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# ARRHYTHMIC SYNCOPE: NEW CONTRIBUTIONS ON ETIOLOGY, MANAGEMENT, AND PROGNOSIS IN COMPLEX SITUATIONS

**Jaume Francisco Pascual**

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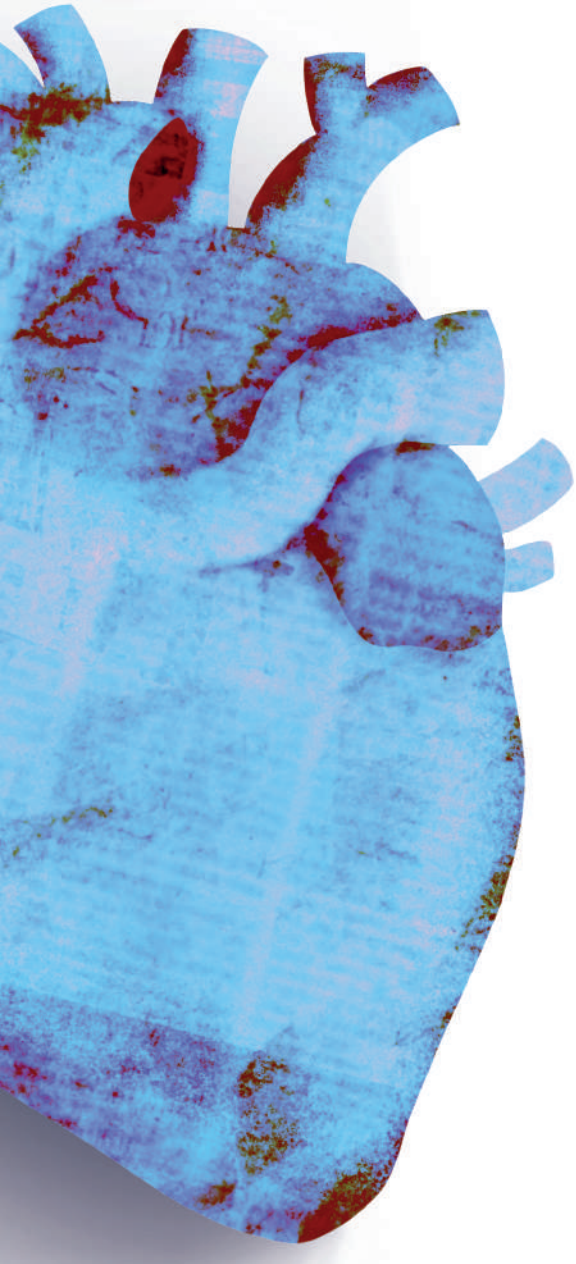
Doctoral Thesis

# Arrhythmic syncope:
## New contributions on etiology, management, and prognosis in complex situations



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# ACKNOWLEDGMENTS

Tot i que aquest és el primer apartat de la tesi, és l'últim que escric i segurament el més difícil, ja que tinc tant a agrair que possiblement aquesta secció es queda curta. No em vull descuidar de cap amic o company que m'hagi acompanyat en aquest viatge, pel que crec que el més oportú és no escriure noms, tot i que molts d'ells estaran implícits en les següents línies.

No tinc suficients paraules per agrair l'esforç de tots els professors que he tingut, des de l'escola i el batxillerat, que em van saber transmetre la passió per la ciència, i sobretot durant la universitat. Molts d'aquests professors, que van contribuir a la meva inclinació cap a la cardiologia, han esdevingut després companys de feina i alguns, fins i tot, bons amics. En aquest punt, cal destacar els directors i tutors de la tesis, que m'han guiat i assessorat de forma magistral durant el transcurs de la mateixa, però al mateix temps m'han concedit la llibertat per investigar allò que m'interessava més i de la manera que considerava més adequada.

Durant aquests anys, he tingut la sort de compartir la meva feina amb magnífics companys, molts dels quals també són grans amics i fan que el dia a dia, dins i fora de l'hospital, passi sense que m'adoni. Crec que sóc molt afortunat de poder dir això. En aquest sentit, vull agrair especialment als companys de la unitat d'arrítmies, on hi ha un equip multidisciplinari difícilment igualable. Ells m'han acompanyat moltes hores al dia, i he pogut aprendre d'ells i amb ells. També hagués estat impossible desenvolupar els treballs d'aquesta tesis sense el seu suport. Tanmateix, em sento afortunat d'haver tingut mentors en cardiologia, especialment en el món de les arrítmies. La seva ajuda és impagable. Moltes gràcies per tots els consells, les ensenyances i per haver-me introduït en el món de la recerca en arrítmies i, especialment, en la síncope. Un agraïment especial a aquells companys que han col·laborat d'una forma o altra en el desenvolupament dels estudis de la tesis, alguns dels quals són coautors dels treballs de la tesis, però cal estendre-ho a tot el servei de Cardiologia que es cuida d'aquests pacients.

Sé que la paraula «amic» ja ha aparegut diverses vegades en aquestes poques línies. Però ningú com jo sap la importància de tenir bons amics, amics de veritat. Sortosament, en tinc diversos, que sempre estan al meu costat, tant en els bons moments com en els més difícils. En alguns casos, sé que estan allà malgrat la distància i que, en èpoques per diverses raons, no puc tenir tot el contacte que desitjaria. Moltes gràcies també per acompanyar-me en aquest viatge.

I el més important, la família. Ho he deixat per l'últim punt perquè se'm neguen els ulls a escriure aquestes línies. M'imagino com es sentirien avui aquells que desafortunadament ja

no hi poden ser: els avis, la tieta, i sobretot el pare, i la cara de joia que posarien en poder llegir aquestes pàgines (suposo que la mateixa que posarà la mare). Sense la família, i sobretot sense l'acompanyament de la mare i el pare, tinc clar que avui no estaria aquí. El seu suport incondicional, a vegades fins i tot desmesurat, és el fonament sobre el qual he pogut construir cada pas d'aquest camí. M'han guiat en el viatge de la vida i m'han ensenyat molt més del que es pot aprendre a l'escola o a la universitat. Moltes gràcies a tots, als que ens veiem menys del que voldríem, i als que em doneu tant d'escalf quan arribo a casa. Us estimo.

# ABBREVIATIONS

aAVB: advanced atrioventricular block

AF: Atrial Fibrillation

AoS: Aortic stenosis

AVB: Atrio-ventricular block

BBB: Bundle branch block

BFB: Bifascicular block

BP: Blood pressure

BrS: Brugada syndrome

CAD: Coronary artery disease

cBBB: complete bundle branch block

CI: confidence interval

CMR: Cardiac magnetic resonance

CPVT: Catecholaminergic Polymorphic Ventricular Tachycardia

CSM: Carotid sinus massage

CSS: Carotid sinus syndrome

DBP: diastolic blood pressure

ECG: Electrocardiogram

ED: Emergency department

ELR: External loop recorders

EPS: Electrophysiology study

ESC: European Society of Cardiology

HCM: Hypertrophic cardiomyopathy

HR: Heart rate

ICD: Implantable cardiac defibrillator

ICM: Implantable cardiac monitor

IHD: Ischemic heart disease

ILR Implantable loop recorders

LBBB: left bundle branch block

MSVT: Monomorphic sustained ventricular tachycardia

OH: orthostatic hypotension

OMT: optimal medical treatment

POTS: postural orthostatic tachycardia syndrome

PVS: programmed ventricular stimulation

PVT: Polymorphic ventricular tachycardia

RBBB: right bundle branch block

RSE: recurrent episodes

SAS: Severe aortic stenosis

SBP: systolic blood pressure

SCD: Sudden cardiac death

SHD: Structural heart disease

SND: Sinus node disfunction

SNRT: sinus node recovery time

SSE: single syncopal episode

SSS: Sick sinus syndrome

T-LOC: Total loss of consciousness

VT: Ventricular tachycardia

VF: Ventricular fibrillation

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# ABSTRACT

**Background:**

A cardiac cause of syncope, especially arrhythmic, is a significant concern for patients and physicians due to its worse prognosis and risk of sudden cardiac death. Arrhythmic causes are more likely in patients with structural heart disease or ECG conduction disturbances. This thesis will focus on four unanswered aspects of managing patients with unexplained syncope at risk of an arrhythmic cause, studying three different cohorts of patients with specific underlying conditions: severe aortic stenosis (SAS), mid-range left ventricular disfunction (MR-LDV) and bundle branch block (BBB). This research will contribute knowledge in the field of syncope that may have a substantial impact on future patients care.

**Main objectives:**

Part 1) To determine the primary etiology of syncope in patients with SAS and assess the prognostic implications of identifying the main cause of syncope. Part 2) To determine the causes of syncope and assess the diagnostic yield and safety of a systematic work-up in patients with MR-LVD. Part 3) To analyze the sex-related differences in patients with syncope and BBB concerning the prevalence of AV block, the diagnostic yield of tests, and clinical outcomes and to analyze potential differences in the arrhythmic risk, diagnostic yield of testing, and clinical outcomes in patients with single vs recurrent unexplained syncope and BBB.

**Methodology:**

Part 1 was based on a retrospective cohort study of patients with syncope and SAS. Parts 2 and 3 studied a prospective cohort of patients with unexplained syncope after initial evaluation and MR-LVD or BBB, respectively, in which a systematic diagnostic work-up for syncope was applied.

**Main results:**

Part 1) In most patients with SAS, syncope is often caused by factors other than the valvulopathy itself, with bradyarrhythmia or reflex causes being the most prevalent. Syncope of unknown etiology is associated with a worse prognosis. Part 2) Arrhythmias are the most common cause of syncope in patients with MD-LVD. A systematic diagnostic strategy leads to a high number of specific diagnoses, which allows for appropriate treatment guidance. Part 3) Compared to men,

women with unexplained syncope and BBB have a lower risk of AV block and of requiring cardiac pacing. In contrast, patients with a single syncopal episode do not significantly differ from those with recurrent episodes in terms of arrhythmic risk and prognosis. A stepwise diagnostic approach has a similar diagnostic yield in all groups studied, and it seems appropriate to guide the treatment and avoid unnecessary pacemaker implantation.

**Conclusions:**

A rhythm disorder, especially bradycardias, is the most common underlying cause of unexplained syncope in the studied groups. The overall arrhythmic risk varies based on patient characteristics. A diagnostic approach with a systematic predefined work-up protocol is not only useful for identifying the etiology but also for guiding treatment and avoiding unnecessary interventions. The results emphasize the importance of appropriately evaluating high-risk patients to improve their prognosis.

# RESUM

**Antecedents:**

Determinar si un síncope es degut a una causa cardíaca, especialment arrítmica, és important degut al seu pitjor pronòstic i risc de mort sobtada. Les causes arrítmiques són més probables en pacients amb malaltia cardíaca estructural o trastorns de la conducció de l'ECG. Aquesta tesi es centrarà en quatre aspectes on no hi havia suficient evidència fins el moment sobre el maneig clínic de pacients amb síncope inexplicat i risc d'una causa arrítmica. S'estudiaran tres cohorts diferents de pacients amb cardiopaties subjacents específiques: estenosi aòrtica severa (EAS), disfunció ventricular esquerra de rang mig (DVREM) i bloc de branques (BB). Aquesta recerca contribuirà al coneixement en el camp del síncope que pot tenir un impacte substancial en el tractament d'aquests pacients.

**Objectius principals:**

Part 1) Determinar l'etiologia principal del síncope en pacients amb EAS i avaluar les implicacions pronòstiques d'identificar la causa principal del síncope. Part 2) Determinar les causes del síncope i avaluar el rendiment diagnòstic i la seguretat d'una investigació sistemàtica en pacients amb DVREM. Part 3) Analitzar les diferències relacionades amb el sexe en pacients amb síncope i BB en relació amb la prevalença del bloqueig AV, el rendiment diagnòstic de les proves i els resultats clínics i analitzar les diferències potencials en el risc arrítmic, el rendiment diagnòstic de les proves i els resultats clínics en pacients amb síncope inexplicat únic vs recurrent i BB.

**Metodologia:**

La part 1 es basa en un estudi de cohort retrospectiu de pacients amb síncope i EAS. Les parts 2 i 3 s'estudia una cohort prospectiva de pacients amb síncope inexplicat després de l'avaluació inicial i DVREM o BB, respectivament, en què es va aplicar una protocol diagnòstic sistematitzat per al síncope.

**Resultats principals:**

Part 1) En la majoria de pacients amb EAS, el síncope és causat per factors diferents de la valvulopatia en si mateixa, sent les bradiarítmies o les causes reflexes les més prevalents. El síncope d'etiologia desconeguda s'associa amb un pronòstic pitjor. Part 2) Les arrítmies són la

causa més comuna de síncope en pacients amb DVREM. L'aplicació d'un protocol diagnòstic sistematitzat aconsegueix un nombre elevat de diagnòstics específics, el que permet orientar el tractament adequadament. Part 3) Comparades amb els homes, les dones amb síncope inexplicat i BB tenen un risc més baix de bloqueig AV i de requerir la implantació d'un marcapassos cardíac. Per altra banda, els pacients amb un episodi sincopal únic no difereixen significativament dels que tenen episodis recurrents en termes de risc arrítmic i pronòstic. Un protocol diagnòstic escalonat i sistematitzat té un rendiment diagnòstic similar en tots els grups estudiats, i sembla apropiat per guiar el tractament i evitar la implantació innecessària de marcapassos.

**Conclusions:**

Un trastorn del ritme, especialment bradiarítmies, és la causa subjacent més comuna del síncope inexplicat en els grups estudiats. El risc arrítmic global varia en funció de les característiques del pacient. Un enfocament diagnòstic amb un protocol d'investigació sistemàtic no només és útil per identificar l'etiologia sinó també per guiar el tractament i evitar intervencions innecessàries. Els resultats destaquen la importància d'avaluar adequadament els pacients de risc elevat per millorar el seu pronòstic.

# SCIENTIFIC ARTICLES OF THE THESIS

The present thesis is presented in the form of a compendium of articles. It consists of 3 parts, corresponding to three subprojects, and 4 articles. Each article addresses a specific aspect related to the objectives and subprojects established in the thesis.

**PART 1:** Etiology and prognosis of syncope in patients with severe aortic stenosis.

Article 1: **Francisco-Pascual J**, Rodenas E, Belahnech Y, Rivas-Gándara N, Pérez-Rodon J, Santos-Ortega A, Benito B, Roca-Luque I, Cossio-Gil Y, Serra Garcia V, Llerena-Butron S, Rodríguez-García J, Moya-Mitjans A, García-Dorado D, Ferreira-González I. Syncope in Patients With Severe Aortic Stenosis: More Than Just an Obstruction Issue. Can J Cardiol. 2021 Feb;37(2):284-291. doi: 10.1016/j.cjca.2020.04.047. Epub 2020 May 18. Erratum in: Can J Cardiol. 2022 Dec;38(12):1979. PMID: 32439473.

*Impact factor at the time of article acceptance: 5.2. Knowledge Area: Cardiology and Cardiovascular Medicine. Quartile: Q1.*

**PART 2:** Etiology and prognosis of syncope in patients with mid-range left ventricular disfunction.

Article 2: **Francisco-Pascual J**, Rodenas-Alesina E, Rivas-Gándara N, Belahnech Y, Olivella San Emeterio A, Pérez-Rodón J, Benito B, Santos-Ortega A, Moya-Mitjans À, Casas G, Cantalapiedra-Romero J, Maldonado J, Ferreira-González I. Etiology and prognosis of patients with unexplained syncope and mid-range left ventricular dysfunction. Heart Rhythm. 2021 Apr;18(4):597-604. doi: 10.1016/j.hrthm.2020.12.009. Epub 2020 Dec 14. Erratum in: Heart Rhythm. 2022 Dec;19(12):2132. PMID: 33326869.

*Impact factor at the time of article acceptance: 6.3. Knowledge Area: Cardiology and Cardiovascular Medicine. Quartile: Q1.*

**PART 3:** Risk of arrhythmic syncope in specific populations with bundle branch block

Article 3: **Francisco-Pascual J**, Rivas-Gándara N, Bach-Oller M, Badia-Molins C, Maymi-Ballesteros M, Benito B, Pérez-Rodon J, Santos-Ortega A, Sambola-Ayala A, Roca-Luque I, Cantalapiedra-Romero J, Rodríguez-Silva J, Pascual-González G, Moya-Mitjans À, Ferreira-González I. Sex-Related Differences in Patients With Unexplained Syncope and Bundle Branch Block: Lower Risk of AV Block and Lesser Need for Cardiac Pacing in Women. Front Cardiovasc Med. 2022 Feb 25;9:838473. doi: 10.3389/fcvm.2022.838473. PMID: 35282384; PMCID: PMC8914040.

*Impact factor at the time of article acceptance: 6.05. Knowledge Area: Cardiology and Cardiovascular Medicine. Quartile: Q1.*

Article 4: **Francisco-Pascual J**, Rivas-Gándara N, Maymi-Ballesteros M, Badia-Molins C, Bach-Oller M, Benito B, Pérez-Rodón J, Santos-Ortega A, Roca-Luque I, Rodríguez-Silva J, Jordán-Marchite P, Moya-Mitjans À, Ferreira-González I. Arrhythmic risk in single or recurrent episodes of unexplained syncope with complete bundle branch block. Rev Esp Cardiol (Engl Ed). 2022 Dec 17:S1885-5857(22)00323-1. English, Spanish. doi: 10.1016/j.rec.2022.11.009. Epub ahead of print. PMID: 36539183.

*Impact factor at the time of article acceptance: 7,05. Knowledge Area: Cardiology and Cardiovascular Medicine. Quartile: Q1.*

Furthermore, additional review article and an editorial of article 4, which are relevant to the topic of this thesis and were published during the preparation of the thesis, are included in the appendix, separate from the main compilation of articles.

- **Francisco Pascual J**, Jordan Marchite P, Rodríguez Silva J, Rivas Gándara N. Arrhythmic syncope: From diagnosis to management. World J Cardiol. 2023 Apr 26;15(4):119-141. doi: 10.4330/wjc.v15.i4.119. PMID: 37124975; PMCID: PMC10130893.
- Pérez-Castellano N, Calvo Cuervo D, Pérez-Villacastín J. Syncope and bundle branch block: a single study with several take-home messages. Rev Esp Cardiol (Engl Ed). 2023 Mar 23:S1885-5857(23)00081-6. English, Spanish. doi: 10.1016/j.rec.2023.01.014. Epub ahead of print. PMID: 36963613.

# 1. INTRODUCTION

## 1.1. General Concepts

### 1.1.1. Definitions and causes

Syncope is a total loss of consciousness (T-LOC) secondary to cerebral hypoperfusion, characterized by rapid onset, short duration, and complete spontaneous recovery[1]. It must be differentiated from other T-LOC that do not meet these characteristics, such as T-LOC of traumatic origin, some types of epilepsy or certain psychiatric disorders.

It is important to note that syncope is a symptom that encompasses a diverse range of pathologies, spanning from benign causes to conditions associated with a high risk of sudden death. Therefore, it should not be considered a definitive diagnosis. Stratifying the risk and attempting to determine the underlying cause are of great importance.

The term "cardiac syncope" is used to describe episodes where the cerebral hypoperfusion is directly attributed to a cardiac disorder, while "arrhythmic syncope" specifically refers to cardiac syncope caused by rhythm disorders. Arrhythmias, in fact, are the most prevalent cause of cardiac syncope (*Table 1*). Both bradyarrhythmias and tachyarrhythmias can result in a sudden reduction in cardiac output, leading to syncope. Non-arrhythmic causes of cardiac syncope are typically associated with structural heart diseases (SHD) that involve the obstruction of blood outflow and/or inflow. These obstructions can limit the ability to increase cardiac output during exercise, rendering this insufficient to maintain the circulation. Severe aortic stenosis (SAS), hypertrophic cardiomyopathy (HCM), mitral stenosis, atrial myxoma or severe pulmonary hypertension are some examples of conditions that can cause cardiac syncope via this mechanism. Furthermore, myocardial ischemia and acute ischemic syndromes may also precipitate syncope through multiple mechanisms. It is important to highlight that most of these heart diseases can also be associated with arrhythmias or reflex syncope, and therefore it is often challenging to determine the main cause of syncope in structural cardiac syncope[1–5]. In other words, the presence of SHD with obstruction alone does not necessarily indicate that syncope is caused by this mechanism. In many cases, it is important to consider and rule out other potential causes, particularly arrhythmic ones.

**Table 1: Main cardiac causes of syncope**

| CARDIAC SYNCOPE |
|---|
| **ARRHYTHMIC CAUSES** |
| • Bradyarrhythmia<br>  • Sick Sinus Syndrome / Sinus node disfunction<br>  • Atrio-ventricular Block<br>• Tachyarrhythmia<br>  • Supraventricular Tachycardia (AVNRT, AVRT, AT, fast AF...)<br>  • Ventricular arrhythmias<br>  Related to Structural Heart Disease<br>  Channelopathies and inherited arrhythmia syndromes |
| **NON-ARRHYTHMIC CAUSES** |
| • Mechanical causes<br>  • Valvulopathies (Aortic Stenosis, Mitral stenosis...)<br>  • HCM<br>  • Atrial Myxoma<br>  • Pulmonary emboli<br>  • Tamponade<br>  • Severe Pulmonary hypertension |
| **ACUTE CORONARY SYNDROME** |

*AT: atrial tachycardia; AF Atrial fibrillation; AVNRT: atrioventricular nodal reentrant tachycardia; AVRT: atrioventricular reentrant tachycardia; HCM: hypertrophic cardiomyopathy.*

### 1.1.2. Epidemiology

It is estimated that almost one in two people will suffer at least one syncopal episode in their lifetime[1,6]. It is a front-line health problem with a high impact on the health system, even though it is known that only a small proportion of patients with syncope seek medical attention. An epidemiological study carried out in the United States showed that the prevalence of patients with syncope in the community requiring medical attention is 9.5 per 100 inhabitants, and that 1 in 10 required hospital admission[7].

The incidence of the first syncopal episode is distributed with a bimodal curve, with a first peak in youth (between 10-30 years of age) and a second peak over 65 years of age. Cardiac syncope is the third most common cause of syncope after reflex and orthostatic hypotension (OH) [1,8,9]. In the emergency department (ED), cardiac syncope accounts for 5–21% of syncope. In the Framingham cohort, the prevalence of syncope and long-term prognosis were analyzed[10]. The incidence of a first report of syncope was 6.2 per 1000 person-years. Reflex or vasovagal syncope is the most common cause in the general population. In the Framingham cohort it

represented 21% of the cases, while cardiac syncope made up only 9.5%[10]. It is remarkable that the prevalence of cardiac syncope increases with advancing age[1,9–11]. Cardiac syncope causes less than 1% of syncope in youth (<40 years)[12] and up to one third in those over 60 years of age[10,12].

### 1.1.3. Prognosis

The prognosis of syncope is mostly related to the underlying cause and the presence of SHD. While reflex syncope has an excellent prognosis in terms of survival, cardiac syncope is associated with an increased risk of mortality, especially if it is not identified and treated properly. Patients with reflex syncope have similar survival to patients without syncope[10], with a mortality rate between 4%-12% after 1 year (depending on the patient's age and comorbidities) [10,13–15]. By contrast, the 1-year mortality rate for cardiac syncope rises to 20-30%[10,13–15]. In the Framingham cohort, cardiac syncope was associated with a 2-fold increase in the risk of death compared with those without a history of syncope, with an approximately 50% 5-year survival[10]. In this study, patients with syncope of unknown origin also had an increased risk of all-cause mortality compared with the general population (HR 1.32, 95% CI 1.09-1.60). This may be due to the fact that there are potentially serious causes for syncope left untreated due to a lack of diagnosis.

Importantly, in patients with syncope of unknown origin, the mere presence of structural cardiac abnormalities or the evidence of a conduction system disorder is associated with a poor prognosis, increasing the risk of death by a factor of more than five[1,9,16–19]. On the other hand, a structurally normal heart with a normal electrocardiogram (ECG) is usually associated with a benign etiology for syncope and a favorable prognosis[1,20–22].

## 1.2. Diagnostic Approach and Test

### 1.2.1. Initial evaluation, clinical history, physical examination, and ECG:

T-LOC is a relatively common cause of presentation to the ED, and half of these episodes can be attributed to syncope [23]. However, it is important to distinguish it from other causes of T-LOC, in order to prevent unnecessary investigations in patients with benign causes and to accurately identify and treat those with cardiac syncope, which can have serious consequences. Epilepsy is probably the most common condition that can be mistaken for syncope. This confusion is an important phenomenon leading to misdiagnosis, with rates ranging from 6-67%[24]. Such incorrect diagnoses significantly contribute to the number of patients with an uncertain epilepsy diagnosis, as well as those labeled as having drug-resistant epilepsy. Syncope can be accompanied by urinary incontinence and/or muscular contractions that may resemble

epileptic seizures, creating challenges in distinguishing between the two diagnoses. While in epilepsy, muscular movements are generalized and occur from the onset of T-LOC and continue for a few minutes, syncope can also involve muscular contractions. However, in syncope, these contractions typically occur a few seconds after the collapse, are often pleomorphic, and last only a brief duration. Certain clinical findings have been proposed to aid in distinguishing between seizures and convulsive syncope. Tongue biting and confusion on awakening are the most useful in predicting an epileptic origin [25]. In addition, clinical clues that should raise the suspicion for psychogenic pseudosyncope include prolonged duration, eye closure during the episode, unusual triggers, no recognizable prodromes and a high frequency of attacks [26].

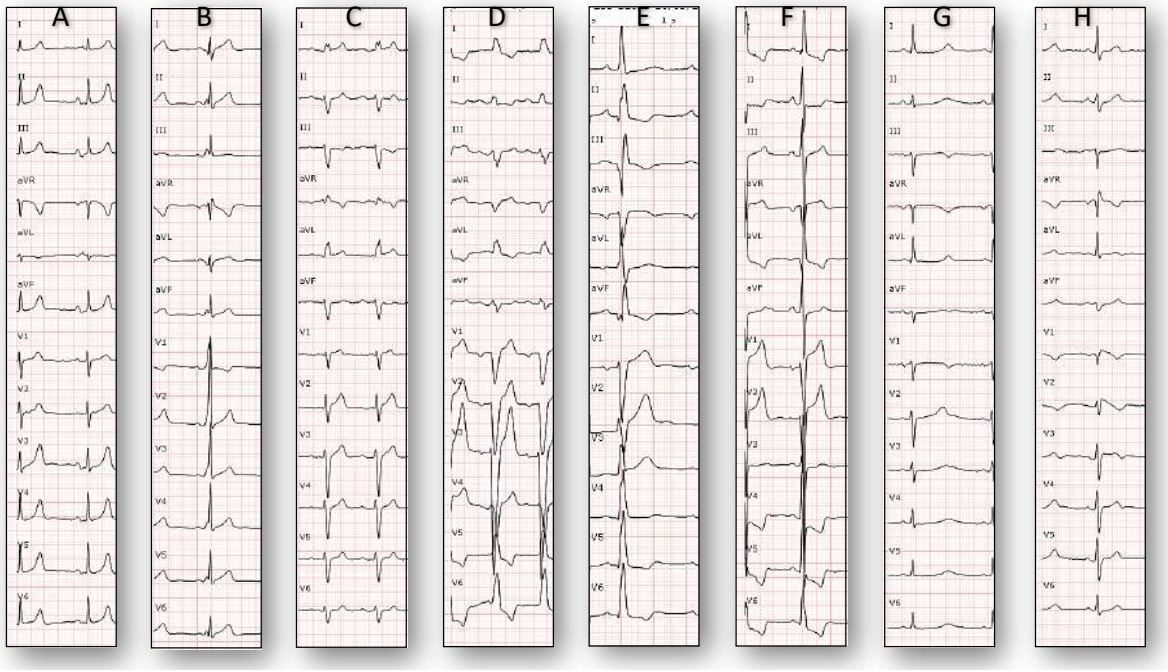
Another common source of confusion in the ED is represented by falls, especially in the elderly population with non-witnessed T-LOC. On the one hand, elderly people with cognitive impairment and muscular weakness can present with falls as a manifestation of another illness, such as infections, or metabolic disorders [27]. On the other hand, these populations are usually treated with medications which can lower blood pressure (BP) and heart rate (HR) and tend to be dehydrated due to reduced water consumption. This combination of factors can promote orthostatic syncope. Additionally, in the elderly, there is a high prevalence of sinus node dysfunction (SND), conduction disturbances and SHD, putting these patients at high risk of presenting with cardiac syncope[2]. For all these reasons, current guidelines recommend that repeated falls in elderly people without a reasonable explanation should be approached like unexplained syncope[1].

Once the syncope diagnosis has been established, special attention should be paid to determining the underlying cause. Syncope can be caused by three main different etiologies: reflex mechanism (also known as neurally mediated syncope), OH or cardiac syncope, which can be due to arrythmia or SHD. The diagnostic approach should prioritize the detection of potential cardiac syncope, as it may be a clinical manifestation of an underlying primary cardiac disease with a high risk of adverse events.

The initial evaluation of any patient presenting with syncope should incorporate three fundamental elements: a thorough history taking regarding the current and prior episodes (including accounts from eyewitnesses), a physical examination, and an ECG. Among these, the clinical history is likely the most crucial component, with a focus on the patient's past medical history, particularly previous cardiac conditions, as well as symptoms related to the episode. Syncope during exertion or in a supine position, accompanied by chest pain or palpitations, have been described as high-risk factors, and should raise the suspicion of cardiac syncope [28,29]. In addition, a family history of sudden cardiac death (SCD) at a young age or personal history of SHD or coronary artery disease (CAD) have been considered high-risk factors. Physical examination does not usually show relevant findings, but it could reveal signs of heart failure

or a systolic murmur suggesting SHD. Performing an ECG is crucial, as it can reveal conduction disturbances, pathological Q waves, or repolarization abnormalities that may indicate an underlying cardiac disease. [15,30–32] (*Figure 1*) It is important to mention that every patient with syncope should have an ECG even if there is clear evidence that is a reflex syncope, since there are some channelopathies such as long QT syndrome that can present with ventricular arrhythmias after emotional stimulus that can be confused with reflex syncope. Additionally, it has been described that patients with Brugada syndrome (BrS) are more prone to vasovagal syncope [33].

**Figure 1: Examples of pathological ECG that should lead to suspicion of an arrhythmic origin of the syncope**




*Suspected supraventricular tachycardia:* **A:** Bayes Syndrome (biphasic p wave in inferior leads compatible with interatrial block, which is related with atrial arrhythmias); **B:** Preexcitation syndrome. *Suspected AV block*: **C:** long PR interval and left anterior fascicular hemiblock. **D:** Left bundle branch block. Suspected VT: **E:** Inferior necrosis (Q waves); **F:** Hypertrophic cardiomyopathy. *Suspected polymorphic VT*: **G:** Long QT syndrome; **H:** Brugada syndrome.

There are several scores developed for risk stratification according to clinical and ECG findings[34]. However, some of them have been tested with external validation cohorts showing poor sensitivity and specificity for detecting cardiac syncope, and they perform no better than clinician judgement at predicting short-term serious outcomes. Therefore, current guidelines do not recommend using them alone to make decisions in the ED. Most items included on these scales are those suggesting cardiac syncope, such as ECG abnormalities or signs or symptoms of SHD.

### 1.2.2. Carotid sinus massage

Carotid sinus massage (CSM) consists of applying external pressure to the area of the neck where the carotid sinus is located and is indicated in patients over 40 with syncope. According to current clinical guidelines, carotid sinus hypersensitivity is defined by a sinus pause longer than 3 seconds or a drop in systolic blood pressure (SBP) higher than 50 mmHg[1,9]. However, this condition is very common among older individuals with cardiovascular disease, even in the absence of syncope. To avoid misdiagnoses, it has been proposed that the diagnosis of carotid sinus syndrome (CSS) requires reproduction of patient's symptoms and a sinus pause longer than 6 seconds or more, or a drop in mean arterial pressure of 60 mmHg or more [35]. Patients fulfilling these criteria have been shown to have recurrent long pauses on monitoring and to respond well to cardiac pacing [36,37]. The worst complication of CSM is stroke, which is extremely uncommon.

### 1.2.3. Orthostatic challenge

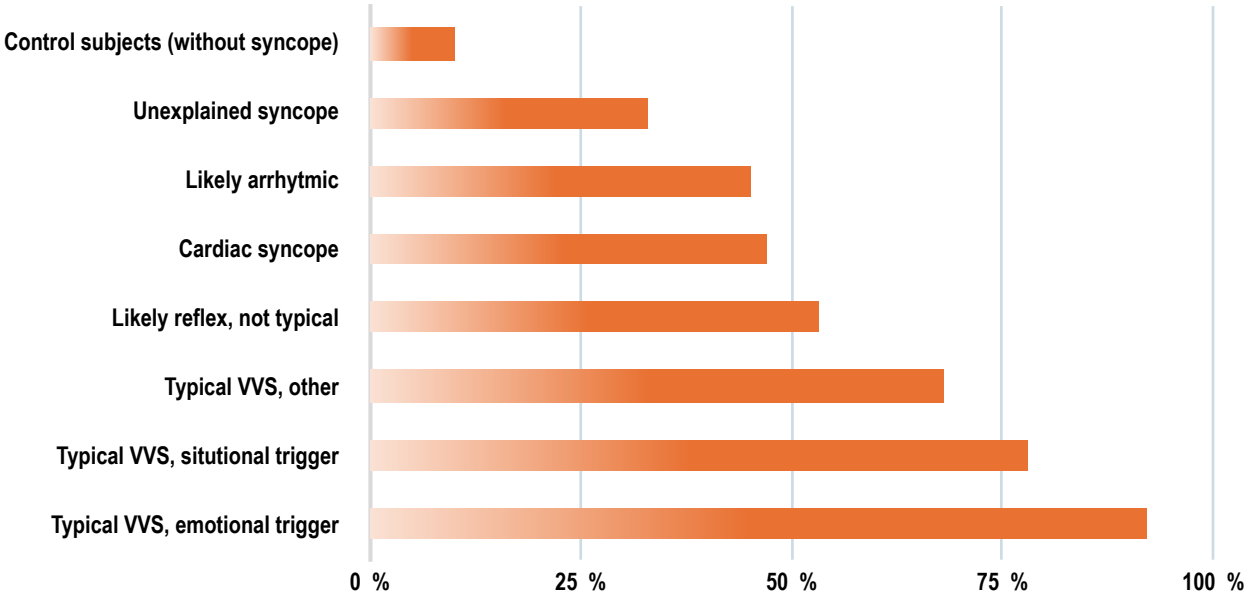
Orthostatic challenge consists of measuring HR and BP, changes between supine and upright positions. It is recommended to measure them during the first three minutes, but it can be extended to the first ten minutes if there is high suspicion of OH, since retarded responses have been described[38]. OH is defined by a drop of more than 20 mmHg in SBP, or a drop of more than 10 mmHg of diastolic blood pressure (DBP), or if SBP becomes lower than 90 mmHg, always accompanied by symptoms[39]. OH is very common among elderly people, especially in patients taking anti-hypertensive medications and/or with autonomous nervous system diseases like Parkinson disease or diabetes, and it represents an important cause of syncope in this population [2,40].

### 1.2.4. Tilt testing

Tilt testing is recommended in patients with suspected reflex syncope or autonomic failure, including delayed forms of OH or postural orthostatic tachycardia syndrome (POTS). The most frequently used protocol is the so called "Italian protocol", which includes a twenty-minute stabilization phase, followed by administration of sublingual nitroglycerin [41]. Recently, a modified shorter Italian protocol has been proposed, demonstrating similar diagnostic accuracy[42]. t is particularly useful in patients with true reflex syncope, as studies have shown that a positive cardioinhibitory response is highly predictive of spontaneous syncope with asystole [43]. However, in patients with SHD or a high risk of arrhythmias, the results of the tilt-table test should be interpreted with extreme caution. This is because it can also yield positive results in a significant percentage of patients with cardiac syncope, thereby providing limited diagnostic value in these populations[44–46] (*Figure 2*). Therefore, routine performance of tilt-table

testing is not recommended in high risk patients.[1] Tilt test has also been tested to evaluate treatment effectiveness, showing little value in this aspect. Finally, in recent years it has been demonstrated that cardiac denervation of parasympathetic ganglia can be highly effective in reducing cardioinhibitory reflex syncope, a technique known as cardioneuroablation[47]. Tilt test might play a crucial role in detecting suitable patients for this promising procedure [48].

**Figure 2: Rates of tilt testing positivity in different clinical conditions [1]**




*VVS: Vasovagal syncope.*

### 1.2.5. Electrophysiological study

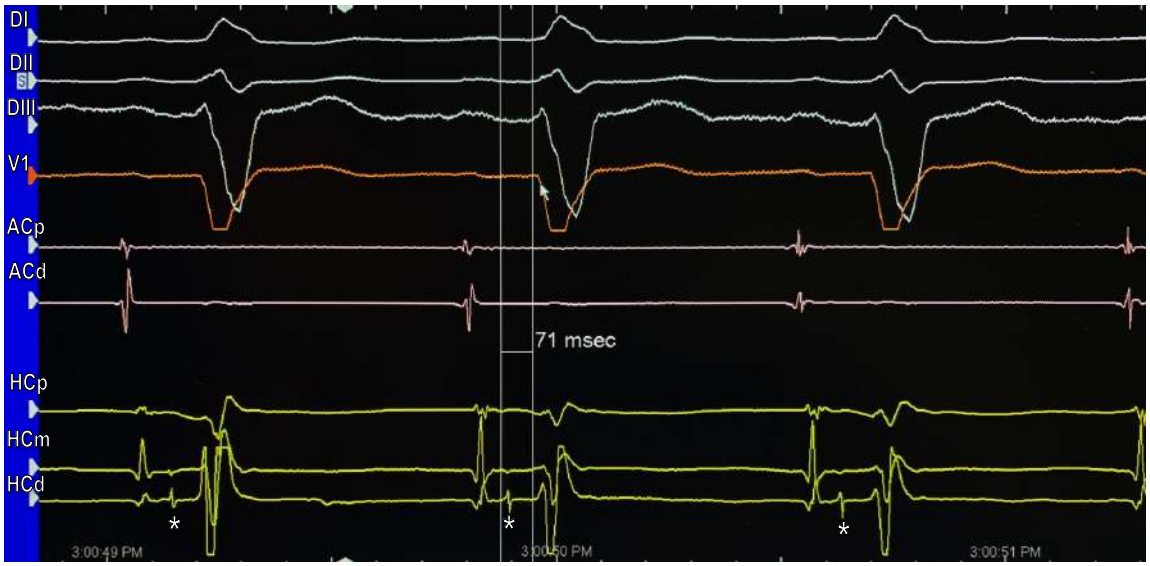
According to current European Guidelines[1], electrophysiological study (EPS) is indicated in patients with syncope and bifascicular block (BFB) or previous myocardial infarction or other scar-related conditions, when the etiology remains unexplained after non-invasive evaluation. It could also be considered when syncope is preceded by palpitations or in patients with sinus bradycardia, when the rest of the study has been negative. However, in patients with normal ECG and no SHD, EPS is of poor diagnostic value, and other options like home monitoring are more appropriate. Additionally, a positive EPS is strongly predictive of the origin of the previous syncope, but a negative result cannot exclude arrhythmic events in the future, so it has a low negative predictive value [49–51].

Sick sinus syndrome (SSS) is a heterogeneous disease characterized by abnormal functioning of the sinus node. It encompasses various types of bradycardia, including sinus pauses and junctional rhythm. These conditions are relatively common in elderly people, and it is crucial to correlate the bradycardia episodes with the patient's symptoms. A sinus node recovery time

(SNRT) longer than 1600 ms is considered abnormal (or corrected SNRT longer than 525 ms) and has been correlated with SSS [52], but its prognostic value remains unclear. Furthermore, there are few data supporting the benefit of pacing in patients with an abnormal SNRT.

Patients with intraventricular conduction disturbances like BFB or nonspecific conduction disturbance with a QRS greater than 120 ms are at higher risk of arrhythmic events due to His-Purkinje system disease, and in this population paroxysmal atrioventricular block (AVB) is the most common cause of syncope [51,53,54]. In these patients with syncope suspected to be related to bradycardia, an HV interval longer than 70 ms or the development of second or third-degree AVB during incremental atrial pacing or pharmacological stress, identifies a group with a high risk of developing AVB in the future [55], and pacing is recommended. In addition, some studies have evaluated the relation between ECG conduction disturbance and the results of EPS, showing that PR interval prolongation and/or BFB patterns make a positive result in EPS more likely, rather than a right bundle branch (RBBB) pattern alone[56]. (*Figure 3*)

**Figure 3: Electrophysiological study of a patient with syncope and LBBB**




Surface electrocardiogram (DI, DII, DIII, V1) (top) and intracardiac electrograms at 100 mm/seg of an EPS to evaluate infra-Hisian conduction. A diagnostic catheter was placed in the right atrium (Pink register: ACp and Acd) and in the His bundle zone (Yellow register: HCp, HCm and HCd).

** indicates the His deflection. HV interval, from the onset of the His deflection to the onset of the QRS, is measured with the caliper (71 milliseconds in this case).*

Another important part of the EPS in the syncope work-up is programmed ventricular stimulation (PVS). In patients with previous myocardial infarction and syncope, the induction of monomorphic sustained ventricular tachycardia (MSVT) is strongly predictive of the cause of syncope and should be managed as spontaneous MSVT [57,58]. In contrast, the induction of polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF) is considered a less

specific finding, especially with aggressive stimulation protocols[59]. However, induction of PVT or VF may play a role in risk stratification of specific populations such as patients with repaired Tetralogy of Fallot (TOF) [19,60–62] or BrS [63,64].

### 1.2.6. Electrocardiographic cardiac monitoring

ECG cardiac monitoring is one of the cornerstones of the etiological diagnosis of arrhythmic syncope. In addition, there are several areas of interest other than unexplained syncope in which monitoring devices have been investigated[60,65–78]. The objective of ECG monitoring is to establish a correlation between the patient's symptoms and the electrocardiographic recordings in order to reach a diagnosis. For this reason, the diagnostic yield of ECG monitoring is primarily related to the duration of monitoring and the frequency of symptoms. Since syncope episodes are often infrequent, long-term monitoring devices are typically necessary to increase the chances of recording a syncopal event. Additionally, the identification of significant asymptomatic arrhythmias (such as advanced AVB) can also be important for diagnosis. Therefore, as a general guideline, ECG monitoring is recommended when there is a high pre-test probability of detecting an arrhythmia associated with syncope, following appropriate risk stratification. The choice of monitoring modality depends on the frequency of the events. In recent years, ECG monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-hour Holter monitor. This evolution of the ECG recording systems include, among other aspects, smaller devices, greater memory capacity for long-term monitoring, better quality of records or remote monitoring capacity[76]. (*Table 2*)

The main current ECG monitoring devices available are the following:

- **In-Hospital telemetry:** In-hospital monitoring should be mandatory in patients with high-risk clinical features, especially if the monitoring is initiated promptly after syncope. A recent study that evaluates the optimal ECG-monitoring duration of ED patients with syncope found that a serious underlying arrhythmia was often identified within the first 2 hours of ED arrival for low-risk patients and within 6 hours for medium- and high-risk patients[79]. The diagnostic yield of ECG monitoring varies from 2–20% depending on the patients' characteristics[1,9,75,79–81].
- **24/48-hour Holter monitoring:** Despite probably being the most frequently used device, the diagnostic yield is as low as 1-2% in unselected patients due to its short monitoring time[75,76]. Even the newest devices with a longer recording capacity (7-14 days) offer a very limited diagnostic yield. In our opinion, at the present time, the 24/48-hour Holter should only be considered in patients with daily or very frequent

symptoms[75,76]. In different circumstances, other modalities offer not only a greater diagnostic yield, but also better cost efficiency per diagnosis.

- **Loop recorders:** These devices allow for longer-term monitoring as they do not store continuous recordings. Although they continuously monitor the ECG, they only store a few minutes of data, which are subsequently overwritten with newer recordings. However, when the device is triggered (either manually or through an automatic arrhythmia detection algorithm), it saves the recording from a few minutes before the start of the event until its end in a separate part of the memory. These recorded episodes are protected from being overwritten and are available for review. This mechanism ensures that several minutes leading up to the activation are stored in the device memory, increasing the likelihood of capturing the ECG trace during the syncope episode. Within this category, we have differentiated between external and implantable devices:

    - *External loop recorders (ELR):* The device uses cutaneous electrodes to record, like the 24hr Holter monitor. The patients themselves position the electrodes daily. Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3 - 4 weeks, although there are reports of more prolonged periods of time[76,82]). For this reason, in the setting of syncope, the diagnostic yield is no greater than 10%. They are especially useful for the investigation of symptoms that occur every two or three weeks. Significantly, it has been found in various studies that early recorder use increased the likelihood of diagnostic events during external ECG monitoring[79,83].

    - *Implantable loop recorders (ILR):* These are small devices which are implanted subcutaneously, usually in the left parasternal region. They have the disadvantage of being minimally invasive, since the latest models have been made significantly smaller. However, these devices allow for a more prolonged continuous monitoring of up to 3 to 4 years, so they are especially useful in patients with syncope. Numerous studies have evaluated the diagnostic value and the usefulness of ILR for the work-up and the diagnostic yield increases up to 30-50%[5,51,65,68,84–88]. In a meta-analysis of five randomized controlled trials, it was found that initial implantation of an ILR in the work-up provided a 3.7-fold [95% confidence interval (CI) 2.7–5.0] increase in the relative probability of a diagnosis compared with the conventional strategy[1,77,89,90] . Different studies have also demonstrated that ILR was more cost-effective than the conventional strategy[75,87,89–91]

- **Skin patches:** They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads that allow for a continuous ECG recording for 7-30 days of monitoring. Diagnostic yield and limitations are similar to ELR.

