to perform the procedure. The guideline has been created based on evidence and consensus at the time of publication and should be updated over time. This guideline describes the recommended indications and procedures as of 2018. Future technological advances will further expand the indications for non-pharmacotherapy of arrhythmia and make the procedures more reliable and convenient.

This guideline is designed to be used as a reference by doctors diagnosing and treating diseases in clinical practice, and the final decision should be made by the attending physicians after ascertaining the patient's condition. Even when selecting a diagnosis or treatment that does not follow the guideline, the decision of the attending physicians should be prioritized in consideration of the individual patient's situation. In actual clinical settings, it is most important for the attending physicians to make the judgment after fully considering the clinical background and social situation of each patient while complying with the guideline.

Arrhythmias and Intraventricular Conduction Disturbances in Patients Hospitalized with Coronavirus Disease 2019[4]

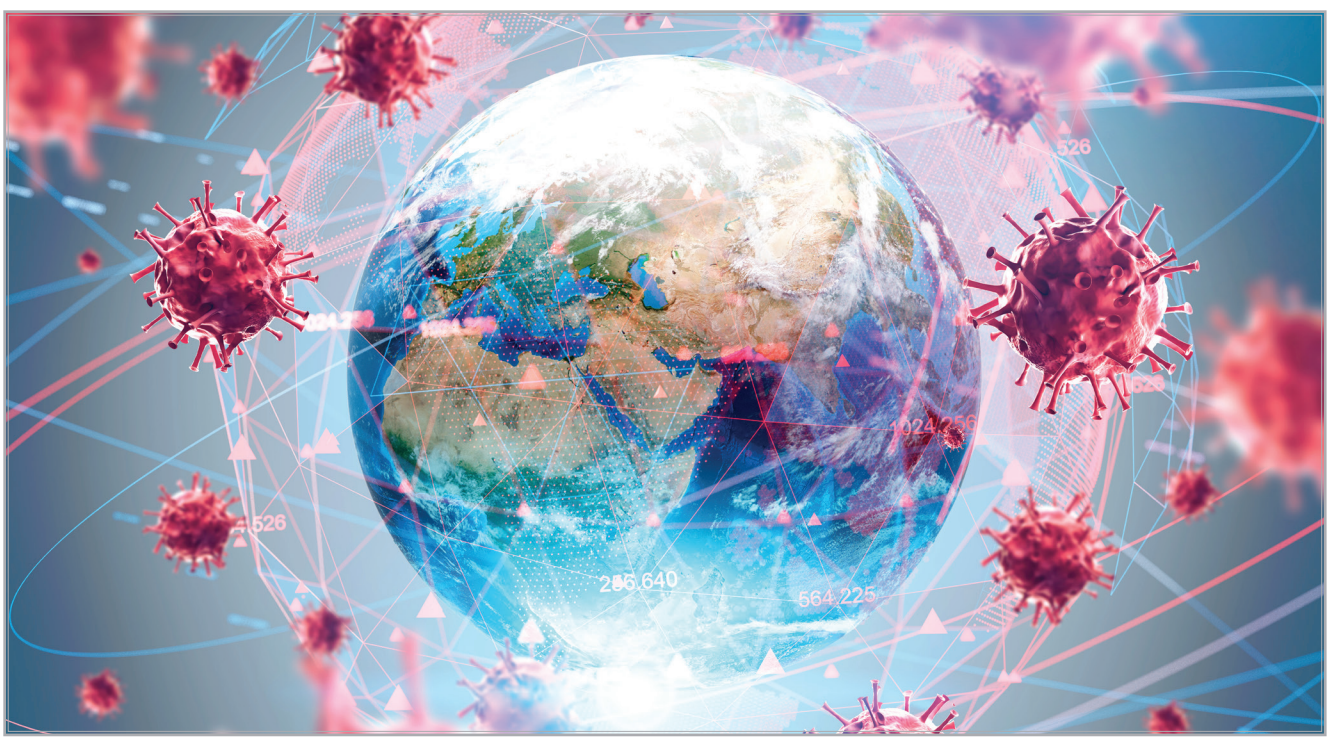
Patel NH, Rutland J, Tecson KM. Arrhythmias and Intraventricular Conduction Disturbances in Patients Hospitalized With Coronavirus Disease 2019. Am J Cardiol. 2022 Jan 1;162:111-115.

Cardiac arrhythmias have been observed in patients hospitalized with coronavirus disease (COVID-19). Most analyses of rhythm disturbances to date include cases of sinus tachycardia, which may not accurately reflect true cardiac dysfunction. Furthermore, limited data exist regarding the development of conduction disturbances in patients hospitalized with COVID-19. Hence, Patel et al performed a retrospective review and compared characteristics and outcomes for patients with versus without incident arrhythmia, excluding sinus tachycardia, as well as between those with versus without incident conduction disturbances.

