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EHRA POSITION PAPER

European Heart Rhythm Association (EHRA) position paper on arrhythmia management and device therapies in endocrine disorders, endorsed by Asia Pacific Heart Rhythm Society (APHRS) and Latin American Heart Rhythm Society (LAHRS)

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Endocrine disorders are associated with various tachyarrhythmias, including atrial fibrillation (AF), ventricular tachycardia (VT), ventricular fibrillation (VF), and bradyarrhythmias. Along with underlying arrhythmia substrate, electrolyte disturbances, glucose, and hormone levels, accompanying endocrine disorders contribute to development of arrhythmia. Arrhythmias may be life-threatening, facilitate cardiogenic shock development and increase mortality. The knowledge on the incidence of tachy- and bradyarrhythmias, clinical and prognostic significance as well as their management is limited; it is represented in observational studies and mostly in case reports on management of challenging cases. It should be also emphasized, that the topic is not covered in detail in current guidelines. Therefore, cardiologists and multidisciplinary teams participating in care of such patients do need the evidence-based, or in case of limited evidence expert-opinion based recommendations, how to treat arrhythmias using contemporary approaches, prevent their complications and recurrence in patients with endocrine disorders. In recognizing this close relationship between endocrine disorders and arrhythmias, the European Heart Rhythm Association (EHRA) convened a Task Force, with representation from Asia-Pacific Heart Rhythm Society (APHRS)

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and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLAECE), with the remit of comprehensively reviewing the available evidence and publishing a joint consensus document on endocrine disorders and cardiac arrhythmias, and providing up-to-date consensus recommendations for use in clinical practice.

Keywords Endocrine disorders • Arrhythmias • Atrial fibrillation • Ventricular arrhythmias • Cardiac implantable electronic device • Pacemaker • Implantable cardioverter-defibrillator • Catheter ablation • Diabetes • Thyroid disorders • Hyperthyroidism • Hypothyroidism • Pheochromocytoma • Growth hormone dysfunction • Hyperaldosteronism • Adrenal insufficiency • Parathyroid disease • Stroke • Oral anticoagulation • EHRA position paper

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Introduction

However, the ultimate judgement on the care of a specific patient must be made by the healthcare provider and the patient in light of all individual factors presented.

Evidence review

This document was prepared by the Task Force with representation from EHRA, APHRS, and SOLAECE and peer-reviewed by official external reviewers representing EHRA, HRS, APHRS, and SOLAECE. Their members made a detailed literature review, weighing the strength of evidence for or against a specific treatment or procedure, and including estimates of expected health outcomes where data exist. In controversial areas, or with respect to issues without evidence other than usual clinical practice, a consensus was achieved by agreement of the expert panel after thorough deliberation.

In contrast to guidelines, we opted for an easier and user-friendly system of ranking using 'coloured hearts' that should allow physicians to easily assess the current status of the evidence and consequent guidance (*Table 1*). This EHRA grading of consensus statements does not have separate definitions of the level of evidence. This categorization, used for consensus statements, must not be considered as directly similar to that used for official society guideline recommendations, which apply a classification (Class I–III) and level of evidence (A, B, and C) to recommendations used in official guidelines.

Thus, a green heart indicates a 'should do this' consensus statement or indicated treatment or procedure that is based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective. A yellow heart indicates general agreement and/or scientific evidence favouring a 'may do this' statement or the usefulness/efficacy of a treatment or procedure. A 'yellow heart' symbol may be supported by randomized trials based on a small number of patients or which is not widely applicable. Treatment strategies for which there is scientific evidence of potential harm and should not be used ('do not do this') are indicated by a red heart.

Mechanisms and pathophysiology of cardiac arrhythmias in endocrine disorders

A number of cardiac arrhythmia mechanisms may underlie ventricular and atrial arrhythmias, such as reentry, abnormal automaticity or triggered activity. Normally, these mechanisms are not active in a normal (young) heart. The only exceptions are inherited arrhythmia syndromes, in which cardiac remodelling may be present that make the heart more vulnerable often under specific circumstances, like the excess of catecholamines.

Acutely, hormones can play a crucial role such as in catecholamine-induced polymorphic VT, induced by exercise or in the long QT syndrome (LQTS), induced either by sleep, fear, or excitement. Often the challenge provided acutely by these hormones exceeds the safety margins (=reserve) of the vulnerable heart to overcome and ventricular arrhythmias ensue. Thus, endocrine disorders may play an acute role in the triggering of cardiac arrhythmias (*Figure 1*).

