



iCARDEA

“An Intelligent Platform for Personalized Remote Monitoring of the Cardiac Patients with Electronic Implant Devices”

SPECIFIC TARGETED RESEARCH PROJECT

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iCARDEA – D4.2.1 Integrative Risk Assessment Model

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1 INTRODUCTION

1.1 Purpose

This document describes the integrative risk assessment model developed for the cardiac arrhythmia patients with implanted CIEDs in order to foresee possible further comorbidities. Since iCARDEA addresses secondary prevention, the risk assessment model focuses on early identification of further complications.

In this regard, as the evaluation of patients is global, despite not being contemplated in the Clinical Guidelines of Management, much of the risk assessment of patients that is being presented in this deliverable has also been implemented in task 4.1 (Adaptable Computer Interpretable Clinical Guideline Models for Executable Personalized CIED Follow-up), and reported in iCARDEA Deliverable D.4.1.1 “Clinical Guideline Definitions and Flowcharts for the Follow-up of CIED Patients”. As in deliverable D.4.1.1, we have focused on three fundamental aspects: management of patients with atrial fibrillation, management of ventricular arrhythmias and technical malfunctions in patients with cardiovascular implantable electronic devices.

1.2 Scope

This document provides detailed information about the risk assessment models developed within the scope of “Task 4.2 Integrative Risk Assessment Models” and will contribute to the milestone “M7 iCARDEA Personalized Adaptive Care Planner for CIED Recipients”.

1.3 Definitions, acronyms and abbreviations

Table 1 List of Abbreviations and Acronyms

Abbreviation/Acronym	DEFINITION
ACS	Acute coronary syndrome
AF	Atrial fibrillation
ARVC	Arrhythmogenic right ventricular cardiomyopathy
AVID	Antiarrhythmics Versus Implantable Defibrillators
BBB	Bundle branch block
CASH	Cardiac Arrest Study Hamburg
CHD	Coronary heart disease
CIDS	Canadian Implantable Defibrillator Study
CIED	Cardiovascular Implantable Electronic Device
CT	Computed tomography
EF	Ejection fraction
EGM	Endocardial electrogram
EHRA	European Heart Rhythm Association
EP	Electrophysiology
ESC	European Society of Cardiology
GPI	Glycoprotein IIb/IIIa inhibitor
GRACE	Global Registry of Acute Coronary Events
HCM	Hypertrophic cardiomyopathy
HF	Heart failure
HIS	Hospital information System
ICD	Implantable Cardioverter Defibrillator
INR	International Normalized Ratio
LA	Left atrium
LAA	Left atrial appendage
LBBS	Left bundle branch block
LMWH	Low-molecular-weight heparin

LQTS	Long QT syndrome
LV	Left ventricle
MADIT	Multicenter Automatic Defibrillator Implantation Trial
MI	Myocardial infarction
MRI	Magnetic Resonance Imaging
MUSTT	Multicenter UnSustained Tachycardia Trial
NSVT	Non-sustained ventricular tachycardia
OAC	Oral anticoagulation
PAD	Peripheral arterial disease
PCI	Percutaneous Coronary Intervention
PVC	Premature ventricular complex
RBBB	Right ventricular cardiomyopathy
RV	Right ventricle
SCD	Sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SMVT	Sustained monomorphic ventricular tachycardia
SPECT	Single photon emission computed tomography
SQS	Short QT syndrome
SR	Sinus rhythm
SVT	Supraventricular tachycardia
TE	Thrombo-embolism
TIA	Transient ischemic attack
TIMI	Thrombolysis In Myocardial Infarction Study
TOE	Transoesophageal echocardiography
UFH	Un-fractionated heparin
VF	Ventricular fibrillation
VKA	Vitamin K antagonist
VT	Ventricular tachycardia
LVH	Left ventricular hypertrophy

2 OVERALL DESCRIPTION

Management of cardiac arrhythmia abnormalities that are not transient or reversible require constant clinical monitoring as a chronic condition. Delays on diagnosis or medical assistance increase risks of adverse outcomes such as heart failure, stroke or sudden cardiac. Therefore, Cardiovascular Implantable Electronic Devices (CIED) have become a part of the standard therapy in patients who are at the risk of life-threatening cardiac arrhythmias.

CIED devices with remote monitoring capabilities can store and transmit cardiac status and device function data. Remote sensor devices are located in patients' homes to transfer stored data from the cardiac implant to a remote monitoring service centre. These remote monitoring service centres, operated by device manufacturers, receive, store, analyze and translate transmitted data into patient-specific reports and allow healthcare professionals to access patient data or to receive alerts in case of unusual persisting data variations. These systems are also capable of providing this valuable information in machine processable form. iCARDEA project has set out to use this information to semi-automate the follow-up of cardiac arrhythmia patients with the care plans based on computer interpretable clinical guideline models by also personalizing the guidelines with the data obtained from patient EHRs.

Clinical guidelines include plans for treatment and aim to reduce inter-practice variations and the cost of the medical services, improve the quality of care and standardize clinical procedures. A variety of government and professional organizations are producing and disseminating clinical guidelines^{1,2}. Several computer interpretable models of Clinical Guidelines have also been proposed such as GLIF³, ASBRU⁴, and ARDEN⁵. Additionally, there are several guideline execution engines processing these models, such as GLEE⁶, GLARE⁷ and DeGel⁸ demonstrating that the guideline definitions can be executed to automate the decision making process. In the iCARDEA system, GLIF is used for the definition of the care plans and an engine is developed to execute them. In this respect, the care plans presented in this deliverable are defined using GLIF Notation.

Currently the CIED data is available from two different sources. The patient may be at the clinic during an in-clinic follow-up, so the data from the CIED can be directly accessed using the CIED Programmer of the vendor. The CIED Programmer is able to export the data into PDF file(s) stored in a configurable directory. Alternatively, the patient may be at home and the data is transmitted (semi-) automatically into the CIED Data Centre of the vendor for a remote follow-up. The physicians then can access the CIED Portal of the vendor that functions as frontend of the CIED Data Centre. It is also possible to export the CIED Data to the clinic, however right now this export has to be triggered manually in the CIED Portal. The data is then either exported using the IHE IDCO/HL7 v2.5 message or it is exported to a vendor system that has to be installed in the clinic. Currently the v2.5 messages transferred by the CIED Vendors usually contain limited information; however the PDF reports that contain the detailed data are embedded in the message. The vendor system in the clinic then automatically stores the data in a single PDF file using a configurable filename and the filename includes additional information such as the Patient name, Patient ID, and the timestamp.

iCARDEA uses "IHE Implantable Device Cardiac Observation Profile (IDCO)"⁹ to automatically expose the CIED data from different vendors in a machine processable format to be used in the care plan of the patients. There are different CIED vendors each with its own device and data centre interfaces. On the other hand, IHE has defined this profile in order to standardize transferring information from an interrogated implantable cardiac device to the healthcare enterprise information management systems. The implant device is interrogated in clinic or home environment using vendor proprietary equipment and the information is transferred to clinic system as structured HL7 v2.5 ORU message using IEEE 11073 IDC nomenclature¹⁰.

In iCARDEA, a care plan is personalized to a patient by also accessing his medical history from the EHR systems. For example, in executing iCARDEA care plans for monitoring CIED patients with Atrial Fibrillation (AF), the history of the non-cardiac conditions, detailed information about severity of each

¹ US National Guideline Clearinghouse, <http://www.guideline.gov/>

² National Institute for Clinical Excellence- England/Wales (\uppercase{NICE}) Published Guidelines, <http://www.nice.org.uk/page.aspx?o=guidelines.completed>

³ Boxwala AA, Peleg M, Tu S et al. GLIF3: a representation format for sharable computer-interpretable clinical practice guidelines. *Journal of Biomed Inform.*, 2004, 37(3), 147-61

⁴ Shahar, Y., Miksch, S., and Johnson, P. The Asgaard project: A task-specific framework for the application and critiquing of time-oriented clinical guidelines. *Artificial Intelligence in Medicine*, 1998, 14: 29-51.

⁵ Jenders RA, Corman R, Dasgupta B. Making the standard more standard: a data and query model for knowledge representation in the Arden syntax. *Proceedings of AMIA Annual Symp.*, 2003, 323-30.

⁶ Wang D, Shortliffe EH. GLEE - a model-driven execution system for computer-based implementation of clinical practice guidelines. *Proceedings of AMIA Symp.*, 2002, 855-9.

⁷ Terenziani P, Montani S, Bottrighi A et al. The GLARE approach to clinical guidelines: main features. *Studies in Health Technology and Informatics*, 2004. 101, 162-6.

⁸ Shahar Y, Young O, Shalom E, Mayaffit A, Moskovitch R, Hessing A, and Galperin M. DeGel: A Hybrid, Multiple-Ontology Framework for Specification and Retrieval of Clinical Guidelines. *Proceedings of the 9th Conference on Artificial Intelligence in Medicine*, Springer-Verlag Heidelberg, 2003, 122 - 131.

⁹ IHE Implantable Device - Cardiac - Observation Profile, http://www.ihe.net/Technical_Framework/upload/IHE_PCD_TF_Supplement_IDCO_2009-08-10.pdf

¹⁰ ISO/IEEE 11073-10101:2004, Point-of-care medical device communication -- Part 10101: Nomenclature, http://www.iso.org/iso/catalogue_detail.htm?csnumber=37890

condition (e.g., record of prior hospitalizations or specifics of therapy for the condition), the medications being taken at the time of spontaneous arrhythmia occurrence or the non-cardiac conditions denoting contraindications to the proposed therapies need to be accessed from the patient EHRs. The major challenge addressed in accessing the EHR systems is the interoperability problem of communicating with very many heterogeneous EHR systems. It should be noted that the care plans in this deliverables are generic in that they are not personalized to a specific patient.

To be able to avoid routinely monitoring a wide variety of clinical data from disparate systems, and developing ad hoc interfaces to access heterogeneous systems, IHE has specified the “Care Management Profile”¹¹ and this profile is used in the iCARDEA system.

2.1 iCARDEA System Architecture

The iCARDEA system aims to automate and personalize the follow-up of cardiac arrhythmia patients with implanted CIED devices with computer interpretable clinical guideline models using standard device interfaces and integrating patient EHRs. Figure 1 shows the overall architecture and the environment in which iCARDEA needs to provide interoperation services. The major components of the system are as follows:

1. Personalized Adaptive Care Planner for the CIED Recipients: In the iCARDEA project, the personalized follow-up of CIED patients is coordinated through a “care plan” which is an executable definition of computer interpretable clinical guideline models. The care plans are represented in GLIF, and the Care Plan Engine is capable of semi-automatically executing the care plan by processing its machine processable definition. The control flow of the care plan is dynamically adapted based on the patient’s context derived from the data coming from CIEDs and the medical context obtained from the EHRs. Through a graphical monitoring tool, the physicians are allowed to follow the execution of the care plan in detail, and coordinate the flow of actions when consultations to physicians are required.
2. The CIED Data Exposure Module uses “IHE Implantable Device Cardiac Observation Profile (IDCO)” to expose the CIED data from different vendors in a machine processable format to be used in the care plan of the patients. For this, it has a component that allows accessing the CIED Portal of the vendor and triggers the CIED data export automatically from the CIED Data Centre (periodically every x hours or each morning at a defined time). The CIED Data Listener Component waits for the exported data. For this it either scans a configurable directory in case of the data is exported directly to a vendor system in the clinic, alternatively it listens a pre-configured port for the exported data using the IHE IDCO/HL7 v2.5 protocol in case of direct network retrieval. In both cases the PDF file(s) need to be processed to extract the CIED data and the Data Translation Service sub-system creates a valid IHE IDCO format (HL7 v2.5 ORU Message) and makes the CIED data available to the iCARDEA Adaptive Care Planner through PCD-09 Send Observation message.
3. EHR Interoperability Infrastructure: To execute the clinical guidelines, it is also necessary to have access to medical history of the patients in the EHR systems. Considering that there are very many EHR systems with proprietary interfaces, in iCARDEA, “IHE Care Management (CM) Profile” is used. In our system, the proprietary hospital information systems export “Discharge Summary” and also “Laboratory Report Summary” CDA documents in conformance to IHE CDA Document templates¹² to an EHR Server which is implemented as an IHE XDS Repository¹³. This EHR Server also acts as a “Clinical Data Source” by implementing the IHE CM Profile. In this way, Adaptive Care Manager can subscribe to receive update notifications for the clinical data that is necessary to

¹¹ IHE Patient Care Coordination (PCC) Technical Framework Supplement, 2008-2009, Care Management (CM), Draft for Trial Implementation, August 22, 2008

¹² IHE Care Coordination Framework, Content Modules, http://wiki.ihe.net/index.php?title=1.3.6.1.4.1.19376.1.5.3.1.1#Medical_Documents_Specification_1.3.6.1.4.1.19376.1.5.3.1.1.1

¹³ IHE Cross Enterprise Document Sharing (XDS) Profile, http://www.ihe.net/Technical_Framework/index.cfm#IT

execute the care plans. IHE Care Management Profile specifies standard interfaces to extract this data that is needed by the care plans from the EHR systems. The two standardized transactions used in the iCARDEA system are as follows:

- “PCC-09 Care Management Data Query” allows querying the clinical data sources such as the EHR systems for the data required to execute the care plan.
- “PCC-10-V3 Care Management Update” allows the clinical data sources (EHR systems) to send the updated clinical data to the subscribed Care management systems as an HL7 V3 messages.

Additionally, IHE has specified “Content Modules” to be used as the payloads of these transactions to transfer clinical data in terms of CDA Sections and Entries. The HL7 Clinical Document Architecture (CDA)¹⁴ is a document mark-up standard that specifies the structure and semantics of "clinical documents" for the purpose of exchange and each CDA document is made up of CDA Sections and each Section is made up of CDA Entries.

Different content module templates for CDA Documents such as Discharge Summary, Referral Summary; CDA Sections such as History of Present Illness, Medications, and CDA Entries such as Problem Entry, Vital Signs Observation have been specified.

While a Care manager queries a clinical data source, it specifies the type of the clinical data required through a code specified in the “careProvisionCode” field, such as “LABCAT”, meaning all lab results. For each code specified in this controlled code list, the IHE content module template (for example “Simple Observations” template is specified for reporting lab results) is also specified through which the clinical data update is sent. The clinical data sources send the updated clinical data to the iCARDEA care plan engine by conforming to these content module templates. In this way the interoperability of the transactions among clinical data sources and care managers is guaranteed.

4. There is also a Patient Empowerment component that aims to provide active and informed involvement of patients in management of their own health. Through the web based PHR, patients will be able to view their medical history, CIED data, and manage their medication summaries, daily nutrition information.

¹⁴ HL7 Clinical Document Architecture (CDA), <http://hl7.org/library/Committees/structure/CDA.ReleaseTwo.CommitteeBallot03.Aug.2004.zip>

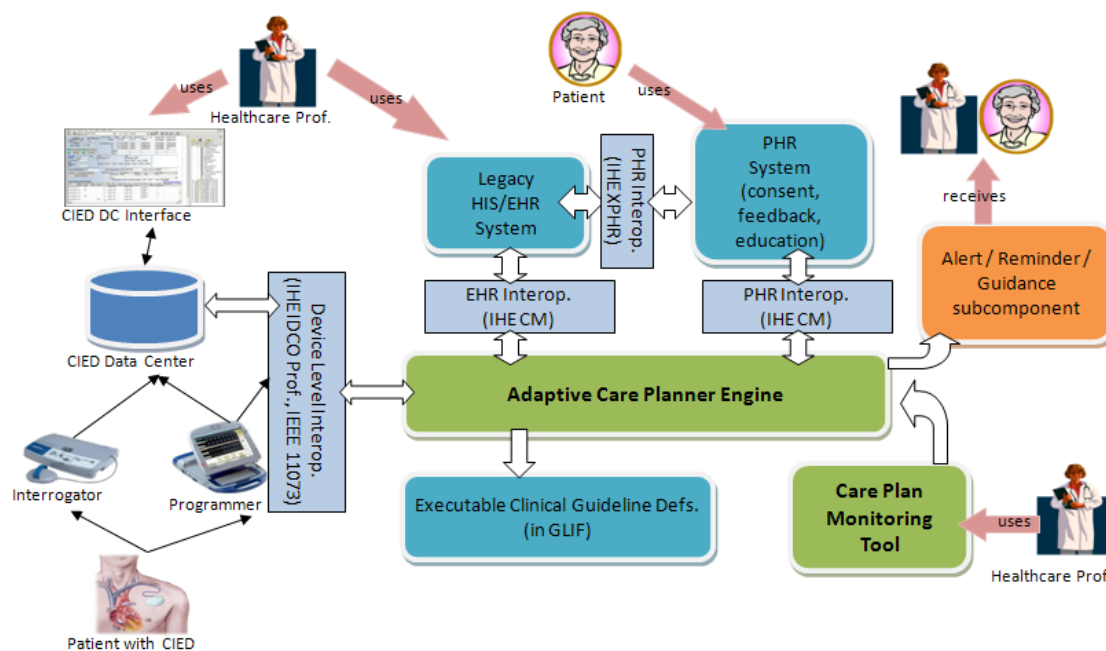


Figure 1 iCARDEA Architecture Overview

3 ICARDEA PILOT APPLICATION MEDICAL CAREPLANS

In iCARDEA Project, the following main aspects are contemplated in the pilot application:

1. AF Care plan: Management of patients with atrial fibrillation,
2. VT/VF Care plan: Management of patients with ventricular arrhythmias, and
3. Technical aspects of device follow-up.

In the following subsections, the care plans are described respectively by emphasizing the risk assessment models. These care plans are represented as flowcharts to be automated by the iCARDEA Care Plan Engine, and presented in Deliverable 4.1.1. Due to the peculiar nature of anticoagulants and antiarrhythmic drugs, a final subsection on contraindications, secondary effects and precautions to have with these drugs, has been included.