**Table 2: Main advantages, limitations, and indications of the most commonly used devices for ECG cardiac monitoring in patients with syncope**

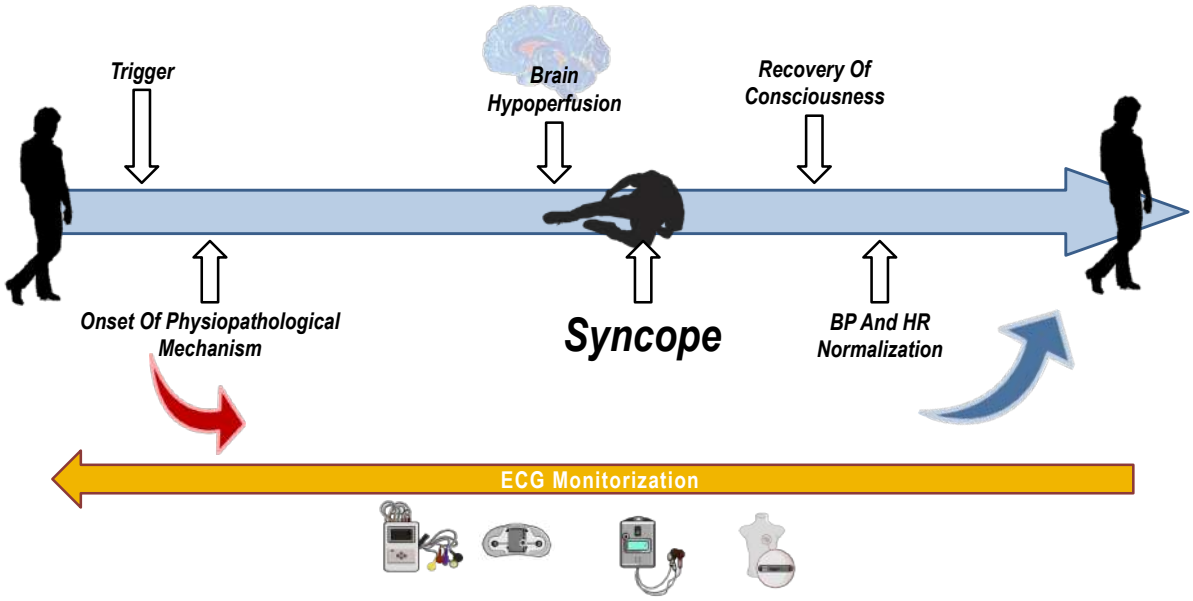
| | ADVANTAGES | DISADVANTAGES | MAIN INDICATIONS |
|---|---|---|---|
|  **24-HR HOLTER** | • Continuous recording<br>• 12 leads with good correlation with surface ECG<br>• Low economic cost per study | • Discomfort for the patient<br>• Artifacts<br>• Maximum recording of 24-48 hrs (low diagnostic yield)<br>• High economic cost per diagnosis | • Very frequent (daily) symptoms<br>• In-Hospital monitoring (if ECG-Telemetry not available) |
|  **SKIN PATCHES** | • Continuous recording of 7-14 days<br>• Good tolerability for patients | • Single-use and greater economic cost<br>• Only one lead*<br>• Low diagnostic yield | • Frequent (weekly) symptoms |
|  **EXTERNAL LOOP RECORDERS** | • Loop recording (includes beginning and end of arrhythmic event)<br>• 4 weeks' monitoring<br>• Low economic cost per study | • Patient discomfort<br>• Requires education from healthcare professional on how to correctly place the electrodes<br>• Relatively low diagnostic yield | • Frequent (weekly-monthly) symptoms |
|  **IMPLANTABLE LOOP RECORDERS** | • Loop recording<br>• Up to 3-year monitoring (good diagnostic yield)<br>• Patient does not have to do anything<br>• Remote monitoring | • Invasiveness and associated complications (infection, bleeding, etc.)<br>• Individual economic cost<br>• Single lead | • Infrequent symptoms<br>• Most useful in syncope |

** There are devices with more leads.*

It should be noted that some new wearable devices like smart-watches or other prospective intermittent ECG event recorders, which are quite popular nowadays, are generally not useful for syncope workup. These devices start recording only when the patient activates them. They have the limitation of not allowing for the recording of the onset of the episodes, which is often

important for diagnosis. Furthermore, if the patient activates the device after recovering from the syncopal episode, in most cases, the possible rhythm disorder would have resolved. (*Figure 4*)

**Figure 4: ECG monitoring of syncope mechanism**




Frequently, patients activate the ECG monitoring device after recovering from syncopal episodes. Only devices that allow retrospective monitoring from the time of activation are useful in syncope patients to record possible rhythm disorders before and during the syncope.

### 1.2.7. Other tests

Autonomic function tests like the Valsalva maneuver or deep breathing test can be considered to diagnose autonomic disfunction, but there is weak evidence that these tests may be useful in patients with syncope. Echocardiography should be performed in all patients with suspected valvular or SHD, as it can detect some conditions that could present with cardiac obstructive syncope (i.e. aortic stenosis (AoS) or cardiac tamponade). Exercise testing is especially useful in patients that have experienced syncope during or shortly after exertion. The main purpose of these tests is to rule out ventricular arrythmias related to CAD or exercise-induced advanced AVB, which is usually located distally to the AV node. Cardiac biomarkers such as high sensitivity troponin and natriuretic peptides can be elevated in patients with syncope and have been associated with worse outcomes in some case series [92] [93]. However, such determinations are highly nonspecific and seldom provide a definitive diagnosis. Additionally, they may indicate serious illness unrelated to myocardial ischemia or heart failure. Therefore, it remains uncertain whether these determinations should be performed as part of routine practice. [94]

## 1.3. Risk Stratification

Cardiac syncope is a life-threatening condition. By consequence, the main goal of risk stratification is to identify those low-risk patients with benign causes that can be discharged home and only require medical education, from those high-risk patients with syncope probably related with cardiac arrythmias or SHD who require hospital admission for further investigation. This initial evaluation is especially necessary in the ED, where most patients with syncope first consult (*Table 3*).

**Table 3: High-risk features suggesting cardiac syncope**

| Past Medical History |
|---|
| Previous myocardial infarction |
| Previous cardiovascular condition (i.e., BrS, Hypertrophic cardiomyopathy, Long QT syndrome…) |
| **Syncopal Event** |
| Syncope during exertion or in supine position |
| Syncope associated with chest pain, palpitations, breathless or abdominal pain |
| **Physical Examination** |
| Signs of heart failure |
| Cardiac murmur suggesting specific condition (i.e., aortic stenosis) |
| Signs of shock |
| **Electrocardiogram** |
| Conduction disturbance (AV block, bundle branch block) |
| Pathological Q waves |
| Long QT interval |
| Pre-excitation syndrome |
| Negative T waves |

*BrS: Brugada syndrome. AV: Atrio-Ventricular.*

For this purpose, several risk scores have been developed. In 2016, the Canadian Syncope Risk Score[34] was published. They included 4030 patients who presented to EDs of three centers in Canada for syncope, and analyzed the occurrence of serious events including death, myocardial infarction, arrythmia, SHD, pulmonary embolism, serious bleeding, and procedural intervention within 30 days from admission. Finally, they included nine predictors: predisposition to vasovagal syncope, heart disease, any systolic pressure reading in the ED < 90 or > 180 mm Hg, troponin level above 99th percentile for the normal population, abnormal QRS axis (< −30° or > 100°), QRS duration longer than 130 ms, QTc interval longer than 480 ms, emergency department diagnosis of cardiac syncope and emergency department diagnosis of vasovagal

syncope. Those items suggesting reflex syncope conferred negative points, and those suggesting cardiac syncope conferred positive points. Each patient obtained a final score, with higher scores representing a greater risk of serious events (-3 – 0 points are considered low risk, while 4 – 11 points are considered high or very high risk, respectively). Recently, the same authors have validated this risk score in another large cohort of 3819 patients, showing great correlation. Setting a threshold score of –1 points, they achieved very good sensitivity (97,8%) but poor specificity (44,3%) for serious events [95]. In addition, another group of researchers have validated the same score in a cohort of 2283 patients from three continents also showing good correlation, and better performance when compared with another European risk score [96]. However, they also observed that a simplified model including only the clinical classification (vasovagal, cardiac, or other), also achieved a similar degree of discrimination regarding the primary outcome, showing that some of the predictors included may have a secondary role.

There are other scales that have been previously developed, such as the San Francisco Syncope Rule [97], or the EGSY score [29]. Both have showed similar results with good sensitivity but poor specificity. However, lack of reproducibility and remarkable heterogeneity in study design, variables, and outcome definitions of primary studies have prevented widespread use of these tools in clinical practice [98]. Moreover, recent studies have compared the EGSY score with clinical judgment, both alone and in combination with cardiac biomarkers. These studies have demonstrated that clinical judgment alone exhibits the highest diagnostic accuracy.[99] In summary, several risk scores have shown good sensitivity but low specificity in predicting short-term serious outcomes. However, they do not outperform clinical judgment, and therefore, they should not be relied upon in isolation for decision-making.

It is also worth mentioning that, apart from risk scores, some other tests such as EPS, cardiac magnetic resonance (CMR) or stress test may be useful for risk stratification in selected groups of patients, as is discussed above in other sections of this article.

## 1.4. Arrhythmic Syncope In Specific Populations

As previously mentioned, syncope could be the presenting symptom of an impending sudden cardiac arrest or can be related to more benign conditions such as neuro-mediated syncope or OH. Thus, it is important to correctly stratify the risk of each patient. For this reason, we need to understand the clinical scenario in which syncope takes place. Patients without overt SHD or conduction disturbances are at a lower risk of subsequent cardiac complications. Nonetheless, we must also consider certain inherited heart diseases, primarily of electrical nature, known as channelopathies, which can occur in the absence of SHD. A summary of the most significant heart conditions associated with a higher risk of ventricular arrhythmias and sudden cardiac arrest follows.

### 1.4.1. Structural heart disease

Syncope in patients with SHD poses a particular challenge for physicians. The presence of SHD has been identified as an independent predictor of cardiac syncope, exhibiting high sensitivity but low specificity [100]. However, the mere presence of cardiac abnormalities does not necessarily imply that the syncopal event is of a cardiac or arrhythmic nature with malignant implications[3,100].

SHD encompasses various factors that predispose individuals to both arrhythmic and non-arrhythmic syncope. For instance, the use of multiple medications commonly prescribed to these patients and autonomic dysfunction, which sometimes accompanies certain cardiomyopathies, are well-known causes of OH and may also trigger vasovagal reflexes[12,101]. On the other hand, the presence of myocardial scar and fibrosis is the most common mechanism underlying ventricular tachycardia (VT) development[19,102,103]. Additionally, it is associated with conduction abnormalities and, thus, AVB[104]. Moreover, in the presence of severe ventricular dysfunction or obstruction, some supraventricular arrhythmias such as atrial fibrillation (AF), which is typically considered a benign condition, can lead to a sudden collapse in patients.

In the subsequent sections, particular characteristics and management approaches for syncope in the most significant types of SHD are discussed.

#### 1.4.1.1. *Ischemic heart disease*

Patients with ischemic heart disease (IHD) are at a higher risk of ventricular arrhythmias. It is necessary to differentiate between 3 stages in the ischemic evolution:

- **Acute ongoing ischemia:** A patient suffering from an acute myocardial infarction might have VF and VT related to the ischemic myocardium[1,19,103,105]. The acute ischemia induces a dispersion of the repolarization that may produce polymorphic ventricular arrhythmias and VF in the acute setting. In the same way, some patients might present with monomorphic ventricular arrhythmias during acute myocardial infarction, in which a macro reentrant circuit involving the ischemic tissue is a more probable mechanism. This latter mechanism is much less frequent than the former[103].
- In the **subacute phase** of ischemia, comprising hours to days after the ischemic event, Purkinje related ectopia is a frequent mechanism for VF and acute cardiac arrest. The premature ventricular complexes are characterized by their very short coupling intervals and by the presence of a normal QT interval. It is believed that the ischemia induces an abnormal calcium release to the cytosol of Purkinje cells, which causes such early post depolarization[103].

- In the **chronic setting**, which accounts for most patients with syncope and IHD. A characteristic mechanism involves the occurrence of ventricular arrhythmias resulting from macro reentry within well-established ventricular scars.[1,19] The risk of ventricular arrhythmias is much higher among those patients with IHD with low ventricular ejection fraction[1,19,106].

Ventricular arrhythmias should be suspected in patients with syncope and IHD [1,6,9,107]. If the patient has an LVEF of < 35% despite optimal medical treatment (OMT), an implantable cardiac defibrillator (ICD) is indicated [18,19,108]. These patients have solid evidence of high arrhythmic risk independently of the invasive risk stratification, and an ICD implantation is strongly indicated even if the etiology of the syncope is treated subsequently. This recommendation is strongly supported by large randomized clinical trials (SCD-HeFT, MADIT-II)[109][110] and class 1A recommendation in the *2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death, The 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure* [111] and the 2019 Guidelines on Chronic Coronary Syndromes [112].

When the cause of the syncope remains unknown after an initial evaluation, and there is no apparent direct indication for ICD, an EPS with PVS should be performed. If MSVT are induced, the implantation of an ICD should be considered. The induction of polymorphic ventricular arrhythmias or VF has not been consistently related with ventricular arrhythmias or sudden cardiac arrest and no recommendation about ICD implantation can be made in this scenario. Despite the absence of solid evidence, the *2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* [19] recommends performing an EPS in patients with syncope and previous STEMI with a class IC recommendation. It is not clear if this recommendation is applicable to patients with history of coronary revascularization without infarction or in the absence of late gadolinium enhancement in the CMR and further studies are needed.

As we previously mentioned, the induction of a monomorphic VT in a patient with previous myocardial infarction presenting with syncope is an indication for an ICD implantation. On the other hand, the induction of VF has been traditionally considered as a non-specific result as these patients appear to have a similar prognosis as patients without any ventricular arrhythmia induction. Brugada et al. demonstrated that non-sustained PVT and VF are nonspecific responses to an aggressive stimulation protocol including three to four extra stimuli[113]. In 2002, Brodsky et al., presenting the results of the AVID trial, were not able to demonstrate that the induction of VF or fast VT (rate > 200 bpm) is related with death or ventricular arrhythmia recurrence (p 0.07) but the induction of slow VTs (HR < 200 bpm) was independently related with recurrences as monomorphic VT.[114] Mittal et al. also evaluated the

prognosis of ventricular arrhythmia induction in a cohort of 118 consecutive patients with CAD presenting with syncope. The mean left ventricular ejection fraction of their cohort was 42 +/- 13%. VF was the only arrhythmia induced in 20 patients (17% of the cohort). There was a survival rate of 89 and 81% at one and two years consecutively in the entire cohort and there were no differences between patients with VF induction or no induced arrhythmia (p 0.39)[59]. By contrast, Link MS et al. found contradictory results in their cohort where they followed 274 consecutive patients with CAD and syncope or presyncope. The risk of arrhythmia occurrence was evaluated at the time of presentation with syncope by an EPS. VF was induced in 23 patients (8%) and ventricular flutter (monomorphic tachycardia with CL < 230 ms) in 24 patients (9%). 41 patients (15% of the cohort) were inducible for monomorphic VTs. After a follow-up of 37+/-25 months, 34 patients had ventricular arrhythmias. Among them, 3 out of 23 patients in whom VF was induced in the initial EPS (13% of this group) and 7 out of 24 patients with induction of ventricular flutter (30% of this group). Considering these results together, the induction of VF/ventricular flutter was predictive of ventricular arrhythmias during follow-up (p <0.001 vs. non-inducible patients). [115] Nonetheless, the *2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death*[19] only has clear recommendations for the induction of sustained monomorphic VT. The induction of polymorphic VT, VF or non-sustained ventricular arrhythmias are considered non-specific responses and considering the absence of solid evidence, no specific recommendations are done.

Even though VT should be ruled out in patients with IHD, many other causes may be present in this set of patients[3,9,100,116]. In fact, VT is not the most common cause of syncope. Patients with IHD have some factors that predispose them to other causes. For example, they are often on different hypotensive drugs that predispose to OH or reflex syncope[2]. Also, some conduction disturbances are more frequent in patients with IHD[30,51,56]. In the presence of conduction disturbances on the ECG, advanced AV block is a common cause of syncope[53,56,117]. Importantly, if the EPS is negative, VT is unlikely to be the cause of syncope, with reflex and OH syncope being the most probable etiologies[3,100].

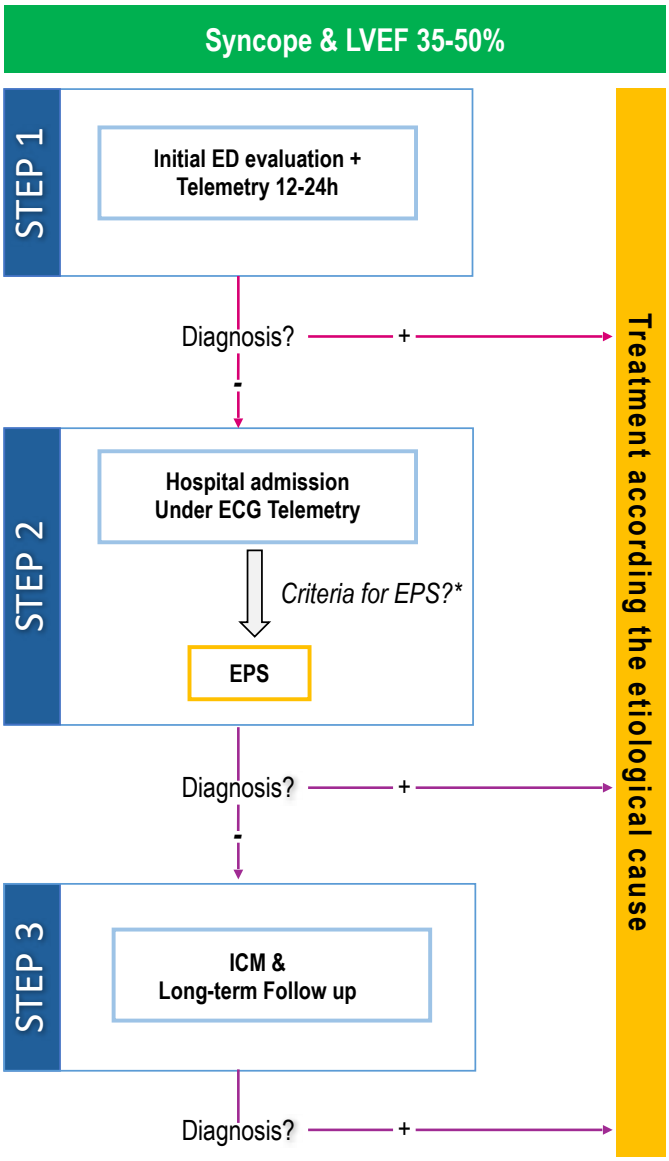
#### 1.4.1.2. *Mid-range left ventricular dysfunction*

Most of the clinical studies available in patients with ventricular dysfunction are focused on heart failure with reduced ejection fraction (LVEF <35-40%) or preserved ejection fraction (LVEF >50-55%). As a result, patients with heart failure with mid-range ejection fraction (LVEF 40-50%) are often excluded [118]. Consequently, there is limited information regarding the clinical characteristics of patients with mid-range ventricular dysfunction, and there is a scarcity of evidence on which to base therapy recommendations in general. This lack of data is particularly notable in cases of syncope.

Patients with left ventricular disfunction are at high risk of cardiac and arrhythmic syncope[6]. In observational studies, unexplained syncope in this population has been associated with an increased risk of sudden death[1,9,85,119,120] although the evidence for the benefit of an ICD is limited. In general, the direct implantation of an ICD is indicated in those patients who fulfil the primary prevention criteria (NYHA class II-III heart failure, with LVEF <35% on optimized pharmacological therapy). The evidence regarding the management of syncope in patients with mid-range LVEF is even more scant. Current *ESC syncope clinical practice guidelines*[1], which are similar to *ACC/AHA/HRS*[9] guidelines, suggest a work-up in line with general recommendations and state that the implantation of an ICD should be considered in patients with systolic dysfunction and unexplained syncope. The use of an implantable cardiac monitor (ICM) is an alternative that may be considered in patients with recurrent episodes (RSE). Newly published *ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death*[19] suggest a most conservative strategy based on risk stratification and ICM implantation in patients with no other direct indication for an ICD.

As discussed in previous sections, EPS serve as a valuable tool not only for diagnosing specific arrhythmic etiologies but also for risk stratification. The EPS has shown significant diagnostic value in patients with myocardial scar or conduction abnormalities. Additionally, ICM have been assessed in patients with SHD. Similar to the evaluation in other patient groups such as those with BBB, a stepwise systematic protocol incorporating EPS and ICM may prove beneficial in managing these patients (*Figure 5*). However, prior to the publication of the studies included in this thesis, there was a lack of evidence regarding their utility and safety.

**Figure 5: Proposed algorithm for the management of syncope in patients with mid-range left ventricular dysfunction**




* Criteria for EPS: 1) Presence of conduction disorder on baseline ECG (1st degree AV block or Mobitz 1 second degree block, complete right or left bundle branch block, left anterior or posterior hemiblock), 2) Evidence of myocardial scar 3) Palpitations prior to the syncopal episode.

*ED: emergency department; LVEF: Left ventricle ejection fraction; EPS: electrophysiological study; ICM: implantable cardiac monitor.*

### 1.4.1.3. *Hypertrophic Cardiomyopathy*

The hallmark of HCM is the abnormal increase of left ventricular wall thickness unrelated with abnormal loading conditions such as high BP, valvular heart diseases or congenital heart disease. At the histopathological level, HCM is characterized by an increase in the size of myocardial cells and disordered myocardial cell organization with interstitial fibrosis that may predispose patients to suffer from ventricular arrhythmias. HCM carries a mortality rate that

ranges from 1-2%. New data from cohorts of patients with ICDs suggest that the mortality rate might be even lower (about 0.8%) and that it is related with several risk factors summarized in the HCM-SCD score. [121] The 8 variables included in the risk score are: age, left ventricle (LV) wall thickness, left atrial size, LVOT gradient, NSVT, unexplained syncope, and family history of SCD.

In a recent systematic review and metanalysis, syncope was reported by 15.8% of HCM patients[122]. HCM patients may have different syncope etiologies such as: hypovolemia, conduction system disorders, sustained ventricular tachycardia, left ventricular outflow tract obstruction (LVOTO), and abnormal vascular reflexes, … [122–124]. After ruling out non-cardiogenic and neurally mediated causes, arrhythmic syncope is one of the more worrisome causes for syncope in those patients. Patients with unexplained syncope should be appropriately studied, including in most cases and exercise echocardiogram to rule out LVOTO on exertion. After an extensive evaluation of causes of syncope in those patients without clear diagnosis, an ILR should be implanted[1,124]. Routine tilt table testing in patients with HCM may be associated with an unacceptable number of false positives and its use should be limited to selected cases[124].

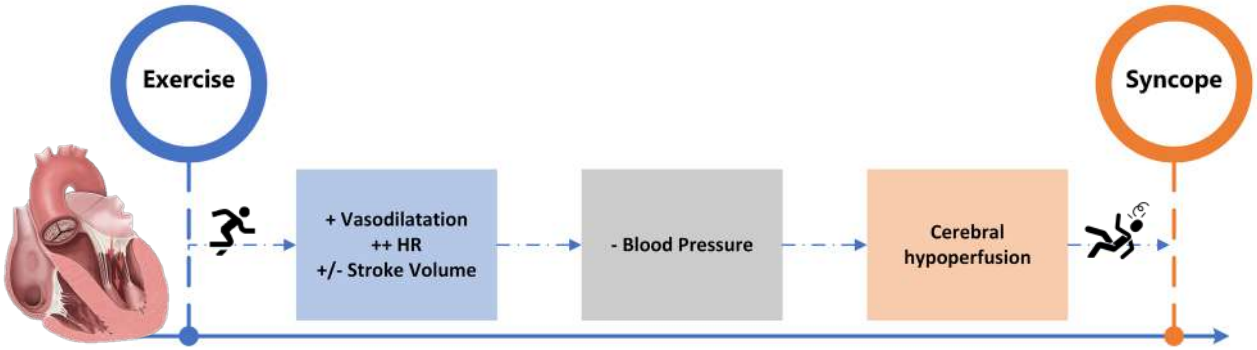
Syncope of unknown origin is included in the risk score with an independent hazard ratio of 2.05 (1.48, 2.82; p< 0.001). [121] Patients with intermediate- and low-risk clinical profiles should be evaluated for additional risk factors not included in the score, following 2022 ESC guidelines. [19] LV systolic dysfunction, apical aneurysm, > 15% of LV mass with late Gadolinium Enhancement on CMR, and several sarcomeric mutations have demonstrated a higher risk of ventricular arrhythmias in different studies and should be considered when evaluating the risk profile of a given patient[122,124]. The risk of ventricular arrhythmias is nonetheless dynamic and needs to be reassessed at every clinical visit. Those patients with syncope and a high-risk clinical profile (SCD HCM risk score > 6%) or intermediate risk and other risk factors should be considered for ICD implantation (IIa B level of recommendation) [123] and those with intermediate risk (SCD HCM risk score 4-6%) may be considered for ICD implantation (IIb B level of recommendation). [19]

#### 1.4.1.4. *Valvulopathies*

A hemodynamic origin of syncope should be suspected in patients with valvular heart disease, however other causes are possible[1,5,9,125–129]. The valvular heart disease with the highest risk of syncope is AoS[5,130,131]. Syncope is more frequent in severe stages of AS but can occur in patients with moderate severity when suffering from other hemodynamic disturbances.Classically, syncope in AS is associated with exertion[125,131]. In AS, the aortic valve becomes calcified and obstructs the forward flow of blood, leading to increased left ventricular afterload. This results in a relatively fixed cardiac output. Consequently, during physical exertion, the heart is unable to augment cardiac output adequately to meet the body's demands, leading to cerebral

hypoperfusion and syncope. This mechanism is exacerbated by systemic hypotension. During exercise, beta-2 receptors induce vasodilation in skeletal muscles, leading to a decrease in BP. Under normal circumstances, baroreceptors detect this change and compensate by increasing HR and stroke volume. However, AoS hinders patients from meeting this increased demand during exertion[130,132]. (*Figure 6*)

**Figure 6: Pathophysiology of exertional syncope in patients with SAS**



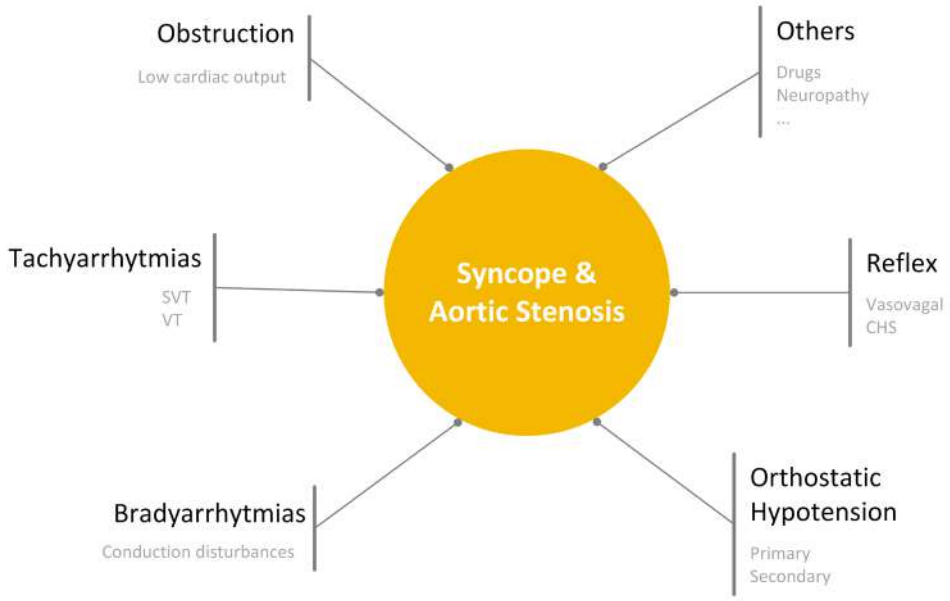

*HR: Heart rate.*

However, AS involves a complex cardiomyopathy, and several other mechanisms of syncope may be present. Valvular stenosis can result in pressure and volume overload of the left ventricle and atria, significantly increasing the risk of AF. The prevalence of AF in severe AS ranges from 16% to 51%[133]. In the setting of severe obstruction, a rapid episode of AF can trigger syncope. Additionally, other arrhythmias may occur. Studies analyzing ventricular arrhythmias in symptomatic SAS prior to transcatheter aortic valve implantation via 24-hour Holter monitoring have shown the presence of premature ventricular complexes in 48% of cases and non-sustained VT in 9-29% of cases[133–137].

The relationship between the aortic valve and the cardiac conduction system is of great importance. The aortic annulus is anatomically close to the His bundle and the left bundle branch. The progressive process of valve calcification and inflammation can directly affect the conduction system through calcification and indirectly through increased pressure afterload on the left ventricle. Ventricular conduction disorders are reported to be more prevalent in patients with AS compared to the general population[138–140].

Pharmacologic hypotension and an increased susceptibility to vasovagal reflexes are also common factors that can provoke syncope in patients with moderate and SAS[127,141,142]. (*Figure 7*)

**Figure 7: Multiple factors that can contribute to syncope in patients with SAS**




*SVT: Supraventricular tachycardia; VT: Ventricular tachycardia, CHS: Carotid hypersensitivity syndrome.*

There is limited literature on the relationship between resting syncope and AoS, which may lead to misinterpretation that the valve is the underlying cause of the syncope. If the true underlying cause is not addressed, the patient may continue to experience syncope even after the valve is repaired[131,143,144].

Importantly, syncope in the setting of a severe AS has been suggested as having prognostic implications. In a study published in 2019, these patients had a greater risk of mortality after aortic valve replacement in both the short-term (HR 2.27; 95% CI 1.04-4.95) and the long-term (HR 2.11 95% CI 1.39-3.21) compared with patients who did not have syncope[145]. Also, in a recent study by San Roman et al., patients with syncope at rest demonstrated a worse prognosis following aortic valve replacement (AVR) compared to patients with exertional syncope[143]. Although patients with syncope had somewhat different characteristics on echocardiography (smaller aortic valve area, smaller cardiac chambers, and lower ejection volumes), we believe that this rise in mortality was also partially due to the presence of other causes for the syncope such as underdiagnosed arrhythmias.

Furthermore, several studies have observed a high incidence of syncope and SCD after TAVR[72,73,78,137,146]. It is theorized that induced conduction system delays after TAVR may predispose patients to suffer from electrical reentry within the His-Purkinje system favoring a rare type of cardiac arrhythmia called Bundle-branch reentry in which the electrical impulse circulates between both branches of the conduction system with a slight delay often happening in the left bundle in the retrograde arm of the tachycardia[19]. This arrhythmia is very rapid and frequently compromises the patient hemodynamically producing syncope or sudden cardiac

arrest. The real incidence of this problem is unknown, but it needs to be kept in mind when evaluating a patient after a TAVR with some degree of conduction system delay.

Another significant but infrequent cause of syncope in patients with valvular heart disease is the presence of VF in patients with mitral valve prolapse which has been named "The malignant mitral valve prolapse syndrome". In a recent meta-analysis carried out by Nalliah C et al., they reported the population prevalence of MVP of 1.2% and the prevalence of MVP in SCD autopsies of 11.7%. Nonetheless an incidence of 0.14 SCD events per 100 patient-year in the community MVP cohort, deserves an in-depth investigation of other risk factors for ventricular arrhythmias such as the presence of myocardial fibrosis or frequent complex ventricular ectopy, as has been proposed. [147]

### 1.4.2. Conduction disturbances

In patients with syncope and conduction disturbances, the presence of bradyarrhythmia is always a concern, although other causes may also be present. For example, in a recent cohort of 503 patients with unexplained syncope and BBB, arrhythmic syncope was identified in 57.9% patients, mostly secondary to AV block (51.3%). However, 12% was due to reflex syncope or an OH mechanism, 1.4% to ventricular tachycardia, and 10% was secondary to other causes[117]

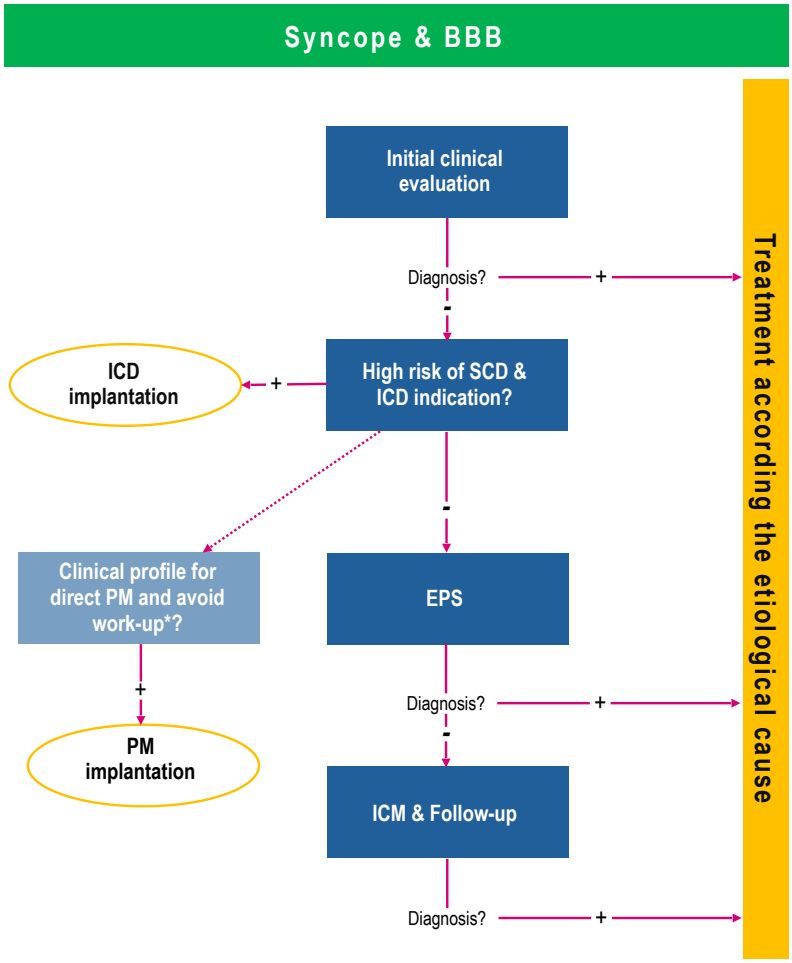
The optimal management of patients with unexplained syncope and bundle branch block (BBB) is still controversial[1,9,51,53,54,148,149]. In fact, the 2017 ACC/AHA Guidelines[9] suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies while ESC guidelines [1] recommend opting for a stepwise approach. The systematic stepwise approach (that includes an EPS and long-term follow-up with an ICM was initially evaluated in the B4 study[54]. This study found that the diagnostic approach is safe and achieves a high rate of etiological diagnosis allowing for the selection of specific treatment and avoiding the implantation of unnecessary pacemakers. The results of the B4 study have been confirmed by several subsequent studies, some of them with a relatively high number of patients and long-term follow-up[86,117,150–152]. On the other hand, the strategy of direct pacemaker implantation was recently evaluated in the SPRITELY trial[153]. This study randomized 105 patients older than 50 years with BFB (41 LBBB and 74 RBBB plus left fascicular block) and at least 1 syncope in the previous year to receive ICM or empirical pacemaker implantation. In the 33-month follow up period, the 57 patients randomized to the pacemaker arm showed a lower primary composite endpoint (cardiovascular death, syncope, bradycardia resulting in an intervention, and device complications.) than the ILR arm; (20 [35%] vs 44 [76%]; chi squared $P < 0.0001$). However, the presence of syncope during follow-up was similar in both groups (29% vs 26%, chi-squared $P = 0.95$)[154]. It must be highlighted that in the SPRITELY trial, EPS was not systematically carried out before ICM implantation, and therefore it cannot be considered as a direct comparison with the stepwise

approach. Similar findings were previously found in the PRESS study[155], where patients were randomized to pacemaker in pacing mode (DDD at 60 bpm) or backup pacing mode (DDI at 30 bpm). The primary endpoint of this study was a composite endpoint of syncope, presyncope with device intervention or documented bradycardia and AVB, and patients allocated to active pacing had a significant reduction of this composite endpoint. However, when only syncope recurrences were analyzed separately, there were no differences between the two groups. Furthermore, there are some studies that have analyzed the recurrence rate in patients with syncope and BBB, in whom a pacemaker has been implanted, showing that syncope recurrence is higher in those patients in whom pacemaker was implanted empirically than in those in whom pacemaker was implanted after a positive EPS or a documented AVB[156,157]

Based on the available evidence, it appears reasonable to continue supporting the stepwise approach in managing these patients. Nevertheless, direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment. (*Figure 8*).

According the newest 2021 ESC guidelines for cardiac pacing and resynchronization [18], in patients with sinus bradycardia and syncope of unclear origin after a thorough work-up, an exercise test to evaluate chronotropic competence and an EPS to evaluate for sinus node overdrive suppression pathologic responses might be indicated. Corrected SNRT (Sinus node recovery time – basal cycle length; normal value 525 ms) has demonstrated good predictive value in patients with sinus bradycardia despite the presence of symptoms (Overall accuracy of cSNRT in predicting serious sinus node disease regardless of the presence of symptoms: 90%; 100% in the presence of symptoms. Sensitivity of the test: 66%). Patients presenting with a ventricular rate below 40 bpm have a 70% probability of having an abnormal cSNRT. In patients with a basal heart rate of 50 to 55 bpm, the probability of finding an abnormal response in cSNRT test is 24%. [158]. However, it should be noted that pacing patients with SND has not demonstrated improved survival so far[18,149].

**Figure 8: Proposed algorithm for the management of syncope in patients with bundle branch block**




*Direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment

*SCD: Sudden cardiac death; ICD: Implantable cardiac defibrillator; PM: Pacemaker; EPS: electrophysiological study; ICM: implantable cardiac monitor*

EPS diagnostic yield is higher in patients with sinus bradycardia or BFB and SHD and is lower in patients with a normal ECG and no SHD [53,56]. Thus, it is preferable to perform EPS in patients with higher pretest probability and implant a loop recorder in those with lower pretest probability. Patients with 1st degree AV block and 2nd degree type I (Wenckebach) block presenting with syncope without a firm diagnosis after extensive study should be offered an EPS. The presence of 2nd degree type II block or 3rd degree AVB constitutes a clear indication for cardiac pacing. Patients with 2:1 AV block can be evaluated by increasing the sinus node rate (Atropine 1 mg or exercise test). If the degree of block increases by increasing of the sinus rate, an infrahisian origin must be suspected and pacemaker implantation should be considered. Patients with syncope and BFB represent a group whose risk of syncope is especially difficult to stratify. Therefore, in patients with BFB and syncope of unknown origin an EPS should

be performed. In the presence of a HV interval longer than 70 ms (basal) or >100 ms after infusion of 2 mg/kg of flecainide (or other Vaughan Williams class I antiarrhythmic drugs), cardiac pacing should be considered[159]. The absence of high-risk characteristics in the EPS of patients with syncope and BBB or BFB does not preclude the development of paroxysmal AV block, and an ILR needs to be considered. Roca-Luque et al. demonstrated that the most predictive combination of conduction disorders was LBBB or RBBB + long PR interval + left fascicular block (Odds ratio 4.5 1.06-20.01; P< 0.042); LBBB plus prolonged PR interval (5.2 1.52-17.74; p < 0.001) and RBBB plus prolonged PR interval (3.8 1.7-8.7; p<0.001) in their 271-patient cohort in 2018.[56]

### 1.4.3. Channelopathies and inherited arrhythmia syndromes:

Cardiac channelopathies are a group of diseases in which a mutation of different regulatory proteins of the action potential may predispose a patient to suffer from ventricular arrhythmias and SCD. Syncopal episodes in these patients might be due to non-sustained polymorphic VT or VF. In this review, we will discuss the implications of the presence of syncope in patients with BrS, Long QT syndrome and Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

#### 1.4.3.1. *Brugada Syndrome*

BrS was first described by the Brugada brothers in their elegant paper published in JACC in 1992. [160]. In their first publication of this syndrome, they described a cohort of 8 patients with RBBB and ST elevation in leads V1-V2-3 that suffered from aborted episodes of SCD. [161]

Even though the mechanism of the electrical dysfunction leading to VF is not completely understood, it is believed that an increase in early repolarizing currents (Ito current) or a reduction in depolarizing currents (INaT) currents may lead to a phase II dispersion of repolarization and early post-depolarizations, which might generate phase II reentries, possibly triggering VF. This electrical disorder seems to be more accentuated in the anterior part of the RVOT, where Ito current has been shown to be higher than in other heart sites. This latter observation might explain the isolated ST elevation in precordial leads and the effectiveness of ablation on the RVOT in patients with BrS and arrhythmic storm.[162]

Patients with BrS pattern on ECG and syncope have a 4-fold risk of sudden cardiac arrest, representing a 1.5% annual risk of sudden cardiac arrest. When the syncope cannot be classified as neuro-mediated or a cardiac origin is a possibility, ICD implantation should be considered[19]. Therefore, it is usually not necessary to perform an EPS to stratify the risk in the presence of unexplained syncope, as it is assumed to be high risk.

However, patients with sodium channel dysfunction may exhibit conduction system dysfunction as well. It is not infrequent for patients with those specific mutations to exhibit sinus bradycardia and/or BBB. Furthermore, reflex syncope is also frequent in young patients with BrS[163]. For these reasons, some authors have also suggested a more conservative approach, where implantation of a loop recorder can be considered in BrS patients with an unexplained syncope (not clearly cardiac) and without other indications for an ICD[19,164]

#### 1.4.3.2. *Long QT Syndrome*

The hallmark of the long QT syndrome is an inadequately prolonged corrected QT interval, measured from the beginning of the QRS complex to the point at which the descending limb of the T wave crosses the isoelectric baseline of the ECG. The measure is frequently performed in leads II or V5-6 where the T wave and the isoelectric baseline are often well demarcated. The diagnosis of LQTS is made in the presence of a cQT interval of ⩾ 480 ms or a Schwartz score (including several clinical and electrocardiographic parameters) of > 3. In the presence of a cardiogenic syncope, the presence of a cQT ⩾ 460 ms is sufficient to reach the diagnosis.

The mechanism of arrhythmogenicity in patients with long QT syndrome seems to be related with dispersion of the repolarization. The prolongation of the repolarization is not homogeneous among the different layers of myocardium. Therefore, early post depolarization occurring over the T wave may generate functional reentry patterns of conduction ultimately generating fibrillatory conduction.

Up to 17 different mutations leading to long QT syndrome have been described. The majority of them are produced by 3 specific mutations. LQTS1 is produced by mutation in the α subunit of the delayed rectifier potassium channel with slow opening kinetics (IKs). This mutation comprises 40-55% of cases. LQTS1 patients are prone to suffering from ventricular arrhythmias during sports or physical activity (especially during swimming). LQTS2 is caused by a mutation in the α subunit of the delayed rectifier potassium channel with rapid opening kinetics (IKr). This mutation is present in up to 30-45% of cases and ventricular arrhythmias are frequent during loud noises and in the postpartum period in women. The activating mutation in the α subunit of the sodium channel (INaT) keeps the channel opened beyond phase 0, increasing late sodium currents (INaL), thus prolonging repolarization and therefore the QT interval. This mutation is present in 5-10% of patients and is related to fatal events during rest or sleep. [165]

It has been observed that LQTS patients respond favorably to betablockers and thus every patient with a diagnosis of LQTS should be treated with betablockers. Apparently, non-specific betablockers, such as propranolol or nadolol, have shown better results with a lower incidence

of ventricular arrhythmias. If patients suffer from syncope despite the use of betablockers, an ICD must be implanted for the prevention of SCD. [166]

#### 1.4.3.3. *Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)*

CPVT is an inherited channelopathy in which several mutations may affect the intracellular handling of calcium release-uptake. The overload of cytoplasmatic calcium leads to cell membrane voltage instability leading to delayed depolarizations that lead to the characteristic arrhythmia of this disorder, bidirectional ventricular tachycardia (also seen in digitalis toxicity), or VF.

The mutation in the ryanodine receptor gene (RYR2) inherited in an autosomal dominant manner, is the cause of 50-55% of cases. A new mutation in the calsequestrin gene (CASQ2) has been described and has an autosomal recessive inheritance pattern.

The RYR2 mutation generates an aberrant ryanodine channel which permeabilizes the channel to calcium release. The calsequestrin proteins work close to the ryanodine channel, regulating its function.

Patients with CPVT are prone to ventricular arrhythmias related with exercise. Ventricular arrhythmias usually occur with HR over 130 bpm. With increasing levels of exercise, patients may exhibit monomorphic ectopy, polymorphic ectopy and non-sustained VT, bidirectional VT and finally, if the exercise continues, VF. CPVT is a highly arrhythmogenic condition with a cardiac event rate of up to 80% at 40 years. Therefore, a low threshold for ICD implantation is advised. The use of non-selective betablockers has been shown to reduce the incidence of ventricular arrhythmias from 25% to 11% at 8 years. [167]

Probably due to small cohorts, no single risk factor has demonstrated sufficient prognostic value to be used routinely. The *2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death* recommend implantation in patients with CPVT who have survived a cardiac arrest (class I-C) and should be considered in patients with CPVT and either arrhythmic syncope or presence of polymorphic VT or bidirectional VT on maximal tolerated doses of betablockers (class IIa-C).[19]

# 2. THESIS STUDIES JUSTIFICATION

This thesis is focused on the study of arrhythmic syncope, examining various aspects that have significant clinical implications and have not been adequately studied before. As we delve into the subsequent sections, the different studies comprising this thesis will concentrate on specific patient groups with unique characteristics that may differentiate them in terms of risk factors, outcomes, prognosis, or management.

Arrhythmic syncope is a clinical condition that presents several challenges, making its study essential. Firstly, arrhythmic syncope is generally associated with a poor prognosis. Understanding the underlying mechanisms and risk factors can help identify high-risk patients and implement appropriate management strategies to improve outcomes. Secondly, diagnosing arrhythmic syncope can be challenging. The transient nature of syncope episodes and the absence of clear diagnostic markers often make it difficult to differentiate arrhythmic syncope from other causes. Consequently, conducting studies to develop more accurate diagnostic tools and algorithms can greatly aid in timely and precise diagnosis. Furthermore, arrhythmic syncope may be underdiagnosed in clinical practice. Raising awareness and conducting studies on arrhythmic syncope can help increase its recognition, leading to appropriate diagnostic evaluation and treatment. Moreover, arrhythmic syncope frequently occurs in patients with underlying SHD or conduction system disorders. These patients require specific attention and tailored management approaches to address the underlying pathology and prevent future syncope episodes. Lastly, the management of arrhythmic syncope in certain patient subgroups remains controversial. Conducting studies can provide valuable insights into the most effective treatment strategies, including the use of antiarrhythmic medications, implantable devices, or catheter ablation, thus guiding clinicians in making informed decisions and improving patient outcomes.