However, there are also chronic adaptations induced by endocrine disorders that can underlie the formation of arrhythmias. The action potential is controlled by numerous ion currents that either provides inward or outward currents. It is this delicate balance that shapes the

Table 1 Scientific rationale of recommendations[a]

Definitions where related to a treatment or procedure	Consensus statement instruction	Symbol
Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial or is supported by strong observational evidence and authors' consensus (as indicated by an asterisk)	'Should do this'	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials based on a small number of patients or which is not widely applicable	'May do this'	
Scientific evidence or general agreement not to use or recommend a treatment or procedure	'Do not do this'	

[a]This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B, and C) to recommendations.

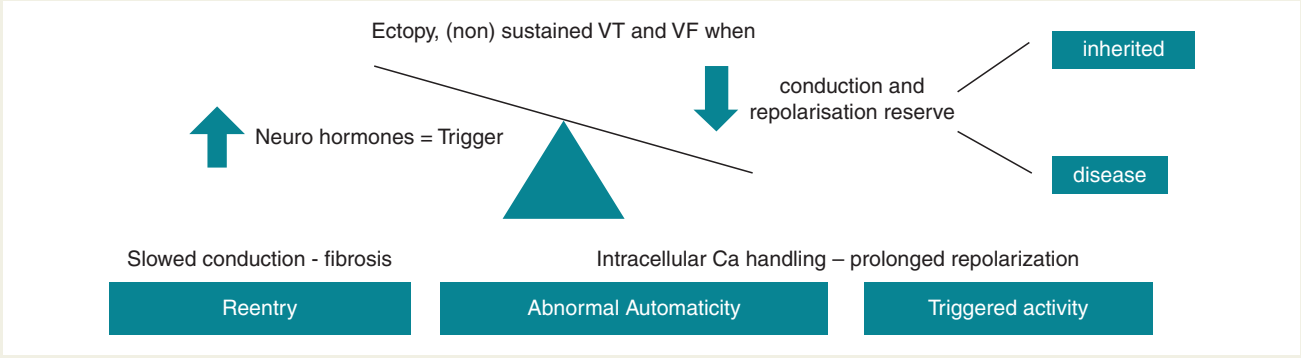

Figure 1 Mechanism of arrhythmias in endocrine disorders: The balance between the strength of the heart to de- or repolarize is often challenged by the autonomic nervous system. When the balance is off, the heart has to allow arrhythmias, which can be based upon numerous arrhythmogenic mechanisms. VF, ventricular fibrillation; VT, ventricular tachycardia.

action potential and determines its duration, often measured as QT-duration. Overexpression or down-regulation of these ion currents can chronically increase or decrease conduction or repolarization reserve.

A few examples have been listed:

Diabetes mellitus: In an experimental model, mimicking diabetes type 1, it was demonstrated that this metabolic disorder reduced repolarization reserve by decreasing the outward current 'slowly delayed rectifier (IKs)' in the rabbit, thereby increasing the liability for drug induced Torsade de Pointes.[1] More recently, it has been suggested that the transcription of ion channels due to the involvement of the P13K pathway is responsible for this reduced transcription.[2]

Gender differences: The incidence and prevalence of AF and sustained ventricular arrhythmias and sudden cardiac death (SCD) are lower in women than in men. However, women have a greater chance to develop Torsade de Pointes arrhythmias.[3] It has been shown that sex hormones account for most of the differences in the cardiac electrophysiological properties observed between females and males. Human data demonstrate that the expression of a number of potassium channels is reduced in females accounting for a prolonged duration of the ventricular action potential.[4] Testosterone reduces the ventricular action potential duration (APD) by enhancing the slow delayed rectifier current and by increasing the l-type calcium current.[4]

Adrenal dysfunction: Glucocorticoid has been reported to be important for the maintenance of membrane Calcium transport in the cardiac sarcoplasmic reticulum and for the regulation of various ion channels, including IKs, and the rapid delayed rectifier (IKr), thereby manipulating QT duration.[5]

Management of arrhythmias in specific endocrine disorders

Diabetes mellitus

Diabetes mellitus (DM) type 1 (reduced insulin production) or type 2 (increased resistance to insulin) may increase the risk of cardiac arrhythmias via many factors including: (i) cardiovascular risk factors (e.g. hypertension), (ii) atherosclerotic cardiovascular disease [i.e. coronary