3.1 Management of patients with atrial fibrillation

Atrial fibrillation is the most common sustained cardiac arrhythmia, occurring in 1–2% of the general population. Over 6 million Europeans suffer from this arrhythmia, and its prevalence is estimated to at least double in the next 50 years as the population ages.

The problem of early recognition of AF is greatly aggravated by the often ‘silent’ nature of the rhythm disturbance. In about one-third of patients with this arrhythmia, the patient is not aware of so-called ‘asymptomatic AF’. Much earlier detection of the arrhythmia might allow the timely introduction of therapies to protect the patient, not only from the consequences of the arrhythmia, but also from progression of AF from an easily treated condition to an utterly refractory problem. Monitoring and screening may help to do this.

The care plan defined for the management of AF has already been described in deliverable 4.1.1. The risk assessment model that has partially already been implemented in this care plan focuses on early identification of further complications in a stepwise manner.

3.1.1 Atrial fibrillation-related cardiovascular events ('outcomes')

AF is associated with increased rates of death, stroke and other thrombo-embolic events, heart failure and hospitalizations, degraded quality of life, reduced exercise capacity, and left ventricular (LV) dysfunction (Table 2).

Table 2. Clinical events (outcomes) affected by AF	
Outcome parameter	Relative change in AF patients
1. Death	Death rate doubled
2. Stroke (includes hemorrhagic stroke and cerebral bleeds)	Stroke risk increased; AF is associated with more severe stroke
3. Hospitalizations	Hospitalizations are frequent in AF patients and may contribute to reduced quality of life
4. Quality of life and exercise capacity	Wide variation, from no effect to major reduction AF can cause marked distress through palpitations and other AF-related symptoms
5. Left ventricular dysfunction	Wide variation, from no change to tachycardiomyopathy with acute heart failure
<i>The prevention of these outcomes is the main therapeutic goal in AF patients</i>	

Death rates are doubled by AF, independently of other known predictors of mortality^{1,2}. Only antithrombotic therapy has been shown to reduce AF-related deaths³.

Stroke in AF is often severe and results in long-term disability or death. Approximately every fifth stroke is due to AF; furthermore, undiagnosed 'silent AF' is a likely cause of some 'cryptogenic' strokes^{1, 4}. Paroxysmal AF carries the same stroke risk as permanent or persistent AF⁵.

Hospitalizations due to AF account for one-third of all admissions for cardiac arrhythmias. Acute coronary syndrome (ACS), aggravation of heart failure, thrombo-embolic complications, and acute arrhythmia management are the main causes.

Cognitive dysfunction, including vascular dementia, may be related to AF. Small observational studies suggest that asymptomatic embolic events may contribute to cognitive dysfunction in AF patients in the absence of an overt stroke⁴.

Quality of life and exercise capacity are impaired in patients with AF. Patients with AF have a significantly poorer quality of life compared with healthy controls, the general population, or patients with coronary heart disease in sinus rhythm⁶.

Left ventricular (LV) function is often impaired by the irregular, fast ventricular rate and by loss of atrial contractile function and increased end-diastolic LV filling pressure. Both rate control and maintenance of sinus rhythm can improve LV function in AF patients.

3.1.2 Cardiovascular and other conditions associated with atrial fibrillation

AF is associated with a variety of cardiovascular conditions^{7, 8}. Concomitant medical conditions have an additive effect on the perpetuation of AF by promoting a substrate that maintains AF. Conditions associated with AF are also markers for global cardiovascular risk and/or cardiac damage rather than simply causative factors^{7,8}.

Ageing increases the risk of developing AF, possibly through age-dependent loss and isolation of atrial myocardium and associated conduction disturbances.

Hypertension is a risk factor for incident (first diagnosed) AF and for AF-related complications such as stroke and systemic thrombo-embolism.

Symptomatic heart failure [New York Heart Association (NYHA) classes II–IV] is found in 30% of AF patients^{7, 8}, and AF is found in up to 30–40% of heart failure patients, depending on the underlying cause and severity of heart failure. Heart failure can be both a consequence of AF (e.g. tachycardiomyopathy or decompensation in acute onset AF) and a cause of the arrhythmia due to increased atrial pressure and volume overload, secondary valvular dysfunction, or chronic neurohumoral stimulation.

Tachycardiomyopathy should be suspected when LV dysfunction is found in patients with a fast ventricular rate but no signs of structural heart disease. It is confirmed by normalization or improvement of LV function when good AF rate control or reversion to sinus rhythm is achieved.

Valvular heart diseases are found in ≈30% of AF patients^{7, 8}. AF caused by left atrial (LA) distension is an early manifestation of mitral stenosis and/or regurgitation. AF occurs in later stages of aortic valve disease. While ‘rheumatic AF’ was a frequent finding in the past, it is now relatively rare in Europe.

Cardiomyopathies, including primary electrical cardiac diseases⁹, carry an increased risk for AF, especially in young patients. Relatively rare cardiomyopathies are found in 10% of AF patients^{7, 8}. A small proportion of patients with ‘lone’ AF carry known mutations for ‘electrical’ cardiomyopathies.

Atrial septal defect is associated with AF in 10–15% of patients in older surveys. This association has important clinical implications for the antithrombotic management of patients with previous stroke or transient ischaemic attack (TIA) and an atrial septal defect.

Other congenital heart defects at risk of AF include patients with single ventricles, after Mustard operation for transposition of the great arteries, or after Fontan surgery.

Coronary artery disease is present in ≥20% of the AF population^{7, 8}. Whether uncomplicated coronary artery disease per se (atrial ischaemia) predisposes to AF and how AF interacts with coronary perfusion¹⁰ are uncertain.

Overt thyroid dysfunction can be the sole cause of AF and may predispose to AF-related complications. In recent surveys, hyperthyroidism or hypothyroidism was found to be relatively uncommon in AF populations^{7, 8}, but subclinical thyroid dysfunction may contribute to AF.

Obesity is found in 25% of AF patients⁸, and the mean body mass index was 27.5 kg/m² in a large, German AF registry (equivalent to moderately obese).

Diabetes mellitus requiring medical treatment is found in 20% of AF patients, and may contribute to atrial damage.

Chronic obstructive pulmonary disease (COPD) is found in 10–15% of AF patients, and is possibly more a marker for cardiovascular risk in general than a specific predisposing factor for AF.

Sleep apnoea, especially in association with hypertension, diabetes mellitus, and structural heart disease, may be a pathophysiological factor for AF because of apnoea-induced increases in atrial pressure and size, or autonomic changes.

Chronic renal disease is present in 10–15% of AF patients. Renal failure may increase the risk of AF-related cardiovascular complications, although controlled data are sparse.

3.1.3 Initial management

A thorough medical history should be obtained from the patient with suspected or known AF (Table 3).

Table 3. Relevant questions to be put to a patient with suspected or known AF
Is there any precipitation factor such as exercise, emotion, or alcohol intake?
Are symptoms during the episodes moderate or severe? The severity of symptoms may be expressed using the EHRA score (see table 4)
Are the episodes frequent or infrequent, and are they long or short lasting?
Is there a history of concomitant disease such as hypertension, coronary heart disease, heart failure, peripheral vascular disease, cerebrovascular disease, stroke, diabetes, or chronic pulmonary disease?
Is there an alcohol abuse habit?
Is there a family history of AF?
<i>AF: atrial fibrillation</i>

The acute management of AF patients should concentrate on relief of symptoms and assessment of AF-associated risk. Clinical evaluation should include determination of the EHRA score (Table 4), estimation of stroke risk, and search for conditions that predispose to AF and for complications of the arrhythmia. The 12-lead ECG should be inspected for signs of structural heart disease (e.g. acute or remote myocardial infarction, LV hypertrophy, bundle branch block or ventricular pre-excitation, signs of cardiomyopathy, or ischaemia).

Table 4. Classification of AF-related symptoms (EHRA score)	
EHRA class	Explanation
EHRA I	No symptoms
EHRA II	Mild symptoms: normal daily activity not affected
EHRA III	Severe symptoms: normal daily activity affected
EHRA IV	Disabling symptoms: normal daily activity discontinued

3.1.3.1 Diagnostic Evaluation

The initial diagnostic work-up is driven by the initial presentation. The **time of onset of the arrhythmia episode** should be established. Most patients with AF <48 h in duration can be cardioverted on low molecular weight heparin (LMWH) without risk for stroke. If AF duration is >48 h or there is doubt about its duration, transoesophageal echocardiogram may be used to rule out intracardiac thrombus prior to cardioversion, although it can be difficult in patients in acute distress and may not be available in emergency settings. The transthoracic echocardiogram can provide useful information to guide clinical decision making, but cannot exclude thrombus in the left atrial appendage.

Patients with AF and signs of **acute heart failure** require urgent rate control and often cardioversion. An urgent echocardiogram should be performed in haemodynamically compromised patients to assess LV and valvular function and right ventricular pressure.

Patients should be assessed for **risk of stroke**. Most patients with acute AF will require anticoagulation unless they are at low risk of thrombo-embolic complications (no stroke risk factors) and no cardioversion is necessary (e.g. AF terminates within 24–48 h).

After the initial management of symptoms and complications, **underlying causes of AF** should be sought (table 5). An *echocardiogram* is useful to detect ventricular, valvular, and atrial disease as well as rare congenital heart disease. *Thyroid function tests* (usually measurement of serum thyroid-stimulating

hormone), a *full blood count*, a *serum creatinine* measurement and analysis for *proteinuria*, measurement of *blood pressure*, and a test for diabetes mellitus (usually a *fasting glucose* measurement) are useful. A serum test for *hepatic function* may be considered in selected patients. A *stress test* is reasonable in patients with signs or risk factors for coronary artery disease. Patients with persistent signs of LV dysfunction and/or signs of myocardial ischaemia are candidates for *coronary angiography*.

Table 5. Clinical evaluation in patients with AF
Minimum evaluation
<p>1. History and physical examination, to define Presence and nature of symptoms associated with AF Clinical type of AF (first episode, paroxysmal, persistent, or permanent) Onset of the first symptomatic attack or date of discovery of AF Frequency, duration, precipitating factors, and modes of termination of AF Response to any pharmacological agents that have been administered Presence of any underlying heart disease or other reversible conditions (e.g., hyperthyroidism or alcohol consumption)</p>
<p>2. Electrocardiogram, to identify Rhythm (verify AF) LV hypertrophy P-wave duration and morphology or fibrillatory waves Preexcitation Bundle-branch block Prior MI Other atrial arrhythmias To measure and follow the R-R, QRS, and QT intervals in conjunction with antiarrhythmic drug therapy</p>
<p>3. Transthoracic echocardiogram, to identify Valvular heart disease LA and RA size LV size and function Peak RV pressure (pulmonary hypertension) LV hypertrophy LA thrombus (low sensitivity) Pericardial disease</p>
<p>4. Blood tests of thyroid, renal, and hepatic function For a first episode of AF, when the ventricular rate is difficult to control</p>
Additional testing (One or several tests may be necessary)
<p>1. Six-minute walk test (if the adequacy of rate control is in question) 2. Exercise testing (if the adequacy of rate control is in question (permanent AF)) To reproduce exercise-induced AF To exclude ischemia before treatment of selected patients with a type IC antiarrhythmic drug 3. Holter monitoring or event recording (if diagnosis of the type of arrhythmia is in question) As a means of evaluating rate control 4. Transesophageal echocardiography To identify LA thrombus (in the LA appendage) To guide cardioversion 5. Electrophysiological study To clarify the mechanism of wide-QRS-complex tachycardia To identify a predisposing arrhythmia such as atrial flutter or supraventricular tachycardia To seek sites for curative ablation or AV conduction block/modification 6. Chest radiograph, to evaluate Lung parenchyma, when clinical findings suggest an abnormality Pulmonary vasculature, when clinical findings suggest an abnormality</p>
<p><i>Type IC refers to the Vaughan Williams classification of antiarrhythmic drugs (see Table 19). AF indicates atrial fibrillation; AV, atrioventricular; LA, left atrial; LV, left ventricular; MI, myocardial infarction; RA, right atrial; RV, right ventricular.</i></p>

3.1.3.2 Clinical Follow-up

Important considerations during follow-up of the AF patient are listed below:

- Has the risk profile changed (e.g. new diabetes or hypertension), especially with regard to the indication for anticoagulation?
- Is anticoagulation now necessary—have new risk factors developed, or has the need for anticoagulation passed, e.g. postcardioversion in a patient with low thrombo-embolic risk?
- Have the patient's symptoms improved on therapy; if not, should other therapy be considered?
- Are there signs of proarrhythmia or risk of proarrhythmia; if so, should the dose of an antiarrhythmic drug be reduced or a change made to another therapy?
- Has paroxysmal AF progressed to a persistent/permanent form, in spite of antiarrhythmic drugs; in such a case, should another therapy be considered?
- Is the rate control approach working properly; has the target for heart rate at rest and during exercise been reached?

At follow-up visits, it is important to document the rhythm and rate, and to investigate disease progression. For those on antiarrhythmic drug therapy it is important to assess potential proarrhythmic ECG precursors such as lengthening of PR, QRS, or QT intervals, non-sustained ventricular tachycardia, or pauses. If any worsening of symptoms occurs, repeated blood tests, long-term ECG recordings and a repeat echocardiogram should be considered.

The patient should be fully informed about the pros and cons of the different treatment options, whether it is anticoagulation, rate control drugs, antiarrhythmic drugs, or interventional therapy. It is also appropriate to inform the patient with 'lone' or idiopathic AF about the good prognosis, once cardiovascular disease has been excluded.

3.1.4 Management

Management of AF patients is aimed at reducing symptoms and at preventing severe complications associated with AF. These therapeutic goals need to be pursued in parallel, especially upon the initial presentation of newly detected AF. Prevention of AF-related complications relies on antithrombotic therapy, control of ventricular rate, and adequate therapy of concomitant cardiac diseases. These therapies may already alleviate symptoms, but symptom relief may require additional rhythm control therapy by cardioversion, antiarrhythmic drug therapy, or ablation therapy (Figure 2).

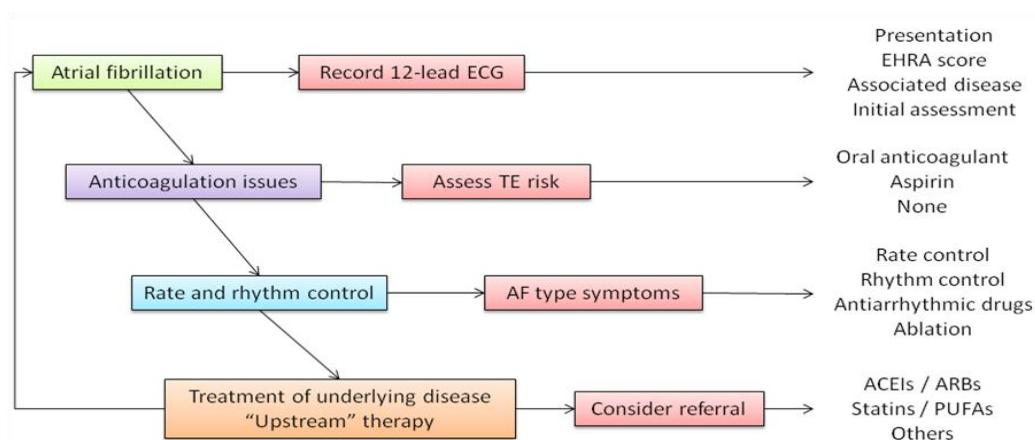


Figure 2. Management cascade for patients with AF.

ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; PUFA = polyunsaturated fatty acid; TE = thrombo-embolism.

3.1.4.1 Anti-thrombotic management

The care plan emphasizes the oral anticoagulation therapy for preventing thromboembolic events like stroke in patients with AF. Anticoagulation therapy is a basic point in the therapy of AF for the early recognition of this arrhythmia and its medical consequences and the remote monitoring creates an important advantage in this respect. The iCARDEA Personal Adaptive care plan engine continuously monitors the CIED patients and provides guidance to the physician for a reliable and fast decision on whether to start anticoagulation by checking the alerts provided by the CIED devices, together with the patient's medical history, his current medications, his recent lab results, and the possible contraindications. The flowcharts of the care plan are specified based on the clinical expertise provided by the clinicians of Salzburg Clinic, and Hospital Clínic de Barcelona, and defined as a computer interpretable clinical guideline definition in GLIF as presented in Deliverable D4.1.1.

Risk stratification for stroke and thrombo-embolism

The identification of various stroke clinical risk factors has led to the publication of various stroke risk schemes. The simplest risk stratification score is the **CHADS₂** [cardiac failure, hypertension, age, diabetes, stroke (doubled)] index is based on a point system in which 2 points are assigned for a history of stroke or TIA and 1 point each is assigned for age >75 years, a history of hypertension, diabetes, or recent cardiac failure (table 7)¹¹. The original validation of this scheme classified a CHADS₂ score of 0 as low risk, 1–2 as moderate risk, and >2 as high risk.

Risk factor	Score
Stroke or transient ischemic accident	2
Age > 75 years	1
Hypertension	1
Diabetes mellitus	1
Heart failure	1

In patients with a CHADS₂ score ≥ 2 , chronic oral anticoagulation (OAC) therapy with a vitamin K antagonist (VKA) is recommended in a dose-adjusted approach to achieve an international normalized ratio (INR) target of 2.5 (range, 2.0–3.0), unless contraindicated. Such a practice appears to translate to better outcomes in AF patients in routine care^{3,12}.

However, various published analyses, have shown that even patients at 'moderate risk' (currently defined as CHADS₂ score = 1, i.e. one risk factor) still derive significant benefit from OAC over aspirin use, often with low rates of major haemorrhage. Also, the CHADS₂ score does not include many stroke risk factors, and other 'stroke risk modifiers' need to be considered in a comprehensive stroke risk assessment (Table 8).