There were 27 of 173 patients (16%) hospitalized with COVID-19 who developed a new arrhythmia. Incident arrhythmias were associated with an increased risk of intensive care unit admission (59% vs 31%, $p = 0.0045$), intubation (56% vs 20%, $p < 0.0001$), and inpatient death (41% vs 10%, $p = 0.0002$) without an associated increase in risk of decompensated heart failure or other cardiac issues.

New conduction disturbances were found in 13 patients (8%). Incident arrhythmias in patients hospitalized with COVID-19 are associated with an increased risk of mortality, likely reflective of underlying COVID-19 disease severity more than intrinsic cardiac dysfunction. Conduction disturbances occurred less commonly and were not associated with adverse patient outcomes.

In conclusion, the authors found that 16% of patients hospitalized with COVID-19 developed an incident arrhythmia, and conduction disturbances occurred in 8%. Development of an incident arrhythmia, but not conduction disturbance, was associated with an increased risk of intubation, ICU admission, and death and is likely more reflective of a severe disease state of COVID-19 rather than intrinsic cardiac dysfunction.



Hypertension

I-ADD Study: Assessment of Efficacy and Safety Profile of Irbesartan/Amlodipine Fixed-Dose Combination Therapy Compared with Irbesartan Monotherapy in Hypertensive Patients Uncontrolled with Irbesartan 150 mg Monotherapy[5]

Bobrie G; I-ADD Study Investigators. I-ADD study: assessment of efficacy and safety profile of irbesartan/amlodipine fixed-dose combination therapy compared with irbesartan monotherapy in hypertensive patients uncontrolled with irbesartan 150 mg monotherapy: a multicenter, phase III, prospective, randomized, open-label with blinded-end point evaluation study. Clin Ther. 2012 Aug;34(8):1720-34.e3.

Hypertension guidelines recommend the use of 2 agents with synergistic action when >1 agent is needed to achieve blood pressure goals. Newer antihypertensive treatment combinations include fixed-dose combinations of an angiotensin receptor blocker and a calcium channel blocker.

The I-ADD study aimed to demonstrate whether the antihypertensive efficacy of fixed-dose combination irbesartan 300 mg/amlodipine 5 mg (I300/A5) was superior to that of irbesartan (I300) monotherapy in lowering home systolic blood pressure after 10 weeks' treatment. The I-ADD was a Phase III study conducted as part of the clinical development program for the registration of a new fixed-dose combination of irbesartan and amlodipine for the treatment of hypertension. Bobrie et al investigated whether the antihypertensive effect, as assessed by using home blood pressure measurements (HBPM), of the fixed-dose combination therapy of irbesartan 300 mg and amlodipine 5 mg(I300/A5) was superior to that of irbesartan 300 mg(I300) alone in hypertensive patients whose condition was insufficiently controlled with I300 monotherapy.

I-ADD study was a 10-week, multicenter, Phase III, prospective, randomized, parallel-group, open-label with blinded-end point study. The main inclusion criterion was essential uncontrolled hypertension (systolic blood pressure ≥145 mm

Hg at office after at least 4 weeks of irbesartan 150 mg [I150] monotherapy administered once daily). Patients continued to receive I150 for 7 to 10 days and were randomized to either monotherapy with I150 for 5 weeks then I300 for the next 5 weeks, or to a fixed-dose combination therapy (I150/A5, then I300/A5). Safety profile was assessed by recording adverse events reported by patients or observed by the investigator.

In this study, treatment with the fixed-dose combination of I150/A5 or I300/A10 resulted in a better BP response than with irbesartan monotherapy, with a similar safety profile. After 10 weeks of study treatment, the reduction in SBP was greater (adjusted mean difference between groups, –8.8 mm Hg) with fixed-dose combination therapy (I150/A5 for 5 weeks, then I300/A5 for 5 additional weeks) than with monotherapy (I150 for 5 weeks, then I300 for 5 additional weeks), with higher proportions of patients attaining mean home SBP<135mmHg (58.9% vs 37.7%) and mean office SBP<140mmHg (61.7% vs 41.1%).

Following enrollment, 325 patients were randomized to treatment, and 320 (mean [SD] age, 56.7 [11.4] years; 41% male) were included in the intention-to-treat analysis: 155 patients treated with I150/A5 then I300/A5, and 165 patients treated with I150 then I300. At randomization, mean home systolic blood pressure was similar in both groups: 152.7 (11.8) mm Hg in the I150/A5 group and 150.4 (10.1) mm Hg in the I150 group. At week 10, the adjusted mean difference in home systolic blood pressure between groups was -8.8 (1.1) mm Hg ($p < 0.001$). The percentage of controlled patients (mean home blood pressure <135 and 85 mm Hg) was nearly 2-fold higher in the I300/A5 group versus the I300 group ($p < 0.001$). Treatment-emergent adverse events were experienced by 10.5% of I300/A5-treated patients and 6.6% of I300-treated patients during the second 5-week period. Three serious adverse events were reported; 2 with monotherapy (1 with I150 and 1 with I300) and 1 with fixed-dose combination I300/A5. All patients affected by serious adverse events made a full recovery.