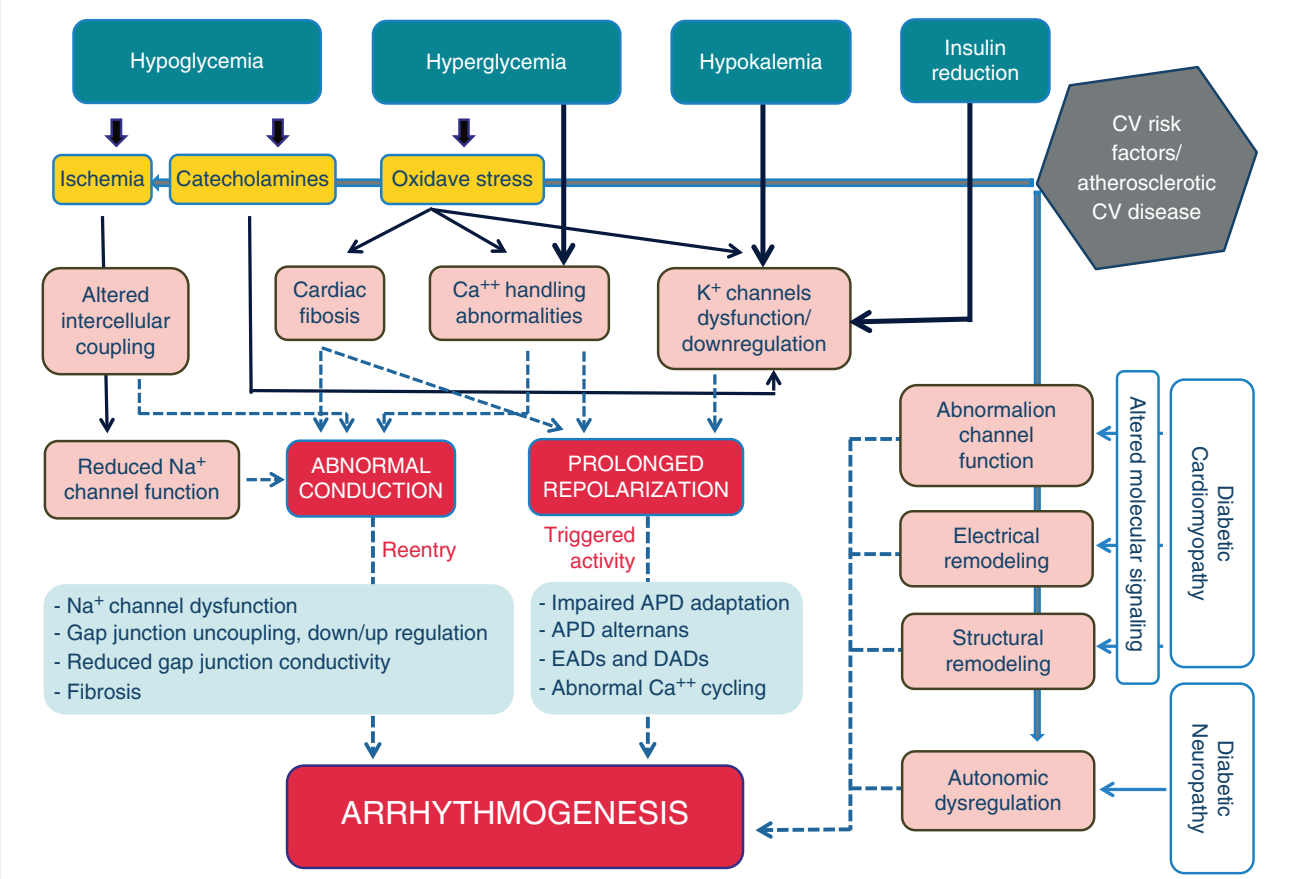

Figure 2 Arrhythmogenesis in diabetes mellitus. APD, action potential duration; CV, cardiovascular; DADs, delayed after depolarizations; EADs, early after depolarizations; dark blue, conditions; white, disorders; yellow, pathophysiologic and physiologic pathways; dark grey, contributing disorders and risk factors; pink, structural, cellular, and ion channel abnormalities; blue, mechanisms of arrhythmogenesis; red, electrophysiological abnormalities and arrhythmogenesis.

artery disease (CAD), prior myocardial infarction (MI), stroke, or peripheral arterial disease],[6–8] and (iii) DM-associated factors such as glucose control, diabetic neuropathy, or cardiomyopathy (*Figure 2*).[6,9,10] The risk for arrhythmias or SCD in DM patients is closely related to the presence and severity of underlying cardiovascular disease,[6,11–13] but the aforementioned DM-related factors could induce arrhythmias independently of cardiovascular comorbidities. Management of cardiac arrhythmias in DM patients is outlined in *Figure 3*.