"Major" risk factors	"Clinically relevant non-major" risk factors
Previous stroke	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF \leq 40%) Hypertension Diabetes mellitus Female sex Age 65 – 74 years Vascular disease
TIA	
Systemic embolism	
Age \geq 75 years	

Thus, the use of antithrombotic therapy is recommended on the basis of the presence (or absence) of stroke risk factors.

‘Major’ risk factors (previously referred to as ‘high’ risk factors) are prior stroke or TIA, or thrombo-embolism, and older age (≥ 75 years). The presence of some types of valvular heart disease (mitral stenosis or prosthetic heart valves) would also categorize such ‘valvular’ AF patients as ‘high risk’.

‘Clinically relevant non-major’ risk factors (previously referred to as ‘moderate’ risk factors) are heart failure [especially moderate to severe systolic LV dysfunction, defined arbitrarily as left ventricular ejection fraction (LVEF) $\leq 40\%$], hypertension, or diabetes. Other ‘clinically relevant non-major’ risk factors (previously referred to as ‘less validated risk factors’) include female sex, age 65–74 years, and vascular disease (specifically, myocardial infarction, complex aortic plaque and PAD). Risk factors are cumulative, and the simultaneous presence of two or more ‘clinically relevant non-major’ risk factors would justify a stroke risk that is high enough to require anticoagulation.

This risk factor-based approach for patients with non-valvular AF can also be expressed as an acronym, **CHA₂DS₂-VASc** [congestive heart failure, hypertension, age ≥ 75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74, and sex category (female)]¹³. This scheme is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥ 75 ; and 1 point each is assigned for age 65–74 years, a history of hypertension, diabetes, recent cardiac failure, vascular disease (myocardial infarction, complex aortic plaque, and PAD, including prior revascularization, amputation due to PAD, or angiographic evidence of PAD, etc.), and female sex (Table 9). Thus, this acronym extends the CHADS₂ scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate.

Table 9. Risk factor-based approach, with the acronym CHA ₂ DS ₂ -Vasc (note: maximum score is 9, since age may contribute 0, 1 or 2 points)	
Risk factor	Score
Congestive heart failure / LV dysfunction	1
Hypertension	1
Age ≥ 75 years	2
Diabetes mellitus	1
Stroke / TIA / thrombo-embolism	2
Vascular disease ^a	1
Age 65 – 74	1
Sex category (i.e. female sex)	1
Maximum score	9
^a Prior myocardial infarction, peripheral artery disease, aortic plaque. Actual rates of stroke in contemporary cohorts may vary from these estimates. AF: atrial fibrillation; LV: left ventricular; TIA: transient ischemic attack.	

Current recommendations for antithrombotic therapy

Recommendations for antithrombotic therapy should be based on the presence (or absence) of risk factors for stroke and thrombo-embolism.

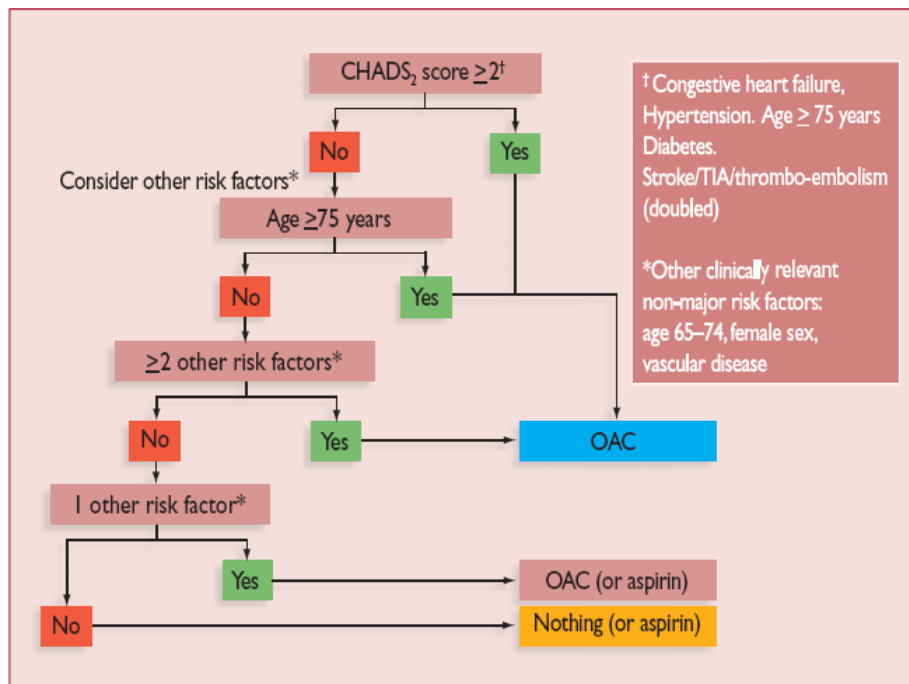


Figure 3. Clinical flowchart for the use of oral anticoagulation for stroke prevention in AF.

The CHADS₂ stroke risk stratification scheme is used as a simple initial means of assessing stroke risk, particularly suited to primary care doctors and non-specialists. In patients with a CHADS₂ score of ≥2, chronic OAC therapy, e.g. with a VKA, is recommended in a dose adjusted to achieve an INR value in the range of 2.0–3.0, unless contraindicated. In patients with a CHADS₂ score of 0–1, or where a more detailed stroke risk assessment is indicated, it is recommended to use a more comprehensive risk factor-based approach, incorporating other risk factors for thrombo-embolism (Table 10 and Figure 3).

Table 10. Approach to thromboprophylaxis in patients with AF		
Risk category	CHA ₂ DS ₂ -Vasc score	Recommended antithrombotic therapy
One “major” risk factor of ≥2 “clinically relevant non-major” risk factor	≥ 2	OAC
One “clinically relevant non-major” risk factor	1	Either OAC ^a or aspirin 75 – 325 mg daily. Preferred: OAC rather than aspirin
No risk factors	0	Either aspirin 75 – 325 mg daily or no antithrombotic therapy. Preferred: no antithrombotic therapy rather than aspirin

^aOAC, such as VKA, adjusted to an intensity range of INR 2.0 – 3.0 (target 2.5). New OAC drugs, may ultimately be considered. For example, should both doses of dabigatran etexilate receive regulatory approval for stroke prevention in AF, the recommendations for thromboprophylaxis could evolve as follows considering stroke and bleeding risk stratification:

(a) Where oral anticoagulation is appropriate therapy, dabigatran may be considered as an alternative to VKA therapy:

(i) If a patient is at low risk of bleeding (e.g. HAS-BLED score of 0 – 2), dabigatran 150 mg b.i.d. may be considered, in view of the improved efficacy in the prevention of stroke and systemic major bleeding events, when compared with warfarin); and

(ii) If a patient has a measurable risk of bleeding (e.g. HAS-BLED score of ≥3), dabigatran etexilate 110 mg b.i.d. may be considered, in view of similar efficacy in the prevention of stroke and systemic embolism (but lower rates of intracranial haemorrhage and of major bleeding compared with VKA).

(b) In patients with one “clinically relevant non-major” stroke risk factor, dabigatran 110 mg b.i.d. may be considered, in view of a similar efficacy with in the prevention of stroke and systemic embolism but lower rates of intracranial haemorrhage and major bleeding compared with the VKA and (probably) aspirin.

(c) Patients with no stroke risk factors (e.g. CHA₂DS₂-Vasc score = 0) are clearly at so low risk, either aspirin 75 – 325 mg daily or no antithrombotic therapy is recommended. Where possible, no antithrombotic therapy should be considered for such patients, rather than aspirin, given the limited data on the benefits of aspirin in this patient group (i.e. lone AF) and the potential adverse effects, especially bleeding.

In all cases where OAC is considered, a discussion of the pros and cons with the patient, and an evaluation of the risk of bleeding complications, ability to safely sustain adjusted chronic anticoagulation and patient preferences are necessary. In some patients, for example, women aged <65 years with no other risk factors (i.e. a CHA₂DS₂-VASc score of 1) may consider aspirin rather than OAC therapy.

Risk of bleeding

The HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly) score allows to assess the bleeding risk in AF patients (table 11), whereby a score of ≥ 3 indicates 'high risk', and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin.

Clinical characteristics comprising the HAS-BLED bleeding risk score		
Letter	Clinical characteristic ^a	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
Maximum 9 points		
<p>^a "Hypertension" is defined as as systolic blood pressure >160 mmHg. "Abnormal kidney function" is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥ 200 $\mu\text{mol/L}$. "Abnormal liver function" is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic dderangement (e.g. bilirrubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). "Bleeding" refers to previous bleeding history and/or predisposition tho bleeding, e.g. bleeding diathesis, anaemia, etc. "Labile INRs" refers to unstable/high INRs or poor time in therapeutic ranges (e.g. <60%). "Drugs/alcohol use" refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR: international normalized ratio.</p>		

Special situations

Perioperative anticoagulation

Patients with AF who are anticoagulated will require temporary interruption of VKA treatment before surgery or an invasive procedure. Many surgeons require an INR <1.5 or even INR normalization before undertaking surgery. The risk of clinically significant bleeding, even among outpatients undergoing minor procedures, should be weighed against the risk of stroke and thrombo-embolism in an individual patient before the administration of bridging anticoagulant therapy.

If the VKA used is *warfarin*, which has a half-life of 36–42 h, treatment should be interrupted ≈ 5 days before surgery (corresponding approximately to five half-lives of warfarin), to allow the INR to fall appropriately. If the VKA is *phenprocoumon*, treatment should be interrupted 10 days before surgery, based on the half-life of phenprocoumon of 96–140 h. It would be reasonable to undertake surgical or diagnostic procedures that carry a risk of bleeding in the presence of subtherapeutic anticoagulation for up to 48 h, without substituting heparin, given the low risk of thrombo-embolism in this period. VKA should be resumed at the 'usual' maintenance dose (without a loading dose) on the evening of (or the morning after) surgery, assuming there is adequate haemostasis. If there is a need for surgery or a procedure where the INR is still elevated (>1.5), the administration of low-dose oral vitamin K (1–2 mg) to normalize the INR may be considered.

In patients with a mechanical heart valve or AF at high risk for thrombo-embolism, management can be problematic. Such patients should be considered for 'bridging' anticoagulation with therapeutic doses of either LMWH or unfractionated heparin (UFH) during the temporary interruption of VKA therapy.

Stable vascular disease

Many anticoagulated AF patients have stable coronary or carotid artery disease and/or PAD, and common practice is to treat such patients with VKA plus one antiplatelet drug, usually aspirin. Adding aspirin to VKA does not reduce the risk of stroke or vascular events (including myocardial infarction), but substantially increases bleeding events.

Acute coronary syndrome (ACS) and/or percutaneous coronary intervention

Current guidelines for ACS and/or percutaneous coronary intervention (PCI) recommend the use of aspirin–clopidogrel combination therapy after ACS, and a stent (4 weeks for a bare-metal stent, 6–12 months for a drug-eluting stent). VKA non-treatment is associated with an increase in mortality and major adverse cardiac events, with no significant difference in bleeding rates between VKA-treated and non-treated patients. The prevalence of major bleeding with triple therapy (VKA, aspirin, and clopidogrel) is 2.6–4.6% at 30 days, which increases to 7.4–10.3% at 12 months. Thus triple therapy seems to have an acceptable risk–benefit ratio provided it is kept short (e.g. 4 weeks) and the bleeding risk is low.

A systematic review and consensus document published by the ESC Working Group on Thrombosis, endorsed by the EHRA and the European Association of Percutaneous Cardiovascular Interventions (EAPCI), suggests that drug-eluting stents should be avoided and triple therapy (VKA, aspirin, and clopidogrel) used in the short term, followed by longer therapy with VKA plus a single antiplatelet drug (either clopidogrel or aspirin) (Table 12)^{14, 15}.

Table 12. Antithrombotic strategies following coronary artery stenting in patients with AF at moderate to high thrombo-embolic risk (in whom oral anticoagulation therapy is required)			
Haemorrhagic risk	Clinical setting	Stent implanted	Anticoagulation regimen
Low or intermediate (e.g. HAS-BLED score 0–2)	Elective	Bare-metal	1 month: triple therapy of VKA (INR 2.0–2.5) + aspirin <–100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	Elective	Drug-eluting	3 (–olimus ^a group) to 6 (paclitaxel) months: triple therapy of VKA (INR 2.0–2.5) + aspirin <–100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal/ drug-eluting	6 months: triple therapy of VKA (INR 2.0–2.5) + aspirin <–100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone
High (e.g. HAS-BLED score >–3)	Elective	Bare-metal ^c	2–4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin <–100 mg/day + clopidogrel 75 mg/day Lifelong: VKA (INR 2.0–3.0) alone
	ACS	Bare-metal ^c	4 weeks: triple therapy of VKA (INR 2.0–2.5) + aspirin <–100 mg/day + clopidogrel 75 mg/day Up to 12th month: combination of VKA (INR 2.0–2.5) + clopidogrel 75 mg/day ^b (or aspirin 100 mg/day) Lifelong: VKA (INR 2.0–3.0) alone

^a*Sirolimus, everolimus, and tacrolimus.*
^b*Combination of VKA (INR 2.0–3.0) + aspirin ≤100 mg/day (with PPI, if indicated) may be considered as an alternative.*
^c*Drug-eluting stents should be avoided as far as possible, but, if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary.*

In patients with stable vascular disease (e.g. with no acute ischaemic events or PCI/stent procedure in the preceding year), VKA monotherapy should be used, and concomitant antiplatelet therapy should not be prescribed. Published data support the use of VKA for secondary prevention in patients with coronary artery disease, and VKA is at least as effective as aspirin.

Elective percutaneous coronary intervention

In elective PCI, drug-eluting stents should be limited to clinical and/ or anatomical situations, such as long lesions, small vessels, diabetes, etc., where a significant benefit is expected compared with bare-metal stents, and triple therapy (VKA, aspirin, and clopidogrel) should be used for 4 weeks. Following PCI with bare-metal stents, patients with AF and stable coronary artery disease should receive long-term therapy (12 months) with OAC plus clopidogrel 75 mg daily or, alternatively, aspirin 75–100 mg daily, plus gastric protection with proton pump inhibitors, H₂-receptor antagonists, or antacids depending on the bleeding and thrombotic risks of the individual patient. Triple therapy (VKA, aspirin, and clopidogrel) should be administered for a minimum of 1 month after implantation of a bare-metal stent, but for much longer with a drug-eluting stent [≥ 3 months for an ‘-olimus’ (sirolimus, everolimus, tacrolimus) type eluting stent and at least 6 months for a paclitaxel-eluting stent] following which VKA and clopidogrel 75 mg daily or, alternatively, aspirin 75–100 mg daily, plus gastric protection with either PPIs, H₂-receptor antagonists, or antacids may be continued.

When anticoagulated AF patients are at moderate to high risk of thrombo-embolism, an uninterrupted anticoagulation strategy can be preferred during PCI, and radial access should be used as the first choice even during therapeutic anticoagulation (INR 2–3).

Non-ST elevation myocardial infarction

In patients with non-ST elevation myocardial infarction, dual antiplatelet therapy with aspirin plus clopidogrel is recommended, but in AF patients at moderate to high risk of stroke, OAC should also be given. In the acute setting, patients are often given aspirin, clopidogrel, UFH, or LMWH (e.g. enoxaparin) or bivalirudin and/or a glycoprotein IIb/IIIa inhibitor (GPI). Drug-eluting stents should be limited to clinical situations, as described above (see Table 12). An uninterrupted strategy of OAC is preferred, and radial access should be used as the first choice.

For medium- to long-term management, triple therapy (VKA, aspirin, and clopidogrel) should be used in the initial period (3–6 months), or for longer in selected patients at low bleeding risk. In patients with a high risk of cardiovascular thrombotic complications [e.g. high Global Registry of Acute Coronary Events (GRACE) or TIMI risk score], long-term therapy with VKA may be combined with clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection) for 12 months.

Acute ST segment elevation myocardial infarction with primary percutaneous intervention

Such patients are often given aspirin, clopidogrel, and heparin in the acute setting. When patients have a high thrombus load, bivalirudin or GPIs may be given as a ‘bail-out’ option. Mechanical thrombus removal (e.g. thrombus aspiration) is encouraged. Given the risk of bleeding with such a combination of antithrombotic therapies, GPIs or bivalirudin would not be considered if the INR is ≥ 2 , except in a ‘bail-out’ option. For medium- to long-term management, triple therapy (VKA, aspirin, and clopidogrel) should be used in the initial period (for 3–6 months), or for longer in selected patients at low bleeding risk, followed by longer therapy (up to 12 months) with VKA plus clopidogrel 75 mg daily (or, alternatively, aspirin 75–100 mg daily, plus gastric protection).

Acute stroke

An acute stroke is a common first presentation of a patient with AF, given that the arrhythmia often develops asymptotically. There are limited trial data to guide their management, and there is concern that patients

within the first 2 weeks after cardioembolic stroke are at greatest risk of recurrent stroke because of further thrombo-embolism. However, anticoagulation in the acute phase may result in intracranial haemorrhage or haemorrhagic transformation of the infarct.

In patients with AF presenting with an acute stroke or TIA, uncontrolled hypertension should be appropriately managed before antithrombotic treatment is started, and cerebral imaging, CT or magnetic resonance imaging (MRI), should be performed to exclude haemorrhage. In the absence of haemorrhage, anticoagulation should begin after 2 weeks, but, in the presence of haemorrhage, anticoagulation should not be given. In patients with AF and acute TIA, anticoagulation treatment should begin as soon as possible in the absence of cerebral infarction or haemorrhage.

Silent stroke

As stroke in patients with AF is primarily embolic, the detection of asymptomatic cerebral emboli would identify patients at high risk of thrombo-embolism. Cerebral imaging studies (CT/MRI) show a higher incidence of silent strokes in AF patients compared with controls in sinus rhythm. Transcranial Doppler ultrasound may identify asymptomatic patients with an active embolic source or patients with prior stroke who are at high risk of recurrent stroke.