Two groups of patients with SHD that require special attention are patients with SAS and those with MD-LVD. In one hand, SAS represents a complex myocardial condition that extends beyond valvular involvement, potentially leading to various disorders with the risk of inducing syncope. However, in clinical practice, syncope is often attributed solely to the valve disease, and potential arrhythmias are not thoroughly investigated. Therefore, there is a significant knowledge gap regarding the prognosis and underlying mechanisms of syncope in this patient population. In the other hand, in patients with MR-LVD, there is a lack of prior research on this

specific subgroup. The management of syncope in these patients remains controversial, and clear general recommendations are currently lacking. Conducting studies in this population can provide valuable insights into the optimal treatment strategies and improve clinical decision-making.

Patients with BBB represent another group that exhibits a high arrhythmic risk. Although this topic has been the subject of interest in previous studies, numerous questions still remain unanswered. For instance, in recent years, there has been a growing interest in evaluating sex differences in various cardiovascular pathologies, and this concern extends to patients with syncope and BBB as well. It has been observed that women often present a distinct pattern of cardiovascular disease compared to men. This distinction could potentially manifest in patients with syncope and BBB, where sex-specific factors may play a significant role in the pathogenesis, clinical presentation, and prognosis of the condition. Therefore, it is necessary to investigate and explore potential sex-related differences to provide tailored and effective management strategies for each patient. Furthermore, in clinical practice, it has been noted that patients experiencing their first syncope episode are often treated more conservatively than those with RSE. This conservative approach may stem from the assumption of a lower risk associated with initial syncope episodes. However, this generalized approach may overlook the individual characteristics and specific risk profile of patients with BBB. By delving deeper into the study of these specific patient subgroups, we can uncover important insights that could help personalize treatment strategies and improve the overall prognosis. For these reasons, the study of patients with BBB remains an important area of research.

In summary, studying arrhythmic syncope is crucial given its prognostic implications, diagnostic challenges, potential underdiagnosis, and controversial management approaches. Through comprehensive research efforts, we can enhance our understanding of this condition and develop evidence-based guidelines to improve its diagnosis, management, and ultimately, patient outcomes.

# 3. HYPOTHESIS

We hypothesize that in patients with complex cardiopathy, syncope can be caused by multiple etiologies that need to be properly identified. An accurate diagnosis of the causes of the syncope and the consequent appropriate management can significantly impact their prognosis. In line with this, we hypothesize that a systematic diagnostic protocol for syncope can achieve a high diagnostic yield, guide treatment, and minimize sudden death while avoiding unnecessary implantation of cardiac devices. Lastly, we propose that certain groups of patients, such as women with BBB, may have a distinct arrhythmic risk and different management needs due to their susceptibility to syncope and varying comorbidities. However, in other groups, arrhythmic risk will not differ. Knowledge of this information would help to improve the clinical management of these complex pathologies.

While this thesis is divided into three parts, each focusing on a different group of patients at high risk of arrhythmic syncope, the specific hypotheses for each part are reported in detail in the respective articles.

# 4. OBJECTIVES

General objective of the thesis are as follows:

## Main Objective:

- To determine the causes of syncope, assess the diagnostic yield and safety of a systematic diagnostic protocol, and identify specific risk groups in different populations at high risk for arrhythmic syncope.

## Secondary Objectives:

- Determine the factors predicting an arrhythmic etiology of syncope in these populations.
- Determine the diagnostic yield of EPS and ICM in these groups of patients and the factors associated with a positive result.
- Investigate the long-term overall prognosis of patients, the factors associated with their prognosis, and the prognostic implications of different etiologies of syncope.
- Evaluate the syncope recurrence rate after a positive diagnosis and its causes.

# 5. COMPENDIUM OF PUBLICATIONS

## 5.1. Publication 1

**Francisco-Pascual J**, Rodenas E, Belahnech Y, Rivas-Gándara N, Pérez-Rodon J, Santos-Ortega A, Benito B, Roca-Luque I, Cossio-Gil Y, Serra Garcia V, Llerena-Butron S, Rodríguez-García J, Moya-Mitjans A, García-Dorado D, Ferreira-González I. Syncope in Patients With Severe Aortic Stenosis: More Than Just an Obstruction Issue. Can J Cardiol. 2021 Feb;37(2):284-291. doi: 10.1016/j.cjca.2020.04.047. Epub 2020 May 18. Erratum in: Can J Cardiol. 2022 Dec;38(12):1979. doi: 10.1016/j.cjca.2022.10.007. PMID: 32439473.

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doi: 10.1016/j.cjca.2022.10.007

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https://linkinghub.elsevier.com/retrieve/pii/S0828-282X(20)30467-0

doi: 10.1016/j.cjca.2022.10.007

https://linkinghub.elsevier.com/retrieve/pii/S0828-282X(20)30467-0

## 5.2. Publication 2

**Francisco-Pascual J**, Rodenas-Alesina E, Rivas-Gándara N, Belahnech Y, Olivella San Emeterio A, Pérez-Rodón J, Benito B, Santos-Ortega A, Moya-Mitjans À, Casas G, Cantalapiedra-Romero J, Maldonado J, Ferreira-González I. Etiology and prognosis of patients with unexplained syncope and mid-range left ventricular dysfunction. Heart Rhythm. 2021 Apr;18(4):597-604. doi: 10.1016/j.hrthm.2020.12.009. Epub 2020 Dec 14. Erratum in: Heart Rhythm. 2022 Dec;19(12):2132. doi: 10.1016/j.hrthm.2022.10.006. PMID: 33326869.

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doi: 10.1016/j.hrthm.2022.10.006

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doi: 10.1016/j.hrthm.2022.10.006

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doi: 10.1016/j.hrthm.2022.10.006

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doi: 10.1016/j.hrthm.2022.10.006

https://linkinghub.elsevier.com/retrieve/pii/S1547-5271(20)31144-9

## 5.3. Publication 3

**Francisco-Pascual J**, Rivas-Gándara N, Bach-Oller M, Badia-Molins C, Maymi-Ballesteros M, Benito B, Pérez-Rodon J, Santos-Ortega A, Sambola-Ayala A, Roca-Luque I, Cantalapiedra-Romero J, Rodríguez-Silva J, Pascual-González G, Moya-Mitjans À, Ferreira-González I. Sex-Related Differences in Patients With Unexplained Syncope and Bundle Branch Block: Lower Risk of AV Block and Lesser Need for Cardiac Pacing in Women. Front Cardiovasc Med. 2022 Feb 25;9:838473. doi: 10.3389/fcvm.2022.838473. PMID: 35282384; PMCID: PMC8914040.

frontiers in Cardiovascular Medicine

ORIGINAL RESEARCH
published: 25 February 2022
doi: 10.3389/fcvm.2022.838473

# Sex-Related Differences in Patients With Unexplained Syncope and Bundle Branch Block: Lower Risk of AV Block and Lesser Need for Cardiac Pacing in Women

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**Objective:** To analyze if there are sex-related differences in patients with unexplained syncope and bundle branch block (BBB).

**Background:** Despite increasing awareness that sex is a major determinant of the incidence, etiology, and the outcomes of different arrhythmias, no studies have examined differences in presentation and outcomes between men and women with syncope and BBB.

**Methods:** Cohort study of consecutive patients with unexplained syncope and BBB was included from January 2010 to January 2021 with a median follow-up time of 3.4 years [interquartile range (IQR) 1.7–6.0 years]. They were evaluated by a stepwise workup protocol based on electrophysiological study (EPS) and long-term follow-up with an implantable cardiac monitor (ICM).

**Results:** Of the 443 patients included in the study, 165 (37.2%) were women. Compared with men, women had less diabetes (25.5 vs. 39.9%, $p = 0.002$) and less history of ischemic heart disease (IHD; 13.3 vs. 25.9%, $p = 0.002$). Left bundle branch block (LBBB) was more frequent in women (55.2 vs. 27.7%, $p < 0.001$) while right bundle branch block (RBBB) was more frequent in men (41.5 vs. 67.7%, $p < 0.001$). His to ventricle (HV) interval in the EPS was shorter in women (58 ms [IQR 52–71] vs. 60 ms [IQR 52–73], $p = 0.035$) and less women had an HV interval longer than 70 ms (28.5 vs. 38.1%, $p = 0.039$), however, EPS and ICM offered a similar diagnostic yield in both sexes (40.6 vs. 48.9% and 48.4% vs. 51.1%, respectively). Women had a lower risk of developing atrioventricular block (AVB) (adjusted odds ratio [OR] 0.44–95% CI 0.26–0.74,

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***Edited by:***
*Jonathan Chrispin, Johns Hopkins Medicine, United States*

***Reviewed by:***
*Ronald Berger, Johns Hopkins University, United States*
*Andreas Barth, Johns Hopkins Medicine, United States*

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***Specialty section:***
*This article was submitted to Sex and Gender in Cardiovascular Medicine, a section of the journal Frontiers in Cardiovascular Medicine*

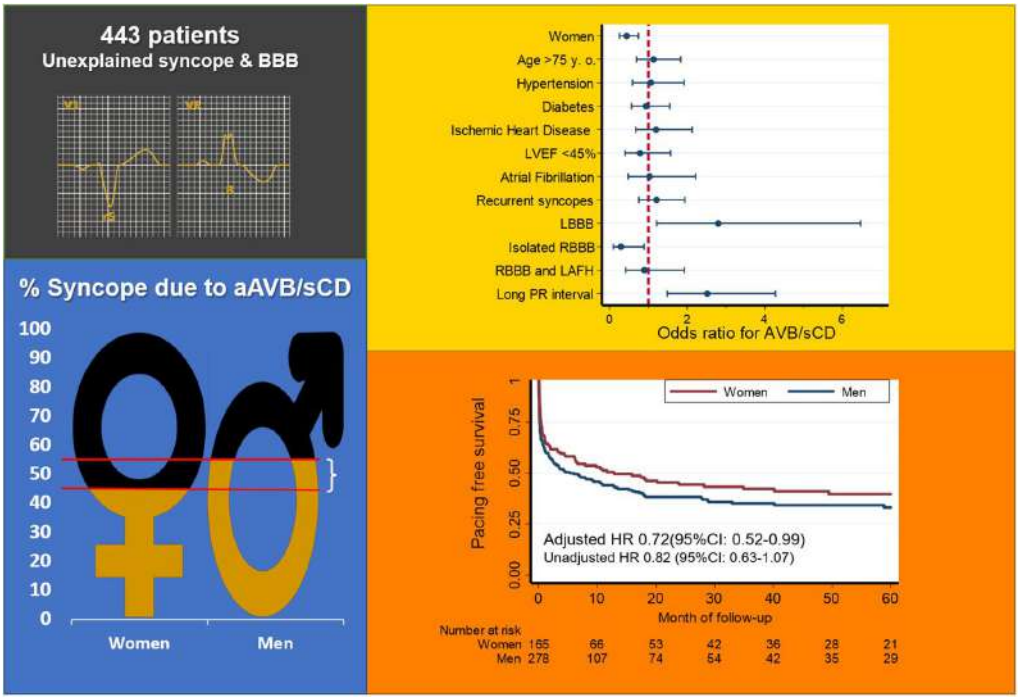
***Received:*** *17 December 2021*
***Accepted:*** *21 January 2022*
***Published:*** *25 February 2022*

***Citation:***
*Francisco-Pascual J, Rivas-Gándara N, Bach-Oller M, Badia-Molins C, Maymi-Ballesteros M, Benito B, Pérez-Rodon J, Santos-Ortega A, Sambola-Ayala A, Roca-Luque I, Cantalapiedra-Romero J, Rodríguez-Silva J, Pascual-González G, Moya-Mitjans À and Ferreira-González I (2022) Sex-Related Differences in Patients With Unexplained Syncope and Bundle Branch Block: Lower Risk of AV Block and Lesser Need for Cardiac Pacing in Women. Front. Cardiovasc. Med. 9:838473. doi: 10.3389/fcvm.2022.838473*

$p = 0.002$) and of requiring permanent pacemaker implantation (adjusted hazard ratio [HR] 0.72–95% CI: 0.52–0.99, $p = 0.046$). The mortality rate was lower in women (4.5 per 100 person-years [95% CI 3.1–6.4 per 100 person-years] vs. 7.3 per 100 person-years [95% CI 5.9–9.1 per 100 person-years]).

**Conclusions:** Compared to men, women with unexplained syncope and BBB have a lower risk of AVB and of requiring cardiac pacing. A stepwise diagnostic approach has a similar diagnostic yield in both sexes, and it seems appropriate to guide the treatment and avoid unnecessary pacemaker implantation, especially in women.

**Keywords: syncope, pacemaker, electrophysiological study, loop recorder, cardiac monitor, gender differences, sex-related differences**




**GRAPHICAL ABSTRACT |** Risk of AVB and need for cardiac pacing. Left: Percentage of patients diagnosed with aAVB/sCD in both sexes. Right-top: Multivariate logistic regression analyses for risk of aAVB/sCD. Odds ratio and 95% CI are plotted. Right-bottom: Kaplan-Meier pacemaker-free survival estimates curves in both sexes. aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; HR, hazard ratio; CI, confidence interval; y.o, years old; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; BBB, bundle branch block; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.

## INTRODUCTION

Although syncope in patients with bundle branch block (BBB) is often due to paroxysmal advanced atrioventricular block (aAVB), other mechanisms may also be involved (1–4). A systematic diagnostic approach based on clinical evaluation, electrophysiological study (EPS), and the Implantable cardiac monitor (ICM) has shown to be safe and provide a high rate of etiological diagnosis (3, 5–7). However, due to the low predictive value of EPS, some investigators suggest that a pacemaker should be implanted on an empirical basis (2, 8), therefore, the best way to manage these patients remains controversial. Increasing knowledge of the disease characteristics can help clinicians to improve their management in specific subgroups of patients. Despite substantial efforts in recent years

**Abbreviations:** aAVB, Advanced atrioventricular block; sCD, Severe conduction disturbances; BBB, Bundle branch block; EPS, electrophysiological study; ICM, Implantable cardiac monitor; SND, Sinus node dysfunction.

to improve the understanding of the sex-related differences in cardiovascular disease, there is still insufficient knowledge of physiology, epidemiology, and outcomes in women, leading to a lack of sex-specific recommendations. In this regard, there is an increasing awareness that sex is a major determinant of the incidence, etiology, and clinical presentation of arrhythmias (9, 10). It is known that women have a major susceptibility to reflex syncope (11–14) and probably to sinus node dysfunction (SND) (9, 10, 15). However, no studies have examined differences between men and women in the presentation and outcomes of unexplained syncope and BBB.

Given the susceptibility of women to syncope due to other mechanisms and the different comorbidities of the female sex, we hypothesize that women with unexplained syncope and BBB would have a different risk of aAVB or severe conduction disturbances (sCDs) and a different risk of needing cardiac pacing compared to men. The aim of this study was to analyze the sex-related differences in patients with syncope and BBB concerning the prevalence of aAVB/sCD, the diagnostic yield of tests, and clinical outcomes.

## METHODS

### Study Population

We performed a prospective observational study on a consecutive patient cohort at a tertiary university hospital that is a reference center for cardiology and arrhythmias [Hospital Universitari Vall d'Hebron, Barcelona (Spain)]. From January 2010 to January 2021, we included those patients admitted for syncope with BBB, in whom no certain diagnosis was reached for the syncope in the initial assessment at the emergency department. We excluded patients under the age of 18 years, those with pacemakers or implantable cardiac defibrillators (ICD) *in situ*, patients with left ventricular ejection fraction (LVEF) <35% or with another ICD direct indication, and those who could not keep to the study's diagnostic protocol due to comorbidities or their own preference. In June 2021, we collected the final follow-up data of the patients. The patient's clinical details, syncope characteristics, therapeutic management, and follow-up were recorded at the time of hospital admission.

The study complies with the Helsinki declaration and was approved by the local ethics committee.

### Study Protocol

Patients were systematically assessed and managed according to the local clinical protocol which is based on recommendations from the European Society of Cardiology (ESC) syncope guidelines (1).

In summary, the diagnostic protocol for syncope in this population was based on 3 phases or steps. Step 1, prior to the patients' inclusion in the study, consisted of the initial assessment in the emergency department. In a systematic manner, clinical history and physical examination were performed, such as testing for orthostatic hypotension and carotid sinus massage (if not contraindicated), general bloodwork, chest x-ray, 12-lead ECG, 12–24-h telemetry monitoring and a transthoracic echocardiogram (in cases where no prior echocardiogram from the last 6 months is available). Those cases with no certain or highly probable diagnosis were then considered unexplained syncope, and these patients were admitted to the hospital with continuous ECG monitoring. Other complementary diagnostic tests, such as exercise stress test, myocardial perfusion gamma scan, or MRI, were carried out at the treating clinician's discretion in line with the suspected diagnosis and applicable recommendations. Step 2 involved the hospital admission with continuous ECG monitoring and an invasive electrophysiology study. Step 3 involved implanting an ICM with subsequent clinical monitoring (**Figure 1**).

### Electrophysiology Study

Two femoral venous accesses were gained and two tetrapolar catheters (Supreme, Abbott, St. Jude Medical, St. Paul, MN, USA) were used for basic measurements, atrial stimulation, and ventricular stimulation. Sinus node recovery time was obtained after 30 s of atrial pacing at 600 and 500 ms, and the highest value was corrected by basal heart rate. Programmed ventricular stimulation protocol utilized up to three extra stimuli delivered after eight paced ventricular cycle lengths at 600, 500, and 400 ms from de right ventricular apex and outflow tract in case no sustained ventricular tachycardia (VT) was induced before.

In cases with basal conduction disturbances where the His to ventricle (HV) interval was <70 ms, a class I drug (procainamide 10 mg/kg or flecainide 2 mg/kg intravenously) was administered. Continuous monitoring of the HV interval and atrial pacing was performed during the class I drug infusion and for 10 min after the infusion.

Electrophysiological study was considered positive according to current ESC guidelines (1) in the following cases: (1) baseline HV interval ≥70 ms or ≥100 ms after class I drug administration. (2) Second- or third-degree infra- or intra-Hisian block (with pacing cycle length above 400 ms) before or during incremental atrial pacing or after class I drug administration. (3) Induction of sustained VT.

### Monitoring With Implantable Cardiac Monitor

In Step 3, a Reveal XT$^{TM}$ (in patients included before 2014) or Linq$^{TM}$ (Medtronic, Inc. Minneapolis, MN, USA) device was implanted. The implantation was performed under local anesthetic at the primary site recommended by the manufacturer (fourth left intercostal space). The patients were instructed on how to use it and were provided with a device for remote monitoring (Medtronic Carelink$^{TM}$). The ICM was programmed with the settings for syncope.

Implantable cardiac monitor was considered diagnostic in the event of being able to correlate recurrence of syncope or presyncope with the ICM's electrocardiographic trace, or when the following rhythm disorders were documented in an asymptomatic patient: complete or advanced AV block, asystole lasting >3 s while awake, or the presence of sustained VT.

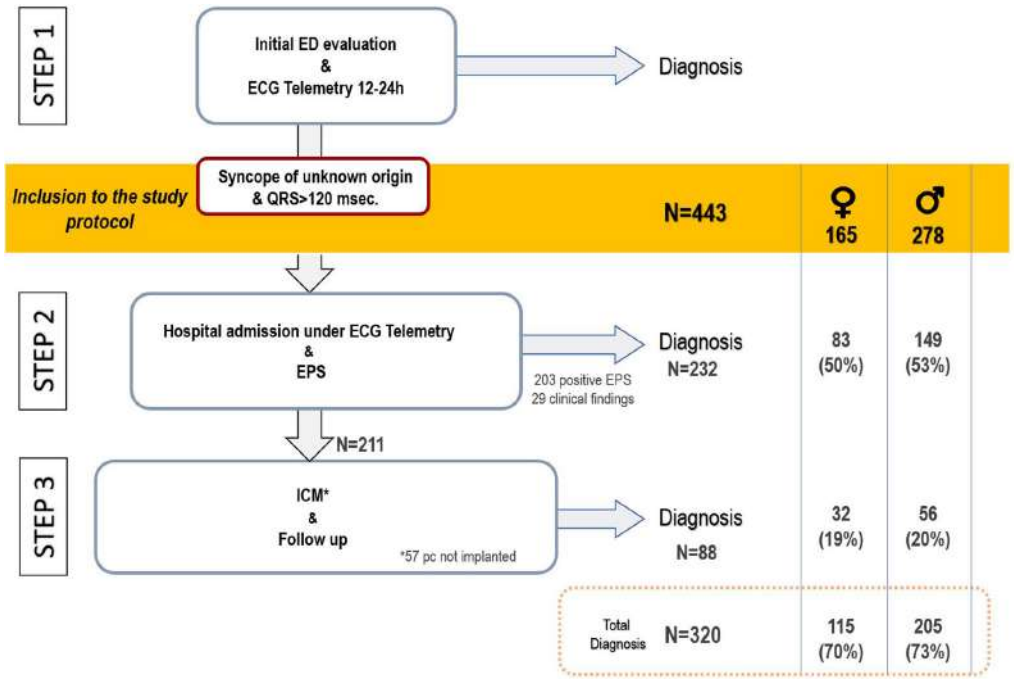



**FIGURE 1 |** Diagnostic protocol schema and flow chart of patient inclusion in the study. ED, emergency department; EPS, electrophysiological study; ICM, implantable cardiac monitor; pc, patients.

## Treatment and Clinical Follow-Up

The syncope was treated appropriately following the clinical practice guidelines according to its etiology. In those patients with syncope secondary to a conduction disorder, the implantation of a cardiac stimulation device was indicated. In patients with syncope secondary to ventricular tachycardia, defibrillator implantation was indicated. The device type (pacemaker, defibrillator, or resynchronizer) and treatments, such as ablation, antiarrhythmic drugs, or angioplasty, were eventually discussed within the "heart team" and individualized according to the patient's functional status, the prior degree of heart failure, and patient preferences. In addition, all patients were educated on syncope and lifestyle changes to prevent and treat reflex syncope.

After hospital discharge, patients were followed up in the outpatient cardiology clinic, and those who had received a cardiac device were also followed up with the corresponding remote function.

## Definitions and Endpoints

The main etiological mechanism of the syncope was established as certain or highly probable according to the definitions in the ESC guidelines on syncope (1) (**Supplementary Table S1**). aAVB/sCD was defined as the documentation of type II second degree, third degree, or high-grade AVB or the following diagnostic findings in the EPS: HV interval ≥ 70 ms or ≥100 ms after class I drug challenge, intra-Hisian, or infra-Hisian block (1, 16). The patient details were analyzed by two cardiologists specialized in syncope to establish the definitive diagnosis according to the definitions. The etiology of syncopal recurrences was defined in the same manner.

Sudden death was defined as death occurring instantaneously or within 1 h of the onset of symptoms, non-sudden cardiac death was defined as a cardiac death occurring 1 h after the onset of symptoms, and non-cardiac death as deaths not directly related to a cardiac or sudden condition.

The primary endpoint of the study was a diagnosis of the main syncope mechanism. The secondary endpoints were test diagnostic yields, need for cardiac pacing related to syncope, syncope recurrences, and mortality.

## Statistical Analysis

The categorical variables are presented as absolute number (N) and percentages. The continuous quantitative variables are presented as the median and interquartile range (IQR). The comparison of numerical variables was performed using Student's *t*-test or Wilcoxon's rank-sum test, depending on the distribution of the variables. The Chi-squared test or Fisher's exact test was used to compare qualitative variables as

**TABLE 1 |** Baseline characteristics of patients included in the study.

| Variable | Total (n = 443) | Men (n = 278) | Women (n = 165) | P |
|---|---|---|---|---|
| Age (years)[+] | 77.9 [70.5–82.1] | 77.0 [70.3–82.20] | 78.7 [71.2–84.6] | 0.122 |
| Age >75 y.o, *n* (%) | 273 (61.6) | 167 (60.1) | 106 (64.2) | 0.383 |
| Hypertension, *n* (%) | 348 (78.6) | 223 (80.2) | 125 (75.8) | 0.269 |
| Diabetes, *n* (%) | 153 (34.5) | 111 (39.9) | 42 (25.5) | 0.002 |
| Dyslipidemia, *n* (%) | 266 (60.1) | 168 (60.4) | 98 (59.4) | 0.829 |
| No SHD, *n* (%) | 346 (78.1) | 212 (76.3) | 134 (81.2) | 0.223 |
| Ischemic heart disease, *n* (%) | 94 (21.2) | 72 (25.9) | 11 (13.3) | 0.002 |
| Old ST elevation infarction, *n* (%) | 25 (5.6) | 20 (7.2) | 5 (3.0) | 0.066 |
| Non-ischemic dilated cardiomyopathy, *n* (%) | 16 (3.6) | 9 (3.2) | 7 (4.2) | 0.584 |
| History of atrial fibrillation, *n* (%) | 90 (20.3) | 62 (22.3) | 28 (17.0) | 0.177 |
| Previous syncope, *n* (%) | 235 (53.1) | 154 (55.4) | 81 (49.1) | 0.199 |
| Use of negative chronotropic drugs, *n* (%) | 149 (34.8) | 95 (35.3) | 54 (34.0) | 0.776 |
| **Characteristics of the syncope** | | | | |
| Prodrome, *n* (%) | 134 (30.5) | 84 (30.3) | 50 (30.8) | 0.776 |
| Severe trauma, *n* (%) | 185 (42.1) | 121 (43.6) | 64 (39.5) | 0.393 |
| **Echocardiogram** | | | | |
| EDD (mm) | 47 [43–52] | 48 [43–53] | 46 [42–50] | <0.001 |
| ESD (mm) | 31 [26–35] | 32 [27–36] | 30 [26–34] | 0.016 |
| Interventricular septum (mm) | 13 [11–14] | 13 [12–14] | 12 [10–15] | 0.021 |
| LVEF (%) | 58 [51–62] | 57 [50–62] | 58 [52–62] | 0.746 |
| LVEF <45%, *n* (%) | 61 (14.7) | 38 (14.8) | 23 (14.7) | 0.970 |
| **ECG on admission** | | | | |
| Heart rate (bpm) | 70 [62–80] | 70 [60–80] | 70 [63–80] | 0.996 |
| Atrial fibrillation, *n* (%) | 78 (17.8) | 49 (17.9) | 29 (17.6) | 0.935 |
| Long PR, *n* (%) | 152 (40.2) | 104 (43.7) | 48 (34.3) | 0.720 |
| QRS duration (msec) | 140 [130–153] | 140 [130–153] | 140 [130–152] | 0.891 |
| LBBB morphology, *n* (%) | 167 (37.9) | 77 (27.7) | 90 (55.2) | <0.001 |
| Long PR and LBBB, *n* (%) | 47 (10.6) | 24 (8.6) | 23 (13.9) | 0.080 |
| RBBB morphology, *n* (%) | 259 (58.6) | 191 (67.7) | 68 (41.5) | <0.001 |
| Isolated RBBB | 50 (11.7) | 34 (12.6) | 16 (10.2) | 0.449 |
| RBBB and LAFB | 159 (35.9) | 116 (41.7) | 43 (26.1) | 0.001 |
| Long PR and RBBB | 96 (21.7) | 75 (27.) | 21 12.7) | <0.001 |
| Long PR, RBBB and LAFB | 71 (16.0) | 52 (18.7) | 19 (11.5) | 0.046 |

[+] *The quantitative variables are expressed as medians [interquartile range].*
*y.o, years old; mm, millimeters; bpm, beats per minute; msec, milliseconds; SHD, structural heart disease; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block. ESD, end-systolic diameter; EDD, end-diastolic diameter; LVEF, left ventricular ejection fraction.*

appropriate. Wald's method was used to calculate the CI for the population rates and proportions. The survival functions were estimated using the Kaplan-Meier method and their comparison was performed by the log-rank test. A multivariable logistic regression model was used to assess the association between sex and aAVB/sCD and to adjust for possible confounder variables. Moreover, a Cox proportional hazards multivariate model was created to determine whether the sex was associated with pacemaker implantation adjusted by possible confounding variables. When we estimated both the Cox proportional hazards model and the logistic regression model, we checked the different possible interactions between pairs of explanatory variables and found no statistically significant results. A saturated model, such as all clinically relevant covariates (1, 4, 5, 7, 17–22), was estimated, and simplified models were evaluated. A relevant confounding effect was judged when the hazard ratios (HRs) or odds ratios (ORs) with and without the adjustment for the potential confounder differed more than 10%. The most precise model with all relevant clinical covariates was finally selected. A $p < 0.05$ was considered statistically significant for all tests. All of the statistical analyses were performed using Stata, version 15.1.0 (StataCorp LLC College Station, TX, USA).

# RESULTS

## Baseline Characteristics

A total of 443 patients were included in the study, of whom 165 (37.2%) were women. The patients' baseline characteristics

and the comparisons between men and women are shown in **Table 1**. The median age was 77.9 years [IQR 70.5–82.1] and 21.2% had ischemic heart disease (IHD). The median LVEF was 58% [IQR 51–62%] and 14.7% of the patients had a depressed LVEF (<45%). The median QRS duration was 140 ms [IQR 130–153 ms]. In the ECG on admission, 37.9% of patients had typical left bundle branch block (LBBB) morphology and 58.6% right bundle branch block (RBBB) morphology.

Compared with men, women had less diabetes (25.5 vs. 39.9%, $p = 0.002$) and less history of IHD (13.3 vs. 25.9%, $p = 0.002$). However, there were no differences regarding atrial fibrillation history and other comorbidities. The rate of conduction disturbances in the ECG on admission differed between both sexes: LBBB was more frequent in women (55.2 vs. 27.7%, $p < 0.001$) while RBBB was more frequent in men (41.5 vs. 67.7%, $p < 0.001$).

## Etiology of the Syncope and Risk of aAVB/sCD

A certain or highly probable diagnosis of the main cause of syncope was reached in 320 patients (72.2%). In 232 (52.4%) patients, the diagnosis of syncope was reached in Step 2 (in 203 patients after a positive EPS and in another 29 due to presenting symptoms with diagnostic criteria during hospital stay). In Step 3, a definitive diagnosis was reached in an additional 88 (19.9%) patients (77 due to the ICM findings and 11 due to clinical criteria; **Figure 1**).

**Table 2** summarizes the etiologies of syncope and the diagnoses reached in each step. Compared to men, women had less frequent aAVB/sCD (44.9 vs. 55.0%, $p = 0.038$), which represents a risk ratio (RR) of 0.81 (95% CI 0.67–0.99). Furthermore, in multivariate analyses, after adjusting for possible confounding variables (such as the type of BBB), women had a lower risk of developing aAVB/sCD than men [OR 0.44 (95% CI 0.26–0.74, $p = 0.002$); **Graphical Abstract** and **Supplementary Table S2**].

## EPS and Implantable Cardiac Monitor

Overall, EPS was positive in 203 (45.8%) patients, and it was due to aAVB/sCD in 193 (43.6%). Details of the EPS results are listed in **Table 3**. Baseline HV interval was shorter in women (58 ms [IQR 52–71] vs. 60 ms [IQR 52–73], $p = 0.035$) than in men. Furthermore, fewer women had a baseline HV interval longer than 70 ms (28.5% vs. 38.1%, $p = 0.039$).

Among those patients with negative EPS at baseline [241 patients (55.1%)], class I drug challenge was positive in 25 (10.3%). No significant differences between men and women were found in the increase of HV interval (Delta HV) or in the positivity of the test (**Figure 2**).

Electrophysiological study had a similar diagnostic yield between women and men (40.6 vs. 48.9%, $p = 0.089$). In addition, EPS negative predictive value (NPV) was similar between both sexes (76.6% [95% CI 67.1–84.0%] vs. 76.6 % [95% CI 69.0–82.8%]).

Among 154 patients who received an ICM, in 77 patients (50% of the implanted patients) a diagnosis was reached, with a similar

**TABLE 2 |** Etiological diagnosis.

| Diagnostic | Total | | | | Step 2 | | | | Step 3 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | All patients (n = 443) | Men (n = 278) | Women (n = 165) | P | All patients (n = 443) | Men (n = 278) | Women (n = 165) | P | All patients (n = 211) | Men (n = 129) | Women (n = 82) | P |
| Unknown, *n* % | 123 (27.8) | 73 (26.3) | 50 (30.3) | 0.358 | 211 (47.6) | 129 (46.4) | 82 (49.7) | 0.502 | 123 (58.3) | 73 (56.6) | 50 (61.0) | 0.529 |
| aAVB/sCD, *n* % | 227 (51.2) | 153(55.0) | 74 (44.9) | 0.038 | 194 (43.8) | 120(46.8) | 64 (38.8) | 0.045 | 33 (15.6) | 23 (17.8) | 10 (12.2) | 0.272 |
| Orthostatic, *n* % | 31 (7.0) | 21 (7.6) | 10 (6.1) | 0.551 | 10 (2.3) | 5 (1.8) | 5 (3.3) | 0.337 | 21 (10.0) | 16 (12.4) | 5 (6.1) | 0.136 |
| SND, *n* % | 22 (5.0) | 11 (4.0) | 11 (6.7) | 0.204 | 3 (0.7) | 2 (0.7) | 1 (0.6) | >0.999 | 19 (9.0) | 9(7.0) | 10 (12.2) | 0.197 |
| Reflex, *n* % | 15 (3.4) | 8 (2.9) | 7 (4.2) | 0.443 | 8 (1.8) | 5 (1.8) | 3 (1.8) | >0.999 | 7 (3.3) | 3 (2.3) | 4 (4.9) | 0.435 |
| Low cardiac output, *n* % | 5 (1.1) | 1 (0.4) | 4(2.4) | | 5 (1.4) | 1 (0.4) | 4 (2.4) | | 0 (0) | 0 (0) | 0 (0) | |
| VT, *n* % | 6 (1.4) | 2 (0.4) | 4 (1.2) | | 5 (1.1) | 2 (0.7) | 3 (1.8) | | 1 (0.5) | 0 (0) | 1 (1.2) | |
| Fast SVT/AF, *n* % | 3 (0.7) | 1 (0.4) | 2 (1.2) | | 1 (0.2) | 0 (0) | 1 (0.6) | | 2 (1.0) | 1 (0.8) | 1 (1.2) | |
| CSH, *n* % | 3 (0.7) | 3 (1.1) | 0 (0) | | 3 (0.7) | 2 (0.7) | 1 (0.6) | | 0 (0) | 0 (0) | 0 (0) | |
| Other, *n* % | 8 (1.8) | 5 (1.8) | 3 (1.8) | | 3 (0.7) | 1 (0.4) | 2 (1.2) | | 5 (2.4) | 4 (3.1) | 1 (1.2) | |

*aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; VT, ventricular tachycardia; SND, sinus node dysfunction; SVT, supraventricular tachycardia; AF, atrial tachycardia; CSH, carotid sinushypersensitivity.*

**TABLE 3 |** Electrophysiological study and implantable cardiac monitor.

| Variable | Total (*n* = 443) | Men (*n* = 278) | Women (*n* = 165) | P |
|---|---|---|---|---|
| **Electrophysiological study** | | | | |
| Baseline HV interval (msec) | 59 [52–73] | 60 [52–73] | 58 [52–71] | 0.035 |
| HV≥70, *n* (%) | 153 (34.5) | 106 (38.1) | 47 (28.5) | 0.039 |
| Intra or infra-Hisian AV block, *n* (%) | 30 (6.9) | 14 (5.1) | 16 (9.9) | 0.06 |
| Basal EPS positive for aAVB/sCD, *n* (%) | 168 (37.9) | 112 (40.3) | 56 (33.9) | 0.183 |
| Class I drug challenge, *n* % | 241 (55.1) | 146 (53.1) | 95 (58.6) | 0.349 |
| Procainamide, *n* % | 93 (21.3) | 59 (21.2) | 34 (21.0) | |
| Flecainide, *n* % | 147 (33.6) | 87 (31.6) | 60 (37.0) | |
| HV interval after class I challenge (msec) | 69 [61-78] | 69 [61-78] | 71 [61-78] | 0.689 |
| Delta HV interval (msec) | 15 [10–22] | 15 [10–22] | 15 [11–21] | 0.77 |
| HV≥100 after class I challenge, *n* (%) | 14 (3.2) | 11 (3.4) | 3 (1.8) | 0.27 |
| Intra or infra-Hisian AV block after IC challenge, *n* (%) | 15 (6.0) | 10 (6.4) | 5 (5.4) | 0.749 |
| Positive class I challenge, *n* (%) | 25 (10.3) | 17 (11.6) | 8(8.4) | 0.433 |
| cSNRT (msec) | 210 [153–280] | 206 [150–278] | 220 [160–294] | 0.492 |
| VT induction, *n* (%) | 6 (3.6) | 2 (1.9) | 4 (6.1) | 0.211 |
| EPS positive for aAVB/sCD, *n* (%) | 193 (43.6) | 129 (46.4) | 64 (37.8) | 0.118 |
| EPS positive for all diagnoses, *n* (%) | 203 (45.8) | 136 (48.9) | 67 (40.6) | 0.089 |
| **Implantable cardiac monitor** | | | | |
| **Patients implanted** | ***n* = 154** | ***n* = 92** | ***n* = 62** | |
| ICM diagnostic, *n* (%) | 77 (50) | 47 (51.1) | 30 (48.4) | 0.742 |
| Asymptomatic finding, *n* (%)* | 23 (29.9) | 14 (29.8) | 9 (30.0) | 0.984 |
| Symptomatic finding, *n* (%)* | 54 (70.1) | 33 (70.2) | 21 (70.0) | |

*% refers to the total of patients diagnosed by ICM.

*HV, His to ventricle; aAVB/sCD, advanced atrio-ventricular block or severe conduction disturbances; VT, ventricular tachycardia; EPS, electrophysiological study; ICM, implantable cardiac monitor; cSNRT, corrected sinus node recovery time; msec, milliseconds.*

diagnostic yield between both sexes (48.4% in women and 51.1% in men, $p = 0.742$; **Table 3** and **Figure 2**).

## Pacemaker Implantation, Clinical Follow-Up, and Prognosis

Patients were followed for a median of 3.4 years [IQR 1.7–6.0 years]. A total of 252 (58.2%) patients required pacing due to bradycardia related to the syncope at the end of follow-up (**Table 4**; **Supplementary Table S3** shows the type of device implanted). Additionally, 2 ICD and 2 CRT-D were implanted due to ventricular tachycardia, 3 pacemakers due to post-surgical AV block, and 3 additional pacemakers because of chronotropic insufficiency. Two patients with VT were treated with antiarrhythmic drugs only due to their comorbidities. In a Cox multivariate analysis, after adjusting for possible confounding variables, women had a lower risk of needing permanent pacemaker implantation compared to men [adjusted HR 0.72 (95% CI: 0.52–0.99, $p = 0.046$); **Table 5** and **Figure 3**].

After the etiological diagnosis and appropriate treatment, 30 patients (8.9%) experienced a syncopal recurrence (**Table 4**), most of them due to a vagal or orthostatic mechanism (**Supplementary Table S4**).

A total of 111 (25.1%) patients died during the follow-up, 73% of them due to non-cardiovascular causes. Only 2 patients experienced sudden death, one 80 years old female with syncope of unknown origin and one 79 years old male with a pacemaker implanted due to AVB 4 years before. The mortality rate in women was 4.5 per 100 person-years (95% CI 3.1–6.4 per 100 person-years) and 7.3 per 100 person-years (95% CI 5.9–9.1 per 100 person-years) in men.

## DISCUSSION

As far as we know, this is the first cohort study to specifically evaluate sex-related differences in patients with unexplained syncope and BBB. In addition, it is one of the largest patient cohorts published evaluating the etiology of syncope and outcomes in this population. The main findings of this study are that women with syncope of unknown origin and BBB are at lower risk of having aAVB/sCD and of requiring pacemaker implantation than men.

In the general population, syncope seems to be more frequent in women (1, 2, 14, 21, 23). In a recent national population-based cohort study that included more than 2.5 million participants, Fedorowsky et al. (21) found that 62% of the patients with syncope were women. However, this proportion is reversed when a cohort of patients with structural heart disease (6, 24, 25) or abnormal ECG (3, 5, 7, 26) is selected, probably because men have a higher prevalence of cardiovascular risk factors and other comorbidities. In our study, which included consecutive patients, 63% were men. Male patients had more diabetes and IHD. Moreover, RBBB was more frequent in men while

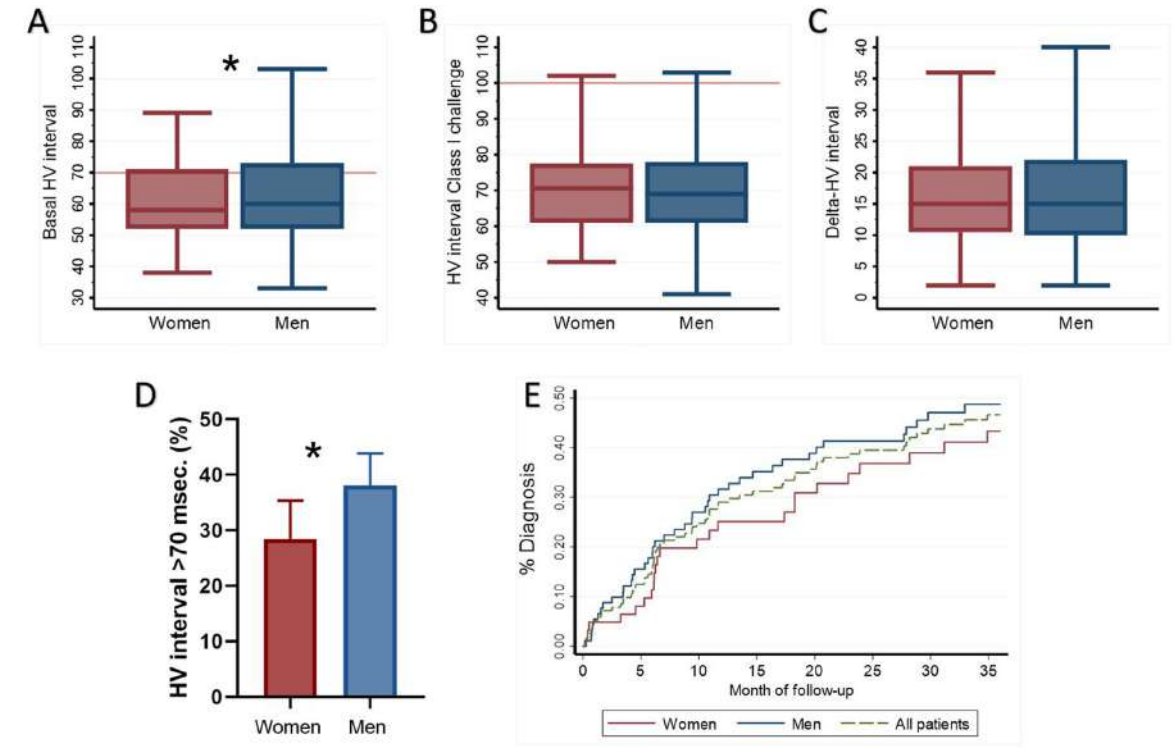



**FIGURE 2 |** Electrophysiological study and implantable cardiac monitor. A comparison between sex of **(A)** baseline HV interval, **(B)** HV interval after class I challenge, and **(C)** absolute increase of HV interval (Delta HV) after class I challenge. **(D)** Percentage of patients with basal HV interval >70 ms in EPS. **(E)** ICM cumulative diagnostic yield according to time of follow-up. *$p < 0.05$. HV, His-ventricular; ICM, implantable cardiac monitor.

LBBB morphology was more frequent in women. These findings in baseline characteristics are consistent with data previously published (3, 5, 7, 26–28), which suggests that patients included in the present study are likely representative of the population with syncope and BBB.

Paroxysmal aAVB is the most likely etiology of syncope in patients with BBB, but other causes also exist. In agreement with previous studies, we found that AVB is the mechanism of syncope in half of these patients, although significant differences were found between the sexes. Women less frequently had aAVB/sCD. In only 44.9% of women, compared to 55.0% of men, aAVB/sCD was found to be the cause of syncope, which represents a risk ratio of 0.81. In other words, women have a 19% lower risk of having aAVB/sCD. Even though there are some differences in patients' baseline characteristics, in multivariate analyses after adjusting for possible confounding variables, female sex was independently associated with a lower risk of advanced AVB (OR 0.44; 95% CI 0.26–0.74). Previous studies had shown that the risk of aAVB in the general population is higher in men (22, 29). For example, in a recent population-based cohort study, Kerola et al. (22) reported that male sex was an independent risk factor for the development of aAVB [adjusted HR 2.04 (95% CI 1.19–3.45)]. Thus, the present study reveals that these findings are also observed in patients with syncope and BBB and it is not explained by differences in the comorbidities alone.

It is well-known that women have a major susceptibility to reflex syncope (11–14). Moreover, previous studies have suggested that SND is also more prevalent in women (9, 10, 15). The higher prevalence of these etiologies in women observed in the general population is also applicable to patients with BBB and it may partially explain the relative lower rate of aAVB in these patients. In our study we only found small and not statistically significant differences in the incidence of these mechanisms between groups, probably because the study is underpowered. Moreover, it should be noted that some of these etiologies were usually diagnosed in Step 1 of the protocol that is not included in the analysis.