Atrial fibrillation

Many epidemiological studies have reported an association of DM with incident AF.[14,15] The duration of DM and glycaemic control were also associated with AF (each year with DM conferred a 3% increase in the risk of AF),[16] whilst HbA1c of >9% was associated with a nearly two-fold increase in AF risk.[17] A meta-analysis of 11 studies with a total of 108 703 AF cases in 1 686 097 subjects showed a 40% greater risk of AF in the presence of DM, but the effect was attenuated after adjustment for multiple risk factors [relative risk 1.24, 95% confidence interval (CI) 1.06–1.44], whilst the population-attributable estimate for AF owing to DM was 2.5% (95% CI 0.1–3.9).[18] In several observational studies, the age-adjusted association of DM with incident AF was no longer significant after multiple adjustments for hypertension, cardiovascular comorbidity, body mass index, or obesity,[19–21] thus suggesting that strategies for AF prevention in DM patients should focus on the control of DM-associated comorbidities (especially the weight and blood pressure control).[19]

Indeed, in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) study, DM patients with AF (7.6%) had significantly greater risks for all-cause death, cardiovascular death, major cerebrovascular events, and heart failure compared with DM patients without AF. Blood pressure lowering yielded similar relative risk reduction in all-cause and cardiovascular mortality but owing to their higher risk of these events, the absolute benefits from blood pressure control appeared much greater in AF patients.[22] In the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) trial, hypertensive patients with new-onset DM had higher rates of new-onset AF compared with non-DM patients and were at higher risk of heart failure.[23] Hence, AF in DM patients should be viewed as a marker of adverse outcome, which should prompt aggressive management of all concomitant risk factors (*Figure 3*).[24] Importantly, intensive glucose lowering (target HbA1c <6.0%) has been associated with similar incident AF rates as a less stringent approach (HbA1c <8.0%), but with increased risk of death and other cardiovascular events.[17]

Since asymptomatic (silent) AF is not uncommon, especially in patients with DM,[25] at least opportunistic screening for AF with pulse palpation should be performed in DM patients, as also recommended