Atrial flutter

The risk of stroke linked to atrial flutter has been studied retrospectively in a large number of older patients, and was similar to that seen in AF. Thus, thromboprophylaxis in patients with atrial flutter should follow the same guidelines as in AF patients.

Cardioversion

Increased risk of thrombo-embolism following cardioversion is well recognized. Therefore, anticoagulation is considered mandatory before elective cardioversion for AF of >48 h or AF of unknown duration. VKA treatment (INR 2.0–3.0) should be given for at least 3 weeks before cardioversion. Thromboprophylaxis is recommended for electrical and pharmacological cardioversion of AF >48 h. VKA should be continued for a minimum of 4 weeks after cardioversion because of risk of thrombo-embolism due to post-cardioversion left atrial dysfunction (so-called ‘atrial stunning’). In patients with risk factors for stroke or AF recurrence, VKA treatment should be continued lifelong irrespective of apparent maintenance of sinus rhythm following cardioversion.

In patients with a definite AF onset <48 h, cardioversion can be performed expediently under the cover of UFH administered i.v. followed by infusion or subcutaneous LMWH. In patients with risk factors for stroke, OAC should be started after cardioversion and continued lifelong. UFH or LMWH should be continued until the INR is at the therapeutic level (2.0–3.0). No OAC is required in patients without thrombo-embolic risk factors.

In patients with AF >48 h with haemodynamic instability (angina, myocardial infarction, shock, or pulmonary oedema), immediate cardioversion should be performed, and UFH or LMWH should be administered before cardioversion. After cardioversion, OAC should be started and heparin should be continued until the INR is at the therapeutic level (2.0–3.0). Duration of OAC therapy (4 weeks or lifelong) will depend on the presence of risk factors for stroke.

The mandatory 3-week period of OAC prior to cardioversion can be shortened if TOE reveals no LA or LAA thrombus. TOE may not only show thrombus within the LAA or elsewhere in the left atrium, but may also identify spontaneous echo-contrast or complex aortic plaque. A TOE-guided cardioversion strategy is recommended as an alternative to 3-week pre-cardioversion anticoagulation if experienced staff and appropriate facilities are available, and, when early cardioversion is needed, pre-cardioversion OAC is not indicated due to patient choice or potential bleeding risks, or when there is a high risk of LA/LAA thrombus.

If no LA thrombus is detected on TOE, UFH or LMWH should be started prior to cardioversion and continued thereafter until the target INR is achieved with OAC. If TOE detects a thrombus in the left atrium or LAA, VKA (INR 2.0–3.0) treatment is required for at least 3 weeks and TOE should be repeated. If thrombus resolution is evident, cardioversion can be performed, and post-cardioversion OAC is continued lifelong. If thrombus is still evident, the rhythm control strategy may be changed to a rate control strategy, especially when AF-related symptoms are controlled, since there is a high risk of thrombo-embolism if cardioversion is performed (Figure 4).

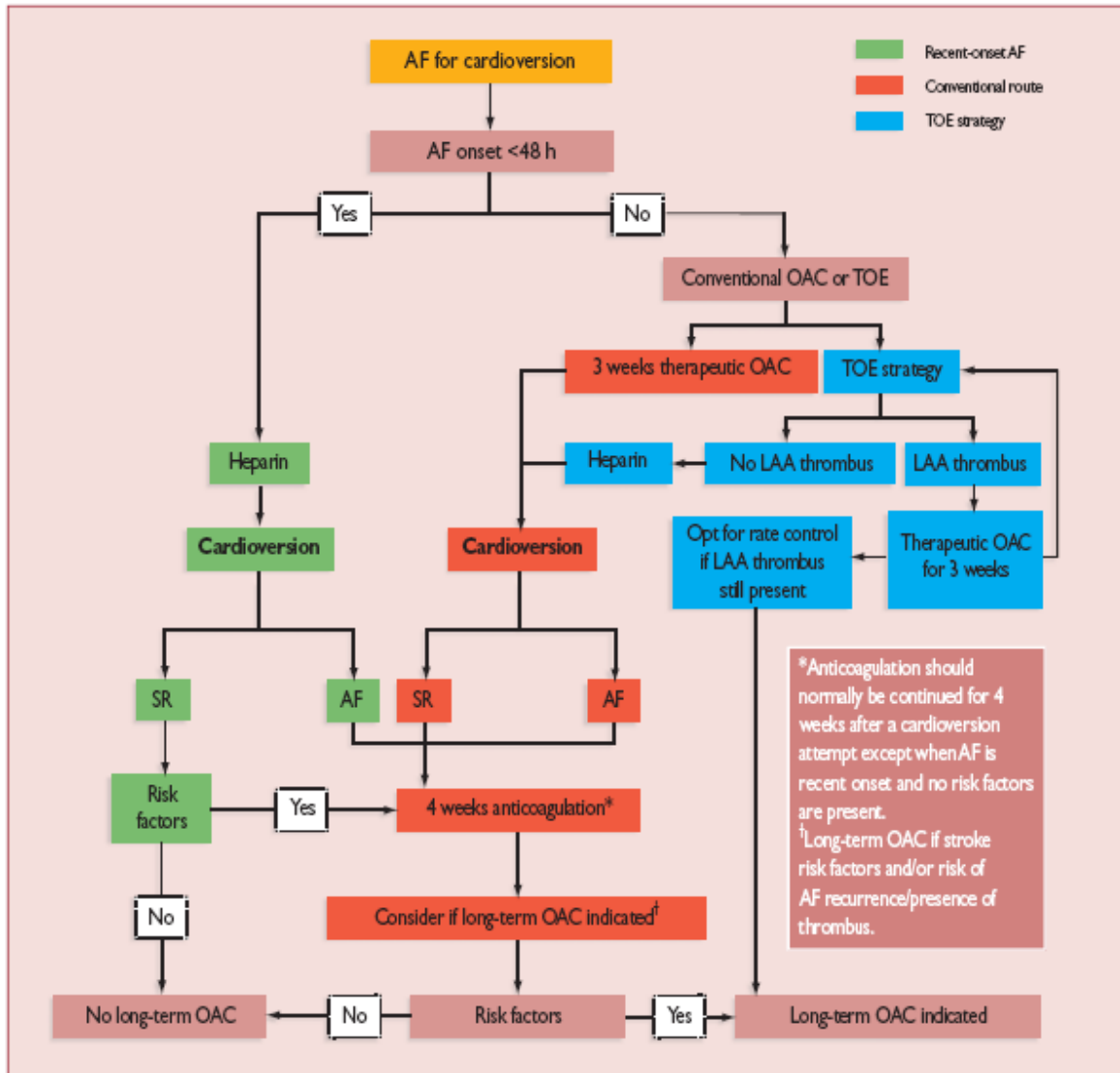


Figure 4. Cardioversion of haemodynamically stable AF, the role of TOE-guided cardioversion, and subsequent anticoagulation strategy.

3.1.4.2 Rate and rhythm management

The acute and long-term management of rate and rhythm in atrial fibrillation have already been described in Deliverable D4.1.1. For specific information on antiarrhythmic drugs, their indications, contraindications, secondary effects and precautions, see section 3.3.

3.2 Care plan for the Management of patients with ventricular arrhythmias: VT/VF

Ventricular arrhythmias range from premature ventricular complexes (PVCs) and non-sustained ventricular tachycardia (NSVT) in normal subjects to sudden cardiac death (SCD) due to ventricular tachyarrhythmias in patients with and without structural heart disease. Epidemiological patterns have implications that help improve profiling risk based on individual subject characteristics¹⁶. Techniques include identification of clinical and lifestyle risk factors for disease development, measurement of risk among subgroups of patients with established disease, and the newly emerging field of genetic epidemiology¹⁶.

3.2.1 Definitions and epidemiology

3.2.1.1 Ventricular Arrhythmias

Among presumably *normal individuals*, estimates of the prevalence of PVCs and NSVT vary according to the sampling technique used and the source of data but it ranges from 0.8-2.2% on standard 12-lead up to a 62% on a 6-h monitor. In contrast to PVCs and monomorphic patterns of NSVT, polymorphic ventricular tachyarrhythmias in the absence of structural heart disease are indicators of risk¹⁶. Many non-sustained polymorphic VT events occurring in individuals free of grossly evident structural abnormalities of the heart are due to abnormalities at a molecular level or a consequence of electrolyte disturbances or adverse drug effects.

PVCs and runs of NSVT in subjects with *structural heart disease* contribute to an increased mortality risk, the magnitude of which varies with the nature and extent of the underlying disease. Among survivors of myocardial infarction (MI), frequent and repetitive forms of ventricular ectopic activity, accompanied by a reduced EF, predict an increased risk of SCD during long-term follow-up¹⁶. However, ventricular arrhythmias during ambulatory recording in patients with HF do not specifically predict risk for SCD. Risk is already high because of the underlying disease. Suppression of ambient ventricular arrhythmias is no longer considered a therapeutic target for prevention of death in the post-MI or nonischemic cardiomyopathy subgroups.

It is important to stress that the clinician's ability to recognize individuals with reversible or transient causes of ventricular tachyarrhythmias is limited¹⁶.

3.2.1.2 Sudden Cardiac Death

The geographical incidence of SCD varies as a function of coronary heart disease (CHD) prevalence in different regions. Estimates for the United States range from less than 200,000 to more than 450,000 SCDs annually, with the most widely used estimates in the range of 300,000 to 350,000 SCDs annually¹⁶. The variation is based, in part, on the inclusion criteria used in individual studies. Overall, event rates in Europe are similar to those in the United States¹⁶, with significant geographic variations reported. Approximately 50% of all CHD deaths are sudden and unexpected, occurring shortly (instantaneous to 1 h) after the onset of a change in clinical status.

Three factors affect the ability to identify subjects and population subgroups at risk and consideration of strategies for prevention of SCD:

- Absolute numbers and event rates (incidence) among population subgroups (Fig. 5).
- Clinical subgroups in which SCDs occur.
- Time dependence of risk.

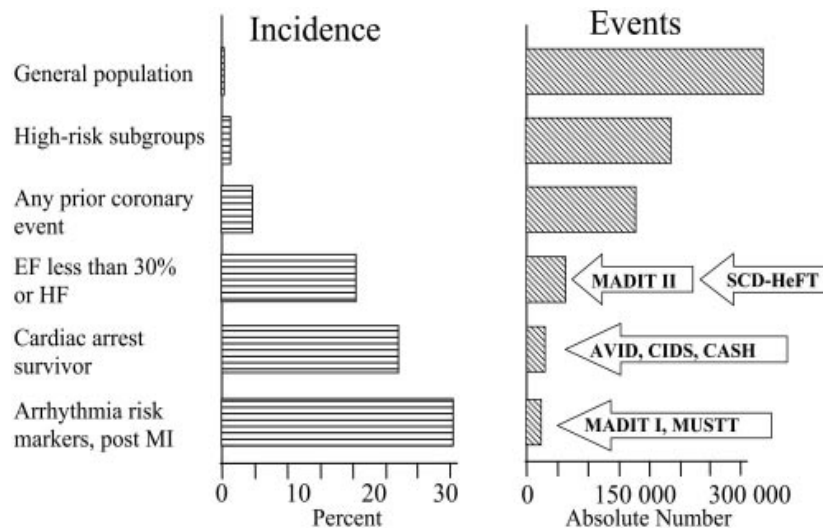


Figure 5. Absolute numbers of events and event rates of SCD in the general population and in specific subpopulations over 1 y¹⁷. *General population* refers to unselected population age greater than or equal to 35 y, and *high-risk subgroups* to those with multiple risk factors for a first coronary event. Clinical trials that include specific subpopulations of patients are shown in the right side of the figure. AVID: Antiarrhythmics Versus Implantable Defibrillators; CASH: Cardiac Arrest Study Hamburg; CIDS: Canadian Implantable Defibrillator Study; MADIT: Multicenter Automatic Defibrillator Implantation Trial; MUSTT: Multicenter UnSustained Tachycardia Trial; SCD-HeFT: Sudden Cardiac Death in Heart Failure Trial.

The overall incidence of SCD in the United States is 1 to 2 per 1000 population (0.1% to 0.2%) annually. This large population base includes those in whom SCD occurs as a first cardiac event, as well as those for whom SCDs can be predicted with greater accuracy because they are included in higher risk subgroups (Fig. 5). Higher levels of risk resolution can be achieved by identification of more specific subgroups. However, the corresponding absolute number of deaths becomes progressively smaller as the subgroups become more focused, limiting the potential impact of interventions to a much smaller fraction of the total population¹⁶. At least 50% of all SCDs due to CHD occur as a first clinical event or among subgroups of patients thought to be at relatively low risk for SCD¹⁶.

3.2.2 Risk Profiles

Biological and behavioral risk profiling for coronary artery disease, using the conventional risk factors for coronary atherogenesis, is useful for identifying levels of population risk but has limited value for distinguishing individual patients at risk for SCD. Multivariate analyses of selected risk factors for atherogenesis have determined that approximately one half of all SCDs occur among the 10% of the population in the highest risk decile. Thus, the cumulative risk associated with conventional risk factors for coronary atherosclerosis exceeds the simple arithmetic sum of the individual risks¹⁶. Markers of risk that move beyond the direct lipid deposition concept of atherogenesis into more complex pathobiology are now being identified, largely focusing on mechanisms responsible for destabilization of lipid-laden plaques. Inflammatory markers, such as C-reactive protein and other indicators of inflammation and destabilization, have entered into risk formulations, offering potentially useful additions to conventional risk marker. In addition, familial clustering of SCD as a specific manifestation of the disease may lead to identification of specific genetic abnormalities that predispose to SCD¹⁶.

Hypertension is an established risk factor for CHD and also emerges as a risk factor for SCD. Both the ECG pattern of left ventricular hypertrophy (LVH) and echocardiographic evidence of LVH are associated with a higher proportion of sudden and unexpected cardiac death. Intraventricular conduction abnormalities such as left bundle branch block (LBBB) are also suggestive of a disproportionate number of SCD^{16, 18, 19}.

There are also meaningful associations between **cigarette smoking, obesity, diabetes, and lifestyle** and SCD.

The Framingham Study demonstrates that **cigarette smokers** have a 2- to 3-fold increase in SCD risk; this is one of the few risk factors in which the proportion of CHD deaths that are sudden increases in association with the risk factor¹⁸. In addition, in a study of 310 survivors of out-of-hospital cardiac arrest, the recurrent cardiac arrest rate was 27% at 3 y of follow-up among those who continued to smoke after their index event, compared with 19% in those who stopped.

Obesity is a second factor that appears to influence the proportion of coronary deaths that occur suddenly^{16, 18}.

Associations between levels of **physical activity** and SCD have been studied, with varying results. A high resting heart rate with little change during exercise and recovery is a risk factor for SCD. Epidemiological observations have suggested a relationship between sedentary activity and increased CHD death risk. The Framingham Study, however, showed an insignificant relationship between low levels of physical activity and incidence of SCD and a high proportion of sudden to total cardiac deaths at higher levels of physical activity. An association between acute physical exertion and SCD demonstrated a 17-fold relative increase for the risk of SCD during vigorous exercise for the entire populations (active and inactive). For the habitually inactive, the relative risk was 74. Habitual vigorous exercise attenuates risk¹⁶. Therefore, these data indicate that, while the risk of cardiac arrest is higher during vigorous exercise (especially among individuals who are usually sedentary), habitual exercise attenuates the risk of cardiac arrest, both during exercise and at rest¹⁶.

The magnitude of **recent life changes** in the realms of health, work, home, and family and personal and social factors have been related to MI and SCD¹⁶. There is an association between significant elevations of life-change scores during the 6 months before a coronary event, and the association is particularly striking in victims of SCD. After controlling for other major prognostic factors, the risk of SCD and total mortality is increased by social and economic stresses, and alteration of modifiable lifestyle factors has been proposed as a strategy for reducing risk of SCD in patients with CHD. Acute psychosocial stressors have been associated with risk of cardiovascular events, including SCD. The risk appears to cluster around the time of the stress and appear to occur among victims at preexisting risk, with the stressor simply advancing the time of an impending event¹⁶.

3.2.3 Clinical presentation of patients with ventricular arrhythmias

There is a great amount of overlap between clinical presentations (Table 13) and the severity and type of heart disease. The prognosis and management are individualized according to symptom burden and severity of underlying heart disease, in addition to the clinical presentation.

Table13. Clinical Presentations of Patients With Ventricular Arrhythmias and Sudden Cardiac Death
<ul style="list-style-type: none"> ● Asymptomatic individuals with or without electrocardiographic abnormalities
<ul style="list-style-type: none"> ● Persons with symptoms potentially attributable to ventricular arrhythmias <ul style="list-style-type: none"> ● Palpitations ● Dyspnea ● Chest pain ● Syncope and presyncope
<ul style="list-style-type: none"> ● Ventricular tachycardia that is hemodynamically stable
<ul style="list-style-type: none"> ● Ventricular tachycardia that is not hemodynamically stable
<ul style="list-style-type: none"> ● Cardiac arrest <ul style="list-style-type: none"> ● Asystolic (sinus arrest, atrioventricular block) ● Ventricular tachycardia ● Ventricular fibrillation ● Pulseless electrical activity

3.2.3.1 Asymptomatic

Ventricular arrhythmias may be detected as an incidental finding during ECG monitoring or physical examination or by an event detection by a CIED. In general, treatment is indicated to prevent potential morbidity, reduce symptom burden, or reduce the risk of SCD. There is no reason to treat asymptomatic ventricular arrhythmias in the absence of such potential benefit. The major determinants of risk of SCD are related more to the type and severity of associated cardiac disease and less to the frequency or classification of ventricular arrhythmia¹⁶.

Certain arrhythmias such as rapid polymorphic VT may be compelling to treat even in the asymptomatic individual without evident heart disease. Nonetheless, such arrhythmias are rarely asymptomatic and are probably related to ionic channel abnormalities yet to be elucidated¹⁶.