The results of this study conducted in a population of adult patients with essential hypertension suggest a greater antihypertensive efficacy of the fixed-dose combination (I150/A5 for 5 weeks, then I300/A5 for 5 additional weeks) compared with irbesartan alone (I150 for 5 weeks, then I300 for 5 additional weeks) in terms of lowering SBP after 10weeks of treatment. Both treatments were well tolerated throughout the study.

Assessment of Suitable Antihypertensive Therapies: Combination with High-Dose Amlodipine/Irbesartan Vs Triple Combination with Amlodipine/Irbesartan/Indapamide (ASAHI-AI Study)[6]

Nakagawa N, Sato N, Saijo Y, Morimoto H, Koyama S, Ogawa Y, Uekita K, Maruyama J, Ohta T, Nakamura Y, Takeuchi T, Hasebe N; ASAHI-AI investigators. Assessment of suitable antihypertensive therapies: Combination with high-dose amlodipine/irbesartan vs triple combination with amlodipine/irbesartan/indapamide (ASAHI-AI study). J Clin Hypertens (Greenwich). 2020 Sep;22(9):1577-1584.

Angiotensin receptor blockers (ARBs) plus calcium channel blockers (CCBs) are a widely used combination therapy for hypertensive patients. In order to determine which combination was better as the next-step therapy for standard-dose combination of ARBs and CCBs, a combination with high-dose CCBs or a triple combination with diuretics, the authors conducted a prospective, randomized, open-label trial to determine which of the following

combination is better as the next-step treatment: a combination with high-dose CCBs or a triple combination with diuretics.

The main finding of this study was that high-dose CCBs combined with ARBs and a triple combination with diuretics combined with CCB/ARBs produced a similar efficacy in reducing the BP. However, the change in the serum uric acid level was advantageous in the ARB + high-dose CCB group (Group 1)

Hypertensive outpatients who did not achieve their target blood pressure (BP) with usual dosages of ARBs and amlodipine 5 mg were randomly assigned to treatment with irbesartan 100 mg/amlodipine 10 mg (Group 1: n = 48) or indapamide 1 mg in addition to ARBs plus amlodipine 5 mg (Group 2: n = 46). The primary end point was changes in the systolic BP (SBP) and diastolic BP (DBP) after the 12-week treatment period, while secondary end points were changes in BP after the 24-week treatment period and laboratory values. At 12 weeks, the SBP/DBP significantly decreased from 152.1/83.4 mm Hg to 131.5/76.1 mm Hg in Group 1 and 153.9/82.1 mm Hg to 132.7/75.9 mm Hg in Group 2. Although both groups produced a similar efficacy in reducing the SBP/DBP (-19.2/-9.2 mm Hg in Group 1 and -21.6/-8.8 mm Hg in Group 2; SBP p=.378, DBP p=.825), high-dose CCBs combined with ARBs controlled hypertension without elevation of serum uric acid.

In conclusion, high-dose CCBs combined with ARBs controlled hypertension without elevation of serum uric acid level, although high-dose CCBs combined with ARBs and a triple combination with diuretics combined with standard-dose CCB/ARBs produced a similar efficacy in reducing the BP throughout the half year. Both combination therapies can be used safely and effectively in hypertensive patients uncontrolled by standard doses of ARBs and CCBs.

I-COMBINE Study: Assessment of Efficacy and Safety Profile of Irbesartan/Amlodipine Fixed-Dose Combination Therapy Compared with Amlodipine Monotherapy in Hypertensive Patients Uncontrolled with Amlodipine 5 mg Monotherapy[7]

Bobrie G; I-COMBINE Study Investigators. I-COMBINE study: assessment of efficacy and safety profile of irbesartan/amlodipine fixed-dose combination therapy compared with amlodipine monotherapy in hypertensive patients uncontrolled with amlodipine 5 mg monotherapy: a multicenter, phase III, prospective, randomized, open-label with blinded-end point evaluation study. Clin Ther. 2012 Aug;34(8):1705-19.