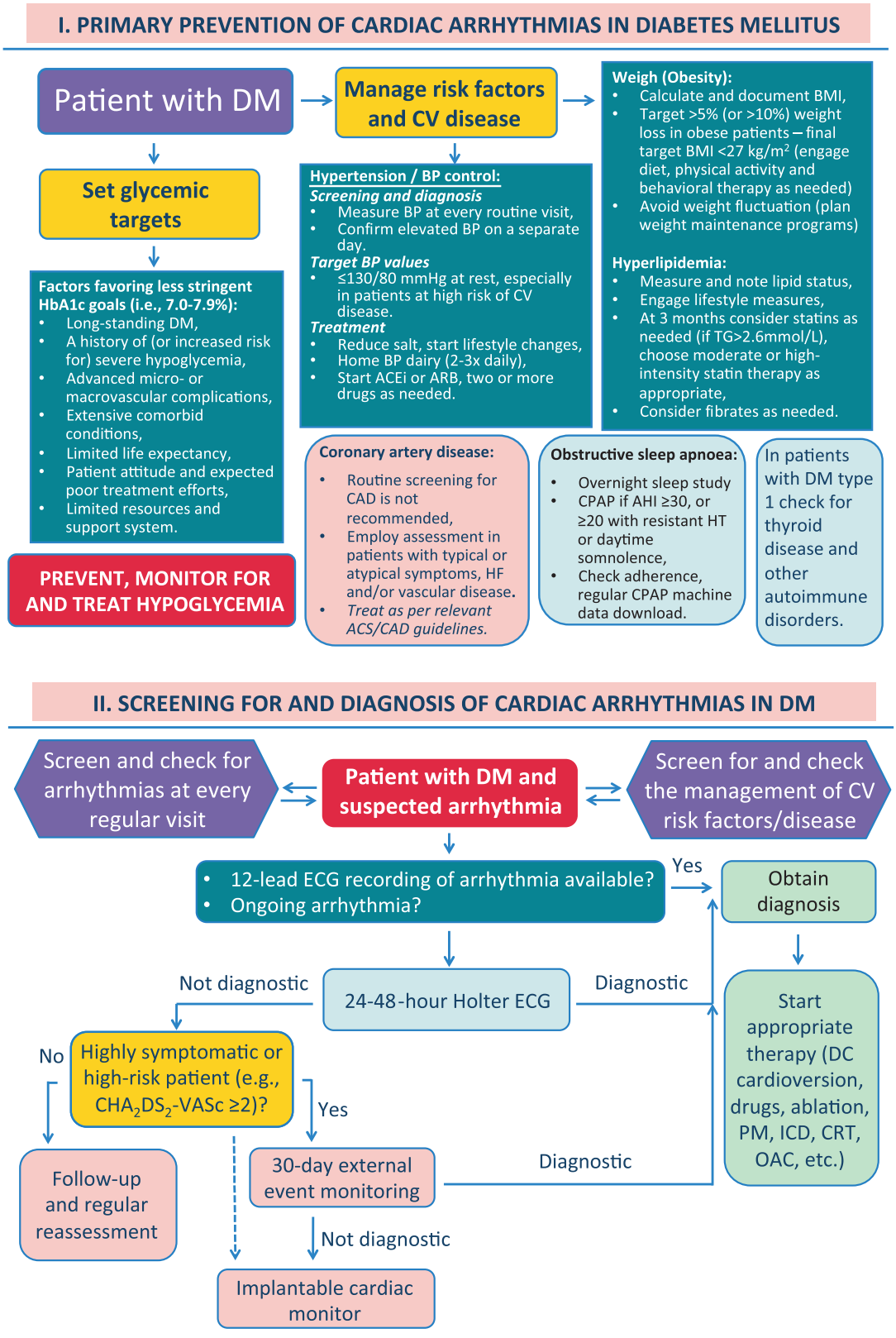

Figure 3 General principles of management of cardiac arrhythmias in patients with diabetes mellitus. AADs, antiarrhythmic drugs; ACEi, angiotensin-converting enzyme inhibitor; AFL, atrial flutter; AHI, apnoea-hypopnea index; ARB, angiotensin receptor blocker; AVNRT, atrioventricular nodal re-entrant tachycardia; AVRT, atrioventricular re-entrant tachycardia; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CPAP, continuous positive airway pressure; CRT, cardiac resynchronization therapy; CV, cardiovascular; DM, diabetes mellitus; ECG, electrocardiogram; HT, hypertension; ICD, implantable cardioverter-defibrillator; LA, left atrium; LV, left ventricle; MRI, magnetic resonance imaging; NOACs, non-vitamin K antagonist oral anticoagulants; OAC, oral anticoagulant therapy; PM, pacemaker; SE, systemic embolism; VKA, vitamin K antagonist; VPBs, ventricular premature beats; VT ns, ventricular tachycardia non-sustained.