NSVT in the patient with previous MI and impaired LV function indicates increased risk of SCD and the need for further evaluation or treatment. The contribution of asymptomatic ventricular arrhythmias to the patient's management is not well established for other cardiac diseases such as dilated cardiomyopathy or hypertrophic cardiomyopathy¹⁶.

3.2.3.2 Symptoms Potentially Related to Ventricular Arrhythmias

Palpitations or a perception of cardiac rhythm irregularity may be caused by the whole spectrum of arrhythmias and are also frequently reported in patients in the absence of any arrhythmia. Less frequently, patients with VT may present with symptoms of paroxysmal dyspnea or chest pain in the absence of a sensation of rapid heart beating. In such instances, the dyspnea or chest pain may be related to the hemodynamic consequences of tachycardia. "Presyncope" is a vague term that is poorly defined but probably is interpreted by most as a feeling of impending syncope. VT may be a cause of undiagnosed syncope, especially in patients with structural heart disease. Patients with poor ventricular function and inducible VT or VF have a high incidence of subsequent appropriate therapies when implanted with an ICD¹⁶. Similar patients with poor ventricular function may be at risk of SCD¹⁶. Patients with sudden onset of very rapid VT such as torsades de pointes with the repolarization syndromes will typically present with syncope or seizure rather than an awareness of rapid heart beating or palpitations¹⁶.

- **Hemodynamically Stable Ventricular Tachycardia:** Patients with slower, stable VT may be asymptomatic but more frequently present with a sensation of rapid heart beating possibly accompanied by dyspnea or chest discomfort. Presentation with stable VT does not in itself indicate a benign prognosis in patients with significant heart disease¹⁶. Incessant VT, although hemodynamically stable, can be a cause of hemodynamic deterioration leading to heart failure. In patients with an ICD, the VT rate can fall below the lower rate of VT detection, causing underdetection of VT that can prevent arrhythmia termination. Immediate reinitiation of the VT following proper ICD therapy can also result in hemodynamic deterioration and early battery depletion¹⁶.
- **Hemodynamically Unstable Ventricular Tachycardia:** The term "hemodynamically unstable" connotes a tachycardia associated with hypotension and poor tissue perfusion that is considered to have the imminent potential to lead to cardiac arrest or shock if left untreated. Hemodynamically unstable VT is usually, but not exclusively, observed in patients with poor ventricular function. Patients with normal ventricular function can have unstable VT or VF if the tachycardia is rapid enough, as in the LQTS and other abnormal repolarization syndromes. Some patients with a normal heart and idiopathic monomorphic VT or even supraventricular tachycardia (SVT) can become hypotensive during the arrhythmia because of a vasovagal reaction.

3.2.3.3 Sudden Cardiac Arrest

Rapid sustained VT or VF results in presentation with markedly impaired tissue perfusion and loss of consciousness as a result of inadequate cardiac output, leading to SCD, if not expediently reversed. Sudden

cardiac arrest may be the presenting symptom with any cardiac disease or even in individuals with no apparent heart disease. The initiating mechanism of sudden cardiac arrest may or may not be related to arrhythmia.

3.2.4 General evaluation of patients with ventricular arrhythmias

3.2.4.1 History and Physical Examination

Palpitations, presyncope, and syncope are the 3 most important symptoms requiring further characterization in patients suspected of having ventricular arrhythmias. Palpitations are usually of a sudden onset/offset pattern and may be associated with presyncope and/or syncope. Sudden episodes of collapse with loss of consciousness without a premonition that usually last for a few seconds must raise the suspicion of conduction defects or ventricular arrhythmias.

Other symptoms related to underlying structural heart disease may also be present, especially chest discomfort, dyspnea, and fatigue. A thorough drug history including dosages used must be included in the evaluation of patients suspected of having ventricular arrhythmias. Physical examination is often unrevealing in patients suspected of having ventricular arrhythmias unless the arrhythmia occurs while the patient is being examined or has other findings indicative of structural heart disease.

3.2.4.2 Non-invasive Evaluation

- **Resting Electrocardiogram:** A standard resting 12-lead ECG allows not only identification of various congenital abnormalities associated with ventricular arrhythmias and SCD (e.g., LQTS, SQTs, Brugada syndrome, arrhythmogenic right ventricular cardiomyopathy) but also identification of various other ECG parameters, such as those due to electrolyte disturbances, or evidence suggesting underlying structural disease, such as bundle-branch block, AV block, ventricular hypertrophy, and Q waves indicative of ischemic heart disease or infiltrative cardiomyopathy. QRS duration and repolarization abnormalities are both independent predictors of SCD. A prolonged QRS duration greater than 120 to 130 ms has been shown in a number of studies to be associated with increased mortality in patients with a reduced LVEF (equal to or less than 30%). Prospective studies have also reported an association between ST-segment depression or T-wave abnormalities and increased risk of cardiovascular death and SCD in particular. A prolonged QTc interval is also an independent predictor of SCD: QTc >420-440 ms has been shown to have a higher risk of cardiovascular death relative to a shorter QTc¹⁶. Although a prolonged QTc interval predicts SCD, it is worth noting that some data suggest that the correlation between QTc and survival may be “J-shaped.” In other words, relatively short QTc intervals have also been associated with increased risk. For instance, it has been reported that patients with a mean QTc <400 ms during 24-h ECG have a more than 2-fold risk of dying suddenly than do patients with a mean QTc between 400 and 440 ms after a 2-y follow-up¹⁶. A QTc <300 ms is often used to define the SQTs, which is an independent predictor of SCD.
- **Exercise Testing:** Exercise-ECG is commonly used in the evaluation of patients with ventricular arrhythmias. Its most common application is for detection of silent ischemia in patients suspected of having underlying CHD. In patients with known or silent CHD or cardiomyopathies, the presence of frequent PVCs during or after exercise has been associated with greater risk for serious cardiovascular events but not specifically SCD. Exercise-induced PVCs in apparently normal individuals should not be used to dictate therapy unless associated with documented ischemia or sustained VT. With the exception of beta blockers, at the present time the use of antiarrhythmic drugs to abolish exercise-induced PVCs has not been proved to be effective in reducing SCD. Exercise testing in adrenergic-dependent rhythm disturbances, including monomorphic VT and polymorphic VT, may be useful in evaluating symptomatic subjects and evaluating response to therapy. Moreover, exercise testing may provide prognostic information in these patients, given that the presence of exercise-induced ventricular ectopy increases mortality at 12 months by 3-fold relative to patients with ectopy at rest only. Patients with exercise-induced paired ventricular

complexes or VT have a lower survival rate than those with exercise-induced simple ventricular ectopy.

- **Echocardiography:** Echocardiography is the imaging technique that is most commonly used because it is inexpensive in comparison with other techniques such as MRI and cardiac CT, it is readily available, and it provides accurate diagnosis of myocardial, valvular, and congenital heart disorders associated with ventricular arrhythmias and SCD (Table 14). In addition, LV systolic function and regional wall motion can be evaluated and, in a majority of patients, EF can be determined. Echocardiography is therefore indicated in patients with ventricular arrhythmias suspected of having structural heart disease and in the subset of patients at high risk for the development of serious ventricular arrhythmias or SCD, such as those with dilated, hypertrophic or RV cardiomyopathies, MI survivors, or relatives of patients with inherited disorders associated with SCD. The combination of echocardiography with exercise or pharmacological stress (commonly known as “stress echo”) is applicable to a selected group of patients who are suspected of having ventricular arrhythmias triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of ECG for ischemia detection. Anomalous origin of coronary arteries can be detected by echocardiography or other imaging techniques.

Disease Entity	Diagnostic Accuracy
Dilated cardiomyopathy	High
Ischemic cardiomyopathy	High
Hypertension with moderate to severe left ventricular hypertrophy	High
Hypertrophic cardiomyopathy	High
Valvular heart disease	High
Arrhythmogenic right ventricular cardiomyopathy	Moderate
Brugada syndrome	Poor

- **Cardiac Computed Tomography:** As with MRI, the field of CT has advanced greatly with the development of fast scanners with better resolution that allow tomographic imaging of the heart and coronary arteries. These systems allow precise quantification of LV volumes, EF, and LV mass with results comparable to MRI but in addition provide segmental images of the coronary arteries from which the extent of calcification can be quantified. The majority of cardiac disorders associated with serious ventricular arrhythmias or SCD are assessed well with echocardiography. Cardiac CT can be used in selected patients in whom evaluation of cardiac structures is not feasible with echocardiography and MRI is not available. There is currently no incremental clinical benefit derived from imaging the coronary arteries by cardiac CT in patients with ventricular arrhythmias.
- **Radionuclide Techniques:** Myocardial perfusion SPECT using exercise or pharmacological agents is applicable for a selected group of patients who are suspected of having ventricular arrhythmias triggered by ischemia and who are unable to exercise or have resting ECG abnormalities that limit the accuracy of ECG for ischemia detection. Myocardial perfusion SPECT can also be used to assess viability in patients with LV dysfunction due to prior MI. Accurate quantification of LVEF is possible with gated radionuclide angiography (multiple gated acquisition scan) and thus this technique may be helpful in patients for whom this measurement is not available with echocardiography.

3.2.4.3 Invasive Evaluation

- **Coronary Angiography:** In patients with life-threatening ventricular arrhythmias or in survivors of SCD, coronary angiography plays an important diagnostic role in establishing or excluding the presence of significant obstructive coronary artery disease. It is common for these patients to undergo this procedure as part of their diagnostic evaluation, particularly if they have an intermediate or greater probability for CHD. Detailed recommendations regarding imaging and exercise testing can be found in the respective guidelines.

- **Electrophysiological Testing:** The sensitivity, specificity, and predictive values of EP testing have been extensively assessed by various authors, usually in small patient groups. EP testing is used to document the inducibility of VT, guide ablation, evaluate drug effects, assess the risks of recurrent VT or SCD, evaluate loss of consciousness in selected patients with arrhythmias suspected as a cause, and assess the indications for ICD therapy. The yield of EP testing varies fundamentally with the kind and severity of the underlying heart disease, the presence or absence of spontaneous VT, concomitant drug therapy, the stimulation protocol, and the site of stimulation. Highest induction rates and reproducibility are observed in patients after MI.
 - *Electrophysiological Testing in Patients with Coronary Heart Disease:* In patients with CHD, asymptomatic NSVT, and an EF <40%, inducibility of sustained VT ranges between 20% and 40%. In CHD patients with a low EF (<30%), non-inducibility does not portend a good prognosis. Persistent inducibility while receiving antiarrhythmic drugs predicts a worse prognosis¹⁶. The prognostic value of inducible ventricular flutter and VF is still controversial. Limited data on the prognostic value of inducible ventricular flutter suggest that it may be an important endpoint¹⁶.
 - *Electrophysiological Testing in Patients with Dilated Cardiomyopathy:* EP testing plays a minor role in the evaluation and management of VT. This is related to low inducibility, reproducibility of EP study, and the predictive value of induced VT¹⁶.
 - *Electrophysiological Testing in long QT Syndrome:* EP testing has not proved useful¹⁶.
 - *Electrophysiological Testing in Brugada Syndrome:* The role of EP testing for risk stratification in Brugada syndrome is debated, and it will probably remain undefined until prospective data are obtained in patients studied with a uniform protocol in a large population with adequate follow-up¹⁶.
 - *Electrophysiological Testing in Hypertrophic Cardiomyopathy:* The value of EP testing is controversial¹⁶.
 - *Electrophysiological Testing in Arrhythmogenic Right Ventricular Cardiomyopathy:* The arrhythmic manifestations of ARVC are variable. The prognostic role of EP testing in patients presenting with isolated PVCs or NSVT is not known. The response to EP testing may be influenced by the severity of the disease. Progression of disease has to be considered.
 - *Electrophysiological Testing in Patients with Outflow Tract Ventricular Tachycardia:* EP testing for the evaluation of outflow tract VT is basically similar to that for other VT entities. It is motivated by the need to establish precise diagnosis to guide curative catheter ablation¹⁶.
 - *Electrophysiological Testing in Patients with Syncope:* EP testing is used to document or exclude the arrhythmic cause of syncope. It is most useful in patients with CHD and LV dysfunction. EP testing is usually not the first evaluation step but rather is complementary to a full syncope work-up. Lack of correlation between symptoms and a documented arrhythmia elicited during EP testing may lead to overinterpretation or underinterpretation of the predictive value of the results. Transient drug effects that can provoke syncope may remain undetected. Other causes such as a neurological aetiology need to be considered in some patients.
 - *Electrophysiological Testing When Bradyarrhythmia Is Suspected:* Syncope can be due to bradyarrhythmias from sinus node dysfunction or AV block. Antiarrhythmic drugs, beta-blocking agents, cardiac glycosides, and calcium channel blockers can induce symptomatic bradycardia. EP testing can be used to document or provoke bradyarrhythmias or AV block when other investigations have failed to provide conclusive information. The diagnostic yield varies greatly with the selected patient populations. EP testing is more useful in the presence of structural heart disease. The diagnostic yield in the absence of structural heart disease or abnormal ECG is low. False-positive results of EP testing can be present in up to 24% of the patients. In syncopal patients with chronic BBB and reduced EF (<45%), EP-induced VT is present in up to 42%. In patients with syncope and BBB, false-negative EP studies are common. EP testing in patients with sporadic bradycardia and syncope has limited sensitivity, even when adding electropharmacological stress such as

intravenous procainamide or atropine. EP testing can provoke nonspecific tachyarrhythmic responses in patients with preserved LV function who do not have structural heart disease.

- *Electrophysiological Testing When Supraventricular Tachyarrhythmia Is Suspected:* The role of EP testing is to document the type of tachyarrhythmia and to guide management of patients. In a mixed population, the diagnostic yield of EP testing was 5%). In supraventricular tachyarrhythmias, syncope is rarely the only symptom and palpitations are usually present as well. Vasodepressive reaction in a few patients with induced SVT, mainly AV node reentry, may be the cause of syncope. Syncope did not correlate with the rate or cycle length of preexcited R-R intervals in WPW syndrome during AF.
- *Electrophysiological Testing When Ventricular Tachycardia Is Suspected:* Syncope in patients with structural heart disease and, in particular, significant LV dysfunction is ominous. NSVT on Holter monitoring, syncope, and structural heart disease are highly sensitive for predicting the presence of inducible VT. Syncope associated with heart disease and reduced EF has high recurrence and death rates, even when EP testing results are negative. EP testing is useful in patients with LV dysfunction due to prior MI (EF <40%) but not sensitive in patients with nonischemic cardiomyopathy. Induction of polymorphic VT or VF, especially with aggressive stimulation techniques, is not specific. In CHD, the diagnostic yield may reach 50%. In HCM, EP testing is not diagnostic in the majority of patients. Induction of nonspecific VTs in 23% of patients with slightly reduced EF has been observed.

3.2.5 Therapies for ventricular arrhythmias

The selection of appropriate therapy for the management of ventricular arrhythmias necessitates an understanding of the aetiology and mechanism of the arrhythmia, an appreciation of the associated medical conditions that may contribute to and/or exacerbate the arrhythmia, the risk posed by the arrhythmia, and risk-to-benefit aspects of the selected therapy. Management of the manifest arrhythmia may involve discontinuation of offending proarrhythmia drugs, specific antiarrhythmic therapy with drugs, implantable devices, ablation, and surgery.

This section provides general comments about drug and interventional therapy for ventricular arrhythmias.

3.2.5.1 Antiarrhythmic drugs

With the exception of beta-blockers, the currently available antiarrhythmic drugs have not been shown in randomized clinical trials to be effective in the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of SCD. As a general rule, antiarrhythmic agents may be effective as adjunctive therapy in the management of arrhythmia-prone patients under special circumstances. Because of potential adverse side effects of the available antiarrhythmic drugs, these agents must be used with caution.

Many marketed cardiac and non-cardiac drugs prolong ventricular repolarization and have the potential to precipitate life-threatening ventricular tachyarrhythmias (see section 3.2.7). Some patients are more susceptible than others to the QT-prolonging effects of these drugs even at an ordinary dosage, possibly due to a genetic propensity or female gender. More commonly, the proarrhythmic effect of the agent is related to elevated drug blood levels as a result of excessive dosage, renal disease, or drug interactions. Once it is appreciated that a patient's ventricular arrhythmia may be due to QT prolongation from one or more prescribed medications, the possible offending therapies should be discontinued and appropriate follow-up monitoring of ventricular repolarization and cardiac rhythm should be carried out.

- **Beta-Blockers:** They are effective in suppressing ventricular ectopic beats and arrhythmias as well as in reducing SCD in a spectrum of cardiac disorders in patients with and without HF. Beta-

blockers are safe and effective antiarrhythmic agents that can be considered the mainstay of antiarrhythmic drug therapy¹⁶.

- **Amiodarone and Sotalol:** The overall long-term survival benefit from amiodarone is controversial, with most studies showing no clear advantage over placebo. Chronic administration of amiodarone is associated with complex drug interactions and a host of adverse side effects involving the lung, liver, thyroid, and skin. As a general rule, the longer the therapy and the higher dose of amiodarone, the greater is the likelihood that adverse side effects will require discontinuance of the drug. Sotalol, like amiodarone, is effective in suppressing ventricular arrhythmias, but it has greater proarrhythmic effects and has not been shown to provide a clear increase in survival; worsening ventricular arrhythmias occur in 2% to 4% of treated patients¹⁶.

Overall, the available antiarrhythmic drugs other than beta-blockers should not be used as primary therapy in the management of ventricular arrhythmias and the prevention of SCD. The efficacy of non-beta-blocker antiarrhythmic drugs is equivocal at best, and each drug has significant potential for adverse events including proarrhythmia¹⁶.

Amiodarone therapy may be considered in special situations; secondary subset analyses indicate possible survival benefit when amiodarone is combined with beta-blockers¹⁶. Both sotalol and amiodarone have also been shown to reduce the frequency of ICD shock therapy¹⁶.