Hypertension guidelines recommend the use of 2 agents with synergistic action when >1 agent is needed to achieve blood pressure goals. Newer antihypertensive treatment combinations include fixed-dose combinations of an angiotensin receptor blocker and a calcium channel blocker. The clinical trial (I-COMBINE) was a Phase III study conducted as part of the clinical development program for the registration of a new fixed-dose combination of irbesartan and amlodipine for the treatment of hypertension. The authors investigated whether the antihypertensive effect, as assessed by using home BP measurements (HBPM), of the fixed-dose combination therapy of irbesartan and amlodipine 150mg/5mg (I150/A5) was superior to that of amlodipine 5mg (A5) alone in hypertensive patients whose condition was insufficiently controlled with A5 monotherapy.

The I-COMBINE study aimed to determine whether the antihypertensive efficacy of the fixed-dose combination irbesartan 150mg/ amlodipine 5mg (I150/A5) was superior to that of amlodipine 5mg (A5) monotherapy in lowering home systolic blood pressure (HSBP) after 5 weeks' treatment.

The I-COMBINE study was a 10-week, multicenter, Phase III, prospective, randomized, parallel-group, open-label with blinded-endpoint study. The main inclusion criterion was essential uncontrolled hypertension (SBP ≥145 mm Hg at office, after at least 4 weeks of A5 monotherapy administered once daily). Patients continued to receive A5 for 7 to 10 days and were randomized to either monotherapy with A5 for 5 weeks then amlodipine 10mg (A10) for the next 5 weeks or to a fixed-dose combination therapy (I150/A5 then I150/A10). Safety profile was assessed by recording adverse events reported by patients or observed by the investigator.

Following enrollment, 290 patients were randomized to treatment, and 287 (mean [SD] age, 57.3 [11.2] years; 48% male) were included in the intention-to-treat analysis: 144 patients treated with I150/A5 then I150/A10, and 143 patients treated with A5 then A10. At randomization, mean HSBP was similar in both groups: 148.5 (10.3)mm Hg in the I150/A5 group and 149.2 (9.7)mm Hg in the A5 group. At week 5, the adjusted mean difference in HSBP between groups was -6.2 (1.0)mm Hg ($p < 0.001$). The proportion of controlled patients (mean home blood pressure <135 and 85mm Hg) was significantly higher in the I150/A5 group than in the A5 group ($p < 0.001$). Treatment-emergent adverse events were experienced by 13.8% of I150/A5-treated patients and 11.9% of A5-treated patients during the first 5-week period, and by 15.8% of I150/A10-treated patients and 17.0% of A10-treated patients during the second 5-week period. Two serious adverse events were reported with the fixed-dose combination; both patients recovered.

This was the first study to assess the antihypertensive efficacy and safety profiles of fixed-dose combination therapy with irbesartan, an ARB, and amlodipine, a dihydropyridine CCB, on BP. Fixed-dose combination therapy with I150/A5 or I150/A10 resulted in increased BP-lowering response and a favorable safety profile compared with amlodipine monotherapy.

Although the study was an open-label design, which could have been a limiting factor, it was performed by using independent evaluation of BP measurements during data management. This allowed a blinded evaluation of BP measurements and supported open-label treatment administration.

Data from this population of adult patients with essential hypertension suggest greater efficacy with the fixed-dose combination I150/A5 over A5 alone in lowering SBP after 5 weeks of treatment. Both treatment regimens were well tolerated throughout the study.

Heart Failure

Torasemide in Hypertension and Heart Failure: Re-inventing Loop Diuretic Therapy?[8]

Manolis A, Kallistratos M, Doumas M. Torasemide in Hypertension and Heart Failure: Re-inventing Loop Diuretic Therapy? Curr Pharm Des. 2021;27(23):2714-2721.

In heart failure (HF) patients, current European Society of Cardiology (ESC) guidelines recommend the use of three loop diuretics (furosemide, torasemide, bumetanide) in order to not only reduce HF hospitalizations but also to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion. In addition, for the first time in hypertensive patients, European Society of Hypertension (ESH) guidelines recommend the use of torasemide.

Loop diuretics represent the cornerstone for the management of edematous disorders, especially HF, chronic kidney disease, proteinuria, and cirrhosis. Loop diuretics exhibit their action by blocking the Na-K-2Cl cotransporter (NKCC) at the apical side of epithelial cells in the thick ascending limb of the loop of Henle, a site where approximately 20-30% of sodium is reabsorbed. The inhibition of NKCC affects the reabsorption of potassium and chlorium along with sodium resulting in increased sodium load to the distal tubule, where in turn the exchange of sodium and potassium is enhanced, leading to increased potassium secretion. The inhibition of NKCC is achieved by reversible binding of the loop diuretics to the chloride site of the cotransporter.