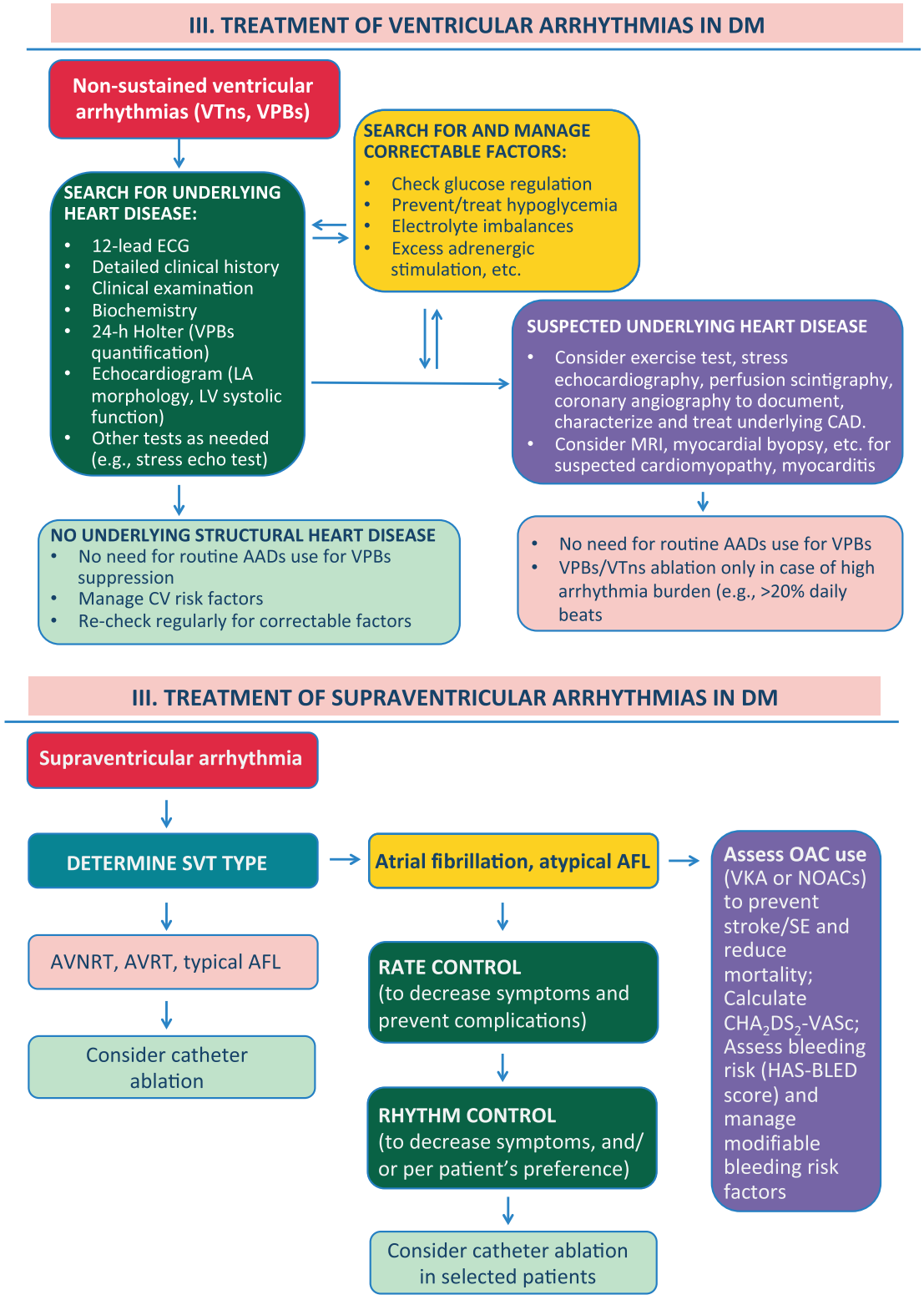

Figure 3 Continued.

Table 2 Randomized controlled trials of intensive vs. standard glycaemic control in adult patients with diabetes mellitus

Study, year	Cohort size	Drug	Intensive glucose control	Follow-up	Study outcomes (intensive vs. standard glucose control)	Significant hypoglycaemia
ADVANCE[72], 2008	11 140 DM type 2	Gliclazide	HbA1c ≤6.5%	Median 5 years	*Microvascular events:* 9.4% vs. 10.9%; HR 0.86 (0.77–0.97), *P* = 0.01 *Macrovascular events:* 10.0% vs. 10.6%; HR 0.94 (0.84–1.06), *P* = 0.32 *Cardiovascular death:* 4.5% vs. 5.2%; HR 0.88 (0.74–1.04), *P* = 0.12 *All-cause death:* 8.9% vs. 9.6%; HR 0.93 (0.83–1.06), *P* = 0.28	2.7% vs. 1.5%; HR 1.86 (1.42–2.40), *P* < 0.001
ACCORD[54], 2008 ACCORD[53], 2011	10 251 DM Type 2, known CV disease or CV risk factors	Various; The intensive regimen stopped early due to increased mortality	HbA1c <6.0%	Mean 3.5 years	*All-cause death:* 1.41% vs. 1.14%; HR 1.22 (1.01–1.46), *P* = 0.04 *Cardiovascular death:* 2.6% vs. 1.8%; HR 1.35 (1.04–1.76), *P* = 0.02 *Fatal arrhythmia:* 0.1% vs. 0.2% *Primary outcome (composite of non-fatal MI, stroke or CV death):* 6.9% vs. 7.2%; HR 0.90 (0.78–1.04), *P* = 0.16 *At 5-year follow-up, the rates of non-fatal MI were lower [1.18% vs. 1.42%, HR 0.82 (0.70–0.96), *P* = 0.01] but the rates of CV death (0.72% vs. 0.57%, HR 1.29 (1.04–1.60), *P* = 0.02) and all-cause death [1.53% vs. 1.27%, HR 1.19 (1.03–1.38), *P* = 0.02] were higher with intensive glucose control. *Fatal arrhythmia:* 0.1% vs. 0.4%	3.1% vs. 1.0%, *P* < 0.001
VADT[73], 2009	1791 military veterans; DM Type 2, 40% with previous CV event	Various; Open-label study	An absolute reduction for 1.5% points in HbA1c compared with standard glucose control	Median 5.6 years	6-year event free rates, standard vs. intensive control: *Cardiovascular death:* 0.96% vs. 0.95%; HR 1.32 (0.81–2.14), *P* = 0.26 *All-cause death:* 0.88% vs. 0.87%; HR 1.07 (0.81–1.42), *P* = 0.62 *Time to first occurrence of a CV event:* HR 0.88 (0.74–1.05), *P* = 0.14	21.2% vs. 9.9%, *P* < 0.001