- Patients with ventricular arrhythmias who do not meet criteria for an ICD: Beta-blockers are the first-line therapy, but if this therapy at full therapeutic dose is not effective, then amiodarone or sotalol can be tried with monitoring for adverse effects during administration.
- Patients with ICDs who have recurrent VT/VF with frequent appropriate shocks: This scenario requires the addition of antiarrhythmic drugs and/or catheter ablation for control of the recurrent VT and associated ICD shocks. Sotalol is effective in suppressing atrial and ventricular arrhythmias; the combination of beta-blockers and amiodarone is an alternative approach. Because many such patients have low EF and poor renal function, amiodarone and beta-blockers rather than sotalol can be the first-line therapy for defibrillator storm. Sotalol should be avoided in patients with severely depressed LV function or significant HF. Intravenous amiodarone has been useful.

3.2.5.2 Ablation

RF ablation can be applied in the treatment of VT in patients with LV dysfunction due to prior MI, cardiomyopathy, bundle-branch reentry, and various forms of idiopathic VT¹⁶.

- **No Apparent Structural Heart Disease:** Specific mapping and ablation techniques that are used differ depending on the type of VT. While patients with no overt structural heart disease account for a small percentage of patients with VT, they are of particular interest for ablation therapy as this technique may be curative. These typically present as a single VT arising from the RV with LBBB inferior axis morphology or from the LV with a right bundle-branch block (RBBB) morphology and, in general, are associated with a good prognosis
- **Bundle-Branch Reentrant VT:** Bundle-branch reentrant VT is often associated with cardiomyopathy. RF catheter ablation of the bundle branches is curative of the arrhythmia but not of the underlying structural abnormality.
- **Structural Heart Disease:** VT is a common complication of structural heart disease and carries significant risk for mortality in CHD patients with low EF. In those with extensive structural abnormalities, especially those with prior MI, multiple morphologies of VT are often present. The newer 3-dimensional mapping systems permit anatomical reconstructions and correlation of EP characteristics with anatomy. These systems have led to an approach whereby circuits can be mapped during sinus rhythm and can facilitate ablation in the ischemic patient who often does not tolerate VT well. Use of these techniques may result in better long-term success rates.
- **Antiarrhythmic Surgery:** In patients with recurrent VT refractory to drugs, ICDs, and RF catheter ablation, direct surgical ablation or resection of the arrhythmogenic focus is an approach that

continues to be used in experienced centres. Surgery requires accurate preoperative and intraoperative mapping to determine the site or sites of the tachycardia. Some centers use a scar-based approach to resecting arrhythmogenic sites.

- **Sympathectomy:** Left cervicothoracic sympathetic ganglionectomy is associated with reduction in the frequency of arrhythmogenic syncope in this syndrome and may be useful as adjunctive therapy in high-risk LQTS patients who have recurrent syncope and/or aborted cardiac arrest despite combined ICD and beta-blocker therapy or in LQTS patients who cannot tolerate beta blockers²⁰.
- **Aneurysmectomy:** Large myocardial aneurysms secondary to MI are associated with hemodynamic compromise and are frequently accompanied by major ventricular arrhythmias. In selected patients, aneurysm resection can improve cardiac function and, along with map-guided EP mapping and resection of arrhythmogenic ventricular myocardium, may reduce or eliminate the accompanying ventricular arrhythmias¹⁶.

In table 15 we summarize the indications for ablation of ventricular arrhythmias according to the most recent consensus by the European Heart Rhythm Association and the Heart Rhythm Society of the American Heart Association.

Table 15. Indications for catheter ablation of ventricular tachycardia²¹.
Patients with structural heart disease (including prior MI, dilated cardiomyopathy, ARVC)
<i>Catheter ablation of VT is recommended</i>
<ol style="list-style-type: none"> 1. for symptomatic sustained monomorphic VT (SMVT), including VT terminated by an ICD, that recurs despite antiarrhythmic drug therapy or when antiarrhythmic drugs are not tolerated or not desired;* 2. for control of incessant SMVT or VT storm that is not due to a transient reversible cause; 3. for patients with frequent PVCs, NSVTs, or VT that is presumed to cause ventricular dysfunction; 4. for bundle branch reentrant or interfascicular VTs; 5. for recurrent sustained polymorphic VT and VF that is refractory to antiarrhythmic therapy when there is a suspected trigger that can be targeted for ablation.
<i>Catheter ablation should be considered</i>
<ol style="list-style-type: none"> 1. in patients who have one or more episodes of SMVT despite therapy with one of more Class I or III antiarrhythmic drugs;* 2. in patients with recurrent SMVT due to prior MI who have LV ejection fraction ≥ 0.30 and expectation for 1 year of survival, and is an acceptable alternative to amiodarone therapy;* 3. in patients with haemodynamically tolerated SMVT due to prior MI who have reasonably preserved LV ejection fraction (>0.35) even if they have not failed antiarrhythmic drug therapy.*
Patients without structural heart disease
<i>Catheter ablation of VT is recommended for patients with idiopathic VT</i>
<ol style="list-style-type: none"> 1. for monomorphic VT that is causing severe symptoms. 2. for monomorphic VT when antiarrhythmic drugs are not effective, not tolerated, or not desired. 3. for recurrent sustained polymorphic VT and VF (electrical storm) that is refractory to antiarrhythmic therapy when there is a suspected trigger that can be targeted for ablation.
VT catheter ablation is contra-indicated
<ol style="list-style-type: none"> 1. in the presence of a mobile ventricular thrombus (epicardial ablation may be considered); 2. for asymptomatic PVCs and/or NSVT that are not suspected of causing or contributing to ventricular dysfunction; 3. for VT due to transient, reversible causes, such as acute ischaemia, hyperkalaemia, or drug-induced torsade de pointes.
<i>ARVC/D, arrhythmogenic right ventricular cardiomyopathy; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; VT, ventricular tachycardia; VF, ventricular fibrillation.</i>
<i>*This recommendation for ablation stands regardless of whether VT is stable or unstable, or multiple VTs are present.</i>

Management Incessant Ventricular Tachycardia

The syndrome of very frequent episodes of VT requiring multiple appropriate ICD shocks cardioversion has been termed “**VT storm**”. While a definition of greater than 2 episodes in 24 h has been used, much more frequent episodes can also occur. Hemodynamically stable VT lasting hours has been termed “incessant”.

Severe underlying heart disease is frequently present. More rarely, VT storm can occur (e.g., in Brugada syndrome, LQTS, catecholaminergic VT, or in drug overdose) in patients who have a structurally normal

heart. “VT storm” can be monomorphic or polymorphic. Polymorphic VT storm in a patient with coronary disease is strongly suggestive of acute myocardial ischemia; pauses may occur prior to polymorphic VT even in the absence of QT prolongation. Pause-dependent VT with marked QT prolongation should be managed as torsades de pointes, although acute ischemia can also present in this fashion. Frequent appropriate ICD shocks may represent part of the natural history of advanced heart disease and may or may not portend a serious deterioration in underlying prognosis.

The first step in VT storm is to identify and correct inciting factors, commonly including drugs, electrolyte disturbances, and acute myocardial. With frequent ICD shocks, electrograms and programming should be reviewed to determine if device reprogramming is desirable.

Intravenous beta-blockade should be considered for a *polymorphic VT* storm as it is the single most effective therapy. Revascularization procedures may be urgently needed. It is of utmost importance to try and understand the substrate of incessant arrhythmias, because if a diagnosis is established, a targeted treatment may be possible. For example, in Brugada syndrome, quinidine or isoproterenol may terminate incessant arrhythmias¹⁶. In acute ischemia, intravenous amiodarone seems more effective than other antiarrhythmic drugs¹⁶. Pacing may be useful especially if the tachycardia onset is pause-dependent. Ablation can be used as an alternative in case of failure of other measures²².

Monomorphic VT storm can be managed by intravenous antiarrhythmics (e.g., amiodarone, procainamide) to slow the rate but may aggravate the tachycardia by promoting frequent or incessant episodes. Ablation can also be effective. ICD therapy may eventually be needed.

3.2.6 Management of ventricular arrhythmias in specific cardiac diseases

The following table (Table 16) summarizes the guidelines for the management of ventricular arrhythmias in specific conditions/cardiomyopathies according to the guidelines of the European Society of Cardiology and the American Heart Association¹⁶.

Table 16. Management of ventricular arrhythmias in relation to specific pathology		
Pathology	Management suggestion	Indication class, Level of evidence
LV dysfunction due to prior myocardial infarction	amiodarone ± beta-blockers	class IIa, level of evidence B
	sotalol	class IIa, level of evidence C
	Catheter ablation	class IIb, level of evidence B
Dilated cardiomyopathy (nonischemic)	amiodarone ± beta-blockers	class IIb, level of evidence C
Hypertrophic cardiomyopathy	Amiodarone	class IIa, level of evidence C
Arrhythmogenic right ventricular cardiomyopathy	Amiodarone	class IIa, level of evidence C
Heart failure	Sotalol	class IIa, level of evidence C
	Amiodarone ± beta-blocker	class I, level of evidence C
	Sotalol	class I, level of evidence C
Long QT syndrome	Beta-blockers	
	Electrical storm: isoproterenol	class IIa, level of evidence C
	Electrical storm: quinidine	class IIb, level of evidence C
Brugada Syndrome	Spontaneous or documented stress-induced ventricular arrhythmias: beta-blocker	class I, level of evidence C
Catecholaminergic polymorphic ventricular tachycardia		
Valvular heart disease	Candidate for valvular repair / replacement? No specific drug suggested by guidelines	
Congenital heart disease	Sustained VT: ablation.	
	Non-sustained VT: EP study.	
	Isolated PVCs: no treatment.	
	No specific drug suggested by guidelines.	

3.2.7 Drug-induced ventricular arrhythmias

Specific syndromes of drug-induced arrhythmias, with diverse mechanisms and management strategies, are described in the sections that follow. Treatment guidelines focus on avoiding drug treatment in high-risk patients, recognizing the syndromes of drug-induced arrhythmia and withdrawal of the offending agent(s). The efficacy of specific therapies is often inferred from anecdotal evidence or preclinical, mechanism-based studies.

High drug concentrations due to overdose or drug interactions generally increase the risk of drug-induced arrhythmias. The largest increases in concentrations occur when a drug is eliminated by a single pathway and that pathway is susceptible to inhibition by the administration of a second drug. Table 17 lists examples of drug interactions that may cause arrhythmias through this mechanism. Interactions can also reduce plasma concentrations of antiarrhythmic drugs and thereby exacerbate the arrhythmia being treated. Additive pharmacological effects may also result in arrhythmias.

Table 17. Drug Interactions Causing Arrhythmias		
Drug	Interacting Drug	Effect
Increased Concentration of Arrhythmogenic Drug		
Digoxin	Some antibiotics	By eliminating gut flora that metabolize digoxin, some antibiotics may increase digoxin bioavailability. Note: some antibiotics also interfere with P-glycoprotein (expressed in the intestine and elsewhere), another effect that can elevate digoxin concentration
Digoxin	Amiodarone Quinidine Verapamil	Increased digoxin bioavailability, reduced biliary and renal excretion due to P-glycoprotein inhibition
Digoxin	Cyclosporine Itraconazole Erythromycin	Digoxin toxicity
Quinidine	Ketoconazole Cisapride Itraconazole Terfenadine, astemizole Erythromycin* Clarithromycin Some calcium blockers* Some HIV protease inhibitors (especially ritanovir)	Increased drug levels
Beta-blockers	Quinidine (even ultra-low dose) Fluoxetine	Increased beta-blockade
Flecainide, propafenone	Some tricyclic antidepressants	Increased adverse effects Decreased analgesia (due to failure of biotransformation to the active metabolite morphine)
Dofetilide	Verapamil Cimetidine Trimethoprim Ketoconazole Megestrol	Increased plasma dofetilide concentration due to inhibition of renal excretion
Decreased Concentration of Antiarrhythmic Drug		
Digoxin	Antacids	Decreased digoxin effect due to decreased absorption
Digoxin	Rifampin	Increased P-glycoprotein activity
Quinidine, mexiletine	Rifampin, barbiturates	Induced drug metabolism
Synergistic Pharmacological Activity Causing Arrhythmias		
QT-prolonging	Diuretics	Increased torsades de pointes risk due to diuretic-induced hypokalemia

antiarrhythmics		
Beta-blockers	Amiodarone, clonidine, digoxin, diltiazem, verapamil	Bradycardia when used in combination
Digoxin	Amiodarone, beta blockers, clonidine, diltiazem, verapamil	
Verapamil	Amiodarone, beta blockers, clonidine, digoxin, diltiazem	
Diltiazem	Amiodarone, beta blockers, clonidine, digoxin, verapamil	
Clonidine	Amiodarone, beta blockers, digoxin, diltiazem, verapamil	
Amiodarone	Beta blockers, clonidine, digoxin, diltiazem, verapamil	
Sildenafil	Nitrates	Increased and persistent vasodilation; risk of myocardial ischemia
*These may also accumulate to toxic levels with co-administration of inhibitor drugs like ketoconazole.		

3.2.7.1 Digitalis Toxicity

Certain arrhythmias are typical: enhanced atrial, junctional, or ventricular automaticity (with ectopic beats or tachycardia) often combined with AV block. Overdose of digitalis causes severe hyperkalemia and cardiac standstill.

The diagnosis is established by the combination of characteristic rhythm disturbances, ancillary symptoms (visual disturbances, nausea, changes in mentation), and elevated serum concentrations. Contributing factors may include hypothyroidism, hypokalemia, or renal dysfunction.

- **Specific Management:** In mild cases, management includes discontinuing the drug, monitoring rhythm and maintaining normal serum potassium. Occasionally, temporary pacing may be needed. For more severe intoxication (serum digoxin concentration > 4 to 5 ng/mL, and with serious arrhythmias), the treatment of choice is digoxin-specific Fab antibody. Side effects include worsening of the underlying disease (increased ventricular rate during AF, exacerbation of HF) and hypokalemia. Digoxin concentration monitoring is unreliable after antidigoxin antibody.

3.2.7.2 Drug-Induced Long QT Syndrome

Marked QT prolongation, often accompanied by the morphologically distinctive polymorphic VT torsades de pointes, occurs in 1% to 10% of patients receiving QT-prolonging antiarrhythmic drugs and much more rarely in patients receiving “non-cardiovascular” drugs with QT-prolonging potential. While many drugs have been associated with isolated cases of torsades de pointes, Table 18 lists those generally recognized as having QT-prolonging potential. An up-to-date list is maintained at www.torsades.org and www.qtdrugs.org.

Table 18. Examples of Drugs Causing Torsades de Pointes*¹⁶

Frequent (greater than 1%): hospitalization for monitoring recommended during drug initiation in some circumstances

- Disopyramide
- Dofetilide
- Ibutilide
- Procainamide
- Quinidine
- Sotalol
- Ajmaline

Less frequent

- Amiodarone
- Arsenic trioxide
- Bepridil
- Cisapride
- Anti-infectives: clarithromycin, erythromycin, halofantrine, pentamidine, sparfloxacin
- Antiemetics: domperidone, droperidol
- Antipsychotics: chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide
- Opioid dependence agents: methadone

*See www.torsades.org for up-to-date listing.

Major risk factors for drug-induced torsades de pointes are listed in Table 19; often more than one is present.

Table 19. Risk Factors for Drug-Induced Torsades de Pointes

- Female gender
- Hypokalemia
- Bradycardia
- Recent conversion from atrial fibrillation
- Congestive heart failure
- Digitalis therapy
- High drug concentrations (*exception: quinidine*), often due to drug interactions
- Rapid rate of intravenous drug administration
- Baseline QT prolongation
- Ventricular arrhythmia
- Left ventricular hypertrophy
- Congenital long QT syndrome
- Certain DNA polymorphisms
- Severe hypomagnesemia
- Concomitant use of 2 or more drugs that prolong the QT interval
- Combination of QT-prolonging drug with its metabolic inhibitor

Presentations of drug-induced QT prolongation include incidental detection in an asymptomatic patient, palpitations due to frequent extrasystoles and non-sustained ventricular arrhythmias, syncope due to prolonged episodes of torsades de pointes, or SCD.

- **Management:** Monitoring high-risk patients during initiation of QT-prolonging antiarrhythmic drugs and recognition of the syndrome when it occurs are the first steps. Maintaining serum potassium between 4.5 and 5 mEq/L shortens QT; no specific data are available on the efficacy of potassium repletion to prevent torsades de pointes. Intravenous magnesium can suppress episodes of torsades de pointes without necessarily shortening QT, even when serum magnesium is normal. Magnesium toxicity (areflexia progressing to respiratory depression) can occur when concentrations reach 6 to 8 mEq/L but is a very small risk with the doses usually used in torsades de pointes, 1 to 2 g intravenously. Temporary pacing is highly effective in managing torsades de pointes that is recurrent after potassium repletion and magnesium supplementation. Isoproterenol can also be used to increase heart rate and abolish post-ectopic pauses¹⁶. Anecdotes have reported that lidocaine, verapamil, and even occasionally amiodarone have been effective. However, amiodarone may itself

cause torsades de pointes, albeit much less commonly than with other QT-prolonging antiarrhythmics¹⁶.

3.2.7.3 Sodium Channel Blocker–Related Toxicity

Arrhythmias caused by sodium channel-blocking drugs are included in Table 20. Antiarrhythmic drugs are the most common precipitants, although other agents, notably tricyclic antidepressants and cocaine, may produce some of their toxicities through these mechanisms. Sodium channel-blocking drugs with slower rates of dissociation tend to generate these adverse effects more commonly; these include agents such as flecainide, propafenone, and quinidine that (as a consequence of the slow dissociation rate) tend to prolong QRS durations even at normal heart rates and therapeutic dosages¹⁶.