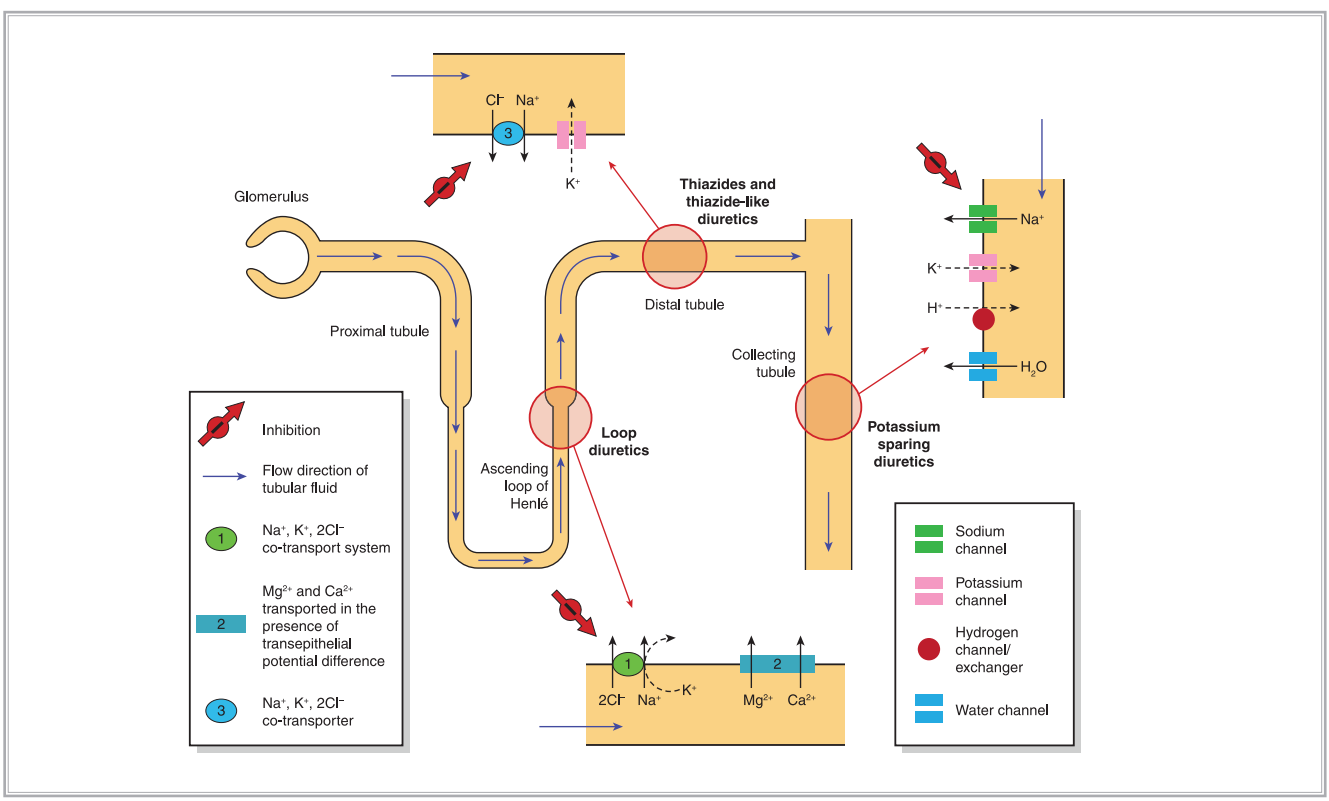
Torasemide is a loop diuretic that is devoid of furosemide limitations. It compares favorably

with hydrochlorothiazide and indapamide. Its mechanism of action may not be entirely based on elimination of salt and water from the body. Torasemide exhibits a favorable side-effect profile, particularly because it does not engender hypokalemia, increases in blood sugar, or serum lipid values.

Torasemide attenuates left ventricular remodeling, may reverse myocardial fibrosis, and reduce collagen synthesis, resulting in an amelioration of cardiac remodeling in patients with HF. In comparison with furosemide, torasemide improves left ventricular function, reduces mortality as well as the frequency and duration of heart failure-related hospitalization, and improves quality of life, exercise tolerance and NYHA functional class in patients with congestive heart failure.

Loop diuretics are the main weapon in the physicians' therapeutic armamentarium for the management of edematous disorders, including CHF. Torasemide possesses significant advantages over furosemide in terms of improved and predictable bioavailability and duration of action. The superior pharmacokinetic profile of torasemide along with its pleiotropic actions render torasemide the preferred loop diuretic for the management of CHF, reminding that the time has come to replace furosemide with torasemide in the management of this devastating disease.