Continued

Table 2 *Continued*

Study, year	Cohort size	Drug	Intensive glucose control	Follow-up	Study outcomes (intensive vs. standard glucose control)	Significant hypoglycaemia
NICE-SUGAR[74], 2009 NICE-SUGAR[51], 2012	6104 critically ill patients	Insulin	Blood glucose 4.5–6.0 mmol/l	90 days	*90-Day all-cause mortality:* 27.5% vs. 24.9%; OR 1.14 (1.02–1.28), $P = 0.02$ *Both moderate and severe hypoglycaemia are associated with increased risk of death: 28.5% vs. 23.5%, HR 1.41 (1.21–1.62), $P < 0.001$ (moderate hypoglycaemia); 35.4% vs. 23.5%; HR 2.10 (1.59–2.77), $P < 0.001$ (severe hypoglycaemia)	6.8% vs. 0.5%, OR 14.7 (9.0–25.9), $P < 0.001$ Moderate hypoglycaemia $n = 2714$ (45.0%); Severe hypoglycaemia $n = 223$ (3.7%)
ORIGIN[52], 2013	12 537 DM Type 2 with additional CV risk factors	Insulin glargine	Normal glycaemia	Median 6.2 years	*Severe hypoglycaemia vs. others:* *Composite of CV death/MI or stroke:* HR 1.58 (1.24–2.02), $P < 0.001$ *All-cause mortality:* HR 1.74 (1.39–2.19), $P < 0.001$ *CV mortality:* HR 1.71 (1.27–2.30), $P < 0.001$ *Arrhythmic death:* HR 1.77 (1.17–2.67), $P = 0.07$	Annual rates of severe hypoglycaemia 0.9% vs. 0.3%

ACCORD, The Action to Control Cardiovascular Risk in Diabetes trial; ADVANCE, The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial; CV, cardiovascular; DM, diabetes mellitus; HR, hazard ratio; MI, myocardial infarction; NICE-SUGAR, The Normoglycaemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation trial; OR, odds ratio; ORIGIN, Outcomes Reduction with an Initial Glargine Intervention; VADT, Veterans Affairs Diabetes Trial.

for all individuals aged ≥65 years.[26] High-risk DM patients would likely benefit from an active screening for AF, but more data are needed to define optimal AF screening strategy(ies) in DM patients.[27] Before treatment initiation, the presence of AF should be documented using a 12-lead electrocardiogram (ECG).[26,28] In DM patients with established AF, ventricular rate control is recommended to decrease symptoms and prevent AF-related complications. In patients with persistent symptoms, despite adequate rate control, or in those with left ventricular dysfunction attributable to poorly controlled high ventricular rate, or as per patient's preference, rhythm control strategy could be attempted[29] including catheter ablation[30–32] or cardioversion. Of note, DM has been associated with increased AF recurrence post successful cardioversion of persistent AF.[33] For AF-related stroke risk management see *Stroke risk assessment and prevention in arrhythmias associated with endocrine disorders.*

Ventricular arrhythmias and sudden cardiac death

Compared with the general population, DM patients have an increased risk of both SCD[13,32–35] and non-SCD.[36] In a meta-analysis of 14 studies involving 346 356 participants and 5647 SCD cases, the risk of SCD was two-fold higher in patients with DM compared with non-DM patients [adjusted hazard ratio (HR) 2.25, 95% CI 1.7–2.97].[29] However, DM patients were also shown to be at nearly three-fold greater risk of non-SCD than non-DM patients (adjusted HR 2.90, 95% CI 1.89–4.46).[36] Observational studies reported marked QTc prolongation,[37] atypical microvolt T-wave alternans patterns,[38] altered heart rate variability,[39–43] or heart rate turbulence[44–46] in DM patients, but none of these tests have been routinely used to stratify the risk for ventricular arrhythmias or SCD in clinical practice.[47] Both hyper- and hypoglycaemia have been independently associated with increased risk of ventricular arrhythmias.[48] Insulin-induced hypoglycaemia has been associated with nocturnal death (so-called 'dead-in-bed syndrome') in DM type 1,[49,50] and arrhythmic deaths were reported in several DM type 2 trials[51–54] (*Table 2*).

There is no DM-specific protocol of screening for SCD[47] but, as shown in *Figure 3*, all patients diagnosed with DM should undergo regular screening for cardiovascular risk factors or structural heart disease, and glycaemic targets should be set individually. Patients with DM and symptoms suggestive of cardiac arrhythmias (e.g. palpitations, pre-syncope, or syncope) should undergo further detailed diagnostic assessment as shown in *Figure 3*.