Interestingly, we found that the HV interval in the EPS was significantly longer in men. In particular, more men had an HV longer than 70 ms, suggesting that men have a more severe conduction disease. Despite these differences, EPS in women still offers a considerable diagnostic yield as has been previously reported (3, 8, 17), and even more importantly, NPV is similar between both sexes. In patients who were not diagnosed in Step 2, the use of an ICM offered a significant additional diagnostic yield in both groups. Remarkably, only a third of the diagnoses

**TABLE 4 |** Outcomes during follow-up.

| Variable | Total ($n$ = 443) | Men ($n$ = 278) | Women ($n$ = 165) | *P* |
|---|---|---|---|---|
| Median follow-up time (years) | 3.4 [1.7–6.0] | 3.4 [1.5–5.8] | 3.2 [1.8–6.2] | 0.845 |
| **Pacing requirements** | | | | |
| Total patients requiring pacing due to the syncope, *n* (%) | 252 (58.2) | 167 (60.7) | 85 (53.8) | 0.159 |
| Devices implanted during admission, *n* (%) | 198 (44.7) | 134 (48.2) | 64 (38.8) | 0.054 |
| Devices implanted during follow up, *n* (%) | 54 (22.5) | 33 (23.24) | 21 (21.4) | 0.741 |
| **Syncope recurrence** | | | | |
| Total syncope recurrence, *n* (%) | 95 (21.4) | 63 (22.7) | 32 (19.4) | 0.418 |
| Syncope recurrence after diagnosis, *n* (%) | 30 (8.9) | 19 (8.9) | 11 (8.9) | 0.998 |
| **Mortality** | | | | |
| Total deaths, *n* (%) | 111 (25.1) | 81 (29.1) | 30 (18.2) | 0.010 |
| Mortality rate, (x100 person-years) | 6.3 | 7.3 | 4.5 | 0.009 |
| Cause of death | | | | |
| Cardiovascular death | 26 (23.4) | 18 (22.2) | 8 (26.7) | 0.686 |
| Non-cardiovascular death | 81 (73.0) | 60 (74.1) | 21 (70.0) | |
| Unknown | 4 (3.6) | 3 (3.7) | 1 (3.3) | |

**TABLE 5 |** Cox proportional hazards multivariate model to assess the association between sex and pacing needs.

| Factor | HR | HR 95% CI | *p*-value |
|---|---|---|---|
| Unadjusted | | | |
| **Women** | **0.82** | **0.63–1.06** | **0.131** |
| Adjusted | | | |
| **Women** | **0.72** | **0.52–0.99** | **0.046** |
| Age>75 y.o | 1.19 | 0.89–1.61 | 0.247 |
| Hypertension | 1.06 | 0.73–1.54 | 0.765 |
| Diabetes | 1.09 | 0.80–1.48 | 0.586 |
| IHD | 1.22 | 0.86–1.75 | 0.266 |
| LVEF<45% | 0.87 | 0.56–1.35 | 0.542 |
| Atrial fibrillation | 1.09 | 0.70–1.70 | 0.698 |
| Recurrent syncope | 1.20 | 0.89–1.61 | 0.236 |
| LBBB | 1.54 | 0.95–2.50 | 0.080 |
| Isolated RBBB | 0.30 | 0.12–0.68 | 0.005 |
| RBBB and LAFH | 1.05 | 0.65–1.69 | 0.846 |
| Long PR interval | 1.62 | 1.20–2.19 | 0.002 |

*CI, confidence interval; HR, hazard ratio; y.o, years old; IHD, ischemic heart disease; LVEF, left ventricular ejection fraction; LBBB, left bundle branch block; RBBB, right bundle branch block; LAFB, left anterior fascicular block.*

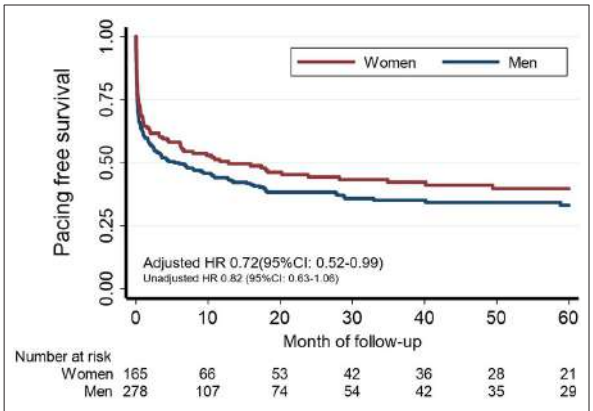



**FIGURE 3 |** Cardiac pacing. Kaplan-Meier pacemaker-free survival estimates curves for women and men.

reached in Step 3 was due to aAVB. This finding supports the systematic use of an ICM in patients where EPS is not diagnostic.

Another key finding of the present study is that women have a lower risk of requiring a permanent pacemaker compared to men [adjusted HR 0.72 (95% CI 0.52–0.99)]. From the clinical point of view, this finding is especially relevant since pacemakers are useful to treat not only syncope due to aAVB/sCD but also due to other types of bradyarrhythmias and some cases of cardioinhibitory reflex syncope. Even though some of these bradyarrhythmias, such as sinus node dysfunction, seem to be more common in women, the overall risk of needing pacing is lower in women compared to men. Ahmed et al. investigated the predictors of pacemaker implantation in patients with syncope receiving an ICM (19). They found that female sex was an independent predictive factor for bradycardia necessitating pacemaker implantation. However, several differences are evident compared to our study. Firstly, only a quarter of the patients included had a BBB and EPS was not routinely performed. Second, less than of half of pacemakers were implanted due to AVB. SND was the most common indication for pacing and as has been commented previously, it seems to be more prevalent in women. Indeed, in the general population, pacemaker implantation is more common in men (9, 15, 29, 30). In a German registry of more than 17,000 patients with primary pacemaker implantation, 53% were men (29). In this large-scale patient cohort, it was found that male patients had more AV blocks when compared with women and less sick sinus syndrome and atrial fibrillation with bradycardia.

Although it was not the aim of the present study, it is remarkable that our results confirm that a systematic stepwise approach to evaluate syncope in patients with BBB, which was initially evaluated in the B4 study (3) and detailed in the ESC guidelines (1), is safe and achieves a high rate of etiological diagnosis allowing to select specific treatment and avoiding the implantation of unnecessary pacemakers. In the present study, once the diagnosis was reached and appropriately treated, only a few patients (8.9%) experienced a syncopal recurrence, most of them due to a vagal or orthostatic mechanism. This finding suggests that the diagnoses were specific. We also found that, compared to men, women had nearly half the mortality rate, probably in relation to a lower comorbidity burden (14).

The optimal management of patients with unexplained syncope and BBB is still controversial (1–4, 8, 18). In fact, the 2017 American College of Cardiology/the American Heart Association (ACC/AHA) guidelines (2) suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies while ESC guidelines (1) recommend opting for a stepwise approach. In light of our results, gender may be an additional factor to be taken into account in the workup of patients with syncope and BBB. A stepwise approach seems reasonable to avoid unnecessary pacemaker implantation, especially in women, given that only half of them will require pacing because of the syncope. Nonetheless, randomized controlled trials are warranted to better answer this important question.

## LIMITATIONS

This study has certain limitations. It is an observational study carried out at a single high-volume center with a dedicated syncope clinic. To minimize potential biases inherent to the study's design, the patients were included consecutively, and possible confounding factors were analyzed. No genetic testing was done systematically to identify certain inherit heart disease that present a higher prevalence of sCD, however, the prevalence of these diseases is low. One aspect worth mentioning is that in our series, the prevalence of reflex/orthostatic syncope was low. It should be noted that some of these episodes were usually diagnosed in Step 1 of the protocol, prior to the patients' inclusion in the study. As such, this series refers not to the global etiology of syncope in this population, rather it focuses on those patients lacking an evident initial diagnosis. The study population was not ethnically diverse. All patients included in the study were from Caucasian or Latin, so the results observed may not be directly extrapolable to other ethnicities. Also, the tilt-test was not used in the workup protocol due to its low specificity in this population (1). However, in selected patients, tilt-test could have revealed an indication for pacing (1). Moreover, the study was not designed to assess predictors of pacemaker implantation in both groups.

## CONCLUSIONS

In this cohort study evaluating sex-specific differences in patients with unexplained syncope and BBB, we found that compared to men, women are at lower risk of having aAVB/sCD and of requiring cardiac pacing. A stepwise diagnostic approach based on EPS and long-term cardiac monitoring have similar diagnostic yield in both sexes and it seems appropriate to guide treatment and avoid unnecessary pacemaker implantation, especially in women.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors upon reasonable request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comitè d'Etica de Vall d'Hebron. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

JF-P prepared the concept, design the study, performed statistical analysis, and draft and editing of the manuscript. NR-G participate in the study design, data review, and manuscript editing. IR-L prepared the clinical database and reviewed the study design. MB-O, CB-M, and MM-B recorded clinical data and revised data in the database. All authors contributed to design the manuscript, patients selection, manuscript review, and agreed with the content of its final version.

## FUNDING

This project was funded by ISCIII, CIBER, and Fundació Marató TV3 and co-funded by the European Regional Development Fund (ERDF-FEDER).

## ACKNOWLEDGMENTS

The authors would like to thank the staff of the Cardiology Department and Arrhythmia Unit for their support in patient management, monitoring, and follow-up.

## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fcvm.2022.838473/full#supplementary-material

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**Conflict of Interest:** The Vall d'Hebron Arrhythmia Unit receives fellowship grants from Boston Scientific and Research grants from Abbott. JF-P receives advisory and speaking honoraria from Abbott and Microport. NR-G receives advisory and speaking honoraria from Abbott. BB, JP-R, and AS-O receive speaking honoraria from Abbott.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## 5.4. Publication 4

**Francisco-Pascual J**, Rivas-Gándara N, Maymi-Ballesteros M, Badia-Molins C, Bach-Oller M, Benito B, Pérez-Rodón J, Santos-Ortega A, Roca-Luque I, Rodríguez-Silva J, Jordán-Marchite P, Moya-Mitjans À, Ferreira-González I. Arrhythmic risk in single or recurrent episodes of unexplained syncope with complete bundle branch block. Rev Esp Cardiol (Engl Ed). 2023 Aug;76(8):609-617. English, Spanish. doi: 10.1016/j.rec.2022.11.009. Epub 2022 Dec 17. PMID: 36539183.

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doi: 10.1016/j.rec.2022.11.009

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doi: 10.1016/j.rec.2022.11.009

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doi: 10.1016/j.rec.2022.11.009

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# 6. OVERALL SUMMARY OF RESULTS

This thesis has provided novel and clinically relevant findings in several aspects of the etiology, management, and prognosis of patients experiencing unexplained syncope that are at high risk of arrhythmic origin. This work aimed to answer specific clinically relevant questions that had not been properly investigated to date. Specifically, the research was focused on three different populations who are at high risk for arrhythmias: patients with SAS, patients with mid-range left ventricular disfunction and patients with BBB.

In summary, the main findings of this research are as follows:

1. Syncope in patients with SAS is a complex condition, not solely related to mechanical outflow tract obstruction. In fact, two-thirds of this population experienced syncope caused by either bradyarrhythmia or reflex syncope.
2. In patients with SAS, syncope of unknown cause was associated with a poor prognosis. Regardless of the treatment for the valve disease, there was an increased short- and medium-term mortality observed in patients with syncope of unknown cause.
3. Arrhythmic syncope was frequent in patients with SAS. Undiagnosed and therefore untreated arrhythmic disorders likely explain the increased mortality observed in patients with syncope of unknown origin.
4. An arrhythmic event is the most common cause of syncope in patients with mid-range left ventricular dysfunction. Among this population, AVB is the most common rhythm disorder, accounting for almost half of the cases, while ventricular arrhythmias were observed in only one out of ten patients.
5. In patients with syncope and MR-LVD without other indications for ICD implantation, the application of a systematic diagnostic protocol based on risk stratification, EPS and/or the implantation of an ICM enables a substantial number of diagnoses to be established and aids in guiding treatment. This approach is safe and helps reduce the unnecessary implantation of ICDs.
6. The presence of conduction disorders in the basal ECG in patients with syncope and MR-LVD is the strongest predictor of AVB.

7. AVB is the primary cause of unexplained syncope in women with BBB. However, when compared to men, the incidence of AVB is lower in women, and in over half of the cases, syncope is attributed to other causes. Additionally, women have a lower risk of requiring pacemaker implantation.
8. The negative predictive value of EPS in patients with BBB is similar in both genders. Moreover, in patients with negative EPS, the implantation of an ICM provides a significant additional diagnostic yield in both sexes.
9. Patients with BBB and unexplained syncope are at a high risk of an arrhythmic etiology, even after the first syncopal episode. Both patients with a SSE and those with RSE exhibit similar arrhythmic risk and prognosis. Additionally, the diagnostic yield of tests, the requirement for pacemaker implantation, and the rate of recurrences after diagnosis are also similar. Due to these reasons, the management approach would be similar, regardless of whether the patient has experienced only one syncopal episode.
10. It is ratified that a stepwise protocol for evaluating patients with syncope and BBB is safe and achieves a high rate of etiological diagnosis. This protocol enables the selection of specific treatment and avoids the implantation of unnecessary pacemakers.
11. The multicausality of syncope is also apparent in patients with SHD. Although a primary cause of syncope can be identified, it cannot be only attributed to a single factor in some of these patients. Instead, it is influenced by a range of factors associated with their underlying heart condition.

# 7. OVERALL SUMMARY OF THE DISCUSSION

## 7.1. General and transversal findings

Despite each of the three parts of this thesis focusing on different types of patients, they share common characteristics and goals. Therefore, when the articles are evaluated together, the overall collection provides interesting cross-cutting findings. In the following sections, the most relevant cross-cutting aspects are reviewed.

### 7.1.1. Syncope work-up based on risk stratification and systematic stepwise approach

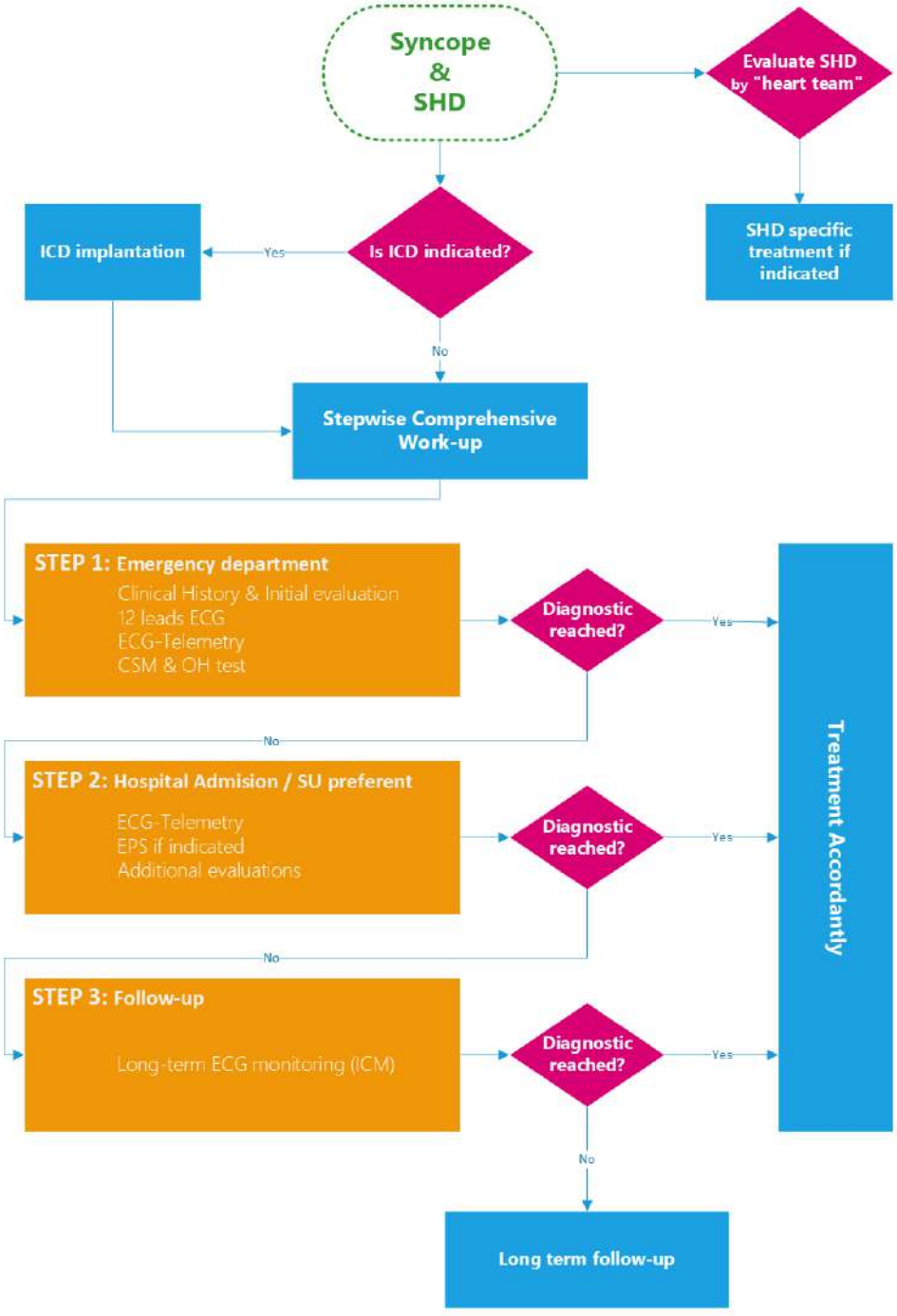
One of the key aspects emphasized by all the studies presented in this thesis is the importance of evaluating patients with syncope and high arrhythmic risk using a stepwise systematic predefined protocol, rather than relying only on a specific exploration or procedure, such as the implantation of an ICM.

As extensively commented in the introduction section, several examinations and tests may be useful for evaluating patients with T-LOC[1]. The diagnostic yield of these explorations depends not only on the specific test itself but also on the subgroup of patients being evaluated and the timing of the assessment[1,38,42,46,49,50,80,88,100,168,169]. For this reason, it is important to systematically perform these tests in a specific order according to the patients' characteristics. This approach aims to increase efficiency and ensure safety. Patient safety is extremely important but also challenging in this population. Syncope can be the first manifestation of a life-threatening arrhythmia, and its misdiagnosis can have catastrophic consequences[1,9,34,120,122,170]. On the other hand, overacting carries a risk of iatrogenic adverse events.

These facts are clearly evident in the compendium of studies included in this thesis. In contrast with the studies in parts 2 and 3, part 1 involved a retrospective analysis where a predefined work-up for syncope was not implemented. Not only do they have a higher proportion of unknown etiologies, but also patients without a final diagnosis carry a worse prognosis. This observation was also noted in the Framingham Heart Study, where an increased risk of death was documented in patients with unexplained syncope (HR = 1.32; 95% CI, 1.09-1.60)[10]. However, this elevated mortality risk was not observed in the prospective studies conducted in parts 2 and 3, where a predefined protocol for syncope work-up was implemented. We

believe that a well-designed systematic protocol facilitates the identification of severe etiologies with prognostic implications, even though more than one in four patients still have an unknown cause of syncope. Consequently, it identifies a group of patients who, despite the undetermined cause of syncope, exhibit a very low risk of adverse events. In other words, the negative predictive value of the work-up for life-threatening arrhythmias must be high.

**Figure 9: Proposed stepwise diagnostic algorithm for the management of syncope in patients with structural heart disease**




*SHD: Structural Heart disease; ICD: Implantable cardiac defibrillator; ECG: Electrocardiogram; CSM: Carotid sinus massage; OH: Orthostatic hypotension; EPS: Electrophysiological study; ICM: Implantable cardiac monitor.*

With possible minor modifications in certain patient subgroups, *Figure 9* provides a comprehensive step-by-step approach that can be beneficial for the majority of high-risk profile syncope patients. It is worth noting that a high-risk profile can be determined based on the clinical history and a baseline 12-lead ECG.

In brief, the diagnostic protocol that we propose for syncope in this population consists of three steps. Importantly, in patients with severe SHD or genetical disease and with criteria for ICD implantation according to specific guidelines, an ICD must be implanted irrespective of the completion of the diagnostic workup for the etiology of syncope. Additionally, the underlying heart disease should be evaluated by the heart team and managed appropriately.

*Step 1* involves an initial assessment, normally done in the ED. A systematic approach is followed, encompassing a thorough clinical history, physical examination, assessment for OH, and CSM (for patients aged 40 and above without contraindications). General bloodwork, chest x-ray, 12-lead ECG, 12-24 hour telemetry monitoring, and transthoracic echocardiogram (if a prior echocardiogram within the last 6 months is unavailable) are performed. In cases where no definite or highly probable diagnosis is reached, the syncope is considered unexplained, and the patient is typically admitted to the hospital with continuous ECG monitoring. Additional diagnostic tests such as exercise stress test, myocardial perfusion gamma scan, or magnetic resonance imaging may be carried out at the discretion of the clinician based on the suspected diagnosis and applicable recommendations.

*Step 2* involves hospital admission with continuous ECG monitoring and consideration of an invasive EPS if the following criteria are met: 1) Presence of conduction disorder on the baseline ECG, 2) Clinical, electrocardiographic, and/or imaging evidence of myocardial scar (history of myocardial infarction, presence of Q waves on surface ECG, presence of late enhancement on cardiac MRI, and/or presence of necrosis on myocardial perfusion SPECT scan), 3) History of palpitations preceding the syncopal episode. If these criteria are not met, an EPS is not performed, and the patient proceeds to Step 3.

*Step 3* involves the implantation of an ICM with subsequent clinical monitoring.

As noted, in addition to the clinical history, the EPS and the ICM play a major role in the work-up. Some consideration must be given. The diagnostic yield of EPS for syncope is typically low, especially in patients with a normal ECG. However, the EPS still plays a significant role in diagnosing syncope in patients with a high clinical risk profile, particularly those with myocardial scar or conduction disturbances. In addition to providing a substantial number of diagnoses, the EPS is likely the most effective tool for identifying patients at lower risk. Numerous studies in various patient subgroups have demonstrated a low risk of arrhythmias following a negative EPS [3,49–51,100,106,163,171]. However, its negative predictive value is suboptimal

(around 70%)[148], and in most cases, further evaluation is still necessary. The implantation of an ICM allows for additional diagnostic yield, and it is safe, as it is shown in the studies presented in the thesis. (*Table 4*)

**Table 4: Electrophysiological study and implantable cardiac monitor diagnostic yields reached in the different populations studied in this thesis**

| Study group | EPS diagnostic yield | ICM diagnostic yield |
|---|---|---|
| **Severe Aortic Stenosis** | 63% (29%-96%) | 50% (9%-90%) |
| **MR-LVD** | 54% (44%-64%) | 35% (21-49%) |
| **Bundle branch block** | 50% (46%-54%) | 47% (40%-55%) |

Data is expressed as Percentage (95% confidence interval)

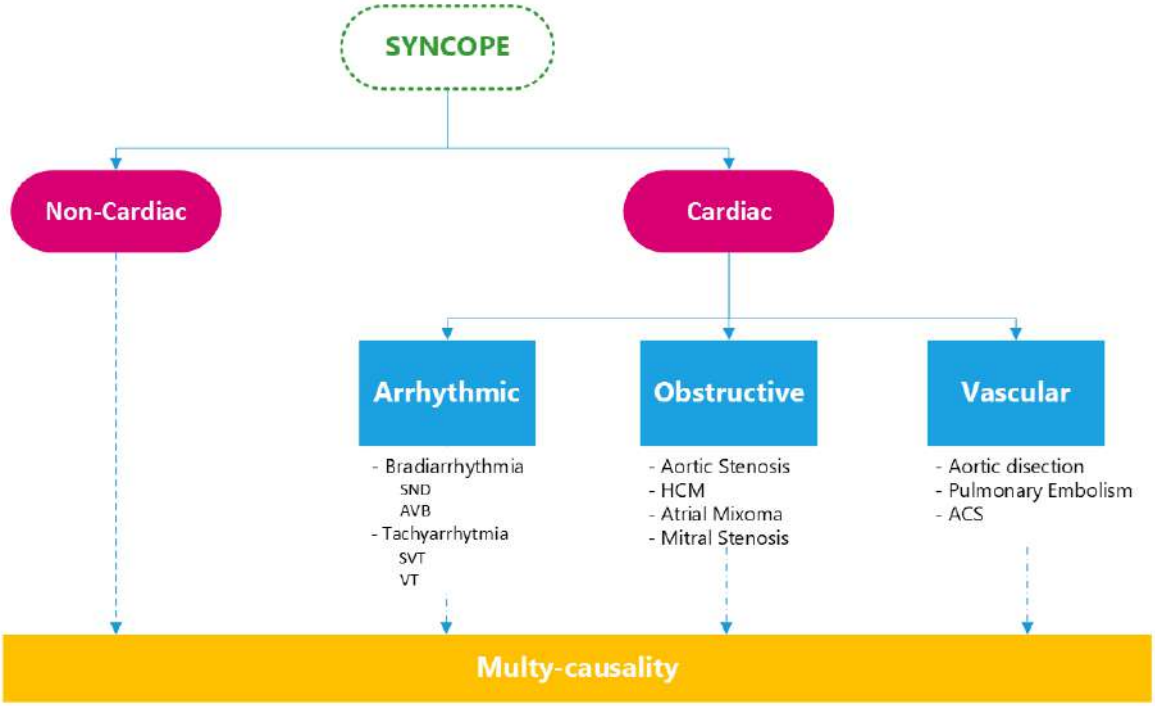
*EPS: Electrophysiological study; ICM: Implantable cardiac monitor, MR-LVD: Mid-range left ventricular dysfunction.*

It is important to emphasize that, in our opinion, and supported by the results of our studies, in patients with arrhythmic risk the implantation of an ICM should be considered as the final step. Although some studies have examined early ICM implantation without other investigations such as an EPS[88,153,172–176], this approach may be less safe. The potential to register the arrhythmic cause of a SCD raises concerns when monitoring high-risk patients. It is likely that the most severe patients at a higher risk of arrhythmic events leading SCD be identified in Steps 1 and 2, which explains the absence of significant adverse events observed in our studies.

### 7.1.2. Arrhythmic and other causes of syncope in patients with structural heart disease

A cardiac cause of syncope, especially arrhythmic, is always a concern in patients with SHD due to its worse prognosis and risk of SCD [1,9,10,15,177–179]. Ventricular arrhythmias are probably the most feared and likely the most typical cause one thinks of in this context[13,180]. However, as mentioned previously, multiple other causes of syncope can be present. In fact, patients with SHD have multiple factors that predispose them to an arrhythmic event, but they also have other factors such as polypharmacy or some degree of autonomic dysfunction that predispose them to more benign causes of syncope[3,100,177]. Furthermore, multicausality is also possible in these patients[2,100,177,181]. (*Figure 10*)

**Figure 10: Possible causes of syncope in patients with SHD**




*ND: Sinus node disfunction, AVB: Atrio-ventricular Block; SVT: Supra-ventricular tachycardia; VT: Ventricular tachycardia; HCM; Hypertrophic cardiomyopathy; ACS: Acute coronary syndrome.*

The studies in this thesis effectively illustrate these facts. The articles in Parts 1 and 2 of the thesis focus on two cohorts of patients with severe SHD, specifically SAS and cardiomyopathy with MR-LVD. While the articles in Part 3 are based on a cohort of patients with BBB, it is noteworthy that approximately one in four patients also had SHD, and in over 15% of the patients, the EF was less than 45%.

*Table 5* summarizes the main causes of syncope identified in our studies. An arrhythmic event was consistently observed as the most frequent cause of syncope in nearly half of the patients, despite the different types of SHD and baseline characteristics across the different studies. Notably, VT accounted for only a small percentage of the arrhythmic events, with AVB being the most commonly documented arrhythmia. Less severe causes such as reflex syncope and OH were also identified, albeit in a significantly smaller proportion. It should be noted that the prospective studies presented in our research excluded patients with an obvious cause of syncope during the initial evaluation. This may explain the lower number of reflex/OH causes detected, as these are often diagnosed based on the initial clinical history and physical examination.

**Table 5: Main causes of syncope in different populations studied in this thesis**

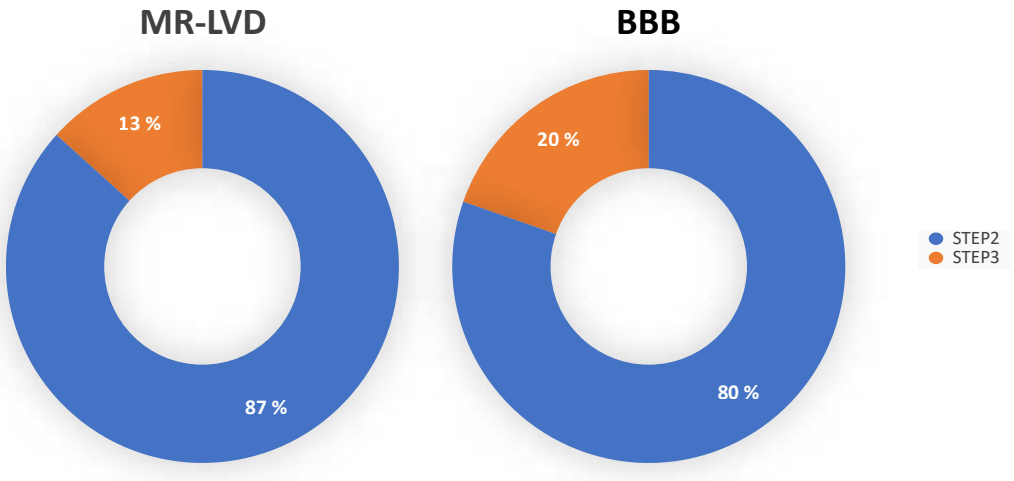
| Cause of syncope | SAS | MD-LVD | BBB |
|---|---|---|---|
| **AVB** | 23% | 45.2% | 51% |
| **SND** | 8.2% | 2.9% | 4.4% |
| **Reflex** | 9.8% | 3.8% | 3.4% |
| **VT** | 0% | 9.6% | 1.4% |
| **Other** | 24.6% | 6.7% | 13.8% |
| **Unknown** | 34.4% | 31.7% | 26% |

Data is expressed as percentage.

*SAS: Severe Aortic Stenosis, MR-LVD: Mid-range left ventricular dysfunction; BBB: Bundle branch block; AVB: AV block; SND: Sinus node disfunction; VT: Ventricular tachycardia.*

A recent study found that reflex syncope was the predominant cause of syncope in patients with negative EPS, SHD and LVEF >30%[3]. In this study, only 1 out of 41 evaluated patients had an arrhythmic cause (AVB). These results contrast with the findings observed in the studies of this thesis. Although the proportion of arrhythmic diagnoses is lower after a negative EPS, it is still significant. For instance, in patients with MR-LVD 10 out of the 16 diagnoses reached in Step 3 of the protocol were arrhythmias. Similarly, in patients with BBB, more than one in four patients monitored with an ICM had arrhythmic events. Therefore, our results justify the implantation of an ICM in patients without a prior diagnosis, despite a negative EPS. (*Figure 11*)

**Figure 11: Percentage of arrhythmic syncope diagnoses reached at each step of the diagnostic algorithm**




The graphics represent the percentage of the total arrhythmic diagnoses reached at each step of the diagnostic algorithm in different populations studied in this thesis.

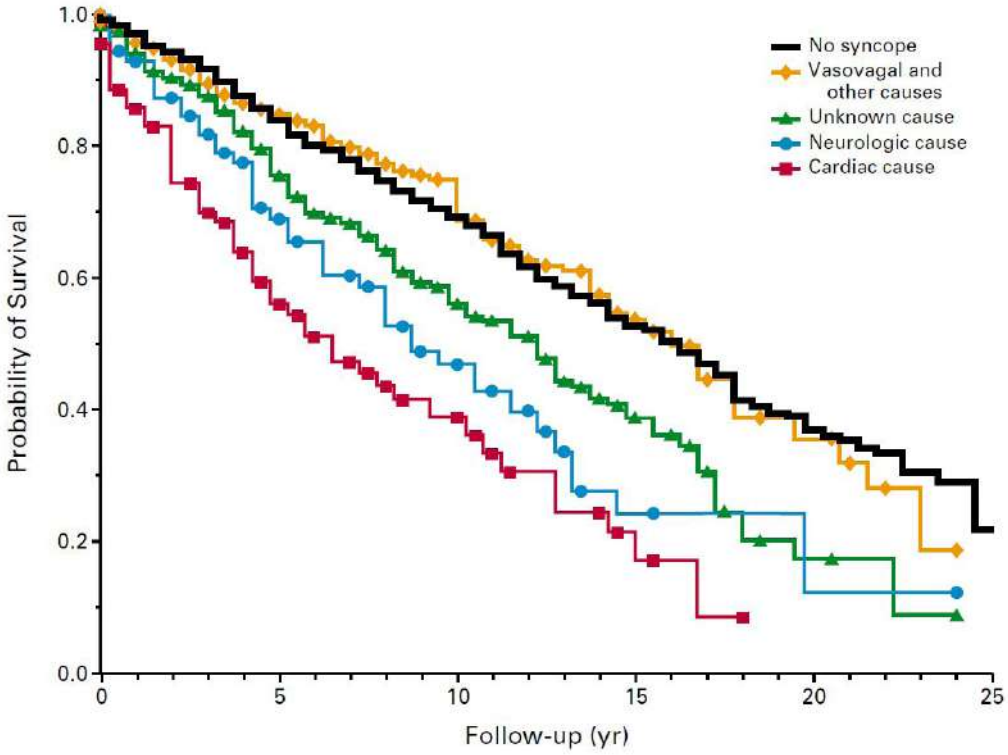
*MR-LVD: Mid-range left ventricular dysfunction; BBB: Bundle branch block.*

In summary, the studies demonstrate that arrhythmic syncope is indeed a common cause of syncope in patients with SHC. However, it is important to note that VT represents only a small percentage of the overall causes, while bradyarrhythmias are more frequently observed. It is crucial to recognize that bradyarrhythmias can also be life-threatening, and their misdiagnosis can have an impact on prognosis. Fortunately, pacing is a highly effective treatment option for these patients, not only improving symptoms but also improving their long-term prognosis[18].

### 7.1.3. Prognosis and long-term outcomes

Syncope is a serious symptom with prognostic implications. In the Framingham Heart Study, individuals with syncope of any cause generally had a higher risk of death from all causes compared to the rest of the study population (HR = 1.31; 95%CI 1.14-1.51)[10]. The highest risk of death was observed in patients with syncope of cardiac origin, accounting for 10% of cases (HR = 2.01; 95%CI 1.48-2.73), whereas patients with vasovagal or orthostatic syncope showed no difference in risk of death compared to the general study population[10]. (*Figure 12*)

**Figure 12: Overall survival of participants with syncope, according to cause, in the Framingham Heart Study**




*Reproduced with permission from* N Engl J Med 2002; 347:878-885 (DOI: 10.1056/NEJMoa012407). Copyright Massachusetts Medical Society.

This prognostic implication is likely more associated with the underlying etiology of syncope and the underlying comorbidities rather than the syncope itself[1,10,15,22,182]. Patients with cardiac syncope have been reported to have an overall mortality rate of approximately 50% within five years, with a 30% incidence of death in the first year[10]. Additionally, in patients with syncope of unknown origin, the presence of SHD or conduction abnormalities is linked to a fivefold increased risk of death[10,15,183]. In the studies included in this thesis, the overall mortality is high, but not as high as previously reported. These differences may be attributed to several factors, such as the specific characteristics of each patient cohort, improvements in the treatment of the underlying disease, and the management of syncope. Illustratively, our studies highlight that mortality is closely associated with the severity of the underlying disease and patients' comorbidities. For instance, in the cohort of patients with SAS, one-third of patients died within a median follow-up of 2.5 years, whereas in the other studies, the mortality rate was approximately 20% with a similar follow-up duration. In this regard, it is important to emphasize that the majority of patients in these studies died from non-cardiovascular causes, underscoring the significance of comorbidities in the overall prognosis. As indicated in the *Table 6*, this proportion was higher in the cohort of patients with BBB, which had a notably lower percentage of severe SHD.

**Table 6: Mortality rate and causes of mortality in the different populations studied in this thesis**

| Study group | Mortality rate+ | Sudden/ Unknown* | Cardiovascular* | Other* |
|---|---|---|---|---|
| **Severe Aortic Stenosis** | 11.7%p-y | 19% | 33.3% | 52,4% |
| **MR-LVD** | 8.1%p-y | 11.1% | 33.3% | 55% |
| **Bundle branch block** | 6.3%p-y | 1.4% | 20.2% | 78.4% |

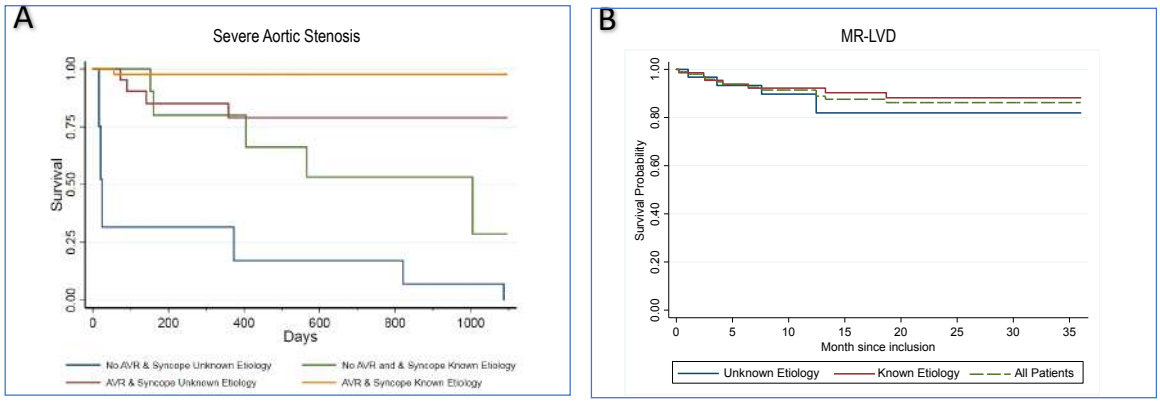
*The percentage values refer to the distribution of the cause of death by category

*%p-y: per 100 person-years; MR-LVD: Mid-range left ventricular dysfunction*

Crucially, the Framingham Heart Study also recorded an elevated risk of death in patients with unexplained syncope (HR = 1.32; 95%CI, 1.09-1.60)[10]. As mentioned earlier, one of the key concepts provided by this thesis is the importance of delving into the diagnosis of the primary cause of syncope, minimizing the use of the term "unexplained syncope" whenever possible. Similar to the observations made in the Framingham Heart Study, in Part 1 of this thesis, which involved a retrospective analysis without a predefined syncope work-up, we found that patients without a final diagnosis had a worse prognosis regardless of the treatment they received for SHD. While there may be various factors contributing to this observation, our hypothesis is that the differences are mainly explained by a significant number of undiagnosed life-threatening arrhythmic events that were not appropriately detected and treated, thereby directly impacting the prognosis. This hypothesis is supported by the findings in Parts 2 and 3, where a systematic

protocol for syncope work-up was implemented with a focus on identifying arrhythmic causes. In these studies, although a quarter of the syncopal episodes remained unexplained, no implications for mortality were observed. It is possible that a well-designed systematic protocol enables the identification of severe etiologies with prognostic implications. Therefore, patients whose syncope cause remains undetermined after ruling out the most important causes that impact prognosis likely have a more benign origin and exhibit a very low risk of adverse events. (*Figure 13*)

**Figure 13: Mortality according to diagnosis of the main cause of syncope in patients with SAS and MR-LVD**




**A:** Survival analysis in patients with syncope and SAS. Kaplan-Meier analysis adjusted for age according to valve replacement and the etiologic diagnosis of the syncope. **B:** Survival analysis in patients with syncope and MR-LVD. Kaplan-Meier analysis according to valve replacement and the etiologic diagnosis of the syncope.

*AVR: Aortic valve replacement; SAS: Severe aortic stenosis; MR-LVD: Mid-range left ventricular dysfunction.*

Noteworthy, the risk of sudden death was low after the syncope work-up, comparable to what can be expected in patients with similar SHD but without syncope, as will be discussed in the following sections. This observation further supports the previously discussed hypothesis.

Regarding syncopal recurrences, the results from all the studies are consistent and indicative. Following the comprehensive work-up and the implementation of appropriate treatment based on the diagnosis, the incidence of syncopal recurrences was low (less than 10%) in all the studied cohorts. Most recurrences were attributed to orthostatic or reflex mechanisms. These findings are relevant as they confirm the accuracy of the diagnoses made through the work-up and demonstrate the effective treatment of most arrhythmic causes.

Finally, it should be noted that when a stepwise diagnostic protocol was implemented, patients diagnosed at Step 2 (hospital admission) had a lower overall recurrence rate compared to those diagnosed at Step 3 (ICM and follow-up). This finding was entirely expected and is a direct consequence of the purpose of Step 3. The objective of an ICM is to record the cardiac rhythm during a spontaneous syncopal episode. Undoubtedly, this provides the most solid

evidence of the primary cause of syncope, but it implies that the patient has experienced a recurrence. Additionally, ICM allows for the detection of asymptomatic findings that may be considered diagnostic, although this is not the most common scenario. Approximately 1 in 3 patients diagnosed through ICM implantation were asymptomatic.

### 7.1.4. Clinical Implications

The thesis addresses questions with direct clinical implications that had remained unanswered until now. Furthermore, beyond the achievement of the primary objectives of each study, the compilation of results has provided additional information that has undoubtfully reinforce the existing clinical evidence. It is worth noting that this fact is emphasized in the editorial accompanying the publication of Study 4 in the thesis.

The most important clinical implications derived from the main aim of each article and have been mentioned in previous sections. By way of summary, the most significant contributions are as follows:

- **The importance of investigating the underlying cause of syncope in high-risk patients.**

  The findings of our studies support the need to conduct in-depth investigations into the primary etiology of syncope to minimize the number of cases labeled as "unexplained syncope". This approach helps in selecting the most appropriate treatment and improving the prognosis for patients at high risk of arrhythmic origin. Also, the importance of other contributing factors or the multicausality of syncope is highlighted, which should also be appropriately managed to reduce the recurrence of syncope.

- **The value of implementing a systematic work-up protocol for diagnosis and treatment guidance.**

  It has been demonstrated that organizing explorations based on the characteristics of patients and tests is highly efficient, resulting in a significant number of diagnoses. Furthermore, our data suggests that this approach is also safe and guides the specific treatment properly and could avoid overtreatment with implantable devices in some patients. The general work-up proposed in the thesis should be useful for most patients with SHD or other high-risk factors.

- **The prognostic implications of appropriately treating arrhythmic syncope.**

  The research suggests that if the cardiogenic syncope is treated appropriately, the overall prognosis seems to be similar to patients without syncope with the same grade of cardiopathy.

- **The need for heightened focus and appropriate management of certain groups of patients that are sometimes overlooked in clinical practice.**

  Specifically, our thesis has highlighted this fact in patients with SAS, women with bundle BBB and patients with isolated syncope episodes. Importantly, it has been demonstrated that in patients with SAS, it is necessary to conduct a thorough investigation into a possible arrhythmic cause, rather than solely indicating AVR as typically done. Furthermore, the studies have shown that although women with BBB have a lower risk of AVB compared to men, the risk is still significant. In this patient group, it is particularly important to manage syncope according to a stepwise protocol rather than immediately resorting to pacemaker implantation. Lastly, our investigation emphasizes not underestimating the risk of the first syncopal episode and highlights the importance of managing them similarly to patients with RSE.

We believe that the data provided by this thesis will be incorporated into future guidelines and recommendations, as well as integrated into the daily clinical practice of physicians, with the aim of improving patient care.

## 7.2. Specific findings of each part

### 7.2.1. PART 1: Etiology and prognosis of syncope in patients with severe aortic stenosis

AoS is currently the most diagnosed acquired valvular disease. Its incidence is increasing due to the greater longevity of the population, and it is already considered by some authors as a true epidemic[184,185]. Most series estimate a prevalence of around 1-3% in patients aged 65-75 years, which increases to over 4% in cohorts of patients over 75 years[184,186,187].

AS causes a progressive obstruction in the LVOT, resulting in a systolic pressure gradient between the left ventricle and the aorta. To overcome this resistance and maintain cardiac output, the LV hypertrophies, typically concentrically[188,189]. In some patients with severe AS, these compensatory mechanisms are not sufficient to overcome the resistance, and despite maintaining good contractile function, they may experience a decrease in cardiac output or an inadequate increase during exercise, resulting in the appearance of symptoms[101,131,145,190].

Cardinal symptoms in SAS (dyspnea, angina, and syncope) typically appear with physical activity. Exertional dyspnea or exercise intolerance is usually the earliest symptom[189,191,192]. Approximately 60% of patients with SAS report angina, which, in half of the cases, occurs without associated obstructive lesions in the epicardial coronary arteries[193]. It often presents later than exertional dyspnea and is due to the ischemia resulting from the

imbalance between increased oxygen demand and decreased supply. Syncope is the third typical symptom, although it is the least frequent. It is present in 5-25% of these patients in published series[130,145,184,194,195]. Classic theories attribute this symptomatology to a decrease in cerebral blood flow caused by a drop in BP during exercise, resulting from vasodilation of the muscular arteries and a fixed cardiac output that fails to compensate for the decrease in resistance[101,125,130,131]. Despite the recognition that other mechanisms may also be involved, it is common in clinical practice to refer patients for AVR without conducting further evaluation of the underlying causes of syncope[196].

To our knowledge, the study we report in this thesis is the largest contemporary series and the first to analyze the main etiology of syncope and its relevance to the prognosis of patients with AS. Our study reveals two main findings. First, there is a high percentage of alternative causes for syncope other than the obstruction caused by AS. Second, performing an etiological diagnosis of syncope has major prognostic implications for short- and medium-term mortality.

In our study, most syncopal episodes occurred at rest or during low-intensity physical activity, indicating that there are other causes besides the obstruction of the LVOT caused by SAS. Patients with severe AS are typically elderly with a high prevalence of cardiovascular risk factors, comorbidities, and multiple pharmacological therapies[2,186,191]. They are also prone to conduction disorders, arrhythmias, vasovagal reflex, and OH, all of which can cause or contribute to syncope[101,127,135,138,139,197].

After an appropriate work-up it is possible to determine the main cause of the syncope in a high proportion of patients. We found a certain or highly probable cause in the 65.6% of the cases. Importantly, in 82.5% of these patients, a primary etiology other than AS-related obstruction was identified. The most common causes were bradyarrhythmia (35% advanced AV block and 12.5% SND), reflex syncope, or OH. These results support the possible pathophysiologic mechanism discussed above. However, it should be noted that while an alternative primary etiology for syncope was found, AS may still play a role in promoting or aggravating the hemodynamic response.

During follow-up, 21.3% of patients experienced a recurrence of syncope, which is similar to other reports[143,198]. Patients who underwent AVR had a lower risk of syncope recurrence, regardless of the etiology of syncope, supporting the notion that obstruction contributes to syncope development. However, achieving an etiological diagnosis for syncope did not reduce the risk of recurrence. This may be due to the presence of multiple mechanisms or the occurrence of different etiologies for recurrent syncope.