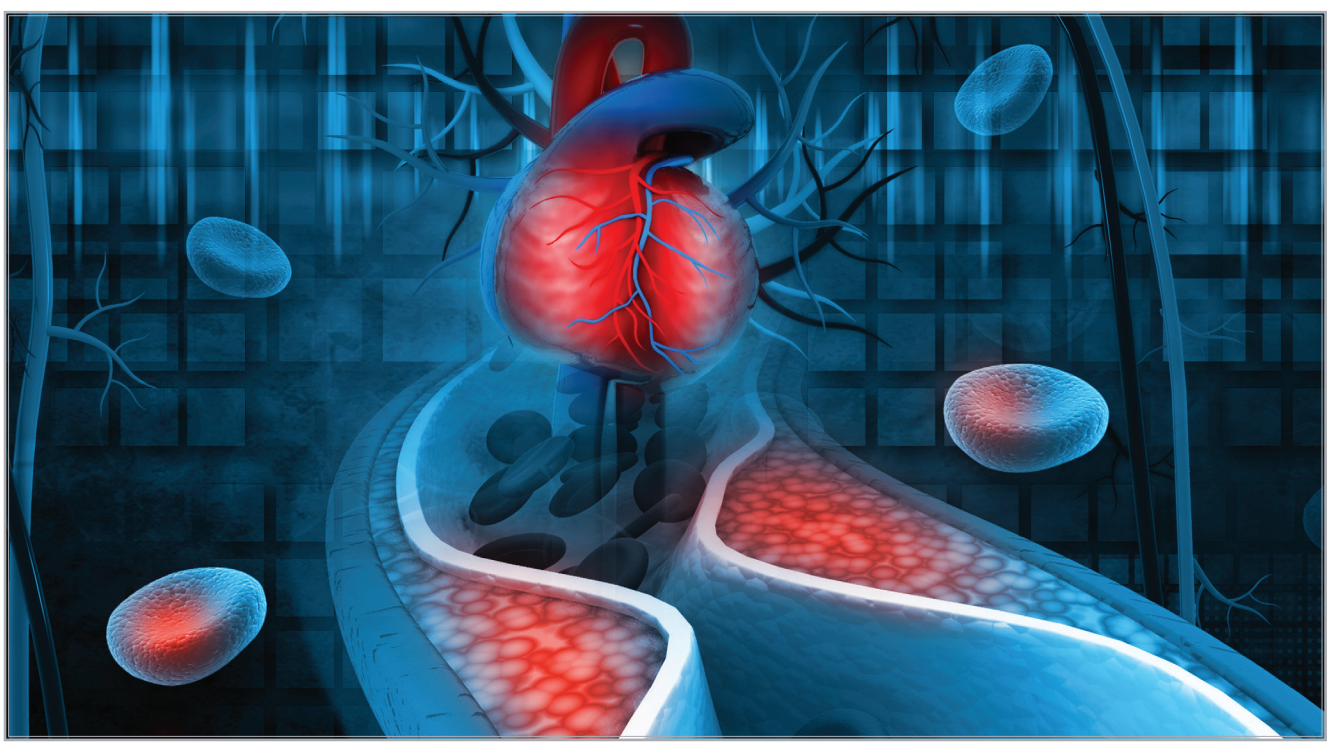
In addition, loop diuretics are currently used for the management of arterial hypertension in patients with impaired renal function. Several lines of evidence indicate that torasemide may also be used in patients with thiazide-induced metabolic alterations. Finally, data from clinical studies demonstrate that torasemide is at least as effective as thiazides and thiazide-like diuretics in terms of blood pressure reduction, suggesting that torasemide is an attractive alternative of thiazide diuretics in the management of patients with arterial hypertension, and paving the pathway for outcome trials comparing the various types of diuretics.



COVID-19 Vaccination in Patients with Heart Failure: A Position Paper of the Heart Failure Association of the European Society of Cardiology[9]

Rosano G, Jankowska EA, Ray R, Metra M, Abdelhamid M, Adamopoulos S, Anker SD, Bayes-Genis A, Belenkov Y, Gal TB, Bωhm M, Chioncel O, Cohen-Solal A, Farmakis D, Filippatos G, Gonzalez A, Gustafsson F, Hill L, Jaarsma T, Jouhra F, Lainscak M, Lambrinou E, Lopatin Y, Lund LH, Milicic D, Moura B, Mullens W, Piepoli MF, Ponikowski P, Rakisheva A, Ristic A, Savarese G, Seferovic P, Senni M, Thum T, Tocchetti CG, Van Linthout S, Volterrani M, Coats AJS. COVID-19 vaccination in patients with heart failure: a position paper of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2021 Nov;23(11):1806-1818.