Table 20. Syndromes of Drug-Induced Arrhythmia and Their Management		
Drugs	Clinical Setting	Management*
Digitalis	Mild cardiac toxicity (isolated arrhythmias only) Severe toxicity: sustained ventricular arrhythmias; advanced AV block; asystole	Anti-digitalis antibody Pacing Dialysis for hyperkalemia
QT-prolonging drugs	Torsades de pointes: few episodes, QT remains long	IV magnesium sulfate (MgSO ₄) Replete potassium (K ⁺) to 4.5 to 5 mEq/L Recurrent torsades de pointes Ventricular pacing Isoproterenol
Sodium channel blockers	Elevated defibrillation or pacing requirement Atrial flutter with 1:1 AV conduction Ventricular tachycardia (more frequent; difficult to cardiovert) Brugada syndrome	Stop drug; reposition leads Diltiazem, verapamil, beta blocker (IV) Beta blocker; sodium Stop drug; treat arrhythmia
*Always includes recognition, continuous monitoring of cardiac rhythm, withdrawal of offending agents, restoration of normal electrolytes (including serum potassium to greater than 4 mEq/L), and oxygenation. The order shown is not meant to represent the preferred sequence when more than one treatment is listed. AV: atrioventricular; IV: intravenous.		

In patients treated for sustained VT, these agents may provoke more frequent, and often more difficult to cardiovert, episodes of sustained VT. While the drugs generally slow the rate of VT, occasionally the arrhythmia becomes disorganized and may be resistant to cardioversion; deaths have resulted¹⁶.

Sodium channel-blocking drugs increase defibrillation energy requirement and pacing thresholds; as a consequence, patients may require reprogramming or revision of pacing or ICD systems or changes in their drug regimens. Sodium channel blockers can “convert” AF to slow atrial flutter, which can show 1:1 AV conduction with wide-QRS complexes. This drug-induced arrhythmia can be confused with VT¹⁶.

Sodium channel blockers can occasionally precipitate the typical Brugada syndrome ECG. This has been reported not only with antiarrhythmic drugs but also with tricyclic antidepressants and cocaine¹⁶.

- **Management:** Sodium channel-blocking drugs should not be used in patients with MI or sustained VT due to structural heart disease. The major indication for these drugs is atrial arrhythmias in patients without structural heart disease; this excludes those with recent or remote MI and any other form of ventricular dysfunction. When used for AF, AV nodal-blocking drugs should be co/administered to prevent rapid ventricular rates should atrial flutter occur; amiodarone may be an exception. Patients presenting with atrial flutter and rapid rates (and in whom VT is not a consideration) should be treated by slowing of AV conduction with drugs such as intravenous diltiazem. Ablation of the atrial flutter and continuation of the antiarrhythmic drug may be an option for long-term therapy¹⁶.

Administration of sodium, as sodium chloride or sodium bicarbonate, may be effective in the reversing conduction slowing or frequent or cardioversion-resistant VT¹⁶.

3.2.7.4 Tricyclic Antidepressant Overdose

Tricyclic antidepressants are second only to analgesics as a cause of serious overdose toxicity. Typical cardiac manifestations include sinus tachycardia, PR and QRS prolongation, and occasionally a Brugada syndrome-like ECG. Hypotension, fever, and coma are other common manifestations of serious toxicity. Torsades de pointes have been associated with tricyclic antidepressant use, but this seems to be very rare¹⁶.

- **Management:** QRS duration can be shortened by administration of NaHCO₃ or NaCl boluses. Antiarrhythmic drugs, including beta-blockers, are generally avoided. Supportive measures, such as pressors, activated charcoal, and extracorporeal circulation, may be required.

3.2.7.5 Other Drug-Induced Toxicity

Anthracycline cardiotoxicity is dose dependent, with intermittent high doses and higher cumulative doses increasing the risk of cardiomyopathy and lethal arrhythmias. Risk factors include younger age, female gender, and use of trastuzumab. This form of cardiomyopathy can occur acutely soon after treatment, within a few months of treatment (the so-called subacute form), or many years later. There is an increase in ventricular ectopy in patients receiving doxorubicin during the acute infusion period, but this is very rarely of any significance. Long-term intermittent cardiac assessment of patients is therefore necessary and cardiac decompensation should be treated conventionally. There is, however, little evidence of reversibility in the anthracycline-induced myopathic process.

5-Fluorouracil causes lethal and potentially fatal arrhythmias irrespective of underlying coronary disease during the acute infusion period, the vast majority occurring during the first administration. Cardiac monitoring during the infusion period, especially the first, is recommended for all patients receiving 5-fluorouracil therapy. Symptoms, with or without corresponding ECG changes compatible with cardiac ischemia, should lead to an immediate discontinuation of the infusion. Ischemia should be treated conservatively or conventionally with anticoagulants, nitrates, and calcium channel and beta-blockade as required. Although this cardiotoxicity is reversible, 5-fluorouracil sensitizes individuals and should be avoided in the future¹⁶.

Toad venom, an ingredient of some traditional Chinese medicines, produces clinical toxicity resembling that of digoxin, and in animal models, digoxin-specific antibodies are successful in reversing the toxicity. **Other herbal products**, including foxglove tea, have been reported to produce similar effects¹⁶.

Cocaine has both slow offset sodium channel-blocking properties and QT-prolonging (IKr-blocking) properties. Arrhythmias associated with cocaine ingestion include wide-complex tachycardias suggestive of sodium channel block (and responding to sodium infusion) as well as torsades de pointes. Cocaine also causes other cardiovascular complications that can lead to arrhythmias, notably myocarditis, and coronary spasm¹⁶.

Ephedrine, the active component, is also detected in a number of street drugs. Coronary spasm has been reported with multiple other medications and can present as VF: certain anticancer drugs (5-fluorouracil), capecitabine, triptans used in the treatment of migraines, recreational agents (e.g., ecstasy, cocaine), inadvertent vascular administration of pressor catecholamines, and anaphylaxis due to any one of a wide range of drugs¹⁶.

3.3 Contraindications, secondary effects and precautions with anticoagulants and antiarrhythmic drugs

3.3.1 Oral anticoagulants

Contraindications for oral anticoagulation are seldom absolute. However, in presence of an absolute contraindication, the clinical decision-making is simple: avoid anticoagulants. In the case of a relative contraindication, a physician should evaluate the pros and cons of this therapy.

The following table summarizes the accepted contraindications for oral anticoagulation:

ABSOLUTE CONTRAINDICATION	RELATIVE CONTRAINDICATION
1. Major bleeding in the previous six months	1. Hemorrhagic retinopathy (depending on its degree it can be an absolute contraindication)
2. Intracranial haemorrhage	2. Active gastroduodenal ulcer
3. Intracranial aneurism	3. Chronic hepatic disease
4. Recent major trauma	4. Active alcoholism
5. Gastrointestinal bleeding	4. Moderate cognitive impairment.
6. Surgery performed or planned within one month	5. Epilepsy
7. Severe hepatic impairment	6. Pericarditis with pericardial effusion
8. Blood dyscrasia	7. Short life-expectancy
9. Severe uncontrolled hypertension	
10. Pregnancy (1 st and 3 rd trimester) or lactation	
11. Severe cognitive impairment (severe dementia or psychiatric disease)	
12. Severe chronic alcoholism	
13. Failure to comply	
14. Hypersensibility	
15. Patient rejection	

This information can be accessed basically from the “recent medical history”, although “recent laboratory” results may also inform us about major pro-hemorrhagic diseases (such as low platelet recount or altered coagulation times). These are:

- Hepatic impairment and chronic hepatic disease: GOT (AST), GPT (ALT), LDH, alkaline phosphatase, gamma-GT
- Blood dyscrasia: erythrocyte count, haemoglobin, platelet count, leukocyte count, PT, TZ, PTT, fibrinogen

A different issue is the potential interaction of anticoagulants with other drugs (“recent medication”, “drug interaction”), which rarely contraindicate this therapy. There are many drugs that enhance the effect of oral anticoagulants and a few other that reduce their efficacy. The need for treatment adjustment/changes should be evaluated by the referring physician.

The following factors, alone or in combination, may be responsible for **increased** response to anticoagulation therapy, and should be checked:

- Endogenous factors: blood dyscrasias, diarrhoea, elevated temperature, hyperthyroidism, poor nutritional state, steatorrhoea, hepatic disorders and vitamin K deficiency.

- Exogenous factors: Potential drug interactions with warfarin are listed below by drug class and by specific drugs.

Table 22. Classes of drugs that may be responsible for increased response to anticoagulation therapy		
5-lipoxygenase Inhibitor	Antiplatelet Drugs/Effects	Leukotriene Receptor Antagonist
Adrenergic Stimulants, Central	Antithyroid Drugs†	Monoamine Oxidase Inhibitors
Alcohol Abuse Reduction Preparations	Beta-Adrenergic blockers	Narcotics, prolonged
Analgesics	Cholelitholytic Agents	Nonsteroidal Anti-Inflammatory Agents
Anaesthetics, Inhalation	Diabetes Agents, Oral	Proton Pump Inhibitors
Antiandrogen	Diuretics†	Psychostimulants
Antiarrhythmics†	Fungal Medications, Intravaginal, Systemic†	Pyrazolones
Antibiotics†	Gastric Acidity and Peptic Ulcer Agents†	Salicylates
Aminoglycosides (oral)	Gastrointestinal Prokinetic Agents	Selective Serotonin Reuptake Inhibitors
Cephalosporins, parenteral	Ulcerative Colitis Agents	Steroids, Adrenocortical†
Macrolides	Gout Treatment Agents	Steroids, Anabolic (17-Alkyl Testosterone Derivatives)
Miscellaneous	Hemorrhologic Agents	Thrombolytics
Penicillins, intravenous, high dose	Hepatotoxic Drugs	Thyroid Drugs
Quinolones (fluoroquinolones)	Hyperglycaemic Agents	Tuberculosis Agents†
Sulfonamides, long acting	Hypertensive Emergency Agents	Uricosuric Agents
Tetracyclines	Hypnotics†	Vaccines
Anticoagulants	Hypolipidemics†	Vitamins†
Anticonvulsants†	Bile Acid-Binding Resins†	
Antidepressants†	Fibric Acid Derivatives	
Antimalarial Agents	HMG-CoA Reductase Inhibitors†	
Antineoplastics†		
Antiparasitic/Antimicrobials		
Table 23. Specific drugs reported that may be responsible for increased response to anticoagulation therapy		
acetaminophen	fenofibrate	oxymetholone
alcohol†	fenoprofen	pantoprazole
allopurinol	fluconazole	paroxetine
aminosalicylic acid	fluorouracil	penicillin G, intravenous
amiodarone HCl	fluoxetine	pentoxifylline
argatroban	flutamide	phenylbutazone
aspirin	fluvastatin	phenytoin†
atenolol	flvoxamine	piperacillin
atorvastatin†	gefitinib	piroxicam
azithromycin	gemfibrozil	pravastatin†
bivalirudin	glucagon	prednisone†
capecitabine	halothane	propafenone
cefamandole	heparin	propoxyphene
cefazolin	ibuprofen	propranolol
cefoperazone	ifosfamide	propylthiouracil†
cefotetan	indomethacin	quinidine
cefoxitin	influenza virus vaccine	quinine
ceftriaxone	itraconazole	rabeprazole
celecoxib	ketoprofen	ranitidine†
cerivastatin	ketorolac	rofecoxib
chenodiol	lansoprazole	sertraline
chloramphenicol	lepirudin	simvastatin
chloral hydrate†	levamisole	stanozolol
chlorpropamide	levofloxacin	streptokinase
cholestyramine†	levothyroxine	sulfamethizole
cimetidine	liothyronine	sulfamethoxazole
ciprofloxacin	lovastatin	sulfinpyrazone
cisapride	mefenamic acid	sulfisoxazole
clarithromycin	methimazole†	sulindac
clofibrate	methyl dopa	tamoxifen

WARFARIN overdose	methylphenidate	tetracycline
cyclophosphamide†	methylsalicylate ointment (topical)	thyroid
danazol	metronidazole	ticarcillin
dextran	miconazole (intravaginal, oral, systemic)	ticlopidine
dextrothyroxine		tissue plasminogen activator (t-PA)
diazoxide	morizine hydrochloride†	tolbutamide
diclofenac	nalidixic acid	tramadol
dicumarol	naproxen	trimethoprim/sulfamethoxazole
diflunisal	neomycin	urokinase
disulfiram	norfloxacin	valdecoxib
doxycycline	ofloxacin	valproate
erythromycin	olsalazine	vitamin E
esomeprazole	omeprazole	zafirlukast
ethacrynic acid	oxandrolone	zileuton
ezetimibe	oxaprozin	

also: other medications affecting blood elements which may modify hemostasis dietary deficiencies prolonged hot weather unreliable PT/INR determinations
†Increased and decreased PT/INR responses have been reported.

The following factors, alone or in combination, may be responsible for **decreased** response to anticoagulation:

- Endogenous factors: edema, hypothyroidism, nephrotic syndrome, hyperlipemia and hereditary warfarin resistance.
- Exogenous factors: potential drug interactions with warfarin are listed below by drug class and by specific drugs.

Table 24 . Classes of drugs that may be responsible for decreased response to anticoagulation		
Adrenal Cortical Steroid Inhibitors	Antithyroid Drugs†	Immunosuppressives
Antacids	Barbiturates	Oral Contraceptives, Estrogen Containing
Antianxiety Agents	Diuretics†	Selective Estrogen Receptor Modulators
Antiarrhythmics†	Enteral Nutritional Supplements	Steroids, Adrenocortical†
Antibiotics†	Fungal Medications, Systemic†	Tuberculosis Agents†
Anticonvulsants†	Gastric Acidity and Peptic Ulcer	Vitamins†
Antidepressants†	Agents†	
Antihistamines	Hypnotics†	
Antineoplastics†	Hypolipidemics†	
Antipsychotic Medications	Bile Acid-Binding Resins†	
	HMG-CoA Reductase Inhibitors†	

Table 25. Specific drugs reported that may be responsible for decreased response to anticoagulation		
alcohol†	Warfarin under dosage	phenobarbital
aminoglutethimide	cyclophosphamide†	phenytoin†
amobarbital	dicloxacillin	pravastatin†
atorvastatin†	ethchlorvynol	prednisone†
azathioprine	glutethimide	primidone
butabarbital	griseofulvin	propylthiouracil†
butalbital	haloperidol	raloxifene
carbamazepine	meprobamate	ranitidine†
chloral hydrate†	6-mercaptopurine	rifampin
chlordiazepoxide	methimazole†	secobarbital
chlorthalidone	morizine hydrochloride†	spironolactone
cholestyramine†	nafcillin	sucalfate
clozapine	paraldehyde	trazodone
corticotropin	pentobarbital	vitamin C (high dose)
cortisone		vitamin K

also: diet high in vitamin K unreliable PT/INR determinations †Increased and decreased PT/INR responses have been reported.

Because a patient may be exposed to a combination of the above factors, the net effect of anticoagulation on PT/INR response may be unpredictable. More frequent PT/INR monitoring is therefore advisable. Medications of unknown interaction with warfarin are best regarded with caution. When these medications are started or stopped, more frequent PT/INR monitoring is advisable.

It has been reported that concomitant administration of warfarin and ticlopidine may be associated with cholestatic hepatitis.

Herbal Medicines

Caution should be exercised when botanical medicines are taken concomitantly with anticoagulation. Few adequate, well-controlled studies exist evaluating the potential for metabolic and/or pharmacologic interactions. Due to a lack of manufacturing standardization with botanical medicinal preparations, the amount of active ingredients may vary. This could further confound the ability to assess potential interactions and effects on anticoagulation. It is good practice to monitor the patient's response with additional PT/INR determinations when initiating or discontinuing botanicals.

Specific botanicals reported to affect warfarin therapy include the following:

- Bromelains, danshen, dong quai (*Angelica sinensis*), garlic, Ginkgo biloba, ginseng, and cranberry products are associated most often with an **increase** in the effects of warfarin.
- Coenzyme Q₁₀ (ubidecarenone) and St. John's Wort are associated most often with a **decrease** in the effects of warfarin.

Some botanicals may cause bleeding events when taken alone (eg, garlic and Ginkgo biloba) and may have anticoagulant, antiplatelet, and/or fibrinolytic properties. These effects would be expected to be additive to the anticoagulant effects of warfarin. Conversely, other botanicals may have coagulant properties when taken alone or may decrease the effects of warfarin.

Some botanicals that may affect coagulation are listed below for reference; however, this list should not be considered all-inclusive. Many botanicals have several common names and scientific names. The most widely recognized common botanical names are listed in the following tables:

Table 26. Botanicals that contain coumarins with potential anticoagulant effects

Agrimony ¹	Celery	Passion Flower
Alfalfa	Chamomile (German and Roman)	Prickly Ash (Northern)
Angelica (Dong Quai)	Dandelion ⁴	Quassia
Aniseed	Fenugreek	Red Clover
Arnica	Horse Chestnut	Sweet Clover
Asafoetida	Horseradish	Sweet Woodruff
Bogbean ²	Licorice ⁴	Tonka Beans
Boldo	Meadowsweet ²	Wild Carrot
Buchu	Nettle	Wild Lettuce
Capsicum ³	Parsley	
Cassia ⁴		

Table 27. Miscellaneous botanicals with anticoagulant properties

Bladder Wrack (Fucus)	Pau d'arco
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Table 28. Botanicals that contain salicylate and/or have antiplatelet properties

Agrimony ¹	Dandelion ⁴	Meadowsweet ²
Aloe Gel	Feverfew	Onion ⁵
Aspen	Garlic ⁵	Policosanol
Black Cohosh	German Sarsaparilla	Poplar

Black Haw	Ginger	Senega
Bogbean ²	Ginkgo Biloba	Tamarind
Cassia ⁴	Ginseng (Panax) ⁵	Willow
Clove	Licorice ⁴	Wintergreen
Table 29. Botanicals with fibrinolytic properties		
Bromelains	Garlic ⁵	Inositol Nicotinate
Capsicum ³	Ginseng (Panax) ⁵	Onion ⁵
Table 30. Botanicals with coagulant properties		
Agrimony ¹	Mistletoe	
Goldenseal	Yarrow	
¹ Contains anticoagulants, has antiplatelet properties, and may have coagulant properties due to possible vitamin K content.		
² Contains anticoagulants and salicylate.		
³ Contains anticoagulants and has fibrinolytic properties.		
⁴ Contains anticoagulants and has antiplatelet properties. ⁵ Has antiplatelet and fibrinolytic properties.		