One of the key findings of our study is the prognostic implications of reaching an etiological diagnosis for syncope. Patients in whom the cause of syncope could not be determined had

significantly higher short- and medium-term mortality rates. Sudden death and cardiovascular death after AVR were concentrated in this subgroup of patients, suggesting untreated serious causes of syncope due to a lack of diagnosis. This emphasizes the importance of identifying the precise cause of syncope to guide appropriate treatment. Specifically, bradyarrhythmia might be one of the main underdiagnosed etiologies according to the results of the study and the fact that they respond very well to stimulation therapy. This observation aligns with the findings of Soteriades et al. in a patient cohort from the Framingham Heart Study, where patients with syncope of unknown origin had a higher risk of all-cause mortality compared to the general population (HR 1.32; 95% CI 1.09-1.60)[10]. In contrast, patients with vasovagal syncope had a mortality rate similar to that of the general population. Goliasch et alt. examined the prognosis of patients undergoing AVR according to their prior symptoms[145]. Of 625 patients, 67 had had one or more episodes of syncope prior to the procedure. These patients had a more than two times risk of mortality after AVR compared with patients who did not have syncope. Although patients with syncope exhibited slightly different characteristics on echocardiography, based on our observations, we believe that the increase in mortality could also be partly due to the presence of other causes for syncope, such as underdiagnosed arrhythmias.

It must be noted, that after the publication of the study included in this thesis, two important new papers have been published regarding this topic referencing our work. Keller et al. found that 7% of the patients in their cohort of 1705 individuals with SAS who underwent TAVR experienced syncope prior to the TAVR procedure[195]. Among these patients, 13% of the syncope cases were attributed to arrhythmic events, while 87% were attributed to valvulopathy. These significant differences compared to our study may be due to variations in the diagnostic approach and definitions utilized in the respective studies. Additionally, they did not observe a statistically significant association between syncope and mortality during the follow-up period, although the mortality rate in patients with syncope was twice as high, suggesting a lack of statistical power in the study. These reflections were discussed in a scientific letter submitted by our group that was published in the same issue of the journal[212]. The second study was conducted by San Román et al[143]. They evaluated 53 patients who had experienced syncope prior to AVR. The study revealed that syncope related to exertion did not recur after AVR, in contrast to syncope occurring at rest. Furthermore, they found that syncope at rest identified a population with higher mortality rates. Although this study had limitations, their observations support the findings of our study and emphasize the importance of assessing syncope before undergoing AVR.

Finally, it is worth mentioning that the study we conducted has some limitations as it is an observational study with a limited number of patients. Also, the investigations performed were based on clinical judgment rather than a specific systematic protocol tailored to AS, which could potentially impact the diagnosis rate and prognosis.

Future studies should aim to determine the optimal management approach for these patients by developing new protocols and guidelines. Additionally, it is important to investigate whether the implementation of these systematic protocols would lead to a reduction in the percentage of syncope cases with unknown origins, and whether it would have any impact on prognosis.

### 7.2.2. PART 2: Etiology and prognosis of syncope in patients with mid-range left ventricular disfunction

Left ventricular dysfunction can have multiple causes, with IHD and primary cardiomyopathies being the most common etiologies[199]. LVEF is the parameter most used in clinical practice to assess systolic function of the left ventricle, and reduced values are known to be associated with a worse prognosis[118,199,200].

The clinical practice guidelines for syncope from the ESC recommend that patients with severely depressed LVEF (<35%) presenting with syncope should undergo implantation of an ICD due to a higher risk of sudden death[1,19,199]. In patients with depressed LVEF but above 35%, there are no clear guidelines for management. Patients with left ventricular dysfunction but LVEF >35% have not ICD indication for primary prevention. So is in this specific subgroup where a serious arrhythmic event can result in sudden death, and syncope could be the first manifestation. It has been proposed that in patients with any type of SHD and a negative EPS who have an ICM, most syncopal events are due to neurally-mediated conditions[3,100]. However, the arrhythmic risk evaluation in patients with MR-LVD has not been standardized so far, and there is a lack of data regarding the prognostic implications of syncope, especially in patients with intermediate LVEF values. Ultimately, the etiology of syncope in patients with LVEF 35-50% had not been thoroughly investigated prior to the study discussed in this thesis.

To our knowledge, our study is the first study assessing the etiology and prognosis of syncope with mid-range LVEF using a systematic protocol based on EPS and/or implantation of an implantable cardiac monitor. The study's main finding is that the application of a systematic protocol has a high diagnostic yield with a low sudden mortality rate.

We implemented a standardized diagnostic protocol consisting of three steps, tailored to this specific patient population, by adapting clinical practice guidelines. The initial step, not evaluated in the study, requires the identification of obvious causes of syncope during the initial assessment, and it is typically carried out in the ED. The second step primarily focuses on performing an EPS in patients with a high pre-test probability of arrhythmia induction and/or conduction disorders, along with continuous electrocardiographic monitoring throughout their hospital admission. For patients who did not meet the criteria for EPS or

had negative results, we systematically implanted an ICM as part of the third step. In our study, the EPS demonstrated a high diagnostic yield (53.6%). This diagnostic yield, slightly higher than the average reported in the literature for patients with SHD, can be attributed to our predetermined inclusion criteria for the study which allowed for appropriate patient selection[49,50,106]. Notably, the presence of myocardial scar and conduction disorders correlated with a higher rate of positive EPS results. The ICM provided an additional diagnostic yield of 34.8%, aligning with previously published data[91,174]. With the combination of both steps, we reached an overall diagnostic yield of 68.3%.

In our cohort of patients, arrhythmia was found to be the most common cause of syncope. Among the total patients, 57.7% were diagnosed with a rhythm disorder as the underlying cause of syncope, with a significant proportion (84.5% of total diagnoses) attributed to bradycardias, primarily AVB (45.2% of patients). Ventricular tachycardia was the second cause but occurred less frequently (9.6%). Other studies investigating syncope in the context of SHD also reported a high prevalence of arrhythmic events, although AV block accounted for a smaller proportion of the diagnoses[3,4,50,120,177]. For instance, Link et al. conducted an EPS evaluation in 186 patients with syncope and IHD, and VT was induced in 78 patients (41.9%), while only 14 patients (7.5%) had a positive test result for AVB[171]. In a recent study by Shenthar et al., involving 63 patients with SHD who underwent EPS for syncope evaluation, VT was induced in 27.0% of cases, while AVB was documented in only 7.9%[3]. These discrepancies are likely due to differences in the characteristics of the study populations. In our project, we specifically focus on patients with MR-LVD, which indicates less severe SHD compared to previous studies. Additionally, more than half of our patients had non-ischemic cardiomyopathy, and 60% of them showed no evidence of myocardial scar. Therefore, the lower rate of VT induction is expected. On the other hand, 65.3% of our patients had BBB, which is strongly associated with AV block. This finding is especially relevant because the management of syncope in patients with BFB can vary among different centers. Some authors advocate for the direct implantation of a cardiac pacing device in these patients, which could have led to potential selection bias in certain historical case series where patients with bundle branch block were immediately prescribed a pacemaker and, therefore, these patients were not selected for EPS[9,153,176]. In our project, we included all patients with BBB, regardless of their conduction abnormalities. The high prevalence of BBB in our population likely reflects the pathophysiological relationship between conduction disorders and the development of syncope in patients with SHD.

It is worth pointing out that most of the arrhythmias, whether AV block or VT, were able to be diagnosed in Step 2. Studies in other populations have shown a high proportion of reflex/orthostatic syncope in patients for whom the EPS was negative. Nonetheless, the proportion

of arrhythmic events are still significant. This was also observed in our study, where, in Step 3, arrhythmic events were present in a significant portion of the diagnoses (10 of 16 diagnoses), which justifies ICM implantation in patients without a prior diagnosis.

One of the main findings of the study is that the diagnoses made enabled effective treatment guidance. Accordingly, we implanted a total of 60 devices (57.7% of the patients), although only 11 cases (10.6%) received devices with defibrillation function (ICD or CRT-D). However, this did not appear to impact the prognosis. The rate of syncope recurrence, once a diagnosis was reached and appropriately treated, was very low and mainly related to vasovagal or orthostatic etiologies. None of the patients experienced a recurrent syncope of arrhythmic origin, indicating the specificity of the diagnoses. Consistent with previous studies, the overall recurrence of syncope was significantly higher in patients who did not receive a diagnosis in Step 2 and required ICM implantation. In most cases, the first recurrence of syncope allowed for a diagnosis to be established in Step 3.

A recent analysis by the ESC Heart Failure Long-Term registry assessed 2212 patients with mid-range LVEF (mean 44+-5), with a mean age of 64.2±14.2 years and a prevalence of IHD of 42%[200]. The study reported an annual global mortality of 7.6%, with 51% of the deaths due to cardiovascular causes. Other recently published case series have showed similar mortality rates in patients with MR-LVD[116,201]. In our study, the overall mortality rate was comparable, with 8.1 deaths per 100 person-years, and a larger proportion of non-cardiovascular causes of death (55.7%), likely due to the older age and presence of various comorbidities in the population. It is worth noting that only one patient experienced sudden death during the follow-up period, and there was one other patient with an unknown cause of death, resulting in a rate of sudden or unknown-cause mortality of 0.9 per 100 person-years. These rates are consistent with those reported in the literature for general case series of patients with mid-range left ventricular dysfunction without syncope[102,116,200–202]. A study by Merlo et al. assessed the risk of arrhythmia and sudden death in patients with mid-range ventricular dysfunction and reported an incidence rate of 0.7 per 100 person-years, with only 2 patients (0.6%) having a history of syncope[102]. Our study, guided by the results of the systematic syncope work-up, did not demonstrate a worse overall prognosis compared to the literature data, indicating the safety of the protocol employed.

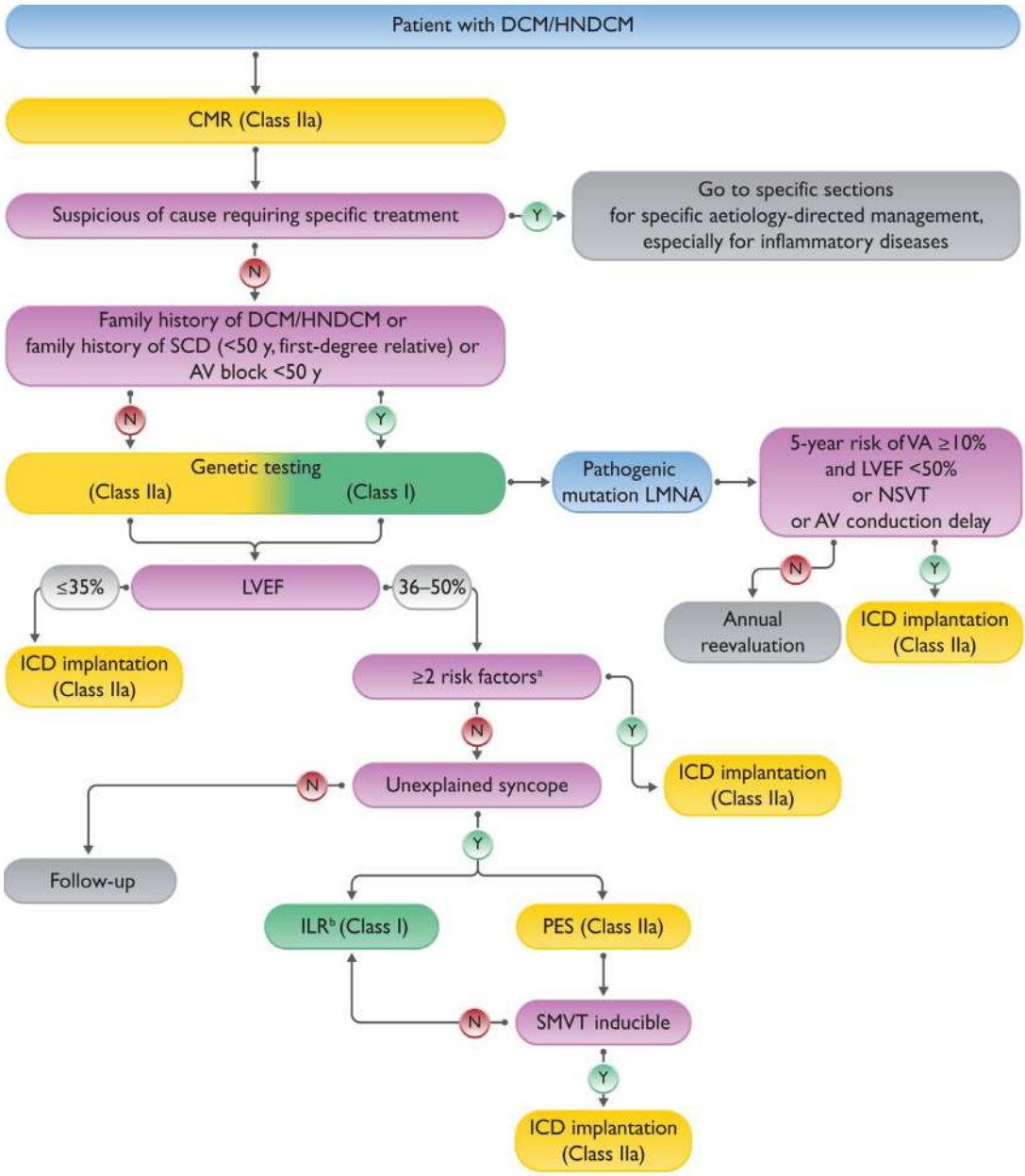
The risk stratification of sudden death in patients with MD-LVD remains a topic of controversy. It is well-established that the absence of sustained VT induction during EPS predicts a lower risk of spontaneous VT and improves prognosis[19,100]. A study by Halliday et al. included 399 patients with dilated cardiomyopathy and LVEF ≥ 40% and found that the presence of late intramyocardial enhancement on magnetic resonance imaging was significantly associated with a higher risk of sudden death (HR 9.2, 95% CI 3.9-21.8)[203]. In our study, the presence of

myocardial scarring did not show an association with increased mortality. However, we did observe a trend towards a higher number of VT inductions during EPS which supports the role of EPS in risk stratification for these patients.

In summary, our study suggests that a stepwise diagnostic strategy and prolonged monitoring may be a safe and effective management alternative, reducing the number of patients requiring an ICD. Nonetheless, the study has certain limitations inherent to its observational design, so it is necessary to conduct randomized controlled trials and continue developing tools that allow for better selection of patients at high risk of sudden cardiac death who may benefit from treatment with an ICD.

It is important to highlight that after the publication of our study, an updated version of the ESC guidelines for the management of VT and prevention of SCD was released[19]. Unlike the current ESC and ACC/AHA/HRS syncope guidelines that suggested an ICD implantation for these patients[1,9], the new ESC VT guidelines propose a therapeutic algorithm based on risk stratification (*Figure 14*). Although it may initially appear similar to the one proposed in our study, there are notable differences. The new ESC VT guidelines recommend ICD implantation (Class IIa) in patients with MR-LVD and two or more risk factors, which include unexplained syncope, LGE on CMR, inducible VT on EPS and certain high-risk genetic variants. If a patient has only unexplained syncope without other factors, the guidelines suggest either the implantation of an ICM (Class I) or performing an EPS (Class IIa). In contrast, in our protocol the presence of LGE on CMR was a criterion for performing an EPS, rather than a direct indication for ICD implantation. We also provided clear indications regarding when an EPS should be performed and when a direct ICM should be implanted. Furthermore, this document does not provide specific recommendations for the investigation of syncope causes, which is crucial for the indication of specific treatments. Therefore, we believe that future recommendations, particularly regarding syncope management, should consider the approach provided in our study.

**Figure 14: 2022 ESC guidelines algorithm for risk stratification and primary prevention of sudden cardiac death in patients with dilated cardiomyopathy/hypokinetic non-dilated cardiomyopathy**




*AV, atrioventricular; CMR, cardiac magnetic resonance; DCM, dilated cardiomyopathy; HNDCM, hypokinetic non-dilated cardiomyopathy; ICD, implantable cardioverter defibrillator; ILR, implantable loop recorder; LMNA: lamin A/C gene; LVEF, left ventricular ejection fraction; N, No; NSVT, non-sustained ventricular tachycardia; PES, programmed electrical stimulation; SCD, sudden cardiac death; SMVT, sustained monomorphic ventricular tachycardia; VA, ventricular arrhythmias; Y, Yes.*

### 7.2.3. PART 3: Risk of arrhythmic syncope in specific populations with bundle branch block

The most common mechanism of syncope in patients with BBB is paroxysmal AVB[1,53,54]. However, it is important to note that these patients may experience syncope due to other mechanisms as well. Consequently, the diagnostic and therapeutic management of these patients poses a challenge, and data in the existing literature regarding the optimal approach is conflicting. Moreover, certain subgroups of patients may exhibit specific characteristics that could alter their arrhythmic risk when compared to the general population[204–206]. In this part of the thesis, we aimed to address two clinically relevant questions. Firstly, whether there are sex-related differences in this population, and secondly, whether patients with RSE have a different risk and prognosis compared to those with a single episode. This is important because, in clinical practice, patients with isolated episodes are often managed more conservatively.

To the best of our knowledge, both articles included in part 3 of this thesis represent the first attempts to address these specific research questions. Additionally, they comprise one of the largest patient cohorts published to date, examining the etiology of syncope and its outcomes in this particular population. As a result, these studies not only address these clinical questions but also validate the initial general findings documented in prior research and provide valuable supplementary data.

The main findings of article 3 (*Sex-Related Differences in Patients With Unexplained Syncope and Bundle Branch Block*) are that women are at lower risk of having AVB and require pacemaker implantation less often than men.

In the general population, syncope appears to be more frequent in women[10,205,207]. However, this proportion is reversed when a cohort of patients with SHD or abnormal ECG is selected, probably because men have a higher prevalence of cardiovascular risk factors and other comorbidities[3]. In our study, which included consecutive patients, 63% were men. Male patients had a higher prevalence of diabetes and IHD. These findings concerning baseline characteristics are consistent with data previously published[54,150,153,155,176], suggesting that patients included in the present study are likely representative of the population with syncope and BBB.

In accordance with prior studies, we observed that AVB is the underlying mechanism of syncope in half of these patients, with notable differences between genders. Women exhibited a lower frequency of AVB, with only 44.9% of women compared to 55.0% of men experiencing AVB as the cause of syncope, resulting in a risk ratio of 0.81. In other words, women had a 19% lower risk of AVB. In multivariate analyses, after adjusting for potential confounding variables, female sex was associated to a lower risk of advanced AVB (OR 0.44; 95%CI 0.26-0.74). Previous investigations have shown a higher risk of AVB in men within the general population. Hence,

this thesis study reveals that these findings also extend to patients with syncope and BBB and cannot be only attributed to differences in comorbidities.

The susceptibility of women to reflex syncope is widely acknowledged[204–206]. Additionally, previous studies have indicated a higher prevalence of SND in women[204,208,209]. The higher prevalence of these conditions among women it may partially explain the relative lower rate of AVB in these patients. In our study we only found small and not statistically significant differences in the incidence of these mechanisms between groups, probably because the study is underpowered. Also, it should be noted that some of these etiologies were usually diagnosed in the Step 1 of the protocol, which is not included in the analysis.

Another important finding of the study is that women have lower risk of requiring a permanent pacemaker compared to men (adjusted HR 0.72(95% CI 0.52-0.99)). From the clinical point of view, this finding is especially relevant since pacemakers are useful to treat not only syncope due to AVB but also due to other types of bradyarrhythmias and some cases of cardioinhibitory reflex syncope. Even though some of these bradyarrhythmias, like SND, seem to be more common in women, the overall risk of needing pacing is lower in women compared to men. Ahmed and col. investigated the predictors of pacemaker implantation in patients with syncope receiving an ICM[30]. They found that, after adjusting for confounders, female sex was an independent predictive factor for bradycardia requiring pacemaker implantation. However, there are evident differences compared to our study. Firstly, only a quarter of the patients included had a BBB and EPS was not routinely performed. Second, less than half of pacemakers were implanted due to AVB. SND was the most common indication for pacing, and as it has been commented previously, it seems to be more prevalent in women. Indeed, in the general population, pacemaker implantation is more common in men[210,211]. In a German registry of more than 17000 patients with primary pacemaker implantation, 53% were male. In this large-scale patient cohort, it was found that male patients had more AV blocks when compared with women and less SSS and AF with bradycardia[210].

The main findings of article 4 (*Arrhythmic risk in single or recurrent episodes of unexplained syncope with BBB*) are as follows: a) Half of patients consulting for syncope had a previous history of at least one other episode; b) The risk of syncope of arrhythmic origin is high and it does not depend on the history of previous episodes; c) EPS and ICM offer a similar diagnostic yield in both groups; d) There are no clinically relevant differences between the two in terms of prognosis after a median of 3 years' follow-up.

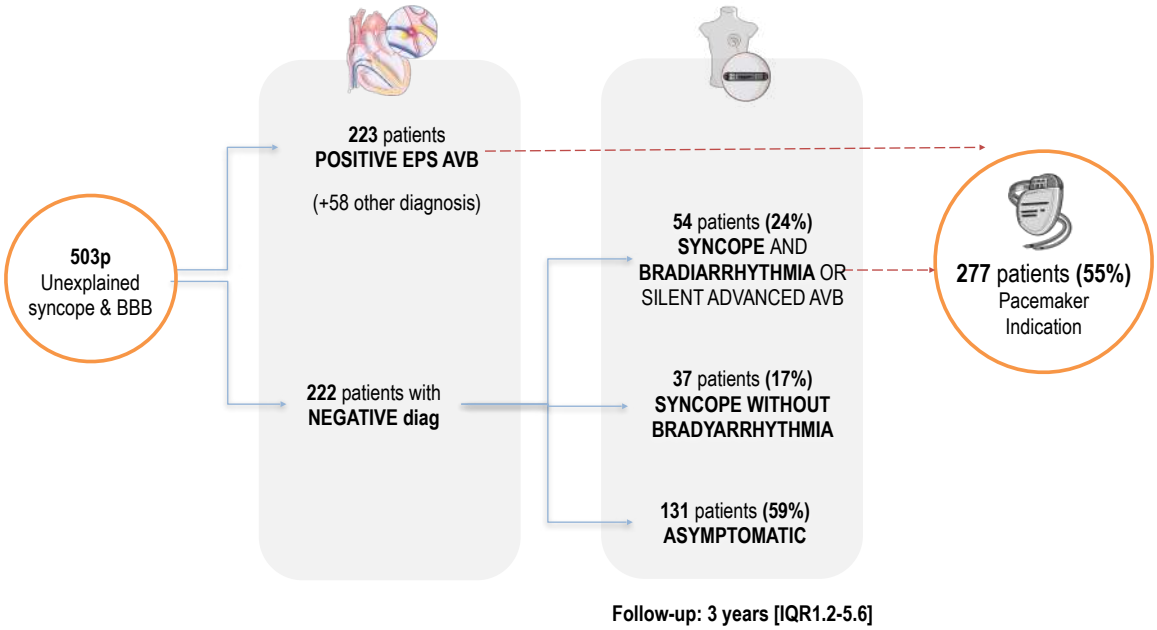
We found that over half of the patients reported one or more previous syncopal events, and up to one third of them had had at least one episode in the preceding 6 months. The risk of syncopal recurrences in the general population has been estimated at between 2 and 30% over

a lifetime. However, the risk is likely much higher in those patients with conduction disturbances and with a higher mean age, as it is the case in our study group.

The key result of our research is that a first syncopal episode in conjunction with the presence of BBB is associated with a high risk of arrhythmic origin, but this risk is comparable to that of patients with RSE. To our knowledge, no previous studies have specifically examined the relationship we are investigating. However, some data on recurrence exist in earlier studies that primarily focused on other aspects and had a smaller patient population. In a prior study conducted by our research group, we found an association between the type of conduction disturbance pattern, PR interval, and the results of the EPS[56]. However, there was no correlation between the number of previous syncopal episodes and the likelihood of a positive EPS. A study by Azocar et al. found that the risk of AVB was higher in patients with prolonged PR intervals or axis deviation, but no significant differences were observed when comparing patients with single or RSE[152]. It is important to note that these earlier studies were not specifically designed to investigate this relationship, and no statistical techniques were employed to evaluate potential confounding factors or interactions. The prognosis was also found to be similar in both groups.

Both articles provide detailed information on the results of the EPS, the diagnostic yield of monitoring with an ICM, and the long-term prognosis of patients. EPS successfully provided a diagnosis for half of the patients. Interestingly, we observed that the HV interval was significantly longer in men. Specifically, men had an HV interval longer than 70 msec more often, suggesting a more severe conduction disease in men. However, there were no significant differences between patients with a first syncopal episode and those with RSE. Importantly, the negative predictive value exceeded 70% in all studied groups, consistent with findings from previous studies[148]. When patients were undiagnosed in Step 2, the use of an ICM significantly enhanced diagnostic yield in all groups, at approximately 50%. Notably, only one-third of the diagnoses made in Step 3 were related to AVB. These findings support the systematic use of an ICM in cases where EPS is inconclusive. (*Figure 15*)

**Figure 15: Diagnostics reached and the number of pacemakers implanted in the cohort of patients with syncope and bundle branch block**




*BBB: bundle branch block; EPS: Electrophysiological study; Diag: Diagnostic; AVB: AV block; IQR: interquartile range*

As expected, patients without a diagnosis in Step 2 had a higher risk of syncope recurrence compared to those diagnosed in Step 2. The first recurrence of syncope often led to the final diagnosis in Step 3. Following an etiological diagnosis, few patients experienced further recurrences, and most were due to non-arrhythmic mechanisms. Since specific treatment is known to reduce the recurrence rate, this finding suggests that the diagnoses were specific and allowed for the effective guidance of treatment in both groups. The absence of an increase in mortality in patients without a final diagnosis observed in our work, in contrast to previous studies[10], may be explained by the appropriate treatment and the likely high capability of the complete protocol to exclude severe causes.

As previously mentioned, a systematic stepwise approach to evaluating syncope in patients with BBB was initially assessed in the B4 study and is highly recommended in the ESC syncope guidelines[1,10,54]. This approach differs from the 2017 ACC/AHA guidelines, which suggest empirical pacemaker implantation after ruling out other causes of syncope[9]. The results of the two studies presented in Part 3 of the thesis support the notion that a stepwise approach is reasonable to avoid unnecessary pacemaker implantation, especially in women, as only half of them will require pacing due to syncope. Furthermore, it emphasizes the importance of managing patients with isolated syncopal episodes in the same manner as those with RSE. Future clinical guidelines and recommendations should consider the findings of this study

to improve patient care, adherence to recommendations, and prevent unnecessary delays in receiving appropriate therapy.

It is important to note that both studies have limitations primarily related to their observational design. Additionally, patients were included after Step 1, which means that initial apparent etiologies of syncope were not studied. Moreover, the reasons why patients did not seek consultation or were not evaluated after their first syncopal episode were not assessed.

# 8. CONCLUSIONS

1. The risk of arrhythmic syncope is high in patients with SHD or conduction disturbances, with a greater risk of AVB than ventricular arrhythmias.
2. Investigating the main cause of the syncopal episode is crucial for guiding treatment and improving prognosis.
3. A validated work-up protocol can be applied to most high-risk patients encountered in daily clinical practice.
4. In patients with syncope and SAS, bradyarrhythmia or reflex causes are more prevalent than obstruction by AS, and patients without an identified etiology have a worse prognosis.
5. For patients with MR-LVD, a systematic diagnostic strategy using EPS and ICM leads to a higher diagnostic yield, effective treatment guidance, and similar prognosis to non-syncope patients.
6. Patients with BBB and unexplained syncope have a high risk of arrhythmic etiology, but women have a lower risk of AVB and needing cardiac pacing compared to men, and patients with SSE and RSE show similar arrhythmic risks and outcomes.

# 9. FUTURE LINES

The results of our research open the door to several future studies that aim to answer additional questions or further validate the initial findings obtained from these observational studies.

Regarding patients with SAS, a prospective study has been designed and is currently underway to validate a stepwise diagnostic protocol specifically for this population. It is hypothesized that implementing this protocol may result in a higher number of specific diagnoses, and like other populations studied, patients with unexplained syncope should not have a worse prognosis after applying it. Additionally, exploring the potential relationship between SAS, fibrosis, and amyloid deposits with conduction disturbances is an interesting research avenue. Further investigation into the additional information that imaging techniques can provide in this field is also warranted.

In patients with MR-LVD, further research is required to validate our approach and identify patients who may benefit from the implantation of an ICD. In this regard, new studies assessing the role of cardiac CMR with late LGE, along with other imaging techniques and biomarkers, should also be taken into consideration.

In patients with BBB, the optimal management strategy remains a topic of debate. Despite the recent publication of the randomized trial SPRITELLY[153], the question of whether it is better to implant a direct pacemaker or adopt a stepwise diagnostic approach remains unanswered. The logical next step would be to design a randomized controlled trial comparing both strategies with appropriate endpoints. Further important research in this area includes studies on the cost-effectiveness of these strategies in selected populations, evaluations of the real-world management of the studied subgroups, and the impact of the findings of this thesis on daily clinical practice.

Furthermore, there is limited information regarding syncope etiologies, prognosis, and outcomes, as well as the optimal management approach for other subgroups of patients like individuals with congenital heart disease (CHD) or specific cardiomyopathies. In this regard, a study has been designed and is currently underway to evaluate these aspects in patients with CHD.

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# 11. ANNEXES

## 11.1. Ethical aspects

The highest ethical standards were applied throughout all phases of the studies, in accordance with the Declaration of Helsinki and the relevant Spanish regulations at the time of the studies. Furthermore, the current regulations regarding the use and confidentiality of data have been adhered to, including the Biomedical Research Law 14/2007 and the Organic Law 3/2018 on Personal Data Protection and Guarantee of Digital Rights. The processing, communication, and transfer of participants' personal data have been conducted in accordance with the provisions of the European General Data Protection Regulation (EU 2016/679). All investigations were approved by the local ethical committee (*Comité de ética de investigación con medicamentos y comisión de proyectos de investigación del hospital universitari Vall d'Hebron*), and their resolutions are attached.

The authors' conflicts of interest are disclosed in each article. Similarly, funding sources are also described in each article.

## *Resolutions local ethical committee Part 1*

**INFORME DEL COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS Y COMISIÓN DE PROYECTOS DE INVESTIGACIÓN DEL HOSPITAL UNIVERSITARI VALL D'HEBRON**

Dra. María Luján Iavecchia, Secretaria en funciones del COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron,

**CERTIFICA**

Que el Comité de Ética de Investigación con Medicamentos del Hospital Universitario Vall d'Hebron, en el cual la Comisión de proyectos de investigación está integrada, se reunió en sesión ordinaria nº 395 el pasado 06/09/2019 y evaluó el proyecto de investigación PR(AG)309/2019 presentado con fecha 01/07/2019, titulado *"Estudi observacional, sobre la incidència, etiologia i predictors de la síncope en pacients amb estenosis aòrtica."* que tiene como investigador principal al Dr. Jaume Francisco Pascual, del Servicio de Cardiología de nuestro Centro.

Versión de documentos:

- Memoria versión 4.0 - Agosto de 2019
- Hoja de información y Consentimiento informado. Versión 2.0. Agosto 2019
- Solicitud de informe. Versión 1. Julio 2019.

El resultado de la evaluación fue el siguiente.

Aprobado

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y su composición actual es la siguiente:

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JOAN SEGARRA SARRIES (Abogado)
**Secretario:**
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VALENTINA BALASSO (Médico)
ESTHER CUCURULL FOLGUERA (Médico Farmacólogo)
INES M DE TORRES RAMÍREZ (Médico)
ELADIO FERNÁNDEZ LIZ (Farmacéutico de Atención Primaria)
INMACULADA FUENTES CAMPS (Médico Farmacólogo)
JAUME GUARDIA MASSÓ (Médico)
JUAN CARLOS HORTAL IBARRA (Profesor de Universidad)
MARIA LUJAN IAVECCHIA (Médico Farmacólogo)
NAYANA JOSHI JUBERT (Médico)
ALEXIS RODRIGUEZ GALLEGO (Médico Farmacólogo)
JUDITH SANCHEZ RAYA (Médico)
MARTA SOLÉ ORSOLA (Enfermera)
PILAR SUÑE MARTÍN (Farmacéutica Hospital)
VÍCTOR VARGAS BLASCO (Médico)
GLORIA GÁLVEZ HERNANDO (Enfermera)
ORIOL ROCA GAS (Médico)
ESPERANZA ZURIGUEL PEREZ (Enfermera)

En dicha reunión del Comité de Ética de Investigación con Medicamentos se cumplió el quórum preceptivo legalmente.

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

IAVECCHIA MARIA LUJAN - X9680234V
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Dra. María Luján Iavecchia

Secretaria en funciones del CEIm

## *Resolutions local ethical committee Part 2*

**INFORME DEL COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS Y COMISIÓN DE PROYECTOS DE INVESTIGACIÓN DEL HOSPITAL UNIVERSITARI VALL D'HEBRON**

Sra. Mireia Navarro Sebastián, Secretaria del COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron,

**CERTIFICA**

Que el Comité de Ética de Investigación con Medicamentos del Hospital Universitario Vall d'Hebron, en el cual la Comisión de proyectos de investigación está integrada, se reunió en sesión ordinaria nº 460 el pasado 16/10/2020 y evaluó el proyecto de investigación PR(AG)511/2020, titulado *"Estudio observacional sobre la etiología y predictores clínicos del síncope en pacientes con función ventricular entre 35-50%"* que tiene como investigador principal al Dr. Jaume Francisco Pascual Servicio de Cardiología de nuestro Centro.

Versión de documentos

| | |
|---|---|
| Memoria de Proyecto | versión 2.0 octubre 2020 |
| HIPVCI | versión 1.0 de julio 2020 |
| Solicitud de evaluación CEIm | versión 1 del 29/07/2020 |

El resultado de la evaluación fue el siguiente:

Aprobado

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y su composición actual es la siguiente:

**Presidente:**
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**Vicepresidente:**
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**Secretario:**
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- INMACULADA FUENTES CAMPS - Médico Farmacólogo
- JAUME GUARDIA MASSÓ - Médico
- JUAN CARLOS HORTAL IBARRA - Profesor de Universidad
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- JUDITH SANCHEZ RAYA - Médico
- MARTA SOLÉ ORSOLA - Personal de Enfermería
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- VÍCTOR VARGAS BLASCO - Médico
- ESTHER CUCURULL FOLGUERA - Médico Farmacólogo
- GLORIA GÁLVEZ HERNANDO - Personal de Enfermería
- ORIOL ROCA GAS - Médico
- ESPERANZA ZURIGUEL PEREZ - Personal de Enfermería
- ANA BELÉN ESTÉVEZ RODRIGUEZ - Abogada experta en protección de datos

En dicha reunión del Comité de Ética de Investigación con Medicamentos se cumplió el quórum preceptivo legalmente.

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

MIREIA NAVARRO SEBASTIAN
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Sra. Mireia Navarro

Secretaria técnica CEIM HUVH

## *Resolutions local ethical committee Part 3*

Vall d'Hebron

**INFORME DEL COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS Y COMISIÓN DE PROYECTOS DE INVESTIGACIÓN DEL HOSPITAL UNIVERSITARI VALL D'HEBRON**

Sra. Mireia Navarro Sebastián, Secretaria del COMITÉ DE ÉTICA DE INVESTIGACIÓN CON MEDICAMENTOS del Hospital Universitari Vall d'Hebron,

CERTIFICA

Que el Comité de Ética de Investigación con Medicamentos del Hospital Universitario Vall d'Hebron, en el cual la Comisión de proyectos de Investigación está integrada, se reunió en sesión ordinaria nº 502 el pasado 01/10/2021 y evaluó el proyecto de investigación **PR(AG)474/2021** promotor Vall d'Hebron Institut de Recerca (VHIR) y titulado *"Estudio observacional sobre la etiología, factores asociados y predictores clínicos del síncope arrítmico"* que tiene como investigador principal al Dr. Francisco Pascual, Jaume del Servicio de Cardiología de nuestro Centro.

Versión de documentos

| | |
|---|---|
| Memoria de Proyecto | versión 1.0 de julio 2021 |
| HIP/CI | versión 1.0 de julio 2021 |
| Solicitud de evaluación CEIm | versión 1 de julio 2021 |

El resultado de la evaluación fue el siguiente:

Aprobado

El Comité tanto en su composición como en los PNT cumple con las normas de BPC (CPMP/ICH/135/95) y con el Real Decreto 1090/2015, y su composición actual es la siguiente:

Presidente:
- SOLEDAD GALLEGO MELCÓN - Médico

Vicepresidente:
- JOAN SEGARRA SARRIES - Abogado

Secretario:
- MIREIA NAVARRO SEBASTIAN - Química

Vocales:
- LLUIS ARMADANS GIL - Médico

Vall d'Hebron

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- ESPERANZA ZURIGUEL PEREZ - Personal de Enfermería
- ANA BELÉN ESTÉVEZ RODRÍGUEZ - Abogada experta en protección de datos

En dicha reunión del Comité de Ética de Investigación con Medicamentos se cumplió el quórum preceptivo legalmente.

En el caso de que se evalúe algún proyecto del que un miembro sea investigador/colaborador, éste se ausentará de la reunión durante la discusión del proyecto.

MIREIA NAVARRO SEBASTIAN

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Secretaria técnica CEIM HUVH

## 11.2. Additional publications related to the topic

### 11.2.1. Review article- Arrhythmic syncope: From diagnosis to management

Francisco Pascual J, Jordan Marchite P, Rodríguez Silva J, Rivas Gándara N. Arrhythmic syncope: From diagnosis to management. World J Cardiol. 2023 Apr 26;15(4):119-141. doi: 10.4330/wjc.v15.i4.119. PMID: 37124975; PMCID: PMC10130893.

World Journal of Cardiology

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*World J Cardiol* 2023 April 26; 15(4): 119-141

DOI: 10.4330/wjc.v15.i4.119

ISSN 1949-8462 (online)

REVIEW

# Arrhythmic syncope: From diagnosis to management

Jaume Francisco Pascual, Pablo Jordan Marchite, Jesús Rodríguez Silva, Nuria Rivas Gándara

**Specialty type:** Cardiac and cardiovascular systems

**Provenance and peer review:** Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

**P-Reviewer:** Moussa BS, Egypt; Soe KK, United States

**Received:** January 6, 2023
**Peer-review started:** January 6, 2023
**First decision:** January 20, 2023
**Revised:** February 2, 2023
**Accepted:** April 10, 2023
**Article in press:** April 10, 2023
**Published online:** April 26, 2023

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## Abstract

Syncope is a concerning symptom that affects a large proportion of patients. It can be related to a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. However, benign causes are the most frequent, and identifying high-risk patients with potentially severe etiologies is crucial to establish an accurate diagnosis, initiate effective therapy, and alter the prognosis. The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope is cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope. Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output and produce syncope. In this review, we summarized the main guidelines in the management of patients with syncope of presumed arrhythmic origin. Therefore, we presented a thorough approach to syncope work-up through different tests depending on the clinical characteristics of the patients, risk stratification, and the management of syncope in different scenarios such as structural heart disease and channelopathies.

**Key Words:** Syncope; Arrhythmia; Electrophysiological study; Loop recorder; Myocardiopathy; Atrioventricular conduction block

**Core Tip:** In this review, we summarized the most important and novel data on arrhythmic syncope, the value of the different diagnostic tests, the management, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. The review emphasized the importance of an appropriate stepwise approach work-up and intervention.

**Citation:** Francisco Pascual J, Jordan Marchite P, Rodríguez Silva J, Rivas Gándara N. Arrhythmic syncope: From diagnosis to management. *World J Cardiol* 2023; 15(4): 119-141
**URL:** https://www.wjgnet.com/1949-8462/full/v15/i4/119.htm
**DOI:** https://dx.doi.org/10.4330/wjc.v15.i4.119

## INTRODUCTION

### *Definition and causes*

Syncope is a total loss of consciousness (T-LOC) secondary to cerebral hypoperfusion, characterized by rapid onset, short duration, and complete spontaneous recovery[1]. It must be differentiated from other T-LOC that do not meet these characteristics, such as T-LOC of traumatic origin, some types of epilepsy, or certain psychiatric disorders. It should be noted that syncope is a symptom that encompasses a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. Therefore, it should not constitute a final diagnosis. It is of great importance to stratify the risk and try to determine the cause.

The term cardiac syncope refers to those episodes where the cause of the cerebral hypoperfusion is directly related to a cardiac disorder, while arrhythmic syncope refers to cardiac syncope specifically due to rhythm disorders. Indeed, arrhythmias are the most common cause of cardiac syncope (Table 1). Both bradyarrhythmia and tachyarrhythmia can cause a sudden decrease in cardiac output, causing the syncope. Non-arrhythmic causes of cardiac syncope are usually related to structural heart diseases with obstruction of outflow and/or inflow of blood. These obstructions can restrict increases in cardiac output on exercise rendering this insufficient to maintain the circulation. Severe aortic stenosis (AoS), hypertrophic cardiomyopathy (HCM), mitral stenosis, atrial myxoma, or severe pulmonary hypertension are some examples of conditions that can cause cardiac syncope *via* this mechanism.

Furthermore, myocardial ischemia and acute ischemic syndromes may also precipitate syncope through multiple mechanisms. It is important to highlight that most of these heart diseases can also be associated with arrhythmias or reflex syncope, and therefore it is often challenging to determine the main cause of syncope in structural cardiac syncope[1-5]. In other words, the mere presence of structural heart disease associated with obstruction does not allow us to conclude that the syncope is due to this mechanism. In many cases, it will be necessary to rule out other possible causes, especially arrhythmic ones.

### *Epidemiology*

It is estimated that almost one in two people will suffer at least one syncopal episode in their lifetime[1,6]. It is a front-line health problem with a high impact on the health system, even though it is known that only a small proportion of patients with syncope seek medical attention. An epidemiological study carried out in the United States showed that the prevalence of patients with syncope in the community requiring medical attention is 9.5 per 100 inhabitants, and that 1 in 10 required hospital admission[7].

The incidence of the first syncopal episode is distributed with a bimodal curve, with a first peak in youth (between 10-30 years of age) and a second peak over 65 years of age. Cardiac syncope is the third most common cause of syncope after reflex and orthostatic hypotension (OH)[1,8,9]. In the emergency department (ED), cardiac syncope accounts for 5%-21% of syncope. In the Framingham cohort, the prevalence of syncope and long-term prognosis were analyzed[10]. The incidence of a first report of syncope was 6.2 per 1000 person-years. Reflex or vasovagal syncope is the most common cause in the general population. In the Framingham cohort it represented 21.0% of the cases, while cardiac syncope made up only 9.5%[10]. It is remarkable that the prevalence of cardiac syncope increases with advancing age[1,9-11]. Cardiac syncope causes less than 1% of syncope in youth (< 40 years)[12] and up to one-third in those over 60 years of age[10,12].

### *Prognosis*

The prognosis of syncope is mostly related to the underlying cause and the presence of structural heart disease. While reflex syncope has an excellent prognosis in terms of survival, cardiac syncope is associated with an increased risk of mortality, especially if it is not identified and treated properly. Patients with reflex syncope have similar survival to patients without syncope[10], with a mortality rate between 4%-12% after 1 year (depending on the patient's age and comorbidities)[10,13-15]. By contrast, the 1-year mortality rate for cardiac syncope rises to 20%-30%[10,13-15]. In the Framingham cohort,

**Table 1 Main cardiac causes of syncope**

| Cardiac syncope | | | |
|---|---|---|---|
| Arrhythmic causes | Bradyarrhythmia | Sick sinus syndrome/sinus node disfunction | |
| | | Atrioventricular block | |
| | Tachyarrhythmia | Supraventricular tachycardia (AVNRT, AVRT, AT, fast AF, *etc.*) | |
| | | Ventricular arrhythmias | Related to structural heart disease |
| | | | Channelopathies and inherited arrhythmia syndromes |
| Non-arrhythmic causes | Mechanical causes | Valvulopathies (aortic stenosis, mitral stenosis, *etc.*) | |
| | | HCM | |
| | | Atrial myxoma | |
| | | Pulmonary emboli | |
| | | Tamponade | |
| | | Severe pulmonary hypertension | |
| Acute coronary syndrome | | | |

AVNRT: Atrioventricular nodal re-entrant tachycardia; AVRT: Atrioventricular re-entrant tachycardia; HCM: Hypertrophic cardiomyopathy; AF: Atrial fibrillation; AT: Atrial tachycardia.

cardiac syncope was associated with a two-fold increase in the risk of death compared with those without a history of syncope, with an approximately 50% 5-year survival[10]. In this study, patients with syncope of unknown origin also had an increased risk of all-cause mortality compared with the general population [hazard ratio = 1.32, 95% confidence interval (CI): 1.09-1.60]. This observation was also made in other studies focused on specific populations[5]. This may be due to the fact that there are potentially serious causes for syncope left untreated due to a lack of diagnosis.

Importantly, in patients with syncope of unknown origin, the mere presence of structural cardiac abnormalities or the evidence of a conduction system disorder is associated with a poor prognosis, increasing the risk of death by a factor of more than five[1,9,16-19]. On the other hand, a structurally normal heart with a normal electrocardiogram (ECG) is usually associated with a benign etiology for syncope and a favorable prognosis[1,20-22].

## DIAGNOSTIC APPROACH AND TEST

### *Initial evaluation, clinical history, physical examination, and ECG*

T-LOC is a relatively common cause of presentation to the ED, and half of these episodes can be attributed to syncope[23]. However, it is important to distinguish it from other causes of T-LOC, to avoid unnecessary investigations in patients with benign causes, and to correctly detect and treat patients with cardiac syncope, which can lead to serious outcomes. The most common condition that can be confused with syncope is probably epilepsy. This confusion is an important phenomenon leading to misdiagnosis with rates ranging from 6%-67%[24]. This misdiagnosis contributes significantly to the numbers of patients with a questionable diagnosis of epilepsy and to those with apparently drug-resistant epilepsy. Syncope can be accompanied with urinary incontinence and/or muscular contractions that can resemble epileptic seizures, making it difficult to differentiate between the diagnoses. While in epilepsy muscular movements are generalized and appear from the beginning of the T-LOC and continue for a few minutes, syncope can also be associated with muscular contractions, which often tend to appear a few seconds after the collapse. They tend to be pleiomorphic and last only a short period of time. Some clinical findings have been suggested to differentiate seizures from convulsive syncope. Tongue biting and confusion on awakening are the most useful in predicting an epileptic origin[25]. In addition, clinical clues that should raise the suspicion for psychogenic pseudo-syncope include prolonged duration, eye closure during the episode, unusual triggers, no recognizable prodromes, and a high frequency of attacks[26].