Patients with heart failure (HF) who contract SARS-CoV-2 infection are at a higher risk of cardiovascular and non-cardiovascular morbidity and mortality. Regardless of therapeutic attempts in COVID-19, vaccination remains the most promising global approach at present for controlling this disease. There are several concerns and misconceptions regarding the clinical indications, optimal mode of delivery, safety and efficacy of COVID-19 vaccines for patients with HF. This document provides guidance to all healthcare professionals regarding the implementation of a COVID-19 vaccination scheme in patients with HF. COVID-19 vaccination is indicated in all patients with HF, including those who are immunocompromised (e.g. after heart transplantation receiving immunosuppressive therapy) and with frailty syndrome. It is preferable to vaccinate against COVID-19 patients with HF in an optimal clinical state, which would include clinical stability, adequate hydration and nutrition, optimized treatment of HF and other comorbidities (including iron deficiency), but corrective measures should not be allowed to delay vaccination. Patients with HF who have been vaccinated against COVID-19 need to continue precautionary measures, including the use of facemasks, hand hygiene and social distancing. Knowledge on strategies preventing SARS-CoV-2 infection (including the COVID-19 vaccination) should be included in the comprehensive educational programs delivered to patients with HF.



Summary of all key messages and guidance statements for patients with heart failure and COVID-19

The diagnosis of HF, particularly when present in an elderly and/or frail subject, is a strong predictor of non-lethal and lethal complications of COVID-19, which include a need for intensive non-invasive and invasive respiratory support, a need for pharmacological and mechanical circulatory support, a longer hospital stay, a longer intensive care unit stay, a high risk of severe pneumonia and respiratory failure, more common thromboembolic events, secondary myocardial damage, circulatory decompensation, neurological complications, and finally increased risk of both CV and non-CV death.

All COVID-19 vaccine trials have recruited cohorts of subjects, including those with CVD and HF, and have confirmed the vaccines to be safe and effective in these groups. Rare cases of thromboembolism and myocarditis need to be acknowledged, but also confronted with overwhelming survival benefits due to COVID-19 vaccinations seen globally.

COVID-19 vaccination is indicated for all patients with HF unless other contraindications exist.

COVID-19 vaccination is indicated in all patients with HF with a compromised immune system, including patients following heart transplantation receiving immunosuppressive therapy.

Patients with HF are indicated also to be vaccinated against influenza and pneumonia in order to reduce the risk of dual infections.

It is suggested not to administer the vaccine to individuals with a known history of a severe allergic reaction (e.g. anaphylaxis) to any component of the COVID-19 vaccine. However, it should not be considered as an absolute contraindication for vaccination against COVID-19.

Intramuscular injection required for COVID-19 vaccines can cause hematomas in patients with platelet defects, thrombocytopenia and/or on anticoagulation therapy. The benefit of COVID-19 vaccination is expected to be greater than the risks of local bleeding.

Therapy with anticoagulants and/or antiplatelets in patients with HF is not a contraindication for vaccination against COVID-19.

COVID-19 vaccination is indicated also for frail patients with HF unless other contraindications exist.

Vaccination against COVID-19 patients with HF is needed as early as possible, preferably in an optimal clinical state and optimized treatment of HF and other comorbidities. However, treatment optimization should not delay COVID-19 vaccination.

Iron repletion prior to COVID-19 vaccination has the potential to optimize vaccine benefits in iron-deficient patients with HF.
Precautionary measures, including the use of facemask, hand disinfection and social distancing, are still needed for patients with HF even after COVID-19 vaccination. Patients with HF, their close contacts (including family members and care providers) and healthcare workers still need to follow locally recommended measures designed to prevent the SARS-CoV-2 spread.
A structured clinical follow-up of vaccinated patients with HF is preferred, but an assessment of anti-SARS-CoV-2 antibodies is not required.
Knowledge on strategies preventing SARS-CoV-2 infection (including the COVID-19 vaccination) forms an important part of comprehensive educational programmes delivered to patients with HF.

CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure.

Diabetes and Prediabetes in Patients with Heart Failure and Preserved Ejection Fraction[10]

Jackson AM, Rxrth R, Liu J, Kristensen SL, Anand IS, Claggett BL, Cleland JGF, Chopra VK, Desai AS, Ge J, Gong J, Lam CSP, Lefkowitz MP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rizkala AR, Rouleau JL, Seferović PM, Tromp J, Van Veldhuisen DJ, Yilmaz MB, Zannad F, Zile MR, Kxber L, Petrie MC, Jhund PS, Solomon SD, McMurray JJV; PARAGON-HF Committees and Investigators.. Diabetes and prediabetes in patients with heart failure and preserved ejection fraction. Eur J Heart Fail. 2021 Dec 17. doi: 10.1002/ejhf.2403. Epub ahead of print.

There is an association between heart failure with preserved ejection fraction (HFpEF) and insulin resistance, but less is known about the diabetic continuum, and in particular about prediabetes, in HFpEF.