Effect on Other Drugs

Anticoagulants may also affect the action of other drugs. Hypoglycemic agents (chlorpropamide and tolbutamide) and anticonvulsants (phenytoin and phenobarbital) may accumulate in the body as a result of interference with either their metabolism or excretion.

3.3.2 Rate control and Antiarrhythmic drugs

- β -blockers:** Beta-Blockers are effective in treating both supraventricular and ventricular tachyarrhythmias. β -Blockers antagonize catecholamine effects in the sinoatrial node, atrioventricular node, His-Purkinje tissue, and atrial and ventricular myocardium. On the ECG, the PR interval is prolonged without any significant effect on the QRS or QT interval. Sotalol with its additional class III antiarrhythmic effect, results in prolongation of the action potential and QT interval. Most of the cardiac side effects of β -blockers are related to their negative chronotropic, dromotropic and inotropic properties. They may cause *sinus node slowing* and *heart block* in patients with sinus node dysfunction or AV conduction disease. The use of β -blockers with intrinsic sympathomimetic activity in these patients may be better because these agents may reduce profound slowing of heart rate at rest, while preventing excessive heart rate increases in response to exercise or other stress. Unlike class I and class III antiarrhythmics, β -blockers have a remarkably good safety record in regard to ventricular proarrhythmia. In patients with severe ventricular systolic dysfunction, *congestive heart failure* may be precipitated, especially in those in whom cardiac output is dependent on sympathetic drive. In carefully selected patients with moderate-to-severe heart failure, however, the safety of β -blockade with proper dose titration and monitoring has been demonstrated in several clinical trials. Other adverse effects, especially with nonselective β -blockers, include *bronchospasm* in patients with history of asthma, *fatigue* and *central nervous system effects*, such as sedation, sleep disturbances, hallucination, depression and rarely psychotic reactions. *Impotence* and *worsening of symptoms* due to severe peripheral vascular or vasospastic disorders may occur.
- Non-dihydropyridine calcium channel antagonists (verapamil and diltiazem):** These are effective for acute and chronic rate control of AF. Adverse effects due to calcium channel blockers are mainly the result of vasodilatation (dizziness, headache, flushing and ankle swelling) and a decrease in heart rate and blood pressure (fatigue and lassitude). Calcium channel blockers can cause or aggravate gastroesophageal reflux due to the inhibition of lower esophageal sphincter contraction. Constipation is also common with verapamil. Occasionally, skin reaction and gingival swelling may occur. These effects are mild and dose-dependent. In patients with underlying sinus node or conduction system disease, verapamil and diltiazem may cause profound slowing of the heart rate and heart block, which may be exacerbated by the concomitant use of digoxin or β -blockers. In patients with significant ventricular systolic dysfunction, calcium channel blockers can precipitate heart failure and should be avoided. With intravenous administration, hypotension is common and can be severe. Short-acting nifedipine has been reported to increase the incidence of myocardial infarction and should not be used orally or sublingually

for urgent reduction of elevated blood pressure. In patients with wide complex tachycardia not definitively known to be supraventricular in origin, calcium channel blockers are contraindicated because they may precipitate hemodynamic collapse in patients with ventricular tachycardia or Wolff-Parkinson-White syndrome. Right ventricular outflow tract idiopathic tachycardia is a rare exception to this rule and may be treated with calcium channel blockers. In patients with atrial fibrillation in the setting of Wolff-Parkinson-White syndrome, calcium channel blockers are ineffective for blocking conduction over the accessory pathway and may accelerate conduction, resulting in hypotension or ventricular rate acceleration. In patients with digitalis toxicity, verapamil is contraindicated because it can increase the blood level of digoxin and lead to complete heart block.

- **Digoxin and digitoxin:** These are effective for control of heart rate at rest, but not during exercise. In combination with a b-blocker either may be effective in patients with or without heart failure. Digoxin may cause (life-threatening) adverse effects and should therefore be instituted cautiously. Interactions with other drugs may occur. Digoxin has a narrow therapeutic index and toxicity can develop readily if not carefully monitored. The toxic effects increase markedly with digoxin levels greater than 2.0 ng/mL. The common side effects with chronic digoxin overdose are *gastrointestinal* (anorexia, nausea, vomiting, diarrhea), visual (colored halos around a light) and *cardiac arrhythmias* (ectopic rhythm and heart block). *Central nervous system effects* (malaise, fatigue, confusion, disorientation, insomnia, and vertigo) and gynecomastia may also occur. Adverse effects may occur even with therapeutic serum levels, especially in the presence of hypokalemia or hypomagnesemia, which can independently increase ventricular automaticity and lower threshold for digoxin-induced cardiac arrhythmias. Digoxin toxicity can result from overdose, decreased excretion, or other factors that may increase the sensitivity of tissue to digoxin even at “therapeutic” serum levels.
- **Flecainide:** It can be safely administered in patients without significant structural heart disease, but should not be used in patients with coronary artery disease or in those with reduced LVEF. Precautions should be observed when using flecainide in the presence of intraventricular conduction delay, particularly left bundle branch block. Upon initiation of flecainide therapy, regular ECG monitoring is recommended. An increase in QRS duration of $\geq 25\%$ on therapy compared with baseline is a sign of potential risk of proarrhythmia when the drug should be stopped or the dose reduced. Similarly, when the flecainide dose is increased, QRS duration should be monitored. Concomitant atrioventricular node blockade is recommended because of the potential of flecainide and propafenone to convert AF to atrial flutter, which then may be conducted rapidly to the ventricles. Other side effects include precipitation of or worsening HF, dizziness, and visual problems. Flecainide is occasionally used for the prevention of atrial flutter or fibrillation or acute conversion, but **caution** is necessary because 1:1 conduction may occur if treatment with drugs that slow atrioventricular node conduction is not enforced.
- **Propafenone:** It can be safely administered in patients without significant structural heart disease. By analogy to flecainide, propafenone should not be used in patients with coronary artery disease or reduced LVEF. Precautions similar to those for flecainide should also be observed with propafenone.
- **Quinidine:** It was among the first cardiovascular drugs to undergo prospective systematic testing. In controlled trials quinidine improved maintenance of sinus rhythm. However, a meta-analysis demonstrated that quinidine increased mortality, very probably due to ventricular proarrhythmia secondary to QT interval prolongation (torsade de pointes). Quinidine is now largely abandoned.
- **Amiodarone:** Unlike most other agents, amiodarone can be safely administered in patients with structural heart disease, including patients with heart failure. Although the risk of proarrhythmia is low, amiodarone has many potential adverse effects on many organ systems. With the exception of the kidney, nearly every organ system can be affected. In general, the risk of adverse effects is associated with daily dose and cumulative dose. The risk of drug-induced torsade de pointes is lower with amiodarone than with ‘pure’ potassium channel blockers, possibly due to multiple ion channel inhibition. However, drug-induced proarrhythmia is seen with amiodarone, and the QT interval should be monitored closely. It may also cause severe extracardiac adverse events including thyroid dysfunction and bradycardia (see table 32).
- **Sotalol:** Drug-induced proarrhythmia with sotalol is due to excessive prolongation of the QT interval and/or bradycardia. Careful monitoring for QT prolongation and abnormal T-Uwaves is mandatory. In patients reaching a QT interval ≥ 500 ms, sotalol should be stopped or the dose reduced. Women, and

patients with marked LV hypertrophy, severe bradycardia, ventricular arrhythmias, renal dysfunction, or with hypokalemia or hypomagnesemia are at increased risk of proarrhythmia.

- **Dronedaron**: The safety profile of dronedarone is advantageous in patients without structural heart disease and in stable patients with heart disease. Specifically, dronedarone appears to have a low potential for proarrhythmia.

Table 31. Antiarrhythmic drugs

Drug	Adverse effects and risks	Contraindications	Main precautions	ECG features prompting lower dose or discontinuation	Interactions
Flecainide	Tremor, blurred vision, headache, ataxia, congestive HF, VT proarrhythmia Not suitable for patients with marked structural heart disease; may prolong QRS duration, and hence the QT interval; and may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles.	If creatinine clearance <50 mg/mL, in coronary artery disease, reduced LV ejection fraction.	Caution in the presence of conduction system disease. ↓ initial dose 50% in renal failure; titrate dose based on QRS complex intervals	QRS duration increase >25% above baseline	<i>Increase flecainide concentrations:</i> amiodarone, cimetidine, propranolol, quinidine, quinine. <i>Risk of arrhythmia increased by:</i> tricyclic antidepressants, clozapine, bupropion, mizolastine, terfenadine, ritonavir, lopinavir, indinavir. <i>Decrease flecainide concentration:</i> fenitoin, fenobarbital, carbamazepine. <i>Cardiac toxicity increased by:</i> diuretics.
Propafenone	Constipation, dizziness, headache, metallic taste, exacerbation of asthma, VT proarrhythmia Not suitable for patients with marked structural heart disease; may prolong QRS duration; will slightly slow the ventricular rate, but may inadvertently increase the ventricular rate due to conversion to atrial flutter and 1:1 conduction to the ventricles	In coronary artery disease, reduced LV ejection fraction.	Caution in the presence of conduction system disease, renal impairment, chronic obstructive pulmonary disease or asthma. ↓ initial dose 50% in renal and hepatic failure, and ↑ dosing interval to every 12 h; monitor QRS complex duration carefully	QRS duration increase >25% above the baseline	<i>Increase propafenone concentrations:</i> digoxin (↓ 25-50%), cimetidine, quinidine, ketoconazol, erythromycin, paroxetine <i>Effect of propafenone potentiated by:</i> local anesthetics, β-blockers, tricyclic antidepressants. <i>Propafenone increases the effect of:</i> metoprolol, propranolol, digoxin, desipramine, cyclosporine, theophylline, oral anticoagulants.
Ibutilide	Can cause prolongation of the QT interval and torsades de pointes; watch for abnormal T-U waves or QT prolongation. Will slow the ventricular rate.	Proarrhythmia appears more likely in patients with depressed left ventricular function.	Administrate in hospital setting with close monitoring and resuscitation facilities available. ECG monitoring should be continued for at least 4 hours after		

			administration. Continue monitoring longer if polymorphic VT occurs or if there is hepatic insufficiency.		
Disopyramide	Risk of hTA when used with β -blockers or verapamil Risk of atropinic effect (glaucoma, prostatic hypertrophy, miastenia gravis)	Systolic heart failure	Caution when using concomitant therapy with QT-prolonging drugs, presence of conduction system disease and renal failure.	QT interval >500 ms	<i>Increases serum levels of:</i> teofiline, ritonavir, indiravir, saquinavir, ciclosporine A, warfarine. <i>Atropinic effects increased by:</i> atropine and anticholinergic drugs (fenotiazines)
Sotalol	Bradycardia, fatigue, bronchospasm, and dyspnea. Heart failure, torsades de Pointes (more common in women, doses >320 mg/day, VT as the presenting rhythm, heart failure, and elevated base-line serum creatinine)	Significant LV hypertrophy, systolic heart failure, pre-existing QT prolongation, hypokaliemia creatinine clearance <50 mg/mL	Moderate renal dysfunction requires careful adaptation of dose. Caution when using concomitant therapy with QT-prolonging drugs, presence of conduction system disease	QT interval >500 ms	<i>Risk of torsade de pointes increased by:</i> vincamine, fenoxedil, IV eritromicine, halofantrine, pentamidine, sultopride, potassium-depriving diuretics, fenotiazines, tricyclic antidepressants, terfenadine, astemizol.
Amiodarone	Phlebitis, hypotension. Will slow the ventricular rate. Delayed AF conversion to sinus rhythm. Risk of hyper- or hypothyroidism. IV: can cause severe hTA, cardiovascular shock, cardiomyopathy, respiratory insufficiency	Iodine hypersensitivity, advanced conduction system disease, thyroid alterations (especially hyperthyroidism), pregnancy, lactancy	Caution when using concomitant therapy with QT-prolonging drugs, heart failure. Caution in advanced age (start with lower dose), hypocalcemia (modifies effects and increases QT prolongation and the risk of torsade de pointes) and anesthesia.	QT interval >500 ms	Dose of vitamin K antagonists and of digitoxin/digoxin should be reduced. <i>Toxicity increased by (increased risk of torsade de pointes):</i> quinidine, dysopiramide, sotalol, bepridil, vincamine, chlorpromazine, levomepomazine, tioridazie, trifluoperazine, haloperidol, amisulpride, sulpiride, tiapride, pimozide, cisapride, IV eritromicine, pentamidine <i>Increases serum levels of:</i> warfarine, digoxine, flecainide, cyclosporine. <i>Increases toxicity of:</i> fentanile, lidocaine, tacrolimus, sildenafil, midazolam, triazolam, dihidroergotamin, ergotamine, simvastatine and other statins with CYP3A4 metabolism

Dronedarone	Elevations in serum creatinine of 0.1 – 0.2 mg/dL are common and do not reflect reduced renal function.	Avoid in NYHA class III-IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, powerful CYP3A4 inhibitors, and creatinine clearance <30 mg/mL.	Caution when using concomitant therapy with QT-prolonging drugs, heart failure.	QT interval >500 ms	Dose of digitoxin/digoxin should be reduced. <i>Increased levels of dronedarone by: erythromycin</i> <i>Increases levels of: tacrolimus and sirolimus</i>
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Table 32. Amiodarone monitoring and recommendations*					
Monitoring					
System	Baseline	Follow-Up	Possible Adverse Effect	Incidence	Recommendation
Cardiac	ECG (at baseline and during loading dose)	Yearly	QT prolongation; torsade de Pointes	<1%	Reduce amiodarone dose or discontinue use
			Symptomatic sinoatrial or conduction system impairment	5%	Reduce amiodarone dose or discontinue use
Dermatologic	Physical examination	As needed for signs / symptoms	Photosensitivity to UV light	25-75%	Avoid sunlight; use sunscreen
			Blue-gray skin discoloration	4-9%	Reduce amiodarone dose or discontinue use
Endocrine	Thyroid function tests	Every 6 months	Hyperthyroidism	3%	Discontinue amiodarone; refer to endocrinologist
			Hypothyroidism	20%	Treat with levothyroxine
Hepatic	Liver function tests	Every 6 months	AST or ALT elevation >x2 upper limit of reference range	15%	Reduce amiodarone dose or discontinue use
Neurologic	Physical examination	As needed for signs / symptoms	Tremor and ataxia, peripheral neuropathy, insomnia, memory disturbances, and delirium	3-30%	Reduce amiodarone dose or discontinue use
Ophthalmologic	Eye examination (if visual impairment or for symptoms)	As needed for signs / symptoms	Corneal microdeposits	>90%	Continue amiodarone treatment
			Optic neuropathy	<1%	Discontinue amiodarone
Pulmonary	Pulmonary function tests (including diffusion capacity of carbon monoxide DC _L O)	As needed for signs / symptoms	Pulmonary toxicity (cough, fever, dyspnea)	<3%	Discontinue amiodarone immediately; consider corticosteroid treatment High resolution CT scan (if clinical suspicion of pulmonary toxicity)
	Chest radiograph	Yearly			

*If clinical circumstances warrant, more frequent follow-up will be necessary.

3.4 Suggestions and information based on data analysis of reference cases

These risk assessment models are integrated in to the care plan definitions defined in Task 4.1, to be automated by a care plan engine as an assistant to the medical professionals. In addition to these, In iCARDEA, a data analysis and correlation tool will be build in order to obtain statistically valid patterns that are inherent in the analysed patient data. The approach is based on the assumption that every data item gathered implicitly contains an amount of domain knowledge. The results can be utilized for making suggestions and predictions for similar cases or for a better understanding of the treated patients.

In order to make sure that the data to be analyzed actually contains the assumed domain knowledge and has no bias in the interpretation of data, the data has to originate from the same sources, where the patterns are going to be used.

For iCARDEA, a prototype of the tools is developed that is evaluated at one specific hospital. For this reason, patient data from all CIED / ICD patients of the last five years of the hospital are considered as input to the data analysis task. The patient data that is considered to be (technically and legally) available will include information about medication, secured diagnosis, age and gender, risk factors and secured arrhythmias / complications.

In more detail, it is planned to use the following values:

- ICD10-GM Codes:
 - o The diagnoses and risk factors of the patient the time he was delivered into the hospital, divided into one major and one or more minor diagnosis
 - o The diagnosis and risk factors of the patient the time when he was discharged from the department, divided into one major and one or more minor diagnosis
 - o The diagnosis and risk factors of the patient the time when he was discharged from the hospital, divided into one major and one or more minor diagnosis
- Medication at discharge:
 - o The medications prescribed when the patient was discharged from the hospital
 - o The prescribed medications identified at the patient's follow-up visits
- Patient Data:
 - o Year of Birth
 - o Gender
- Technical Data
 - o Used ICD / CIED device (vendor and type)
 - o Used electrodes (left, right and atrium) and type (active or passive) if applicable
- Surgery:
 - o Month and year of device implantation
- Identification of heart problems
 - o Occurred arrhythmias and other documented complications
- Time:
 - o Since the chronology and time span of all events is important for data analyses all data should be time stamped. Due to legal (privacy) reasons this can not be done on a fine-grained basis. However, at least month and year will be used.

If additional data is available from the hospital and is identified as potentially useful, it will be included into the analysis. In order to obtain reliable results, all data will have to be preprocessed to ensure high data quality and reliability.

As the first exemplary question stated from the involved hospital professionals, statistics about the possible correlation between presence of arrhythmias and different medications will be generated.

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