Another common source of confusion in the ED is represented by falls, especially in the elderly population with non-witnessed T-LOC. On the one hand, elderly people with cognitive impairment and muscular weakness can present with falls as a manifestation of another illness, such as infections or

metabolic disorders[27]. On the other hand, these populations are usually treated with medications that can lower blood pressure (BP) and heart rate (HR) and tend to be dehydrated due to reduced water consumption. This combination of factors can promote orthostatic syncope. Additionally, in the elderly, there is a high prevalence of sinus node dysfunction, conduction disturbances, and structural heart disease, putting these patients at high risk of presenting with cardiac syncope[2]. For all these reasons, current guidelines recommend that repeated falls in elderly people without a reasonable explanation should be approached like unexplained syncope[1].

Once the syncope diagnosis has been established, special attention should be paid to determining the underlying cause. Syncope can be caused by three main different etiologies: Reflex mechanism (also known as neural-mediated syncope); OH; or cardiac syncope, which can be due to arrythmia or structural heart disease. The diagnostic approach should focus on detecting potential cardiac syncope, as it could be clinical manifestation of a primary cardiac disease with high risk of events.

Initial evaluation of any patient presenting with syncope should include three basic elements: (1) Careful history taking regarding the current and previous episodes (including eyewitness accounts); (2) Physical examination; and (3) ECG. Clinical history is probably the most important one, and it should be focused on past medical history, especially previous cardiac conditions, and symptoms related to the episode. Syncope during exertion or in a supine position accompanied by chest pain or palpitations have been described as high-risk factors and should raise the suspicion of cardiac syncope[28,29]. In addition, a family history of sudden cardiac death (SCD) at a young age or personal history of structural heart disease or coronary artery disease (CAD) have been considered high-risk factors. Physical examination does not usually show relevant findings, but it could reveal signs of heart failure or a systolic murmur suggesting structural heart disease. Performing an ECG is crucial, as it can show conduction disturbances, pathological Q waves, or repolarization abnormalities reflecting an underlying cardiac disease[15,30-32] (Figure 1). It is important to mention that every patient with syncope should have an ECG even if there is clear evidence that is a reflex syncope since there are some channelopathies such as long QT syndrome (LQTS) that can present with ventricular arrhythmias after emotional stimulus that can be confused with reflex syncope. Additionally, it has been described that patients with Brugada syndrome (BrS) are more prone to vasovagal syncope[33].

There are several scores developed for risk stratification according to clinical and ECG findings[34]. However, some of them have been tested with external validation cohorts showing poor sensitivity and specificity for detecting cardiac syncope, and they perform no better than clinician judgement at predicting short-term serious outcomes. Therefore, current guidelines do not recommend using them alone to make decisions in the ED. Most items included on these scales are those suggesting cardiac syncope, such as ECG abnormalities or signs or symptoms of structural heart disease.

### *Carotid sinus massage*

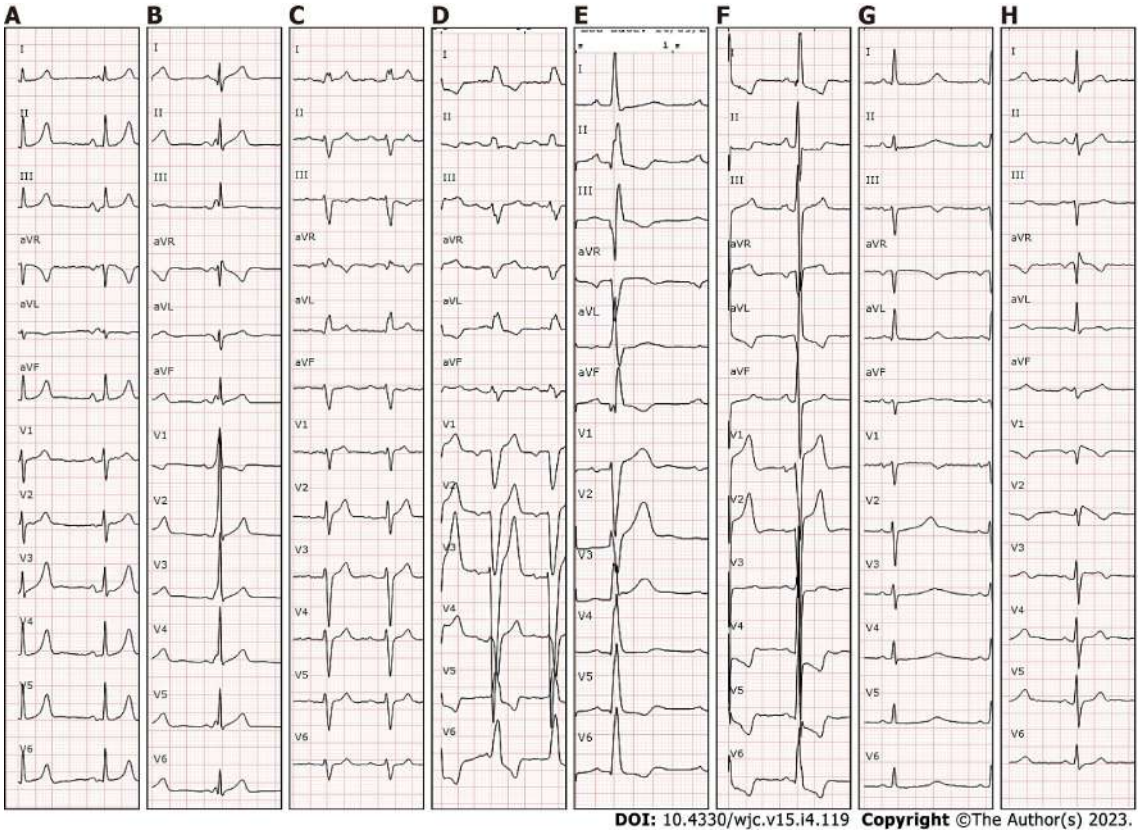
Carotid sinus massage (CSM) consists of applying external pressure to the area of the neck where the carotid sinus is located and is indicated in patients over 40 with syncope. According to current clinical guidelines, carotid sinus hypersensitivity is defined by a sinus pause longer than 3 s or a drop in systolic BP (SBP) higher than 50 mmHg[1,9]. However, this condition is very common among older individuals with cardiovascular disease, even in the absence of syncope. To avoid misdiagnoses, it has been proposed that the diagnosis of carotid sinus syndrome requires reproduction of patient's symptoms and a sinus pause longer than 6 s or more or a drop in mean arterial pressure of 60 mmHg or more[35]. Patients fulfilling these criteria have been shown to have recurrent long pauses on monitoring and to respond well to cardiac pacing[36,37]. The worst complication of CSM is stroke, which is extremely uncommon.

### *Orthostatic challenge*

Orthostatic challenge consists of measuring HR and BP changes between supine and upright positions. It is recommended to measure them during the first 3 min, but it can be extended to the first 10 min if there is a high suspicion of OH since retarded responses have been described[38]. OH is defined by a drop of more than 20 mmHg in SBP, or a drop of more than 10 mmHg of diastolic BP, or if SBP becomes lower than 90 mmHg, and always accompanied by symptoms[39]. OH is very common among elderly people, especially in patients taking anti-hypertensive medications and/or with autonomous nervous system diseases like Parkinson's disease or diabetes, and it represents an important cause of syncope in this population[2,40].

### *Tilt testing*

Tilt testing is recommended in patients with suspected reflex syncope or autonomic failure, including delayed forms of OH or postural orthostatic tachycardia syndrome. The most frequently used protocol is the so called "Italian protocol," which includes a 20-min stabilization phase, followed by administration of sublingual nitroglycerin[41]. It is useful in patients with true reflex syncope, as it has been demonstrated that a positive cardioinhibitory response is highly predictive of asystolic spontaneous syncope[42]. However, it can also be positive in a high percentage of patients with unexplained syncope and even in patients with cardiac arrhythmic syncope. Therefore, it offers little diagnostic value in these




DOI: 10.4330/wjc.v15.i4.119 

**Figure 1 Examples of pathological electrocardiogram that should lead to suspicion of an arrhythmic origin of the syncope.** A: Bayes Syndrome (biphasic p wave in inferior leads compatible with interatrial block, which is related with atrial arrhythmias); B: Pre-excitation syndrome; C: Long PR interval and left anterior fascicular hemiblock; D: Left bundle branch block; E: Inferior necrosis (Q waves); F: Hypertrophic cardiomyopathy; G: Long QT syndrome; H: Brugada syndrome. Suspected supraventricular tachycardia (A and B), suspected atrioventricular block (C and D), suspected ventricular tachycardia (E and F), and suspected polymorphic ventricular tachycardia (G and H).

populations and should not be performed routinely[1]. It has also been tested to evaluate treatment effectiveness, showing little value in this aspect. Finally, in recent years it has been demonstrated that cardiac denervation of parasympathetic ganglia can be highly effective in reducing cardioinhibitory reflex syncope, a technique known as cardioneuroablation[43]. Tilt test might play a crucial role in detecting suitable patients for this promising procedure[44].

### *Electrophysiological study*

According to current European Guidelines[1], electrophysiological study (EPS) is indicated in patients with syncope and bifascicular block (BFB) or previous myocardial infarction or other scar-related conditions, when the etiology remains unexplained after non-invasive evaluation. It could also be considered when syncope is preceded by palpitations or in patients with sinus bradycardia, when the rest of the study has been negative. However, in patients with normal ECG and no structural heart disease, EPS is of poor diagnostic value, and other options like home monitoring are more appropriate. Additionally, a positive EPS is strongly predictive of the origin of the previous syncope, but a negative result cannot exclude arrhythmic events in the future. Therefore, it has a low negative predictive value [45,46].

Sick sinus syndrome is a heterogenous disease where sinus node does not function normally and includes some different kinds of bradycardia such as sinus pauses or junctional rhythm. However, these conditions are relatively common in elderly people, and it is crucial to correlate the bradycardia episodes with the patient's symptoms. A sinus node recovery time (SNRT) longer than 1600 ms is considered abnormal [or corrected SNRT (cSNRT) longer than 525 ms] and has been correlated with sick sinus syndrome[45], but its prognostic value remains unclear. There are few data supporting the benefit of pacing in patients with an abnormal SNRT.

Patients with intraventricular conduction disturbances like BFB or nonspecific conduction disturbance with a QRS greater than 120 ms are at higher risk of arrhythmic events due to His-Purkinje system disease, and in this population paroxysmal atrioventricular block (AVB) is the most common

cause of syncope[46-48]. In these patients with syncope suspected to be related to bradycardia, an HV interval longer than 70 ms or the development of second or third-degree AVB during incremental atrial pacing or pharmacological stress identifies a group with a high risk of developing AVB in the future [49], and pacing is recommended. In addition, some studies have evaluated the relationship between ECG conduction disturbance and the results of EPS, showing that PR interval prolongation and/or BFB patterns make a positive result in EPS more likely rather than a right bundle branch block (RBBB) pattern alone[50] (Figure 2).

Another important part of the EPS in the syncope work-up is programmed ventricular stimulation. In patients with previous myocardial infarction and syncope, the induction of monomorphic sustained ventricular tachycardia (MSVT) is strongly predictive of the cause of syncope and should be managed as spontaneous MSVT[51,52]. In contrast, the induction of polymorphic ventricular tachycardia (PVT) or ventricular fibrillation (VF) is considered a less specific finding, especially with aggressive stimulation protocols[53]. However, induction of PVT or VF may play a role in risk stratification of specific populations such as patients with repaired tetralogy of fallot[19,54-56] or BrS[57,58].

### *Electrocardiographic cardiac monitoring*

ECG cardiac monitoring is one of the cornerstones of the etiological diagnosis of arrhythmic syncope. In addition, there are several areas of interest other than unexplained syncope in which monitoring devices have been investigated[54,59-72]. The objective of ECG monitoring is to correlate the patient's symptoms with the electrocardiographic recordings to reach an objective diagnosis. For this reason, the diagnostic yield of ECG monitoring is primarily related to the duration of monitoring and the frequency of symptoms. Since syncope is often an infrequent event, a long-term monitoring device is usually needed to have a chance of recording a syncopal episode. Moreover, the identification of significant asymptomatic arrhythmias (such as advanced AV block) can be important for the diagnosis. Therefore, as a general rule, ECG monitoring is indicated when there is a high pre-test probability of identifying an arrhythmia associated with syncope and after appropriate risk stratification. The choice of monitoring modality depends on the frequency of events.

In recent years, ECG monitoring systems have incorporated many technical upgrades allowing for improvement in several of the limitations presented by the 24-hr Holter monitor. This evolution of the ECG recording systems include, among other aspects, smaller devices, greater memory capacity for long-term monitoring, better quality of records, or remote monitoring capacity[70] (Table 2).

The main current ECG monitoring devices available are the following:

(1) In-hospital telemetry. In-hospital monitoring should be mandatory in patients with high-risk clinical features, especially if the monitoring is applied immediately after syncope. A recent study that evaluates the optimal ECG monitoring duration of ED patients with syncope found that a serious underlying arrhythmia was often identified within the first 2 h of ED arrival for low-risk patients and within 6 h for medium-risk and high-risk patients[73]. The diagnostic yield of ECG monitoring varies from 2%-20% depending on the patients' characteristics[1,9,69,73-75].

(2) 24/48-hr Holter monitoring. Despite likely being the most frequently used device, the diagnostic yield is as low as 1%-2% in unselected patients due to its short monitoring time[69,70]. Even the newest devices with a longer recording capacity (7-14 d) offer a very limited diagnostic yield. In the opinion of the authors of this review, at the present time, the 24/48-hr Holter should only be considered in patients with daily or very frequent symptoms[69,70]. In different circumstances, other modalities offer not only a greater diagnostic yield but also better cost efficiency per diagnosis.

(3) Loop recorders. These allow for more prolonged monitoring since they do not store a continuous recording. Even though they continuously monitor the ECG, the device just stores a few minutes, which is subsequently overwritten with a newer recording. Only when the device is activated (be it *via* manual activation or through an automatic arrhythmia detection algorithm), it stores from a few minutes before the start of the event until its end in another part of the memory. These stored episodes are protected from overwriting and available for review. In this way, several minutes before activation are stored in the device memory, and the likelihood of recording the trace at the time of the syncope episode is relatively high. Within this category, we have differentiated between external and implantable devices.

External loop recorders. The device uses cutaneous electrodes to record, like the 24 hr Holter monitor. The patients themselves position the electrodes daily. Due to the characteristics of these devices, these systems tend to be worn by patients for no more than a few weeks (usually 3-4 wk, although there are reports of more prolonged periods of time[70,76]). For this reason, in the setting of syncope, the diagnostic yield is no greater than 10%. They are especially useful for the investigation of symptoms that occur every 2-3 wk. Significantly, it has been found in various studies that early recorder use increased the likelihood of diagnostic events during external ECG monitoring[73,77].

Implantable loop recorders (ILR). These are small devices that are implanted subcutaneously, usually in the left parasternal region. They have the disadvantage of being minimally invasive since the latest models have been made significantly smaller. However, these devices allow for a more prolonged continuous monitoring of up to 3 to 4 years, making them especially useful in patients with syncope. Numerous studies have evaluated the diagnostic value and the usefulness of ILRs for the work-up and the diagnostic yield increases up to 30%-50%[5,48,59,62,78-82]. In a meta-analysis of five randomized controlled trials, it was found that initial implantation of an ILR in the work-up provided a 3.7-fold

**Table 2 Main advantages, limitations, and indications of the most commonly used devices for electrocardiogram cardiac monitoring in patients with syncope**

| | Advantages | Disadvantages | Main indications |
|---|---|---|---|
| 24-hr holter | Continuous recording: 12 leads with good correlation with surface ECG; low economic cost per study | Discomfort for the patient; artifacts; maximum recording of 24-48 h (low diagnostic yield); high economic cost per diagnosis | Very frequent (daily) symptoms; in-hospital monitoring (if ECG-telemetry not available) |
| Skin patches | Continuous recording of 7-14 d; good tolerability for patients | Single-use and greater economic cost; only one lead[1]; low diagnostic yield | Frequent (weekly) symptoms |
| External loop recorders | Loop recording (includes beginning and end of arrhythmic event); monitoring for 4 wk; low economic cost per study | Patient discomfort; requires education from healthcare professional on how to correctly place the electrodes; relatively low diagnostic yield | Frequent (weekly-monthly) symptoms |
| Implantable loop recorders | Loop recording; up to 3-yr monitoring (good diagnostic yield); patient does not have to do anything; remote monitoring | Invasiveness and associated complications (infection, bleeding, *etc.*); individual economic cost; single lead | Infrequent symptoms; most useful in syncope |

[1]There are devices with more leads.
ECG: Electrocardiogram.

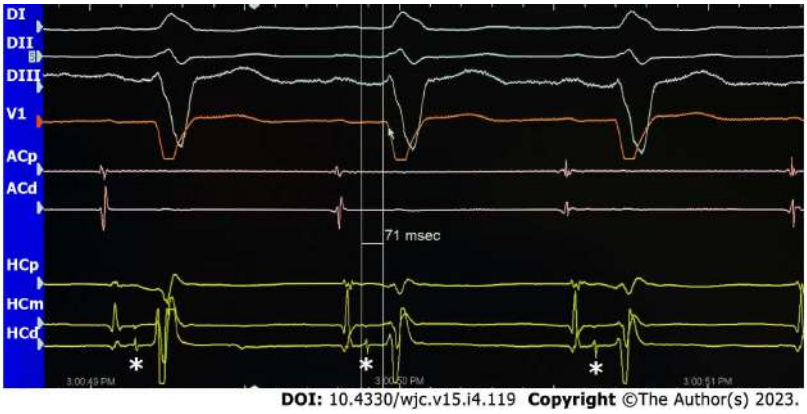



**Figure 2 Electrophysiological study of a patient with syncope and left bundle branch blocked.** Surface electrocardiogram (DI, DII, DIII, V1) (top) and intracardiac electrograms at 100 mm/seg of an electrophysiological study to evaluate infra-Hisian conduction. A diagnostic catheter was placed in the right atrium (pink register: ACp and Acd) and in the His bundle zone (yellow register: HCp, HCm and HCd). *Indicates the His deflection. HV interval, from the onset of the His deflection to the onset of the QRS, is measured with the caliper (71 milliseconds in this case).

(95%CI: 2.7-5.0) increase in the relative probability of a diagnosis compared with the conventional strategy[1,71,83,84]. Different studies have also demonstrated that ILR was more cost-effective than the conventional strategy[69,81,83-85].

(4) Skin patches. They consist of patches of different materials, which adhere to the skin and contain electrodes to obtain one (the most common) or two ECG leads that allow for a continuous ECG recording for 7-30 d of monitoring. Diagnostic yield and limitations are similar to external loop recorders. It should be noted that some new wearable devices like intelligent watches or other ECG prospective intermittent event recorders, which are quite popular nowadays, are generally not useful for syncope workup. These devices start recording only when the patient activates them. They have the limitation of not allowing for the recording of the onset of the episodes, which is often important for diagnosis. Furthermore, if the patient activates the device after recovering from the syncopal episode, in most cases the possible rhythm disorder would have resolved.

### *Other tests*

Autonomic function tests like the Valsalva maneuver or deep breathing test can be considered to diagnose autonomic disfunction, but there is weak evidence that these tests may be useful in patients with syncope. Echocardiography should be performed in all patients with suspected valvular or structural heart disease, as it can detect some conditions that could present with cardiac obstructive syncope (*i.e.,* AoS or cardiac tamponade). Exercise testing is especially useful in patients that have experienced syncope during or shortly after exertion. The main purpose of these tests is to rule out ventricular arrythmias related to CAD or exercise-induced advanced AVB, which is usually located distally to the AV node. Cardiac biomarkers such as high sensitivity troponin and natriuretic peptides

can be elevated in patients with syncope and have been associated with worse outcomes in some case series[86,87]. However, such determinations are highly non-specific and rarely contribute to a certain diagnosis, and they may indicate serious illness rather than myocardial ischemia or heart failure. Therefore, it remains unclear whether they should be determined on a routine basis[88].

## RISK STRATIFICATION

Cardiac syncope is a life-threatening condition. By consequence, the main goal of risk stratification is to identify those low-risk patients with benign causes that can be discharged home and only require medical education from those high-risk patients with syncope likely related with cardiac arrythmias or structural heart disease who require hospital admission for further investigation. This initial evaluation is especially necessary in the ED, where most patients with syncope first consult (Table 3).

For this purpose, several risk scores have been developed. In 2016, the Canadian Syncope Risk Score [34] was published. They included 4030 patients who presented to EDs of three centers in Canada for syncope and analyzed the occurrence of serious events including death, myocardial infarction, arrythmia, structural heart disease, pulmonary embolism, serious bleeding, and procedural intervention within 30 d from admission. Finally, they included nine predictors: (1) Predisposition to vasovagal syncope; (2) Heart disease; (3) Any systolic pressure reading in the ED < 90 or > 180 mmHg; (4) Troponin level above 99$^{th}$ percentile for the normal population; (5) Abnormal QRS axis (< -30° or > 100°); (6) QRS duration longer than 130 ms; (7) QTc interval longer than 480 ms; (8) ED diagnosis of cardiac syncope; and (9) ED diagnosis of vasovagal syncope. Those items suggesting reflex syncope conferred negative points, and those suggesting cardiac syncope conferred positive points. Each patient obtained a final score, with higher scores representing a greater risk of serious events (-3-0 points are considered low risk, while 0-3 points and 4-11 points are considered high and very high risk, respectively).

Recently, the same authors have validated this risk score in another large cohort of 3819 patients, showing very good correlation. Setting a threshold score of -1 point, they achieved very good sensitivity (97.8%) but poor specificity (44.3%) for serious events[89]. In addition, another group of researchers validated the same score in a cohort of 2283 patients from three continents also showing good correlation and better performance when compared with another European risk score[90]. However, they also observed that a simplified model including only the clinical classification (vasovagal, cardiac, or other), also achieved a similar degree of discrimination with regard to the primary outcome, showing that some of the predictors included may have a secondary role.

There are some other scales previously developed, such as the San Francisco Syncope Rule[91] or the EGSY score[29]. Both have shown similar results with good sensitivity but poor specificity. However, lack of reproducibility and remarkable heterogeneity in study design, variables, and outcome definitions of primary studies have prevented widespread use of these tools in clinical practice[92]. Moreover, recently some authors compared the EGSY score with clinical judgement, both alone and in addition to cardiac biomarkers, showing that clinical judgement has the highest diagnostic accuracy[93].

In summary, multiple risk scores have shown good sensitivity but poor specificity for predicting short-term serious outcomes, and they performed no better than clinical judgement. Therefore, they should not be used in isolation for the purposes of decision-making. It is also worth mentioning that, apart from risk scores, some other tests such as EPS, cardiac magnetic resonance (CMR), or stress test may be useful for risk stratification in selected groups of patients, as is discussed above in other sections of this article.

## ARRHYTHMIC SYNCOPE IN SPECIFIC POPULATIONS

As previously mentioned, syncope could be the presenting symptom of an impending sudden cardiac arrest or can be related to more benign conditions such as neuro-mediated syncope or OH. Thus, it is important to correctly stratify the risk of each patient. For this reason, we need to understand the clinical scenario in which syncope takes place. Patients without overt structural heart diseases are at a lower risk of subsequent cardiac complications. Nonetheless, we must also consider some inherited heart diseases, which are primarily electrical, known as channelopathies and that can take place themselves in the absence of structural heart disease. In the following paragraphs we summarized some of those heart conditions that are associated with a higher risk of ventricular arrhythmias and sudden cardiac arrest.

### *Structural heart disease*

**Ischemic heart disease:** Patients with ischemic heart disease (IHD) are at a higher risk of ventricular arrhythmias. It is necessary to differentiate between three stages in the ischemic evolution: (1) Acute ongoing ischemia. A patient suffering from an acute myocardial infarction might have VF and ventricular tachycardia related to the ischemic myocardium[1,19,94,95]. The acute ischemia induces a dispersion of the repolarization that may produce polymorphic ventricular arrhythmias and VF in the

**Table 3 High-risk features suggesting cardiac syncope**

| High-risk features |
|---|
| Past medical history |
| Previous myocardial infarction |
| Previous cardiovascular condition (*i.e.*, BrS, hypertrophic cardiomyopathy, Long QT syndrome, *etc.*) |
| Syncopal event |
| Syncope during exertion or in supine position |
| Syncope associated with chest pain, palpitations, breathless, or abdominal pain |
| Physical examination |
| Signs of heart failure |
| Cardiac murmur suggesting specific condition (*i.e.*, aortic stenosis) |
| Signs of shock |
| Electrocardiogram |
| Conduction disturbance (AV block, bundle branch block) |
| Pathological Q waves |
| Long QT interval |
| Pre-excitation syndrome |
| Negative T waves |

BrS: Brugada syndrome; AV: Atrio-ventricular.

acute setting. In the same way, some patients might present with monomorphic ventricular arrhythmias during acute myocardial infarction, in which a macro re-entrant circuit involving the ischemic tissue is a more probable mechanism. This latter mechanism is much less frequent than the former[94]; (2) In the subacute phase of ischemia, comprising hours to days after the ischemic event, Purkinje-related ectopia is a frequent mechanism for VF and acute cardiac arrest. The premature ventricular complexes are characterized by their very short coupling intervals and by the presence of a normal QT interval. It is believed that the ischemia induces an abnormal calcium release to the cytosol of Purkinje cells, which causes such early post depolarization[94]; and (3) In the chronic setting, which accounts for most patients with syncope and IHD, a frequent mechanism is a ventricular arrhythmia due to macro re-entry in well-established ventricular scars[1,19]. The risk of ventricular arrhythmias is much higher among those patients with IHD with low ventricular ejection fraction[1,19,96].

Ventricular arrhythmias should be suspected in patients with syncope and IHD[1,6,9,97]. If the patient has a left ventricle ejection fraction (LVEF) of < 35% despite optimal medical treatment, an implantable cardiac defibrillator (ICD) is indicated[18,19,98]. These patients have solid evidence of high arrhythmic risk independently of the invasive risk stratification, and an ICD implantation is strongly indicated even if the etiology of the syncope is treated subsequently. This recommendation is strongly supported by large randomized clinical trials (SCD-HeFT, MADIT-II)[99,100] and class 1A recommendation in the 2022 European Society of Cardiology (ESC) guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD, the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure[101], and the 2019 Guidelines on Chronic Coronary Syndromes[102].

When the cause of the syncope remains unknown after an initial evaluation, and there is no apparent direct indication for ICD, an EPS with programmed ventricular stimulation should be performed. If MSVT are induced, the implantation of an ICD should be considered. The induction of polymorphic ventricular arrhythmias or VF has not been consistently related with ventricular arrhythmias or sudden cardiac arrest and no recommendation about ICD implantation can be made in this scenario. Despite the absence of solid evidence, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] recommends performing an EPS in patients with syncope and previous ST elevation myocardial infarction with a class IC recommendation. It is not clear if this recommendation is applicable to patients with a history of coronary revascularization without infarction or in the absence of late gadolinium enhancement in the CMR, and further studies are needed.

As we previously mentioned, the induction of a monomorphic VT in a patient with previous myocardial infarction presenting with syncope is an indication for an ICD implantation. On the other hand, the induction of VF has been traditionally considered as a non-specific result as these patients

appear to have a similar prognosis as patients without any ventricular arrhythmia induction. Brugada *et al*[103] demonstrated that non-sustained PVT and VF are nonspecific responses to an aggressive stimulation protocol including three to four extra stimuli. Brodsky *et al*[104], presenting the results of the AVID trial, were not able to demonstrate that the induction of VF or fast VT (rate > 200 bpm) is related with death or ventricular arrhythmia recurrence ($P$ = 0.07), but the induction of slow VTs (HR < 200 bpm) was independently related with recurrences as monomorphic VT.

Mittal *et al*[53] also evaluated the prognosis of ventricular arrhythmia induction in a cohort of 118 consecutive patients with CAD presenting with syncope. The mean LVEF of their cohort was 42% ± 13%. VF was the only arrhythmia induced in 20 patients (17% of the cohort). There was a survival rate of 89% and 81% at 1 year and 2 years consecutively in the entire cohort, and there were no differences between patients with VF induction or no induced arrhythmia ($P$ = 0.39). By contrast, Link *et al*[105] found contradictory results in their cohort where they followed 274 consecutive patients with CAD and syncope or presyncope. The risk of arrhythmia occurrence was evaluated at the time of presentation with syncope by an EPS. VF was induced in 23 patients (8%) and ventricular flutter (monomorphic tachycardia with CL < 230 ms) in 24 patients (9%). Overall, 41 patients (15% of the cohort) were inducible for monomorphic ventricular tachycardias. After a follow-up of 37 ± 25 mo, 34 patients had ventricular arrhythmias. VF was induced in the initial EPS in 3 out of 23 patients (13% of this group) and in ventricular flutter in 7 out of 24 patients (30% of this group). Considering these results together, the induction of VF/ventricular flutter was predictive of ventricular arrhythmias during follow-up ($P \leq$ 0.001 *vs* non-inducible patients)[105].

Nonetheless, the 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] only have clear recommendations for the induction of sustained monomorphic ventricular tachycardia. Thus, an ICD is recommended in patients with CAD and unexplained syncope with MSVT induced during EPS with a IIa B level of recommendation. The induction of polymorphic VT, VF, or non-sustained ventricular arrhythmias are considered non-specific responses, and considering the absence of solid evidence, no specific recommendations can be made.

Despite the fact that VT should be ruled out in patients with IHD, many other causes may be present in this set of patients[3,9,106,107]. In fact, VT is not the most common cause of syncope. Patients with IHD have some factors that predispose them to other causes. For example, they are often on different hypotensive drugs that predispose to OH or reflex syncope[2]. Also, some conduction disturbances are more frequent in patients with IHD[30,48,50]. In the presence of conduction disturbances on the ECG, advanced AV block is a common cause of syncope[46,50,108]. Importantly, if the EPS is negative, VT is unlikely to be the cause of syncope, with reflex and OH syncope being the most probable etiologies[3,107].

### *Mid-range left ventricular dysfunction*

Patients with left ventricular disfunction are at high risk of cardiac and arrhythmic syncope[6]. In observational studies, unexplained syncope in this population has been associated with an increased risk of sudden death[1,9,79,109,110], although the evidence for the benefit of an ICD is limited. In general, the direct implantation of an ICD is indicated in those patients who fulfil the primary prevention criteria (NYHA class II-III heart failure, with LVEF < 35% on optimized pharmacological therapy). The evidence regarding the management of syncope in patients with mid-range LVEF is even more scant. Current ESC syncope clinical practice guidelines[1], which are similar to ACC/AHA/HRS [9] guidelines, suggest a work-up in line with general recommendations and state that the implantation of an ICD should be considered in patients with systolic dysfunction and unexplained syncope. The implantation of a cardiac monitor (ICM) is an alternative that may be considered in patients with recurrent episodes. Newly published ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD[19] suggest a conservative strategy based on risk stratification and ICM implantation in patients with no other direct indication for an ICD.

Our group has recently investigated a similar strategy based on a stepwise protocol[79]. In summary, the diagnostic work-up for syncope in this population is based on three steps. Step 1 consists of the initial assessment in the ED. In a systematic manner, a clinical history and physical examination are performed, including testing for OH and CSM (if not contraindicated), general bloodwork, chest x-ray, and 12-lead ECG, as well as 12-24-h telemetry monitoring and a transthoracic echocardiogram. In cases where no certain or highly probable diagnosis is reached, it is considered unexplained syncope, and the patient is admitted to the hospital. Step 2 involves the hospital admission with continuous ECG monitoring and carrying out an invasive EPS if the following criteria are fulfilled: (1) Presence of conduction disorder on baseline ECG [1$^{st}$ degree AV block, Mobitz type 1 s degree AV block, complete RBBB or left bundle branch block (LBBB), BFB, left anterior or posterior fascicular block]; (2) Clinical, electrocardiographic, and/or imaging evidence of myocardial scar (history of myocardial infarction, presence of Q waves on surface ECG, presence of late enhancement on cardiac magnetic resonance imaging, and/or presence of necrosis on myocardial perfusion single-photon emission computed tomography scan); and (3) History of palpitations prior to the syncopal episode. If these criteria are not fulfilled, the EPS is not carried out, and the patient moves on to Step 3. Step 3 involves implanting an implantable cardiac monitor with subsequent clinical monitoring (Figure 3).

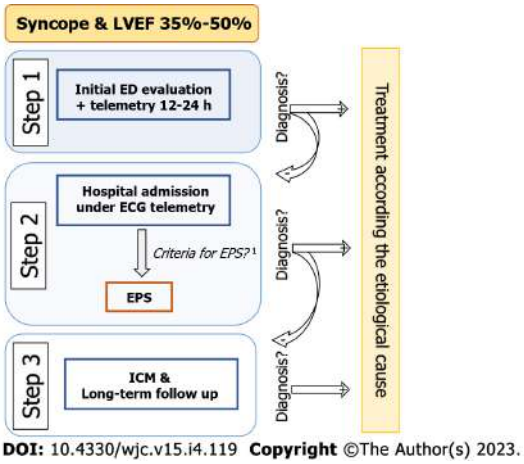



**Figure 3 Proposed algorithm for the management of syncope in patients with mid-range left ventricular dysfunction.** [1]Criteria for electrophysiological study: (1) Presence of conduction disorder on baseline electrocardiogram (1st degree atrioventricular block or Mobitz 1 s degree block, complete right or left bundle branch block, left anterior or posterior hemiblock); (2) Evidence of myocardial scar; and (3) Palpitations prior to the syncopal episode. ECG: Electrocardiogram; ED: Emergency department; LVEF: Left ventricle ejection fraction; EPS: Electrophysiological study; ICM: Implantable cardiac monitor.

In a recent published study that evaluated patients with unexplained syncope (excluding patients diagnosed in step 1), it was found that the application of this systematic protocol had a high diagnostic yield with a low rate of sudden death[79]. The overall diagnostic yield with both steps was 68.3%. Of note, the most common cause was arrhythmia. In 60 patients (57.7% of the total patients and 84.5% of the total diagnoses), a rhythm disorder was identified as the cause of the syncopal episode, with a high proportion of bradycardias, mostly due to AV block (47 patients, 45.2%). VT was the second most frequent cause, although it was significantly less common (9.6%). Most of the arrhythmias, be they AV block or VT, were able to be diagnosed in step 2. Another key finding of the study was that the diagnoses reached allowed treatment to be effectively guided. The sudden or unknown cause mortality rate of 0.9 per 100 person-years was comparable with general mortality rates published in the literature in patients with mid-range left ventricular dysfunction without syncope[106,111-113]. The findings of this study, in line with others on patients with structural heart disease[3,107,114], suggest that a stepwise diagnostic strategy and prolonged monitoring may be a safe and effective management alternative, reducing the number of patients requiring an ICD.

### *HCM*

The hallmark of HCM is the abnormal increase of left ventricular wall thickness unrelated to abnormal loading conditions such as high BP, valvular heart diseases, or congenital heart disease. At the histopathological level, HCM is characterized by an increase in the size of myocardial cells and disordered myocardial cell organization with interstitial fibrosis that may predispose patients to suffer from ventricular arrhythmias. HCM carries a mortality rate that ranges from 1%-2%. New data from cohorts of patients with ICDs suggest that the mortality rate might be even lower (about 0.8%) and that it is related with several risk factors summarized in the HCM-SCD score[115]. The eight variables included in the risk score are: Age, LV wall thickness, left atrial size, left ventricular outflow tract (LVOT) gradient, nonsustained ventricular tachycardia, unexplained syncope, and family history of SCD.

HCM patients may have different syncope etiologies such as: Hypovolemia, conduction system disorders, sustained ventricular tachycardia, LVOT obstruction, and abnormal vascular reflexes, *etc*[116-118]. After ruling out non-cardiogenic and neural-mediated causes, arrhythmic syncope is one of the more worrisome causes for syncope in those patients. Patients with unexplained syncope should be tested with at least 24-hr Holter recording and exercise time-to-exhaustion to rule out LVOT obstruction on exertion. After an extensive evaluation of causes of syncope in those patients without clear diagnosis, an ILR should be implanted[1,117]. Routine tilt table testing in patients with HCM may be associated with an unacceptable number of false positives, and its use should be limited to selected cases[117].

Syncope of unknown origin is included in the risk score with an independent hazard ratio of 2.05 (1.48, 2.82; $P < 0.001$)[115]. Patients with intermediate-risk and low-risk clinical profiles should be evaluated for additional risk factors not included in the score, following 2022 ESC guidelines[19]. LV systolic dysfunction, apical aneurysm, > 15% of LV mass with late gadolinium enhancement on CMR, and several sarcomeric mutations have demonstrated a higher risk of ventricular arrhythmias in different studies and should be considered when evaluating the risk profile of a given patient[117,118]. The risk of ventricular arrhythmias is nonetheless dynamic and needs to be reassessed at every clinical

visit. Those patients with syncope and a high-risk clinical profile (SCD HCM risk score > 6%) or intermediate risk and other risk factors should be considered for ICD implantation (IIa B level of recommendation)[116], and those with intermediate risk (SCD HCM risk score 4%-6%) may be considered for ICD implantation (IIb B level of recommendation)[19].

### *Valvulopathies*

A hemodynamic origin of syncope should be suspected in patients with valvular heart disease. However, other causes are possible[1,5,9,119-123]. The valvular heart disease with the highest risk of syncope is AoS[5,124,125]. Syncope is more frequent in severe stages of AoS but can occur in patients with moderate severity when suffering from other hemodynamic disturbances. Pharmacologic hypotension and atrial arrhythmias are also a frequent cause of syncope in patients with moderate and severe AoS[5,72,121,126]. In a recent study performed by our group in a cohort of patients with severe AoS and syncope, we observed that in 65% of the patients, the stenosis per se was initially identified as the likely cause of syncope, but later only 17.5% of the total cohort of patients was confirmed as having AoS as their final diagnosis. Conduction system disease and vasovagal etiologies were a more frequent cause of syncope in this population[5]. Importantly, syncope in the setting of a severe AoS has been suggested as having prognostic implications.

In a study published in 2019, these patients had a greater risk of mortality after aortic valve replacement in both the short-term (hazard ratio = 2.27; 95%CI: 1.04-4.95) and the long-term (hazard ratio = 2.11; 95%CI: 1.39-3.21) compared with patients who did not have syncope[127]. Although patients with syncope had somewhat different characteristics on echocardiography (smaller aortic valve area, smaller cardiac chambers, and lower ejection volumes), we believe that this rise in mortality was also partially due to the presence of other causes for the syncope such as underdiagnosed arrhythmias. In the cohort studied by Francisco-Pascual *et al*[5], those patients in whom it was not possible to precisely determine the cause of the syncope had more than triple short-term and medium-term mortality.

Furthermore, several studies have observed a high incidence of syncope and SCD after transcatheter aortic valve replacement (TAVR)[66,67,72,126,128]. It is theorized that induced conduction system delays after TAVR may predispose patients to suffer from electrical re-entry within the His-Purkinje system favoring a rare type of cardiac arrhythmia called bundle-branch re-entry in which the electrical impulse circulates between both branches of the conduction system with a slight delay often happening in the left bundle in the retrograde arm of the tachycardia. This arrhythmia is very rapid and frequently compromises the patient hemodynamically producing syncope or sudden cardiac arrest. The real incidence of this problem is unknown, but it needs to be kept in mind when evaluating a patient after a TAVR with some degree of conduction system delay.

Another significant but infrequent cause of syncope in patients with valvular heart disease is the presence of VF in patients with mitral valve prolapse, which has been named "the malignant mitral valve prolapse syndrome". In a recent meta-analysis carried out by Nalliah *et al*[129], they reported the population prevalence of mitral valve prolapse (MVP) of 1.2% and the prevalence of MVP in SCD autopsies of 11.7%. Nonetheless an incidence of 0.14 SCD events per 100 patient-years in the community MVP cohort, deserves an in-depth investigation of other risk factors for ventricular arrhythmias such as the presence of myocardial fibrosis or frequent complex ventricular ectopy, as has been proposed.

### *Conduction disturbances*

In patients with conduction disturbances and syncope, the presence of bradyarrhythmia is always a concern although other causes may also be present. For example, in a recent cohort of 503 patients with unexplained syncope and BBB, arrhythmic syncope was identified in 57.9% patients, mostly secondary to AV block (51.3%). However, 12% were due to reflex syncope or an OH mechanism, 1.4% were due to ventricular tachycardia, and 10% were secondary to other causes[108].

The optimal management of patients with unexplained syncope and BBB is still controversial[1,9,46-48,130,131]. In fact, the 2017 ACC/AHA Guidelines[9] suggest empirical direct pacemaker implantation after exclusion of other syncope etiologies, while ESC guidelines[1] recommend opting for a stepwise approach. The systematic stepwise approach (that includes an EPS and long-term follow-up with an ICM) was initially evaluated in the B4 study[47]. This study found that the diagnostic approach is safe and achieves a high rate of etiological diagnosis allowing for the selection of specific treatment and avoiding the implantation of unnecessary pacemakers. The results of the B4 study have been confirmed by several subsequent studies, some of them with a relatively high number of patients and long-term follow-up[80,108,132-134].

On the other hand, the strategy of direct pacemaker implantation was recently evaluated in the SPRITELY trial. This study randomized 105 patients older than 50 years with BFB (41 LBBB and 74 RBBB plus left fascicular block) and at least one syncope in the previous year to receive ICM or empirical pacemaker implantation. In the 33-mo follow-up period, the 57 patients randomized to the pacemaker arm showed a lower primary composite endpoint (cardiovascular death, syncope, bradycardia resulting in an intervention, and device complications) than the ILR arm; [20 (35%) *vs* 44 (76%); $P < 0.0001$]. However, the presence of syncope during follow-up was similar in both groups (29% *vs* 26%; $P = 0.95$)[135].

It must be highlighted that in the SPRITELY trial, EPS was not systematically carried out before ICM implantation, and therefore it cannot be considered as a direct comparison with the stepwise approach. Similar findings were previously found in the PRESS study[136], where patients were randomized to pacemaker in pacing mode (DDD at 60 bpm) or backup pacing mode (drug-drug interaction at 30 bpm). The primary endpoint of this study was a composite endpoint of syncope, presyncope with device intervention, or documented bradycardia and AVB, and patients allocated to active pacing had a significant reduction of this composite endpoint. However, when only syncope recurrences were analyzed separately, there were no differences between the two groups. Furthermore, there are some studies that have analyzed the recurrence rate in patients with syncope and BBB, in whom a pacemaker has been implanted, showing that syncope recurrence is higher in those patients in whom a pacemaker was implanted empirically than in those in whom a pacemaker was implanted after a positive EPS or a documented AVB[137,138].

With the available evidence, the authors of this review continue to support the stepwise approach to manage these patients. Nevertheless, direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment (Figure 4). According to the newest 2021 ESC guidelines for cardiac pacing and resynchronization[18], in patients with sinus bradycardia and syncope of unclear origin after a thorough work-up, an exercise test to evaluate chronotropic competence and an EPS to evaluate for sinus node overdrive suppression pathologic responses might be indicated. cSNRT (basal cycle length; normal value 525 ms) has demonstrated good predictive value in patients with sinus bradycardia despite the presence of symptoms (overall accuracy of cSNRT in predicting serious sinus node disease regardless of the presence of symptoms: 90%, 100% in the presence of symptoms; sensitivity of the test: 66%). Patients presenting with a ventricular rate below 40 bpm have a 70% probability of having an abnormal cSNRT. In patients with a basal HR of 50 to 55 bpm, the probability of finding an abnormal response in cSNRT test is 24%[139]. However, it should be noted that pacing patients with sinus node dysfunction has not demonstrated improved survival so far[18,131].

EPS diagnostic yield is higher in patients with sinus bradycardia or BFB and structural heart disease and is lower in patients with a normal ECG and no structural heart disease[46,50]. Thus, it is preferable to perform EPS in patients with higher pretest probability and implant a loop recorder in those with lower pretest probability. Patients with first degree AV block and second degree type I (Wenckebach) block presenting with syncope without a firm diagnosis after extensive study should be offered an EPS. The presence of second degree type II block or third degree AVB constitutes a clear indication for cardiac pacing. Patients with 2:1 AV block can be evaluated by increasing the sinus node rate (atropine 1 mg or exercise test). If the degree of block increases by increasing of the sinus rate, an infra-Hisian origin must be suspected, and pacemaker implantation should be considered. Patients with syncope and BFB represent a group whose risk of syncope is especially difficult to stratify. Therefore, in patients with BFB and syncope of unknown origin an EPS should be performed.

In the presence of an HV interval longer than 70 ms (basal) or > 100 ms after infusion of 2 mg/kg of flecainide (or other Vaughan Williams class I antiarrhythmic drugs), cardiac pacing should be considered[140]. The absence of high-risk characteristics in the EPS of patients with syncope and BBB or BFB does not preclude the development of paroxysmal AV block, and an ILR needs to be considered. Roca-Luque *et al*[50] demonstrated that the most predictive combination of conduction disorders were LBBB or RBBB + long PR interval + left fascicular block [odds ratio = 4.5 (1.06-20.01); $P < 0.042$], LBBB + prolonged PR interval [5.2 (1.52-17.74); $P < 0.001$], and RBBB + prolonged PR interval [3.8 (1.7-8.7); $P < 0.001$] in their 271 patient cohort in 2018.

### *Channelopathies and inherited arrhythmia syndromes*

Cardiac channelopathies are a group of diseases in which a mutation of different regulatory proteins of the action potential may predispose a patient to suffer from ventricular arrhythmias and SCD. Syncopal episodes in these patients might be due to non-sustained polymorphic VT or VF. In this section, we discussed the implications of the presence of syncope in patients with BrS, LQTS, and catecholaminergic PVT.

### *BrS*

BrS was first described by the Brugada *et al*[141] in their elegant paper published in JACC in 1992. In their first publication of this syndrome, they described a cohort of 8 patients with RBBB and ST elevation in leads V1-V2-3 that suffered from aborted episodes of SCD[142].