Patients aged ≥50years with LVEF ≥45%, structural heart disease and elevated NT-proBNP were eligible. Patients were classified according to HbA_{1c}: (1) normal HbA_{1c}, <6.0%; (2) prediabetes, 6.0-6.4%; (3) diabetes, ≥6.5% or history of diabetes. The primary outcome was a composite of cardiovascular (CV) death and total HF hospitalizations (HFH). Of 4796 patients, 50% had diabetes and 18% had prediabetes. Compared to patients with normal HbA_{1c}, patients with prediabetes and diabetes more often were obese, had a history of myocardial infarction and had lower KCCQ scores, while patients with diabetes had more clinical evidence of congestion, but similar NT-proBNP concentrations.

Diabetes and prediabetes together affect around two thirds of HFpEF patients, highlighting the highly dysglycemic character of this HF phenotype, globally. Diabetes, and to lesser extent prediabetes, was associated with worse clinical status and higher risk of adverse cardiovascular outcomes. Although a focus on developing safe and effective glucose-lowering therapies for patients with HF is clearly important, attempts to prevent the development of, and even to reverse, diabetes (and, perhaps, even prediabetes) should not be neglected.

The risks of the primary composite outcome (RR 1.59, 1.35-1.88), total HFH (RR 1.67, 1.39-2.02) and CV death (HR 1.35, 1.07-1.71) were higher among patients with diabetes, compared to those with normal HbA_{1c}. Patients with prediabetes had a higher risk (which was intermediate between that of patients with diabetes and those with normal HbA_{1c}) of the primary outcome (1.27, 1.00-1.60) and HFH (1.35, 1.03-1.77), but not of CV death (1.02, 0.75-1.40). Patients with diabetes treated with insulin had worse outcomes than those not, and those with «lean diabetes» had similar mortality rates to those with a higher BMI, but lower rates of HFH.

In this *post-hoc* analysis of the PARAGON-HF trial the authors found that diabetes and prediabetes together affect around two thirds of patients with HFpEF, highlighting the highly dysglycemic character of this HF phenotype, globally. Patients with each of prediabetes and diabetes had higher rates of HF hospitalization than patients with normal $HbA_{1c,}$ with the risk of patients with prediabetes intermediate between that of patients with diabetes and those with normal HbA_{1c}. The risk of all-cause mortality and cardiovascular death were significantly higher in patients with diabetes but similar in patients with prediabetes and those with normal HbA_{1c}.

The authors concluded that prediabetes is common in patients with HFpEF and is associated with worse clinical status and greater risk of HFH.

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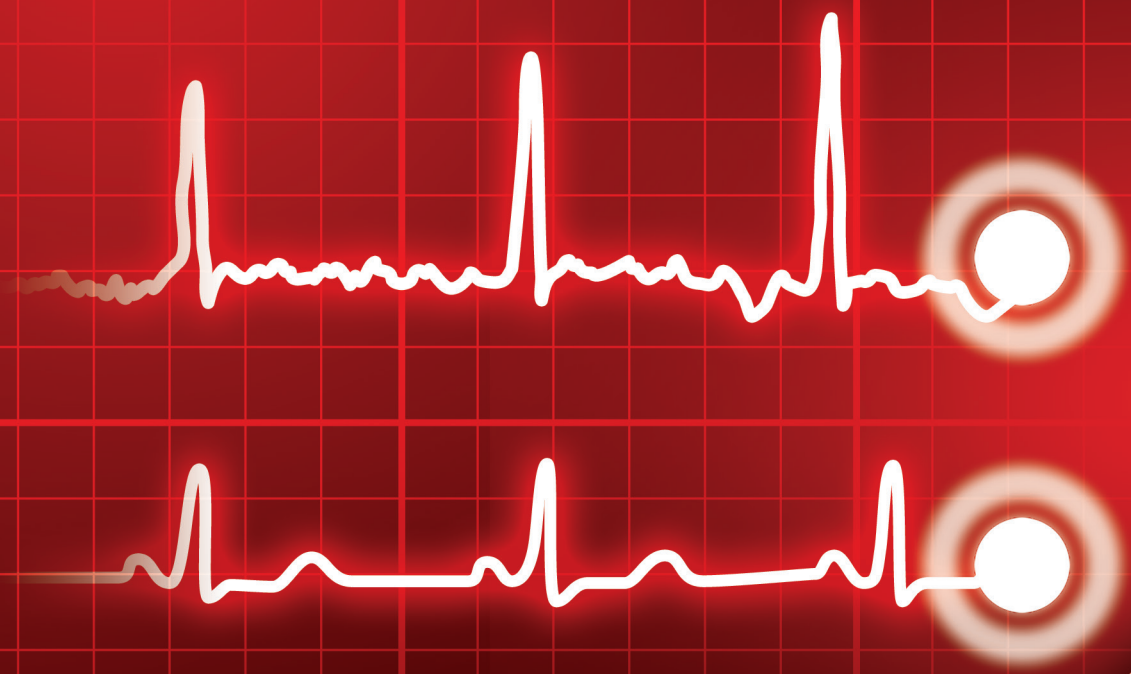

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