Even though the mechanism of the electrical dysfunction leading to VF is not completely understood, it is believed that an increase in early repolarizing currents (Ito current) or a reduction in depolarizing currents (INaT) may lead to a phase II dispersion of repolarization and early post-depolarizations, which might generate phase II re-entries, possibly triggering VF. This electrical disorder seems to be more accentuated in the anterior part of the right ventricular outflow tract obstruction, where Ito current has been shown to be higher than in other heart sites. This latter observation might explain the isolated ST elevation in precordial leads and the effectiveness of ablation on the right ventricular outflow tract in patients with BrS and arrhythmic storm[143].

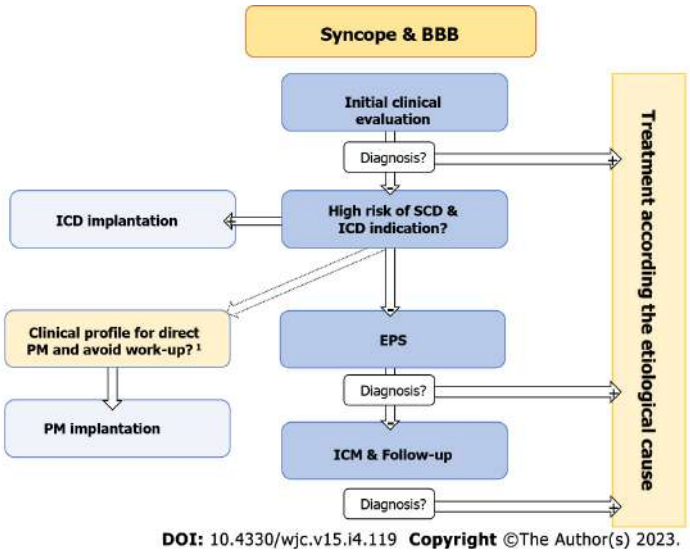



**Figure 4 Proposed algorithm for the management of syncope in patients with bundle branch block.** [1]Direct pacemaker implantation should be considered in some patients, especially in elderly or frail patients after an individual risk/benefit assessment. SCD: Sudden cardiac death; BBB: Bundle branch block; EPS: Electrophysiological study; ICD: Implantable cardiac defibrillator; PM: Pacemaker; ICM: Implantable cardiac monitor.

Patients with BrS pattern on ECG and syncope have a four-fold risk of sudden cardiac arrest, representing a 1.5% annual risk of sudden cardiac arrest. When the syncope cannot be classified as neuromediated or a cardiac origin is a possibility, ICD implantation should be considered[19]. Therefore, it is usually not necessary to perform an EPS to stratify the risk in the presence of unexplained syncope, as it is assumed to be high risk.

However, patients with sodium channel dysfunction may exhibit conduction system dysfunction as well. It is not infrequent for patients with those specific mutations to exhibit sinus bradycardia and/or BBB. Furthermore, reflex syncope is also frequent in young patients with BrS[144]. For these reasons, some authors have also suggested a more conservative approach, where implantation of a loop recorder can be considered in BrS patients with an unexplained syncope (not clearly cardiac) and without other indications for an ICD[19,145].

### *LQTS*

The hallmark of the LQTS is an inadequately prolonged corrected QT interval, measured from the beginning of the QRS complex to the point at which the descending limb of the T wave crosses the isoelectric baseline of the ECG. The measure is frequently performed in leads II or V5-6 where the T wave and the isoelectric baseline are often well demarcated. The diagnosis of LQTS is made in the presence of a cQT interval of ≥ 480 ms or a Schwartz score (including several clinical and electrocardiographic parameters) of > 3. In the presence of a cardiogenic syncope, the presence of a cQT ≥ 460 ms is sufficient to reach the diagnosis.

The mechanism of arrhythmogenicity in patients with LQTS seems to be related with dispersion of the repolarization. The prolongation of the repolarization is not homogeneous among the different layers of myocardium. Therefore, early post depolarization occurring over the T wave may generate functional re-entry patterns of conduction ultimately generating fibrillatory conduction.

Up to 17 different mutations leading to LQTS have been described. The majority of them are produced by three specific mutations. LQTS1 is produced by mutation in the α subunit of the delayed rectifier potassium channel with slow opening kinetics. This mutation comprises 40%-55% of cases. LQTS1 patients are prone to suffering from ventricular arrhythmias during sports or physical activity (especially during swimming). LQTS2 is caused by a mutation in the α subunit of the delayed rectifier potassium channel with rapid opening kinetics. This mutation is present in up to 30%-45% of cases, and ventricular arrhythmias are frequent during loud noises and in the postpartum period in females. The activating mutation in the α subunit of the sodium channel (INaT) keeps the channel opened beyond phase 0, increasing late sodium currents (INaL), thus prolonging repolarization and therefore the QT interval. This mutation is present in 5%-10% of patients and is related to fatal events during rest or sleep [146].

It has been observed that LQTS patients respond favorably to beta-blockers; thus every patient with a diagnosis of LQTS should be treated with beta-blockers. Apparently, non-specific beta-blockers, such as propranolol or nadolol, have shown better results with a lower incidence of ventricular arrhythmias. If patients suffer from syncope despite the use of beta-blockers, an ICD must be implanted for the

prevention of SCD[147].

### *Catecholaminergic PVT*

Catecholaminergic PVT (CPVT) is an inherited channelopathy in which several mutations may affect the intracellular handling of calcium release-uptake. The overload of cytoplasmatic calcium leads to cell membrane voltage instability leading to delayed depolarizations that lead to the characteristic arrhythmia of this disorder, bidirectional ventricular tachycardia (also seen in digitalis toxicity), or VF.

The mutation in the ryanodine receptor gene, inherited in an autosomal dominant manner, is the cause of 50%-55% of cases. A new mutation in the calsequestrin gene has been described and has an autosomal recessive inheritance pattern. The ryanodine receptor gene mutation generates an aberrant ryanodine channel that permeabilizes the channel to calcium release. The calsequestrin proteins work close to the ryanodine channel, regulating its function.

Patients with CPVT are prone to ventricular arrhythmias related to exercise. Ventricular arrhythmias usually occur with HR over 130 bpm. With increasing levels of exercise, patients may exhibit monomorphic ectopy, polymorphic ectopy, non-sustained VT, bidirectional VT, and finally, if the exercise continues, VF. CPVT is a highly arrhythmogenic condition with a cardiac event rate of up to 80% at 40 years. Therefore, a low threshold for ICD implantation is advised. The use of non-selective beta-blockers has been shown to reduce the incidence of ventricular arrhythmias from 25% to 11% at 8 years[148].

Probably due to small cohorts, no single risk factor has demonstrated sufficient prognostic value to be used routinely. The 2022 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD recommend implantation in patients with CPVT who have survived a cardiac arrest (class I C) and should be considered in patients with CPVT and either arrhythmic syncope or presence of polymorphic VT or bidirectional VT on maximal tolerated doses of beta-blockers (class IIa C)[19].

## CONCLUSION

Syncope is a symptom that involves a heterogeneous group of pathologies ranging from trivial causes to diseases with a high risk of sudden death. The highest mortality and SCD risk occur when syncope is associated with underlying cardiac disease, in particular when the main cause of syncope is not well established and treated properly. Arrhythmia is the most common cause of cardiac syncope. Appropriate risk stratification and work-up to determine the main cause of the event is warranted to improve the prognosis of patients. This review provided an update on the important and novel data about arrhythmic syncope, the value of the different diagnostic tests, and the specific characteristics in some particular populations such as patients with cardiomyopathies or channelopathies. This review emphasized the importance of an appropriate stepwise approach work-up and interventions.

## ACKNOWLEDGEMENTS

The authors would like to thank Mr. S Venegas for his help with the illustrations and language editing.

## FOOTNOTES

**Author contributions:** Francisco Pascual J prepared the concept and design and drafted and edited the manuscript; Jordan Marchite P and Rodríguez Silva J contributed to collecting data, creating the tables and figures, and writing part of the manuscript; and all other authors contributed to design and reviewed the manuscript and approved the content of the final version of the manuscript.

**Conflict-of-interest statement:** The Arrhythmia Unit receives fellowship grants from Boston Scientific and research grants from Abbott. Francisco Pascual J receives advisory and speaking honoraria from Abbott and Microport. Rivas Gándara N receives advisory and speaking honoraria from Abbott. The other authors report no conflicts.



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**S-Editor:** Wang JJ
**L-Editor:** Filipodia
**P-Editor:** Zhao S

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## 11.2.2. Revista Española de Cardiologia Editorial about Article 4

Pérez-Castellano N, Calvo Cuervo D, Pérez-Villacastín J. Syncope and bundle branch block: a single study with several take-home messages. Rev Esp Cardiol (Engl Ed). 2023 Aug;76(8):582-584. English, Spanish. doi: 10.1016/j.rec.2023.01.014. Epub 2023 Mar 23. PMID: 36963613.

Rev Esp Cardiol. 2023;**76(8)**:582–584

Editorial

# Syncope and bundle branch block: a single study with several take-home messages

## Síncope y bloqueo de rama: un estudio y varios mensajes para recordar

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*Article history:*
Available online 23 March 2023

Syncope is defined as transient loss of consciousness due to cerebral hypoperfusion and is a prevalent symptom, estimated to affect 1 in 5 people older than 45 years at some point in their lives.[1] The cumulative incidence is 6.2 per 1000 person yearsm,[2] and syncope is a common cause of emergency department attendance (1%-2% of patients) and of hospital admission (50% of patients attending the emergency department for syncope are admitted).[3] Another frequent symptom in the general population is bundle branch block (BBB), which triggers late depolarization of the ipsilateral ventricle and eventually generates a wide QRS complex. Right BBB affects 1.5% of the population,[4] and left BBB affects 0.3% to 0.4%.[5]

Syncope and BBB often occur together in clinical practice and, in a recent article in *Revista Española de Cardiología*, Francisco-Pascual et al.[6] show that complete BBB increases the risk of arrhythmic syncope. This finding highlights the importance of investigating the possible co-occurrence of BBB in patients with syncope, and in light of this and other published studies, as well as the experience accumulated by practicing cardiologists, we can outline a number of observations and clinical practice recommendations, as outlined below.

### IT IS IMPORTANT TO STUDY THE CAUSE OF SYNCOPE CO-OCCURRING WITH BUNDLE BRANCH BLOCK

Patients with a first syncopal episode are frequently managed more conservatively than those with recurrent episodes; moreover, a history of unexplained syncope is common in patients assessed in routine practice for any cause. Using a detailed protocol based on current clinical practice guidelines, Francisco-Pascual et al.[6] analyzed a cohort of more than 500 patients presenting with syncope and BBB for possible differences in etiology, diagnostic yield, treatment, and prognosis according to whether the syncope was a first or a recurrent episode. The study found no differences between the 2 patient groups in etiological diagnosis, electrophysiological study results, implantable cardiac monitor (ICM) diagnostic yield, prognosis, or appropriate treatment, thus demonstrating that there is no justification for treating these patient groups differently.[6] All patients with BBB and experiencing syncope, whether a first or recurrent episode, should undergo a detailed, systematic workup to establish the cause, as this information is essential for determining appropriate treatment and prognosis.

### AVOID THE DIAGNOSIS OF "SYNCOPE OF UNKNOWN CAUSE"

Syncope is a serious symptom with prognostic implications. In the Framingham Heart Study, individuals with syncope of any cause generally had a higher all-cause risk of death than the rest of the study population (hazard ratio [HR] = 1.31; 95% confidence interval [95%CI], 1.14-1.51).[2] The highest risk of death was found in patients with syncope of cardiac origin (10% of cases; HR = 2.01; 95%CI, 1.48-2.73), whereas patients with vasovagal or orthostatic syncope showed no difference in risk of death from the general study population.[2] Crucially, the Framingham Heart Study also recorded an elevated risk of death in patients with unexplained syncope (HR = 1.32; 95%CI, 1.09-1.60).[2] This finding underlines the need to pursue an etiological diagnosis and to reject the diagnostic category of "syncope of unknown cause", since the situation of some patients in this category is serious and possibly even life-threatening. It is nevertheless important to recognize that diagnosing the cause of syncope is challenging; despite the use of systematic diagnostic protocols based on current clinical practice guidelines, the cause of syncope remains undetermined in as many as a third of patients experiencing a first syncopal episode.[2]

### THE WIDER THE QRS COMPLEX, THE WORSE THE PROGNOSIS

Historically, right BBB has been viewed as benign and left BBB as malign, since the latter is a marker of structural heart disease. However, more recent studies show that right and left BBB are both associated with an increased risk of cardiac death (HR = 1.9 [95%CI,

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https://doi.org/10.1016/j.rec.2023.01.014

1.2-3.0] vs HR = 2.4 [95%CI, 1.3-4.7]) and demonstrate a direct correlation between the width of the QRS complex and the increase in risk.[4,7]

## SYNCOPE WITH BUNDLE BRANCH BLOCK IS GENERALLY BRADYARRHYTHMIC, BUT VENTRICULAR ARRHYTHMIA SHOULD BE SUSPECTED IN THE PRESENCE OF HEART DISEASE

The most common syncope mechanism in patients with BBB is atrioventricular (AV) block. AV conduction is mostly preserved in BBB and remains stable over many years; however, serial electrophysiological studies have shown progression of the AV conduction disorder in up to 30% of BBB patients, with second- or third-degree AV block appearing in 20% of these patients.[8] The incidence is even higher when the BBB alternates between the right and left branches, which is a more severe form of conduction system disease. AV block in patients with BBB is not always located below the His bundle, and a supra-Hisian location is detected in as many as 40% of patients.[8]

Nevertheless, patients with BBB, especially of the left branch, have a relatively high prevalence of structural heart disease.[7] In patients with syncope and BBB, the presence of structural heart disease indicates an elevated risk of sudden cardiac death due to ventricular tachycardia, especially if there is ventricular dysfunction or the patient has a history of myocardial infarction. This situation should prompt attending physicians to consider placement of an implantable cardioverter-defibrillator (ICD) without requiring an etiological diagnosis. In other patients, the cause of syncope should be diagnosed through a systematic stepwise approach similar to that used by Francisco-Pascual et al., including a general clinical and cardiological assessment, electrocardiographic monitoring, an electrophysiological study, and, if necessary, placement of an ICM.[6]

In the series presented by Francisco-Pascual et al., electrocardiographic monitoring and electrophysiological study on admission identified the cause of syncope in 56% of patients (with the cause being arrhythmic in 83% of these patients). Subsequent ICM placement identified the cause of syncope in 41% of the patients with no etiological diagnosis on admission (arrhythmic in 64% of these patients). The overall diagnostic yield of the stepwise protocol was 74% (arrhythmic in 78% of these patients). The most frequent diagnoses were AV block (51%), orthostatic syncope (9%), and sinus dysfunction (4%). Syncope was attributed to ventricular tachycardia in just 1% of the patients; however, it should be noted that the study excluded patients with a direct indication for ICD placement or an ejection fraction $< 35\%$.[6]

## ELECTROPHYSIOLOGICAL STUDY OF PATIENTS WITH SYNCOPE AND BBB: A HALF FULL GLASS

Electrophysiological study for syncope generally has a low diagnostic yield, especially in patients with a normal electrocardiogram and echocardiogram. Nevertheless, the electrophysiological study retains an important role in syncope diagnosis in specific patient groups, such as those with structural heart disease or ventricular scarring, especially if the patient has a history of myocardial infarction (indication class I, level of evidence B) or BBB (class IIa, level B).[9]

The electrophysiological study can identify specific features of AV conduction disorder, such as prolongation of the HV interval or induction of infra-Hisian block with atrial stimulation. The sensitivity of the electrophysiological study can be increased by intravenous administration of procainamide or flecainide. Findings compatible with a supra-Hisian AV conduction disorder are harder to define and depend on extrinsic factors such as the neurovegetative balance and the degree of patient sedation during the test.

Scheinman et al.[10] followed 401 patients with BBB for an average of 30 months after electrophysiological study. Patients with a baseline HV interval $\geq$ 70 ms had a higher risk (12%) of progression to second- or third-degree AV block than patients with an HV interval $<$ 70 ms (3.5%). Of the patients with an HV interval $\geq$ 100 ms, 1 out of 4 developed second- or third-degree AV block during follow-up.

The study by Francisco-Pascual et al.[6] provides a meticulously detailed presentation of electrophysiological findings from more than 500 patients with BBB and syncope. This valuable analysis identified the cause of syncope in half of these patients, largely because it detected a severe AV conduction disorder in 44% of them. Programmed stimulation in patients without structural heart disease carries a low risk of inducing ventricular tachycardia, but in patients with BBB the risk can be as high as 5% to 10%.[6,11]

## DIAGNOSIS WITH AN IMPLANTABLE CARDIAC MONITOR: GOOD, BUT LATE

The ICM is a useful and powerful tool for syncope diagnosis. In a randomized clinical trial of patients with BBB and syncope of unknown cause after clinical assessment and electrophysiological study, cardiac monitoring with an implantable device performed significantly better than conventional follow-up, identifying the cause of syncope in 37% of these patients (vs 11% by conventional follow-up).[12] This is comparable to the 41% added diagnostic yield reported by Francisco-Pascual et al. in patients receiving an ICM and followed up for an average of 2.9 years,[6] and similar yields have been reported for other series.[11] Among patients with an ICM diagnosis, the most prevalent cause of syncope was AV block, and the likelihood of ventricular tachycardia being identified as the cause was less than 1%.

Given the low diagnostic sensitivity of electrophysiological study, one might be tempted to recommend monitoring with an ICM as the primary diagnostic text. However, omitting the electrophysiological study of syncope co-occurring with BBB would, at the very least, delay diagnosis of the cause of syncope in half the patients. This delay would put patients at risk of further syncopal episodes, which are linked to significant morbidity in 5% of patients and minor traumatic consequences in 7%. Moreover, delayed diagnosis would also increase the risk of death, since up to 10% of electrophysiological studies identify a ventricular arrhythmia as the potential cause of syncope even in patients with no structural heart disease.[11,13]

## EMPIRICAL PACEMAKER IMPLANTATION IS LIKELY NOT THE BEST OPTION FOR PATIENTS WITH SYNCOPE AND BUNDLE BRANCH BLOCK

After excluding patients with an indication for immediate ICD placement, the most frequent cause of syncope in patients with BBB is bradyarrhythmia, with the most prominent type being AV block. Francisco-Pascual et al. report pacemaker implantation in 60% of patients with syncope and BBB over a mean follow-up of 3 years, and 20% of these patients had previously been monitored with an ICM. This raises the question as to whether it would be safer and more cost effective to directly indicate placement of a permanent pacemaker for patients with syncope and BBB and no indication for ICD placement.[6]

However, such a strategy seems unwise given the excessively high rate of recurrent syncope after empirical pacemaker implantation in patients with BBB, which ranges from 14% to

27%.[14] In a recent small randomized trial in patients with syncope, BBB, and preserved ejection fraction, empirical permanent pacing did not reduce syncope recurrence vs ICM recording.[15] In current European Society of Cardiology guidelines, empirical pacing in patients with syncope and BBB is a class IIb recommendation (level of evidence B).[9]

The article by Francisco-Pascual et al.[6] contains information of immense value to the readership of *Revista Española de Cardiología*. The authors are to be congratulated not only for the main study conclusions, but also for providing a thorough and memorable summary of the factors that determine the correct approach to the treatment of patients with syncope and BBB.

## FUNDING

No funding was received for the preparation of this article.

## CONFLICTS OF INTEREST

None of the authors has conflicts of interest to declare.

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## 11.3. Abstract presentation related to the topic

### 11.3.1. HV interval cutoff should be different in women and men with syncope and bundle branch block. EHRA congress 2024. Berlin 7-9th Arpil 2024

J Francisco Pascual, J M Medina Maguina, A Santos Ortega, J Perez Rodon, R Adelino, E Seder, B Benito, P Jordan, N Lal-Trehan Estrada, N Mallofre, I Ferreira Gonzalez, N Rivas Gandara, HV interval cutoff should be different in women and men with syncope and bundle branch block, EP Europace, Volume 26, Issue Supplement_1, May 2024, euae102.283, https://doi.org/10.1093/europace/euae102.283

Europace 2024 Volume 26 Supplement 1 i1061

*Arrhythmias and Device Therapy – Syncope and Bradycardia, Diagnostic Methods*

# HV interval cutoff should be different in women and men with syncope and bundle branch block

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**Funding Acknowledgements:** Type of funding sources: None.

**Background:** Determining the optimal HV interval cutoff for predicting the need for pacemaker (PM) implantation has been a recent focus of research. Current ESC guidelines recommend HV > 70 msec based on initial studies; however, new data suggest that a cutoff of >60 msec could appropriately identify patients at high risk for requiring PM implantation. While previous studies have indicated that women with bundle branch block (BBB) have a lower risk of AV block (AVB), gender differences in the optimal cutoff for considering a positive EPS have not been thoroughly investigated.

**Methods:** This cohort study included consecutive patients with unexplained syncope and BBB, enrolled from January 2010 to October 2021, with a median follow-up time of 3 years. Patients underwent a stepwise workup protocol involving an electrophysiological study (EPS) and long-term follow-up with an implantable cardiac monitor (ICM).

**Results:** Of the 503 patients in the study, 185 (38%) were women. The median age was 78 years (IQR 71-83), the median LVEF was 58% (IQR 50-62), and 110 (22%) had ischemic heart disease. The ECG showed LBBB in 194 (39%) patients and RBBB in 287 (57%). Among these, 177 (35%) also had left anterior hemiblock. The median HV interval was 60 msec (IQR 52-73), and EPS was diagnostic in 252 (50%) patients, with the majority (221, 44%) for AVB. In 91 patients with initially negative EPS, a diagnosis was made during follow-up with an ICM, and in 35, AVB was documented. In patients with negative EPS, an HV interval >60 msec was associated with an increased risk of AVB during follow-up (HR 2.5, 95% CI 1.6-4). However, significant gender differences were found. The risk of AVB was 2.5 times higher in men (95% CI 1-6) (Figure 1). Furthermore, sensitivity, specificity, PPV, and NPV for the cutoff of 60 msec were 47%/84%/51%/82% in men and 21%/78%/21%/78% in women. The AUC to predict AVB was 0.72 (95% CI 0.6-0.8) in men and 0.51 (95% CI 0.4-0.6) in women (Figure 2).

**Conclusions:** In patients with initially negative EPS, an HV interval >60 msec was associated with a higher risk of AVB during follow-up; however, significant gender differences were observed in diagnostic accuracy. In women, a cutoff of HV interval >60 msec presented poor diagnostic accuracy compared to men. Moreover, the HV interval did not adequately predict the development of AVB in women with a basal HV interval <70 msec, suggesting it may not be suitable for considering PM implantation in female patients.

FIGURE 1

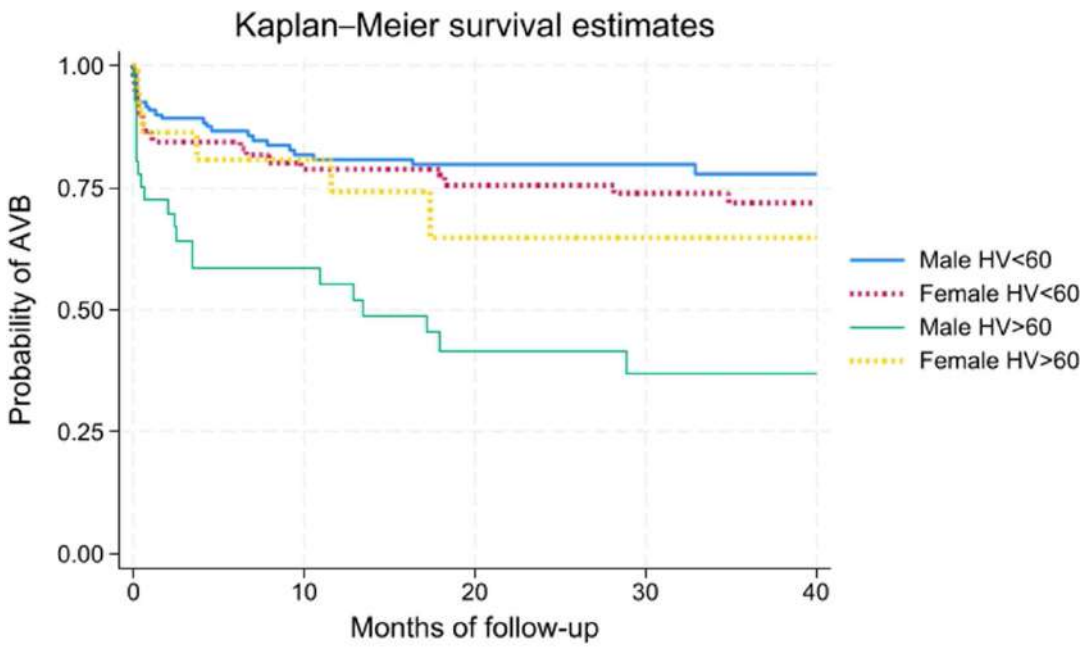

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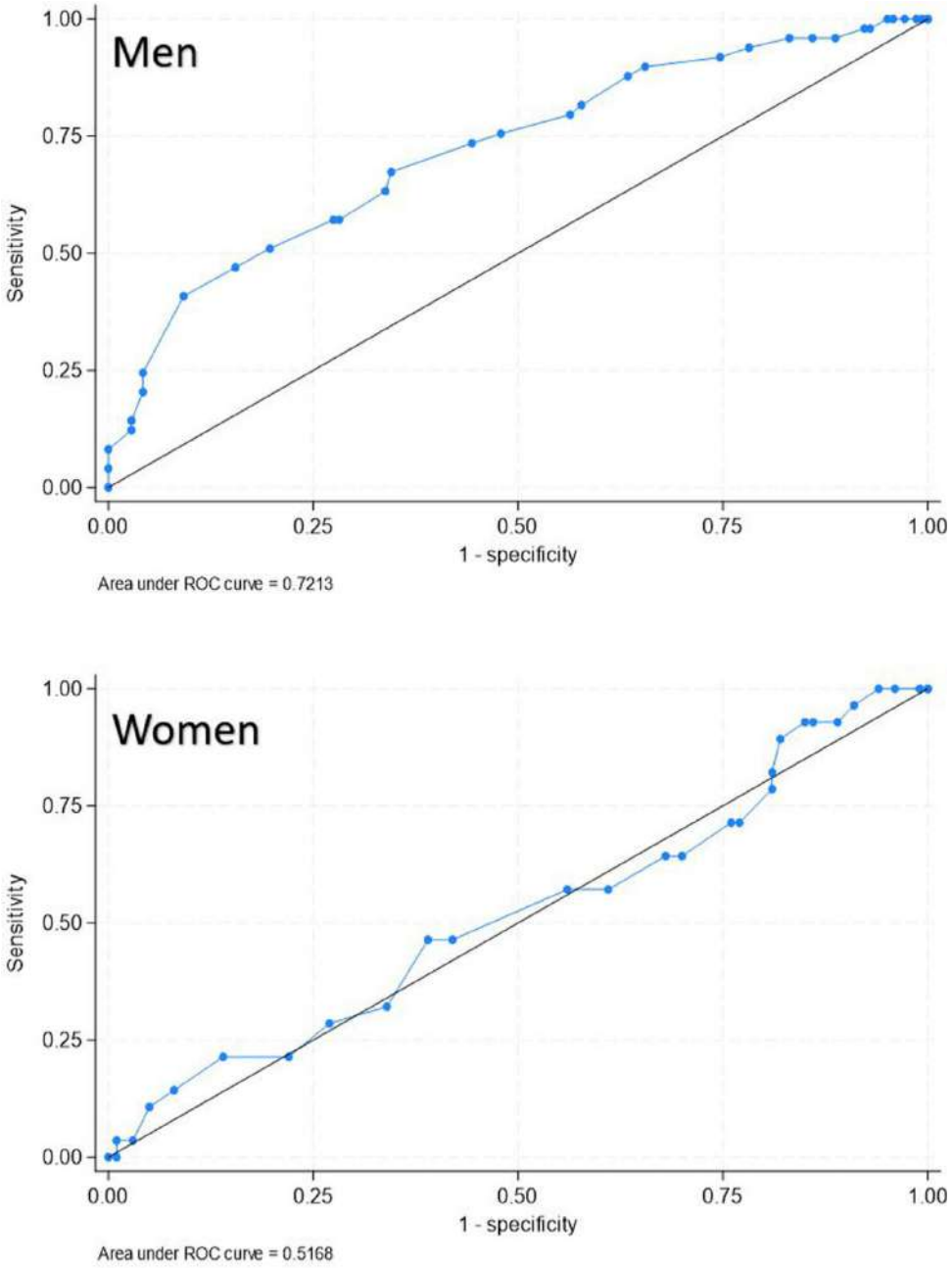
FIGURE 2



### 11.3.2. Síncope único o recurrente en pacientes con QRS ancho: ¿tienen el mismo riesgo arrítmico? Congreso de la salud cardiovascular SEC 21 – Zaragoza 28-30th October 2021

Manel Maymi Ballesteros, Jaume Francisco-Pascual, Clara Badia Molins, Jordi Pérez-Rodón, Begoña Benito, Alba Santos-Ortega, Ivo Roca-Luque, Montserrat Bach-Oller, Gerard Oristrell Santamaría, Javier Cantalapiedra-Romero, Jenson Maldonado, Ignacio Ferreira-González, Nuria Rivas-Gándara. *Síncope único o recurrente en pacientes con QRS ancho: ¿tienen el mismo riesgo arrítmico?* Rev Esp Cardiol. 2021;74(Supl 1):556

Rev Esp Cardiol. 2021;74(Supl 1):556

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# 6027-3 - SÍNCOPE ÚNICO O RECURRENTE EN PACIENTES CON QRS ANCHO: ¿TIENEN EL MISMO RIESGO ARRÍTMICO?

*Manel Maymi Ballesteros, Jaume Francisco-Pascual, Clara Badia Molins, Jordi Pérez-Rodón, Begoña Benito, Alba Santos-Ortega, Ivo Roca-Luque, Montserrat Bach-Oller, Gerard Oristrell Santamaría, Javier Cantalapiedra-Romero, Jenson Maldonado, Ignacio Ferreira-González y Nuria Rivas-Gándara*

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## Resumen

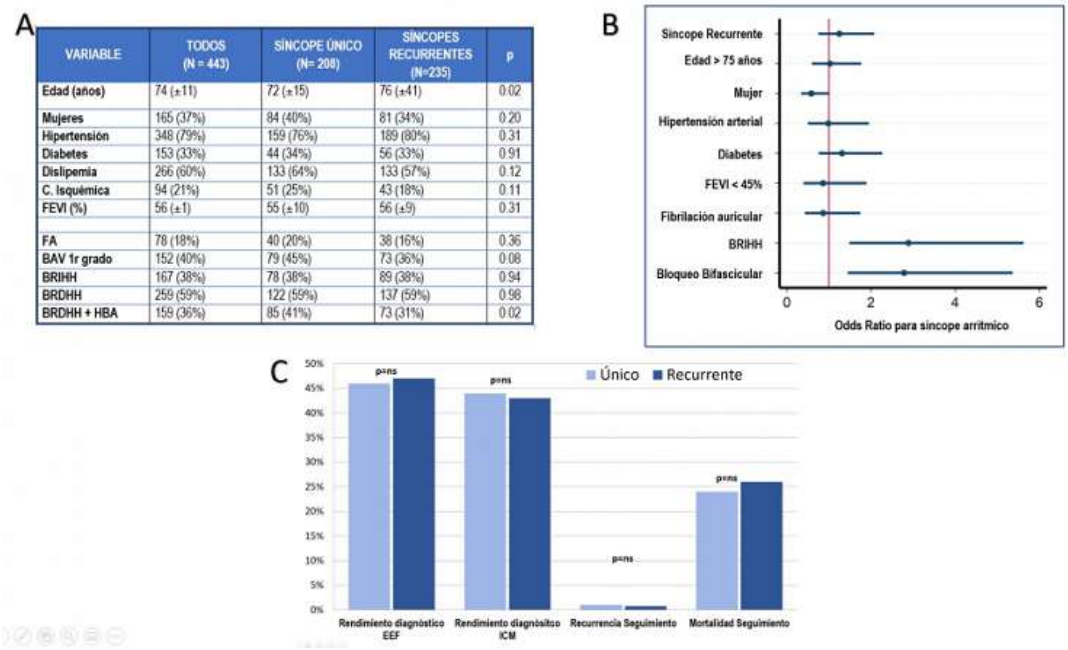
**Introducción y objetivos:** Los pacientes con bloqueo de rama (BR) tienen un elevado riesgo de presentar un síncope arritmogénico (SA). En pacientes con episodios sincopales recurrentes (ESR) un estudio completo incluyendo un estudio electrofisiológico (EEF) o monitor cardiaco implantable (MCI) está recomendado, sin embargo pacientes con un primer episodio sincopal también tienen riesgo de presentar un SA. El objetivo del estudio es determinar si los pacientes con BR y episodio sincopal único (ESU) tienen un elevado riesgo de presentar un SA y compararlo con los pacientes con episodios sincopales recurrentes (ESR).

**Métodos:** Estudio de cohortes llevado a cabo en un hospital terciario, centro de referencia en síncopes. Desde enero 2008 hasta diciembre de 2020 se incluyen todos los pacientes con BR y síncope de origen desconocido tras la evaluación inicial y sin indicación directa de desfibrilador automático implantable (DAI). El manejo se realizó de acuerdo con las guías europeas de práctica clínica.

**Resultados:** Se incluyeron 443 pacientes (74 ± 12 años, 37% mujeres). Seguimiento medio de 3,4 ± 2 años. 249 pacientes se diagnosticaron de AS [115 (55%) en el grupo ESR y 134 (57%) en el grupo ESU, p = 0,7], 239 se debían a bradiarritmias (bloqueo auriculoventricular o disfunción sinusal). No se encontraron diferencias en las características basales de ambos grupos, a excepción del bloqueo bifascicular que fue ligeramente más prevalente en los pacientes con ESU (41 vs 31%, p = 0,02) (fig. Panel A). El riesgo de SA fue del 55% en pacientes con ESU y del 57% en pacientes con ESR (p = 0,8). Los ESR no se asociaron con un incremento del riesgo de SA en el análisis univariante (OR 1,1, IC95% 0,7-1,6) ni en el multivariante (fig. Panel B). El rendimiento diagnóstico del EEF y del MCI fue del 46/44% respectivamente en el grupo ESU y del 47/43% en el grupo ESR (p = 0,8) (fig. Panel C). Después de un tratamiento adecuado, la tasa de recurrencia del síncope fue del 8% en el grupo ESU y del 10% en el grupo ESR (p = 0,7). No se encontraron diferencias significativas en la mortalidad.

A

| VARIABLE | TODOS (N = 443) | SÍNCOPE ÚNICO (N= 208) | SÍNCOPES RECURRENTES (N=235) | p |
|---|---|---|---|---|
| Edad (años) | 74 (±11) | 72 (±15) | 76 (±41) | 0.02 |
| Mujeres | 165 (37%) | 84 (40%) | 81 (34%) | 0.20 |
| Hipertensión | 348 (79%) | 159 (76%) | 189 (80%) | 0.31 |
| Diabetes | 153 (33%) | 44 (34%) | 56 (33%) | 0.91 |
| Dislipemia | 266 (60%) | 133 (64%) | 133 (57%) | 0.12 |
| C. Isquémica | 94 (21%) | 51 (25%) | 43 (18%) | 0.11 |
| FEVI (%) | 56 (±1) | 55 (±10) | 56 (±9) | 0.31 |
| FA | 78 (18%) | 40 (20%) | 38 (16%) | 0.36 |
| BAV 1r grado | 152 (40%) | 79 (45%) | 73 (36%) | 0.08 |
| BRIHH | 167 (38%) | 78 (38%) | 89 (38%) | 0.94 |
| BRDHH | 259 (59%) | 122 (59%) | 137 (59%) | 0.98 |
| BRDHH + HBA | 159 (36%) | 85 (41%) | 73 (31%) | 0.02 |




1. *A) Características basales de los grupos; B) Odds ratio para síncopes arrítmicos; C) Rendimiento diagnóstico, recurrencia y mortalidad.*

**Conclusiones:** Los pacientes con BR y ESU tienen un elevado riesgo de SA y es similar al de los pacientes con ESR. El EEF y el MCI ofrecen un rendimiento diagnóstico similar en ambos grupos. Se recomienda un estudio completo del síncope en estos pacientes pese a presentar un único episodio.

### 11.3.3. ¿Existen diferencias de género en pacientes con síncope y bloqueo de rama? Congreso de la salud cardiovascular SEC 21 – Zaragoza 28-30th October 2021

Montse Bach Oller , Jaume Francisco Pascual , Nuria Rivas Gándara , Manel Maymi Ballesteros , Clara Badia Molins , Jordi Pérez Rodón , Begoña Benito Villabriga , Alba Santos Ortega , Ivo Roca Luque , Javier Cantalapiedra Romero , Jenson Maldonado , Gerard Oristrell Santamaría , Antonia Sambola Ayala , Ángel Moya Mitjans y Ignacio Ferreira González *¿Existen diferencias de género en pacientes con síncope y bloqueo de rama?* Rev Esp Cardiol. 2021;74(Supl 1):331

Rev Esp Cardiol. 2021;74(Supl 1):331

Revista Española de Cardiología

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# 5005-5 - ¿EXISTEN DIFERENCIAS POR SEXO EN PACIENTES CON SÍNCOPE Y BLOQUEO DE RAMA?

*Montse Bach Oller, Jaume Francisco Pascual, Nuria Rivas Gándara, Manel Maymi Ballesteros, Clara Badia Molins, Jordi Pérez Rodón, Begoña Benito Villabriga, Alba Santos Ortega, Ivo Roca Luque, Javier Cantalapiedra Romero, Jenson Maldonado, Gerard Oristrell Santamaría, Antonia Sambola Ayala, Ángel Moya Mitjans e Ignacio Ferreira González*

*Hospital Universitario Vall d'Hebron, Barcelona.*

## Resumen

**Introducción y objetivos:** En los últimos años se ha realizado un esfuerzo sustancial para mejorar la comprensión de las diferencias de género en las enfermedades cardiovasculares. Sin embargo, ningún estudio ha examinado las diferencias entre mujeres y varones que presentan síncope y bloqueo de rama. El objetivo de este trabajo fue determinar si existen diferencias específicas por sexo en las características y resultados del síncope en pacientes con bloqueo de rama.

**Métodos:** Estudio de cohorte realizado entre enero de 2008 y febrero de 2021 en un hospital de tercer nivel centro de referencia en síncope. Se incluyeron pacientes con bloqueo de rama y síncope de origen desconocido tras la evaluación inicial, sin indicación directa de DAI. Los pacientes fueron manejados de acuerdo con las guías actuales de la ESC. A todos los pacientes se les realizó un estudio electrofisiológico (EEF) y en caso de no ser diagnóstico se implantó un registrador de bucle implantable (ILR).

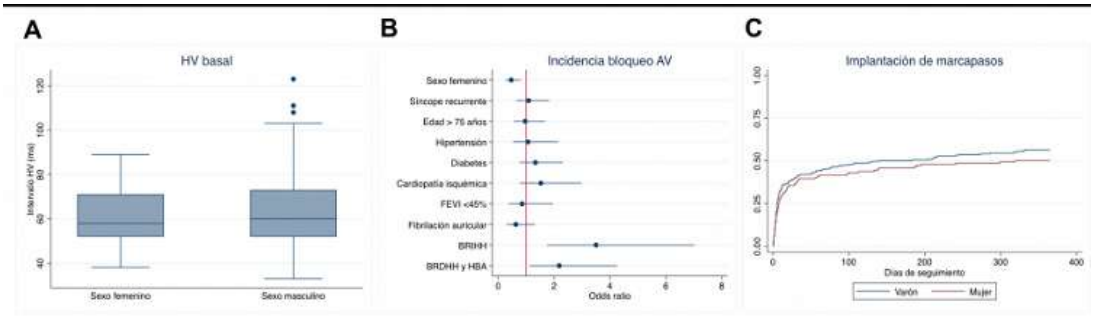
**Resultados:** Se incluyeron 443 pacientes, con una edad media de 73,9 años (DE 15,9), con 165 pacientes de sexo femenino (37,2%). El seguimiento medio fue de 4,0 años (DE 2,9). Los pacientes varones presentaban una mayor prevalencia de diabetes y cardiopatía isquémica. El bloqueo de rama izquierda (BRIHH) fue más prevalente en el sexo femenino y el bloqueo de rama derecha (BRDHH) en el sexo masculino (tabla). El rendimiento diagnóstico del EEF e ILR fue 43,0% y 41,8% respectivamente en mujeres y 48,2% y 45,3% en varones, siendo las diferencias no significativas. Sin embargo, el intervalo HV basal en el EEF fue significativamente más corto en el sexo femenino, 59,5 ms (DE 11,5) respecto a 63,3 ms (DE 15,3) (p = 0,007) (fig. A). En los análisis multivariados, el sexo femenino se asoció con un riesgo significativamente menor de bloqueo AV (fig. B) y con una menor necesidad de implantación de marcapasos al año (HR 0,72; IC95% 0,53-0,98) (fig. C). No se encontraron diferencias significativas entre sexos en la tasa de recurrencia de síncope, pero sí se observó una mayor mortalidad en el sexo masculino (28,8 vs 18,8%; p = 0,019).

Características basales de la muestra

| Variable | Todos los pacientes (n = 443) | Mujeres (n = 165) | Varones (n = 278) | p |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| Edad (años) | 73,9 (± 15,9) | 74,2 (± 17,6) | 73,7 (± 14,8) | 0,125 |
| Hipertensión | 348 (78,6%) | 125 (75,8%) | 223 (80,2%) | 0,269 |
| Diabetes | 153 (34,5%) | 42 (25,5%) | 111 (39,9%) | 0,002 |
| Dislipidemia | 266 (60,1%) | 98 (59,4%) | 168 (60,4%) | 0,829 |
| C. isquémica | 94 (21,2%) | 22 (13,3%) | 72 (25,9%) | 0,002 |
| FEVI (%) | 55,8% (± 10,0) | 55,8 (± 10,3) | 55,8 (± 9,9) | 0,982 |
| Síncope recurrente | 235 (53,1%) | 81 (49,1%) | 154 (55,4%) | 0,199 |
| Fibrilación auricular | 78 (17,8%) | 29 (17,6%) | 49 (17,9%) | 0,935 |
| Bloqueo AV 1º | 152 (40,2%) | 48 (34,3%) | 104 (43,7%) | 0,072 |
| BRIHH | 167 (37,9%) | 90 (55,2%) | 77 (27,7%) | < 0,001 |
| BRDHH | 259 (58,6%) | 68 (41,5%) | 191 (68,7%) | < 0,001 |
| BRDHH + HBA | 159 (35,9%) | 43 (26,1%) | 116 (41,7%) | 0,001 |
| BRDHH aislado | 50 (11,7%) | 16 (10,2%) | 34 (12,6% | 0,449 |
| Duración QRS (ms) | 143,1 (± 16,5) | 142,9 (± 15,3) | 143,3 (± 17,2) | 0,827 |
| QRS > 150 ms | 159 (36,0%) | 59 (36,0%) | 100 (36,0%) | 0,999 |

FEVI: fracción eyección ventrículo izquierdo; Bloqueo AV: bloqueo auriculoventricular; BRIHH: bloqueo rama izquierda del haz de His; BRDHH: bloqueo rama derecha del haz de His; HBA: hemibloqueo anterior izquierdo.




*Representación gráfica de los resultados del estudio.*

**Conclusiones:** Las mujeres con síncope y bloqueo de rama tienen un riesgo menor de bloqueo AV y una menor necesidad de implantación de marcapasos al año de seguimiento. Debe evitarse una estrategia de implantación directa de marcapasos, especialmente en mujeres.

### 11.3.4. Are there sex differences in patients with syncope and bundle branch block? ESC congress 2021, digital, August 2021

J Francisco Pascual, N Rivas Gandara, C Badia Molins, M Maymi Ballesteros, J Perez Rodon, B Benito, A Santos Ortega, I Roca Luque, M Bach Oller, J Cantalapiedra Romero, J Maldonado, G Oristrell Santamaria, A Sambola Ayala, A Moya Mitjans, I Ferreira Gonzalez, Are there sex differences in patients with syncope and bundle branch block?, *European Heart Journal,* Volume 42, Issue Supplement_1, October 2021, ehab724.0603, https://doi.org/10.1093/eurheartj/ehab724.0603

## Are there sex differences in patients with syncope and bundle branch block?

J. Francisco Pascual[1], N. Rivas Gandara[2], C. Badia Molins[1], M. Maymi Ballesteros[1], J. Perez Rodon[2], B. Benito[2], A. Santos Ortega[2], I. Roca Luque[3], M. Bach Oller[1], J. Cantalapiedra Romero[4], J. Maldonado[1], G. Oristrell Santamaria[2], A. Sambola Ayala[2], A. Moya Mitjans[2], I. Ferreira Gonzalez[4]

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**Funding Acknowledgement:** Type of funding sources: None.

**Background:** In the last years a substantial effort has been made to improve the understanding of the sex-differences in cardiovascular disease. However, no studies have examined differences in presentation and outcomes between men and women presenting with syncope and bundle branch block (BBB).

**Aim:** To determinate if there are sex-specific differences in the characteristics and outcomes of syncope in patients with BBB

**Methods:** Cohort study carried out in a tertiary hospital that is a reference center for syncope from January 2008 to February 2021. Patients (p.) with BBB and syncope of unknown origin after the initial evaluation without direct indication of an ICD were included. They were managed according to the current ESC guidelines. All patients underwent to an EPS and an ILR was implanted if it was not diagnostic.

**Results:** 374p. were included (75±1 y. o; 135 (36%) female). Mean follow up was 2.3±1.6 y.o. No differences in baseline characteristics where found comparing both groups, except that LBBB was more prevalent in female and RBBB in male (Figure 1A). EPS and ILR diagnostic yield was 44%/44% respectively in females and 50% /40% in males (p=ns). However, basal HV interval in EPS was significant shorter in females (Figure 2A). In the multivariate analyses female sex was associated with a significant lower risk of AV block (Figure 1B), and with a trend of less need of a pacemaker implantation (PM) (53% in females, 60% in males) (Log-rank 0.1) (Figure 2B). No significant differences in recurrences neither in mortality rate were found.

**Conclusions:** Female patients with syncope and BBB have lower risk of AV block compared to males, and only half of them required a pacemaker implantation. A strategy of direct PM implantation should be avoided, specially in woman.

A

| VARIABLE | ALL PATIENTS (N = 374) | FEMALE (N= 135) | MALE (N=239) | p |
|---|---|---|---|---|
| Age (y.o.) | 75 (±1) | 76 (±1) | 74 (±1) | 0.11 |
| Hypertension | 298 (80%) | 103 (76%) | 195 (82%) | 0.22 |
| Diabetes | 130 (35%) | 35 (26%) | 95 (40%) | 0.01 |
| Dyslipidaemia | 226 (60%) | 79 (59%) | 147 (62%) | 0.57 |
| IHD | 78 (21%) | 14 (10%) | 64 (27%) | <0.01 |
| LVEF (%) | 56 (±1) | 56 (±1) | 56 (±1) | 0.59 |
| Recurrent syncope | 206 (55%) | 72 (53%) | 134 (56%) | 0.58 |
| Atrial Fibrillation | 63 (17%) | 22 (16%) | 41 (18%) | 0.78 |
| 1st degree AVB | 122 (36%) | 38 (33%) | 84 (41%) | 0.18 |
| LBBB | 143 (38%) | 77(57%) | 66 (28%) | <0.01 |
| RBBB | 219 (59%) | 54 (40%) | 165 (69%) | <0.01 |
| RBBB + HBA | 135 (36%) | 33 (24%) | 102 (43%) | <0.01 |
| Isolate RBBB | 47 (13%) | 15 (12%) | 32 (14%) | 0.52 |
| QRS duration | 142 (±1) | 142 (±) | 144 (±1) | 0.32 |
| QRS> 150 ms | 133 (36%) | 44 (33%) | 89 (37%) | 0.39 |

B

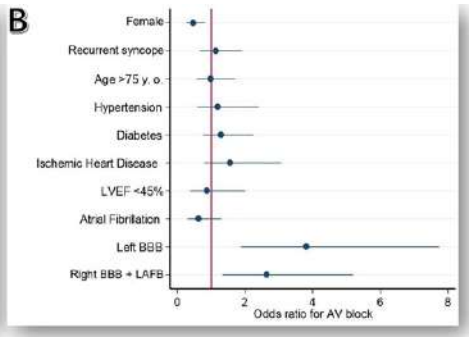
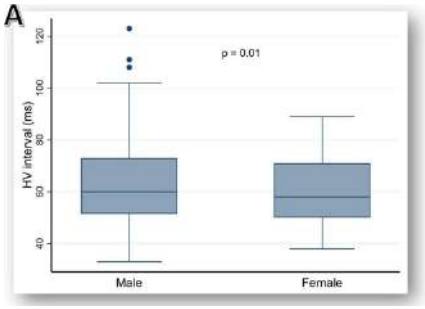



Figure 1

A




B

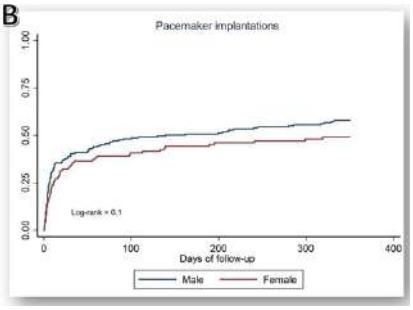



Figure 2

### 11.3.5. First Vs Recurrent Syncope In Patients With Structural Heart Disease Or Bundle Branch Block. EHRA Congress 2021, digital. May 2021

J Francisco Pascual, N Rivas Gandara, A Santos Ortega, J Perez Rodon, B Benito, I Roca, J Cantalapiedra Romero, J Maldonado, P Jordan Marchite, L Herrador Galindo, I Ferreira Gonzalez, First Vs Recurrent Syncope In Patients With Structural Heart Disease Or Bundle Branch Block, *EP Europace*, Volume 23, Issue Supplement_3, May 2021, euab116.316, https://doi.org/10.1093/europace/euab116.316

Europace 2021 Volume 23 Supplement 3 iii355

Syncope and Bradycardia - Diagnostic Methods

# First Vs Recurrent Syncope In Patients With Structural Heart Disease Or Bundle Branch Block

Francisco Pascual J.[1]; Rivas Gandara N.[1]; Santos Ortega A.[1]; Perez Rodon J.[1]; Benito B.[1]; Roca I.[2]; Cantalapiedra Romero J.[1]; Maldonado J.[1]; Jordan Marchite P.[1]; Herrador Galindo L.[1]; Ferreira Gonzalez I.[3]

[1]University Hospital Vall d"Hebron & Vall d"Hebron Institut de Recerca, Servei de Cardiologia. - Universitat autònoma de Barcelona. CIBER-CV, Barcelona, Spain, Barcelona, Spain
[2]Hospital Clinic de Barcelona, Barcelona, Spain
[3]University Hospital Vall d"Hebron, Servei de Cardiologia. - VHIR- Universitat autònoma de Barcelona. CIVERESP, Barcelona, Spain

**Funding Acknowledgements:** Type of funding sources: Public hospital(s). Main funding source(s): Hospital Universitari Vall d"Hebron - Vall d"Hebron Institut de Recerca. CIBERCV

**BACKGROUND:** Patients with structural heart disease (SHD) or bundle branch block (BBB) are at high risk of having an arrhythmic syncope (AS). In patients with recurrent syncope episodes (RSE) complete work-up including electrophysiological study (EPS) and/or implantation of a loop recorder (ILR) is recommended, however patients with their first episode may also be at risk of an AS.

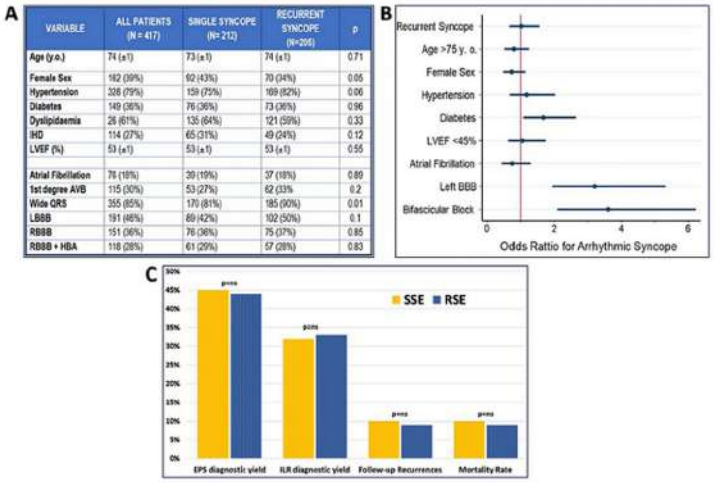
**AIM:** To determinate if the patients with SHD or BBB with a single syncope episode (SSE) are at high risk of having an AS and compare it with patients with recurrent episodes (RSE).

**METHODS** Cohort study carried out in a tertiary hospital that is a reference centre for syncope. From January 2008 to August 2020 patients with SHD or BBB with syncope of unknown origin after the initial evaluation and without direct indication of an ICD were included. They were managed according the current ESC guidelines.

**RESULTS:** 417patients were included (74 ±11 y. o; 39% female). Mean follow up was 2.5 ±1 y. 223 patients were diagnosed from an AS [113 (53%) in SSE group and 110 (54%) in RSE group, p = 0.9], 210 were due to bradyarrhythmia (AV block or sinus arrest). No differences in baseline characteristics where found comparing both groups, except that BBB was slightly more prevalent in patients with RSE (81% vs 90%, p = 0.01) (FIGURE- PANEL A). Risk of AS was 53% in patients with SE and 54% (p = 0.9). RSE were not associated with an increased risk of AS in univariate analyses (OR 1.01 IC95% 0.7-1.5) neither in the multivariate (FIGURE- PANEL B). EPS and ILR diagnostic yield was 45% / 32% respectively in SSE group and 44% / 33% in RSE group (p = 0.8) (FIGURE - PANEL C). After appropriate treatment, recurrence syncope rate was 10% in SSE group and 9% in RSE group (p = 0.8). No significant differences in mortality rate were found.

**CONCLUSIONS:** Patients with SHD or BBB and single syncope episode are at a high risk of having AS, and similar to those with RSE. EPS and ILR offer a similar diagnostic yield in both groups. Complete syncope work-up must be recommended in these patients despite having had only a single episode.

Abstract Figure



### 11.3.6. Impacto pronóstico de encontrar un diagnóstico etiológico del síncope en pacientes con estenosis aórtica severa. Congreso de la sociedad Española de Cardiología 2019. Barcelona. 17-19 de Octubre de 2019

Yassin Belahnech Pujol, Jaume Francisco Pascual, Eduardo Ródenas Alesina, Nuria Rivas Gándara, Jordi Pérez Rodón, Alba Santos Ortega, Sandra Isabel Llerena Butrón, Julián Rodríguez García, Yolima Cossio Gil, Vicente Serra García, David García-Dorado, Ignacio Ferreira González. Impacto pronóstico de encontrar un diagnóstico etiológico del síncope en pacientes con estenosis aórtica severa. *Rev Esp Cardiol*. 2019;72(Supl 1):596

Rev Esp Cardiol. 2019;72(Supl 1):596

Revista Española de Cardiología

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# 6005-60 - IMPACTO PRONÓSTICO DE ENCONTRAR UN DIAGNÓSTICO ETIOLÓGICO DEL SÍNCOPE EN PACIENTES CON ESTENOSIS AÓRTICA GRAVE

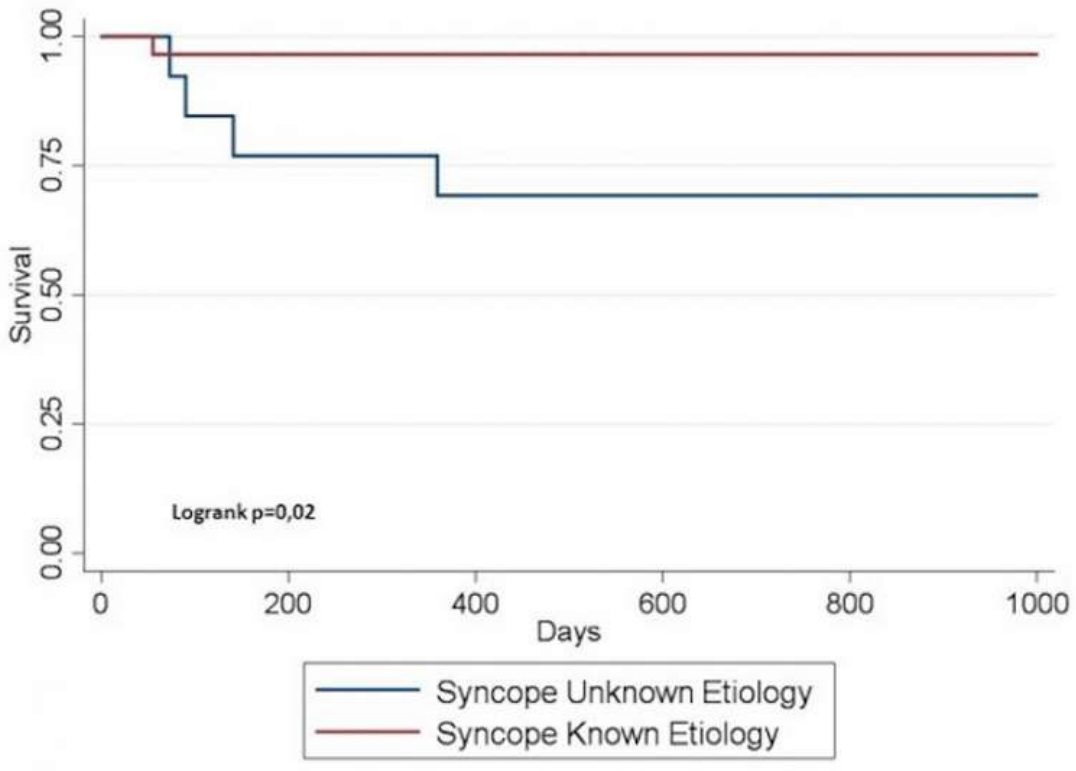
*Yassin Belahnech Pujol[1], Jaume Francisco Pascual[2], Eduardo Ródenas Alesina[1], Nuria Rivas Gándara[2], Jordi Pérez Rodón[2], Alba Santos Ortega[2], Sandra Isabel Llerena Butrón[2], Julián Rodríguez García[2], Yolima Cossio Gil[3], Vicente Serra García[1], David García-Dorado[1] e Ignacio Ferreira González[1], del [1]Servicio de Cardiología, Hospital Universitario Vall d'Hebron, Barcelona, [2]Servicio de Cardiología, Unidad de Arritmias, Hospital Universitario Vall d'Hebron, Barcelona y [3]Hospital Universitario Vall d'Hebron, Barcelona.*

## Resumen

**Introducción y objetivos:** El síncope se asocia a un peor pronóstico después del recambio valvular aórtico (RVAo) en comparación con otras indicaciones clínicas para el RVAo. Sin embargo no se ha evaluado el impacto pronóstico de encontrar una etiología del síncope. El objetivo de este estudio fue evaluar el impacto pronóstico de encontrar una etiología del síncope en pacientes con estenosis aórtica (EAo) grave.

**Métodos:** Se realizó un estudio observacional retrospectivo de una serie de pacientes y se incluyeron de forma consecutiva a todos los pacientes con diagnóstico al alta hospitalaria de síncope y EAo grave entre enero de 2010 y agosto de 2018 con un seguimiento realizado hasta febrero de 2019. Los enfermos fueron evaluados por un equipo multidisciplinar según las recomendaciones vigentes de las guías europeas de síncope y valvulopatías.

**Resultados:** Se evaluaron 336 pacientes con diagnóstico de síncope y EAo de los cuales 61 (18,2%) presentaban EAo grave en el momento del síncope. De estos 27 (44,3%) eran mujeres y la media de edad fue de 79 ± 10 años. Se encontró una etiología del síncope altamente probable o definitiva en 40 pacientes (65,6%) de los cuales 21 (34,4%) fueron de causa arrítmica, 7 (11,5%) fueron refleja, 7 (11,5%) debida a la propia EAo, 4 (6,6%) ortostática y 1 (1,6%) en contexto de síndrome coronario agudo. Los pacientes recibieron tratamiento según su etiología, se implantaron un total de 18 marcapasos y la mayoría fueron sometidos a RVAo. En el análisis multivariante se constató que el hecho de encontrar un diagnóstico etiológico del síncope fue el único factor asociado a mortalidad después del RVAo (HR = 0,11; IC95% 0,12-0,97) (figura).




*Curva de supervivencia Kaplan-Meier según diagnóstico del síncope en pacientes con recambio valvular aórtico.*

**Conclusiones:** En una gran proporción de los enfermos la EAo grave no es la causa principal del síncope. Encontrar un diagnóstico etiológico del síncope permite aplicar un tratamiento específico y esto tiene un importante impacto en el pronóstico después del RVAo.

### 11.3.7. Etiology of syncope in patients with severe aortic stenosis. ESC Congress. München August 2018

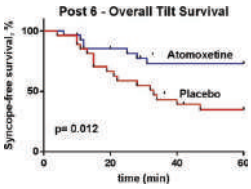
Francisco Pascual, E Rodenas Alesina, Y Belahnech Pujol, N Rivas Gandara, I Roca Luque,J Perez Rodon,A Santos Ortega,Y Cossio Gil,V Serra Garcia,S Llerena,G Oristrell Santamaria, A Moya Mitjans, D Garcia-Dorado. Etiology of syncope in patients with severe aortic stenosis, *European Heart Journal,* Volume 39, Issue suppl_1, August 2018, ehy563.P4834, https://doi.org/10.1093/eurheartj/ehy563.P4834

## SYNCOPE

### P4832
### Norepinephrine transporter inhibition prevents tilt-induced vasovagal syncope: a randomized, placebo controlled trial

S.R. Raj[1], J.C. Guzman[2], T. Kus[3], F.A. Araya-Paredes[4], J. Angihan[1], L. Lei[1], G. Bennett[1], C. Maxey[1], R.S. Sheldon[1]. *[1]Libin Cardiovascular Institute of Alberta, Cardiac Sciences, Calgary, Canada; [2]McMaster University, Medicine, Hamilton, Canada; [3]Hospital du Sacre-Coeur, Cardiologie, Montreal, Canada; [4]University Hospital of Sherbrooke (CHUS), Cardiologie, Sherbrooke, Canada.* On behalf of POST6 Investigators

**Background:** The norepinephrine transporter (NET) is a clearance mechanism in sympathetic neurons. Pharmacological NET inhibition increases sympathetic tone, and this has been shown to decrease tilt induced syncope in healthy subjects. There is a paucity of effective therapies for vasovagal syncope (VVS). Atomoxetine (ATOX) is a potent NET inhibitor.
**Objectives:** We tested the hypothesis that NET inhibition with ATOX would prevent tilt-induced syncope in VVS.
**Methods:** The POST6 study was a placebo-controlled, parallel-group, randomized trial of ATOX (40mg PO BID; n=27) vs. matched placebo (PLAC; n=29). VVS patients were given 2 doses of study drug followed by a 60 min drug-free head-up tilt table test.
**Results:** Patients were 35±14 years (73% F) with a median of 12 lifetime faints, and 3 faints in the last year. VVS patients fainted significantly less with ATOX than PLAC (24% vs. 63%; P=0.003), but there was no difference in the rates of presyncope (76% vs. 78%; P=0.87). The mean time to faint was longer with ATOX than PLAC (49.9±18.8 min vs. 35.9±21.1 min; P=0.01). The logrank Hazard ratio for fainting with ATOX:PLAC was 0.40 (95% CI: 0.18–0.87).



POST6 Syncope Survival

**Conclusion:** NET inhibition with ATOX significantly decreased the risk of tilt-induced syncope in VVS patients. This is a promising novel pharmacological strategy for treating VVS.
**Funding Acknowledgements:** Cardiac Arrhythmia Network of Canada (CANet)

### P4833
### Risk predictors of supraventricular tachycardia and bradycardia necessitating therapy in patients with unexplained syncope receiving implantable loop recorder

T. Onuki[1], T. Gokan[1], Y. Nakamura[1], N. Okada[2], Y. Chiba[1], S. Kawasaki[1], Y. Onishi[1], Y. Munetsugu[1], H. Ito[1], M. Shoji[1], N. Watanabe[1], Y. Minoura[1], T. Adachi[1], M. Kawamura[1], Y. Kobayashi[1]. *[1]Showa University Hospital, Division of Cardiology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [2]Showa University Hospital, Department of hospital pharmaceutics, Tokyo, Japan*

**Background:** Implantable loop recorders (ILR) allow for prolonged cardiac rhythm monitoring and improved diagnostic yield in syncope patients. We sometimes diagnose epilepsy as unexplained syncope because these situations of loss of consciousness are similar. Thus, unexplained syncope patients we diagnosed include epilepsy patients. Predictive factors for supraventricular tachycardia (SVT), bradycardia and epilepsy necessitating therapy in the ILR population with unexplained syncope are not well known. We investigated these predict factors.
**Methods:** We retrospectively reviewed medical records of consecutive patients with ILR implantation for unexplained syncope between February 1, 2009 and December 31, 2017. The medical records of participants were reviewed for clinical history, including activity at the time of syncope, situation and characteristics of syncope, comorbidities (e.g., hypertension, diabetes mellitus, dyslipidemia, prior stroke/transient ischemic attack, ischemic heart disease), medications, blood pressure on consultation, body mass index, smoking, and ECG results. We then performed cox stepwise logistic regression analysis to identify significant independent factor.
**Results:** Eighty-four patients were implanted with ILR for unexplained syncope. During 18 months follow-up period, 6 patients (7%) and 14 patients (15%) had clinically SVT and bradycardia, respectively. Stepwise logistic regression analysis indicated that syncope during effort (OR 4.69; 95% CI 1.23–17.9, $p<0.05$) and injury secondary to syncope (OR 4.74; 95% CI 1.30–17.5, $p<0.05$)) were independent risk factors for bradycardia necessitating PM or discontinuance of culprit drug. Palpitation before syncope (OR 15.7; 95% CI 1.30–369, $p<0.05$) and history of atrial fibrillation (OR 18.9; 95% CI 2.53–388, $p<0.05$) were identified as significant independent prognostic factors for SVT. Finally, syncope while supine (OR 10.0; 95% CI 1.34–74.2, $P<0.05$) was identified as significant independent prognostic factors for epilepsy.
**Conclusions:** Palpitation, atrial fibrillation, syncope during effort and injury were independent risk factors for SVT or bradycardia. Syncope while supine was independent risk factors for epilepsy.

### P4834
### Etiology of syncope in patients with severe aortic stenosis

J. Francisco Pascual[1], E. Rodenas Alesina[2], Y. Belahnech Pujol[2], N. Rivas Gandara[1], I. Roca Luque[1], J. Perez Rodon[1], A. Santos Ortega[1], Y. Cossio Gil[3], V. Serra Garcia[2], S. Llerena[1], G. Oristrell Santamaria[2], A. Moya Mitjans[1], D. Garcia-Dorado[2]. *[1]University Hospital Vall d'Hebron, Unitat d'Arritimes. Servei de Cardiologia. - Universitat autònoma de Barcelona. CIVER-CV, Barcelona, Spain; [2]University Hospital Vall d'Hebron, Servei de Cardiologia. - Universitat autònoma de Barcelona. CIVER-CV, Barcelona, Spain; [3]University Hospital Vall d'Hebron, Barcelona, Spain*

**Background:** Despite aortic stenosis (AoS) have been describe itself as a cause of syncope, other etiologies can be present. Few studies in the literature have evaluated the causes of syncope in this population
**Aim:** To evaluate the etiology of syncope in patients with severe aortic stenosis
**Methods:** We conducted an observational cohort study. All consecutive patients with the diagnosis at hospital discharge of syncope and AoS from January 2010 to December 2017 were included. All patients were referred for evaluation of unexplained syncope, and were examined by a multidisciplinary team according the current European syncope and valvular heart diseases guidelines.
**Results:** Of 293 patients with the diagnosis of syncope and AoS, 41 (13.9%) presented severe AoS at the moment of the syncope. (19 (46.3%) female, mean age 77±11 y. o.) A definitive or highly probable etiology of the syncope was found in 25 (61,0%) patients, in 22 during the initial hospitalization and in 3 of them in the outpatients clinic follow up. Causes of syncope are summarized in the table. Only in 3 patients (7.3%) AoE was considered itself the main cause of syncope, while in other cases AoE was only a bystander or a contributing factor. In 22 (88.0% of patients with diagnosis) the diagnosis was achieved with the initial clinical history, physical exploration, ECG and telemetry ECG monitoring. The presence of wide QRS complex (43.4%.vs11.1% p=0.03) or any grade of AV block (33.3%vs0% p 0.01) in the admission ECG and a lower mean aortic gradient (48.27±12.0 vs 64.78±16.5 mmHg p 0.01) are predictors of achieving an etiological diagnosis.

Table 1

| Main cause of syncope | Total diagnosis | Diagnosis during initial hospitalization | Diagnosis during follow up |
|---|---|---|---|
| Advance AV block | 8 (19.5%) | 7 | 1 |
| Vasovagal syncope | 5 (12.2%) | 4 | 1 |
| Sinus node dysfunction | 4 (9.8%) | 4 | 0 |
| Low cardiac output during exercise | 3 (4.3%) | 3 | 0 |
| Fast atrial arrhythmias | 2 (4.9%) | 2 | 0 |
| Carotid sinus hypersensitivity | 1 (2.4%) | 1 | 0 |
| Orthostatic hypotension | 1 (2.4%) | 0 | 1 |
| Acute coronary syndrome | 1 (2.4%) | 1 | 0 |
| Unknown | 16 (39.0%) | | |

**Conclusions:** In a large proportion of patients severe aortic stenosis is not the main cause of syncope. Systematic evaluation must be done to assess the real etiology of the syncope
**Funding Acknowledgements:** Instituto de Salud Carlos III, grant FIS PI14/1431, PI15/1655 co-financed by the European Regional Development Fund (ERDF-FEDER); CIBERCV

### P4835
### High incidence of injury due to vasovagal and bradyarrhythmic syncope

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**Introduction:** Recurrent syncope raises concerns about future risk of injury.
**Purpose:** We aimed to determine the incidence, severity, and predictors of injuries due to syncope in patients (pts) with syncope in 3 clinical trials.
**Methods:** POST studies are multi-centered randomized syncope treatment trials. POST 2 and 4 studied fludrocortisone and midodrine for vasovagal syncope, and POST 3 studied management strategies for bifascicular block and syncope. Injuries were recorded up to 1 year after enrollment. Injury was defined as minor (bruising, scrapes), moderate (lacerations), and severe (fracture, burns, joint pain). Time-dependent survival were tested with predictors Wilcoxon, and injury severity predictors with ANOVA.
**Results:** Of 459 pts, 183 had at least 1 faint. Fully 97/210 (46%), 30/115 (26%), and 56/128 (44%) pts fainted in POST2, POST3 and POST 4 respectively, with a total 645 faints. Median ages were 34 yr, 74 yr, and 27 yr respectively, and total median age was 35 yr. The median prior yr syncope frequency was 3, with 85/183 (46%) having >3 faints/yr. Fully 58/183 pts (32%) had at least 1 injury related to syncope, and 95/645 faints (15%) resulted in injury. Of 58 injured pts, minor, moderate and severe injuries were reported by 47 (81%), 7 (12%), and 4 (7%) pts respectively. Of 95 injuries, 75 (79%), 16 (17%), and 4 (4%) were

### 11.3.8. Etiología del síncope en pacientes con estenosis aórtica severa. (Oral abstract) Congreso SEC 2018. Sevilla. Octubre 2018

Yassin Belahnech Pujol, Jaume Francisco Pascual, Eduardo Ródenas Alesina, Nuria Rivas Gándara, Ivo Roca Luque, Jordi Pérez Rodón, Alba Santos Ortega, Sandra Isabel Llerena Butrón, Ángel Moya i Mitjáns, Vicente Serra García, Yolima Cossio Gil y David García Dorado. *Etiología del síncope en pacientes con estenosis aórtica severa*. Rev Esp Cardiol. 2018;71(Supl 1):47

Rev Esp Cardiol. 2018;71(Supl 1):47

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# 5000-5 - ETIOLOGÍA DEL SÍNCOPE EN PACIENTES CON ESTENOSIS AÓRTICA GRAVE

*Yassin Belahnech Pujol, Jaume Francisco Pascual, Eduardo Ródenas Alesina, Nuria Rivas Gándara, Ivo Roca Luque, Jordi Pérez Rodón, Alba Santos Ortega, Sandra Isabel Llerena Butrón, Ángel Moya i Mitjáns, Vicente Serra García, Yolima Cossio Gil y David García Dorado, del Hospital Universitario Vall d&#39Hebron, Barcelona.*

## Resumen

**Introducción y objetivos:** A pesar de que la estenosis aórtica (EAo) se ha descrito como causa de síncope, otras etiologías pueden estar presentes. La identificación de una causa arrítmica subyacente tiene implicaciones clínicas y pronósticas evidentes. Pocos estudios en la literatura han evaluado los predictores de una causa arrítmica en esta población. Nuestro objetivo fue evaluar factores clínicos y electrocardiográficos que podrían predecir una etiología arrítmica del síncope en pacientes con EAo grave.

**Métodos:** Se realizó un estudio observacional con todos los pacientes con diagnóstico al alta de síncope y EAo entre enero de 2010 y diciembre de 2017. Los pacientes fueron examinados por un equipo multidisciplinar según las guías de práctica clínica actuales sobre síncope y valvulopatías de la ESC y, según las mismas, se definió la causa del síncope.

**Resultados:** De los 293 pacientes con diagnóstico de síncope y EAo, 41 (13,9%) presentaron EAo grave en el momento del síncope. De estos, 14 pacientes (34,1%) tuvieron un síncope arrítmico (8 (30,7%) bloqueo auriculoventricular avanzado, 4 (15,4%) disfunción sinusal, 2 (7,7%) arritmias auriculares rápidas y 30 pacientes presentaron un síncope no arrítmico: 16 (39%) inexplicado, 7 (17,1%) reflejo u ortostático y 4 (9,6%) por otras causas. Entre pacientes con y sin sincope arrítmico no hubo diferencias significativas en el sexo (46,7 frente a 45,5% mujeres, p = 0,94), la edad (77,5 ± 12,5 frente a 76,9 ± 8,9 años, p = 0,16), el tratamiento antihipertensivo (73,3 frente a 81,8% p = 0,57) o comorbilidades basales. El QRS ancho en el ECG al ingreso (16,7 frente a 63,6%, RR 3,76, p < 0,01) y la frecuencia cardiaca más baja al ingreso (80,1 ± 22,2 frente a 60,24 ± 21,1 lpm, p = 0,02) se asociaron con un mayor riesgo de síncope arrítmico, mientras que la presencia de un desencadenante clínico identificable (56,7 frente a 9,1%, RR 0,15, p < 0,01) fue un predictor de síncope no arrítmico. Los pacientes con síncope no arrítmico presentaron una tendencia a tener gradiente pico más elevado en el ecocardiograma (88,5 ± 24,2 frente a 71,3 ± 27,2 mmHg, p = 0,07).

**Conclusiones:** El síncope arrítmico es una causa común de síncope en pacientes con EAo grave. La presencia de un complejo QRS ancho y una frecuencia cardiaca menor en el ECG de ingreso se asocian con un mayor riesgo de síncope arrítmico, mientras que la presencia de una desencadenante clínico identificable es un predictor de un síncope no arrítmico.

### 11.3.9. Predictores clínicos y electrocardiográficos del síncope en pacientes con estenosis aórtica severa (comunicación oral) Congreso SEC 2018. Sevilla. Octubre 2018

Eduardo Ródenas Alesina, Jaume Francisco Pascual, Yassin Belahnech Pujol, Nuria Rivas Gándara, Ivo Roca Luque, Jordi Pérez-Rodón, Alba Santos Ortega, Yolima Cossio Gil y David García-Dorado. *Predictores clínicos y electrocardiográficos del síncope en pacientes con estenosis aórtica severa*. Rev Esp Cardiol. 2018;71(Supl 1):48

Rev Esp Cardiol. 2018;71(Supl 1):48

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# 5000-6 - PREDICTORES CLÍNICOS Y ELECTROCARDIOGRÁFICOS DEL SÍNCOPE EN PACIENTES CON ESTENOSIS AÓRTICA GRAVE

*Eduardo Ródenas Alesina, Jaume Francisco Pascual, Yassin Belahnech Pujol, Nuria Rivas Gándara, Ivo Roca Luque, Jordi Pérez-Rodón, Alba Santos Ortega, Yolima Cossio Gil y David García-Dorado, del Hospital Universitario Vall d&#39Hebron, Barcelona.*

## Resumen

**Introducción y objetivos:** Pese a que la estenosis aórtica (EAo) se ha descrito como causa de síncope, otras etiologías pueden estar presentes. Pocos estudios han evaluado la etiología del síncope en esta población. Nuestro objetivo fue evaluar la etiología del síncope en pacientes con EAo grave.

**Métodos:** Realizamos un estudio observacional que incluyó a todos los pacientes con diagnóstico al alta de síncope y EAo entre enero de 2010 y diciembre de 2017. Los pacientes fueron examinados por un equipo multidisciplinario según las guías de práctica clínica actuales sobre síncope y valvulopatías de la ESC, y según las mismas, fue definida la causa del síncope.

**Resultados:** De 293 pacientes con el diagnóstico de síncope y EAo, 41 (13,9%) presentaron EAo grave en el momento del síncope (19 mujeres (46,3%), edad promedio 77 ± 11 años). Se encontró una etiología del síncope definitiva o altamente probable en 25 pacientes (61%), en 22 durante la hospitalización inicial y en 3 de ellos en el seguimiento ambulatorio. Solo en 3 pacientes (7,3%) la EAo se consideró la principal causa de síncope, mientras que en otros casos la EAo fue solo un factor contribuyente. En 22 casos (88,0% de los pacientes con diagnóstico) el diagnóstico se logró con la historia clínica inicial, la exploración física, el ECG y la monitorización del ECG por telemetría. La presencia en el ECG de ingreso de un complejo QRS ancho (43,4 frente a 11,1%, p = 0,03) o cualquier grado de bloqueo AV (33,3 frente a 0%, p < 0,01) y un gradiente aórtico medio más bajo (48,27 ± 12,0 frente a 64,78 ± 16,5 mmHg, p < 0,01) son predictores para lograr un diagnóstico etiológico.

Etiología del síncope en pacientes con estenosis aórtica grave

| Causa principal del síncope | Total diagnosis | Diagnóstico al ingreso | Diagnóstico en el seguimiento |
|---|---|---|---|
| Bloqueo auriculoventricular avanzado | 8 (30,7%) | 7 | 1 |
| Síncope vasovagal | 5 (19,2%) | 4 | 1 |
| Disfunción del nódulo sinusal | 4 (15,4%) | 4 | 0 |
| Arritmia auricular rápida | 2 (7,7%) | 2 | 0 |
| Gasto cardiaco bajo durante el ejercicio | 2 (7,7%) | 2 | 0 |

| | | | |
|---|---|---|---|
| Hipersensibilidad del seno carotídeo | 1 (3,8%) | 1 | 0 |
| Hipotensión ortostática | 1 (3,8%) | 0 | 1 |
| Síndrome coronario agudo | 1 (3,8%) | 1 | 0 |
| Desconocido | 17 (41,5%) | | |

**Conclusiones:** En una gran proporción de pacientes la estenosis aórtica grave no es la causa del síncope, por lo que debe realizarse una evaluación sistemática para investigar la etiología real del síncope.

### 11.3.10. Factores asociados que contribuyen al síncope en pacientes con estenosis aórtica grave. Congreso SEC 2018. Sevilla. Octubre 2018

Yassin Belahnech Pujol, Jaume Francisco Pascual, Eduardo Ródenas Alesina, Nuria Rivas Gándara, Ivo Roca Luque, Jordi Pérez Rodón, Alba Santos Ortega, Sandra Isabel Llerena Butrón, Ángel Moya i Mitjáns, Vicente Serra García, Yolima Cossio Gil y David García Dorado. Factores asociados que contribuyen al síncope en pacientes con estenosis aórtica grave. *Rev Esp Cardiol.* 2018;71(Supl 1):747

Rev Esp Cardiol. 2018;71(Supl 1):747

Revista Española de Cardiología

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# 6005-94 - FACTORES ASOCIADOS QUE CONTRIBUYEN AL SÍNCOPE EN PACIENTES CON ESTENOSIS AÓRTICA GRAVE

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## Resumen

**Introducción y objetivos:** La estenosis aórtica (EAo) grave afecta frecuentemente a pacientes de edad avanzada con múltiples comorbilidades. El síncope en esta población puede responder a múltiples causas y pueden existir factores asociados que contribuyan al síncope más allá de la causa principal. Pocos estudios en la literatura han evaluado las principales causas y los factores asociados al sincope en esta población.

**Métodos:** Realizamos un estudio observacional que incluyó a todos los pacientes con diagnóstico al alta de síncope y EAo entre enero de 2010 y diciembre de 2017. Un equipo multidisciplinar examinó a los pacientes según las guías de práctica clínica actuales sobre síncope y valvulopatías de la ESC y, según las mismas, se definió la causa del síncope.

**Resultados:** Se incluyó a 293 enfermos, de los cuales 41 presentaban EAo grave. En 25 (61,0%) se objetivó una clara causa de síncope (14 síncope arrítmico, 7 reflejo u ortostático y 4 otros) y en 16 (39%) la etiología fue desconocida. Más allá de la causa primaria, un promedio de 2,5 ± 1,16 factores asociados contribuyeron al síncope en nuestra población. Los factores asociados más frecuentes fueron: fármacos antihipertensivos (75,6%), desencadenantes clínicos (43,9%), alteraciones de la conducción eléctrica (41,5%), psicofármacos (19,9%) y cardiopatía isquémica (19,5%). Las alteraciones de la conducción fueron significativamente más prevalentes en el grupo de pacientes con síncope conocido (65,2% en pacientes con síncope conocido frente a 11,1% en pacientes con etiología desconocida, p < 0,01). No se encontraron diferencias significativas en el resto de factores asociados teniendo en cuenta si la etiología era conocida o no.

Prevalencia de factores asociados al síncope según causa principal conocida o desconocida

| Factores asociados | Pacientes (n = 41) | Causa principal conocida (n = 25) | Causa principal desconocida (n = 16) | p |
|---|---|---|---|---|
| Antihipertensivos | 75,6% | 73,9% | 77,8% | NS |
| Psicofármacos | 19,5% | 21,7% | 16,7% | NS |
| Cardiopatía isquémica | 19,5% | 17,4% | 22,2% | NS |
| Miocardiopatía primaria | 4,9% | 0,0% | 11,1% | NS |
| Desencadenantes clínicos | 43,9% | 55,2% | 33,3% | NS |

| | | | | |
|---|---|---|---|---|
| Alteraciones de la conducción | 41,5% | 65,2% | 11,1% | < 0,01 |

NS: no significativo.

**Conclusiones:** La mayoría de los pacientes con síncope y EAo grave tenían varios factores asociados añadidos a la causa principal, siendo los antihipertensivos y los trastornos de conducción los más frecuentes. Únicamente los trastornos de conducción fueron significativamente más prevalentes en el grupo con etiología conocida del síncope.

### 11.3.11. Clinical and electrocardiographic predictors of arrhythmic syncope in patients with severe aortic stenosis. ESC Congress. München August 2018

J Francisco Pascual, E Rodenas Alesina, Y Belahnech Pujol, N Rivas Gandara, I Roca Luque, J Perez Rodon, A Santos Ortega, S Llerena, A Moya Mitjans, V Serra Garcia, Y Cossio Gil, G Oristrell Santamaria, D Garcia-Dorado. Clinical and electrocardiographic predictors of arrhythmic syncope in patients with severe aortic stenosis, *European Heart Journal*, Volume 39, Issue suppl_1, August 2018, ehy566.P6635, https://doi.org/10.1093/eurheartj/ehy566.P6635

mV2 discriminated between NMS and controls with a sensitivity of 82% and specificity of 77% (AUC=0.81).
**Conclusions:** The presence of isolated very low QRS voltage in frontal plane ECG leads, as well as of small and elongated frontal QRS loops on the vectorcardiogram may help identify predisposition to NMS.

### P6633
### Pacing as a treatment for recurrent cardioinhibitory vasovagal syncope: systematic review with meta-analysis

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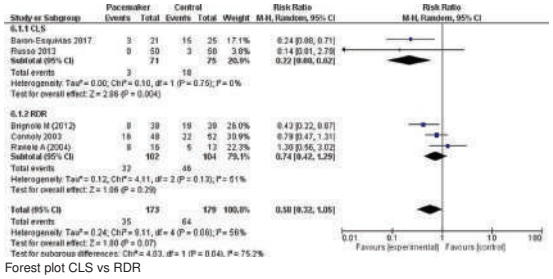
**Introduction:** Vasovagal reflex is the most common cause of syncopal episodes, mostly considered a benign condition. However, some patients have recurring episodes and/or major trauma associated with syncope, thus compromising quality-of-life. Pacemaker with rate drop response (RDR) and Closed-Loop Stimulation (CLS) algorithms have been investigated in recurrent vasovagal syncope (R-VVS). The latter has shown promise in cardioinhibitory R-VVS (defined as heart rate <40 bpm >10 seconds and/or asystole >3 seconds).
**Purpose:** To define the role of cardiac pacing in cardioinhibitory R-VVS.
**Methods:** MEDLINE, Cochrane Library and registered clinical trials were searched for single or double-blinded placebo-controlled randomized controlled trials (RCT) on cardiac pacing treatment for R-VVS and systematically reviewed for inclusion and further analysis.
**Results:** Five clinical trials met the eligibility criteria, with a total of 254 patients included. Four trials were double-blinded and four had a follow-up of at least one year. Two of them investigated the CLS and three the RDR algorithms. The analysis of all trials (N=5) as well as that of the double-blinded with a follow-up greater than a year (N=3) did not find a significant reduction in recurring syncopal events (RR: 0,53; 95% IC: 0,21–1,34; RR: 0,58; 95% IC: 0,32–1,05, respectively). When analyzing the trials by algorithm, the RDR pacemaker has shown no significant advantage (RR: 0,74; 95% IC: 0,42–1,29). However, the CLS algorithm was associated with a 22% reduction in the syncopal events (RR: 0,22; 95% IC: 0,08–0,62).



Forest plot CLS vs RDR

**Conclusions:** The results of this meta-analysis suggest that the pacemaker DDD-CLS may have a role in cardioinhibitory R-VVS. The published data thus far is limited and pacemaker implantation should be reserved to carefully selected patients with refractory cardioinhibitory R-VVS and compromised quality-of-life.

### P6634
### Novel method of analysing heart rate variability at rest predicts a positive tilt table testing in patients with syncope of unknown origin

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**Background/Introduction:** Syncope is a common clinical entity, which is often challenging to explain. Head-up tilt test (HUTT) is a useful surrogate investigation in the diagnostic workup of syncope and can unveil a neurally-mediated syncope (NMS) in a considerable proportion of patients. The autonomic nervous system modulates both the heart rate variability (HRV) and the NMS events, the link however between HRV and HUTT outcome has not yet been elucidated.
**Purpose:** To investigate the association of HRV at rest with the HUTT outcome in patients with syncope of unknown origin (SUO).
**Methods:** We assessed 26 patients (15 females, age 46.5±21.8 years) with SUO who underwent a HUTT. We calculated three indices of HRV during a 5-minute ECG recording at the resting stage of HUTT before bed tilt. We employed a wavelet higher order spectral analysis (WHOS) in the low frequency band LF: 0.075–0.15 Hz which is an index of sympathetic and parasympathetic activity, using the wavelet bispectrum method to assess for nonlinear interactions in the HRV signal. To capture the time variations of bifrequency pairs, we applied the wavelet bispectrum in equal-length parts of the HRV signal. The bifrequency peaks F1 and F2 provide the evidence of frequency interactions and the wavelet biamplitude quantifies their strength. In all signal parts, maxA is the maximum of wavelet biamplitude, maxFc1 the maximum of wavelet bifrequency Fc1 and maxFc2 the maximum of wavelet bifrequency Fc2. HUTT response was classified as positive or negative.
**Results:** Positive HUTT was seen in 11 patients and negative in 15. Positive tests lasted for 30.0±9.2 minutes and negative tests were completed in 40 minutes. Patients with positive HUTT exhibited higher maxA (5.49±3.59 vs. 2.95±1.88, p=0.04) and lower maxFc2 (0.12±0.02 vs. 0.14±0.01, p=0.004). No difference across groups was seen in maxFc1 (Table).

HRV indices at rest and HUTT outcome

| Features | Positive HUTT | Negative HUTT | p |
|---|---|---|---|
| maxA | 5.49±3.59 | 2.95±1.88 | 0.04 |
| maxFc1 | 0.14±0.02 | 0.15±0.004 | 0.62 |
| maxFc2 | 0.12±0.02 | 0.14±0.01 | 0.004 |

**Conclusion(s):** We provide a novel approach in the diagnosis of NMS by analysing HR dynamics in the frequency domain using a nonlinear and non-stationary method based on WHOS analysis. In patients with SUO, data from the rest stage before bed tilt, reveal subtle changes in HRV that are associated with a positive HUTT outcome suggestive of NMS. Further studies will confirm if this methodology can supplement HUTT thereby contributing to a cost- and time-effective diagnosis of NMS.

### P6635
### Clinical and electrocardiographic predictors of arrhythmic syncope in patients with severe aortic stenosis

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**Background:** Despite aortic stenosis (AoS) has been described itself as a cause of syncope, multiple other aetiologies can be present. Identification of an underlying arrhythmic cause of the syncope has evident clinical and prognostic implications. Few studies in the literature have evaluated the main causes of syncope in this population and the predictors of an arrhythmic cause.
**Aim:** To evaluate the clinical and electrocardiographic factors that could predict an arrhythmic aetiology of syncope in patients with severe AoS
**Methods:** We conducted an observational cohort study. All consecutive patients with the discharge hospital diagnosis of syncope and AoS from January 2010 to December 2017 were included. All patients were referred for evaluation of unexplained syncope, and were examined by multidisciplinary team according the current ESC syncope and valvular heart diseases guidelines. Main cause of syncope was defined according ESC syncope guidelines.
**Results:** Out of 293 patients with diagnosis of syncope and AoS, 41 (13.9%) presented severe AoS at the moment of the syncope. Fourteen (34.1%) patients had an arrhythmic syncope (8 (30.7%) advance AV block, 4 (15.4%) sinus node dysfunction, 2 (7.7%) fast atrial arrhythmias) and 30 patients had non-arrhythmic syncope (16 (39%) unexplained syncope, 7 (17.1%) Reflex/orthostatic syncope, 4 (9.6%) other causes). There were no significance differences in sex (46.7% vs 45.5% female, p=0.94), age (77.5±12.5 vs 76.9±8.9 y. o, p=0.16), treatment with antihypertensive drugs (73.3% vs 81.8% p=0.57) and basal comorbidities in patients with and without arrhythmic syncope. The presence of a wide QRS complex in the ECG on admission (16.7% vs 63.6%, RR 3.76 p<0.01) and lower heart rate on admission (80.1±22.2 vs 60.24±21.1 bpm p=0.02) were associated with a higher risk of arrhythmic syncope, while the presence of an identifiable clinical trigger (56.7% vs 9.1%, RR 0.15, p<0.01) was a predictor for a non-arrhythmic syncope. Patients with non-arrhythmic syncope had a trend in having a higher peak gradient in the echocardiogram (88.5±24.2 vs 71.3±27.2 mmHg p=0.07)
**Conclusions:** Arrhythmic syncope is a common cause of syncope in patients with severe aortic stenosis. The presence of a wide QRS complex in the admission ECG and lower heart rate on admission are associated with a higher risk of arrhythmic syncope, while the presence of an identifiable clinical trigger is a predictor for a non-arrhythmic syncope.
**Funding Acknowledgements:** Instituto de Salud Carlos III, grant FIS PI14/1431, PI15/1655 co-financed by the European Regional Development Fund (ERDF-FEDER); CIBERCV

### P6636
### Association of angiotensin-converting enzyme I/D gene variant rs1799752 and autonomic dysfunction with cardiovascular profile in syncope patients

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**Introduction:** The symptoms of autonomic dysfunction were strongly associated

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