Hypoglycaemia-associated arrhythmias are difficult to document, but observational studies using continuous glucose monitoring (CGM) and Holter monitoring in small DM type 2 cohorts ($n = 25$) showed that hypoglycaemic episodes were common, often asymptomatic and associated with various arrhythmias.[55,56] Compared with daytime hypoglycaemia, nocturnal episodes were more common and associated with greater risk for bradycardia or atrial ectopy, whilst ventricular arrhythmias were equally common.[55] In contrast to animal studies,[57] in a recent retrospective analysis of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial, the use of beta-blockers in DM patients was associated with increased risk of severe hypoglycaemia and cardiovascular events,[58] but more evidence is needed to inform optimal use of beta-blockers in DM patients without established CAD.[59] Otherwise, the use of antiarrhythmic drugs should follow the general principles and precautions related to pharmacological treatment of cardiac arrhythmias.[26,47]

In high-risk patients with established cardiovascular disease and/or long-standing sub-optimally controlled DM type 2, a less stringent glycaemic control (i.e. a target HbA1c of ≤8%) is recommended,[60] since intensive glycaemic control has been associated with increased risk of severe hypoglycaemic episodes counterbalanced by significant reduction only in microvascular but not macrovascular complications (e.g. MI, stroke, and mortality). The addition of empagliflozine[61] or liraglutide[62] to standard care should be considered in order to reduce cardiovascular and all-cause mortality or hospitalization for heart failure.[63] In addition, the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial data suggested that liraglutide may have a renal protective effect.[62,64] Although cardiac arrhythmias were not specifically investigated in either LEADER or EMPA-REG OUTCOME (Empagliflozine Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)[60] trial, an antiarrhythmic effect of these drugs (perhaps mediated via glucagon release stimulation) has been hypothesized to contribute to the reduced risk for cardiovascular death.[61,62]

The CANVAS Program data showed that the use of another sodium-glucose co-transporter 2 (SGLT2) inhibitor, canagliflozin, was associated with significantly lower risk of cardiovascular events and a renal protective effect compared with placebo in patients with DM type 2 and an elevated risk of cardiovascular disease.[65] The incidence of cardiovascular events with dapagliflozine is currently investigated in the DECLARE-TIMI 58 trial,[66] and a meta-analysis of 21 trials with this drug[67] suggested the potential for a beneficial cardiovascular effect consistent with the multifactorial benefits on cardiovascular risk factors associated with other SGLT2 inhibitors.[68,69] Concerning the cardiovascular effects of the SGLT1 inhibitors other than liraglutide (i.e. exenatide and lixisenatide), there was no significant difference in the rates of cardiovascular events with these agents compared with placebo in the respective trial.[70,71]

Consensus statements	Consensus statement instruction	Level of evidence	References
Diagnostic assessment of patients with DM type 1 and type 2 requires aggressive screening for and a detailed characterization of underlying cardiovascular risk factors, atherosclerotic cardiovascular disease and DM-related factors (i.e. glucose regulation, diabetic neuropathy, and cardiomyopathy), all of which may increase the risk of cardiac arrhythmias and SCD in DM patients	'Should do this'		6
Glycaemic targets in patients with DM and cardiac arrhythmias should be defined individually, taking into account patient age, individual risk profile, life expectancy and patient values and preferences	'Should do this'		60
Severe hypoglycaemia should be avoided in DM patients at risk of cardiac arrhythmias, owing to increased risk of malignant, potentially lethal ventricular arrhythmias and all-cause death	'Should do this'		60
Intensive glucose control with target HbA1c of <7.0% (or even <6.0%) should not be attempted in elderly and/or high-risk DM patients, owing to increased risk of severe hypoglycaemia and neutral (or negative effect) on all-cause mortality	'Do not do this'		60
Intense management of cardiovascular risk factors (e.g. obesity, dyslipidaemia, hypertension, obstructive sleep apnoea, etc.) in DM patients reduces the risk of cardiac arrhythmias (e.g. AF) by preventing (or slowing) the development of atherosclerotic cardiovascular disease and arrhythmogenic substrate	'Should do this'		26
Incident AF in DM patients should be viewed as a marker of increased risk of adverse cardiovascular events and mortality. Intensive glucose control does not reduce the risk of AF, but aggressive management of cardiovascular risk factors may delay or prevent AF	'Should do this'		26
Screening for silent AF by pulse palpation (with ECG confirmation) should be performed in all DM patients at each regular visit.	'Should do this'		26,27
The use of (non-selective) beta-blockers in DM patients without established CAD may be weighed against the risk of severe hypoglycaemia	'May do this'		58,59

Table 3 Definitions of thyroid dysfunction[6]

	TSH levels (mIU/L)	Free thyroxine (pmol/L)	Total thyroxine (mmol/L)
Thyroid function			
Euthyroidism	0.2–5.0	9–22	60–140
Overt hypothyroidism	>5.0	<9	<60
Subclinical hypothyroidism	>5.0	9–22	60–140
Overt hyperthyroidism	<0.2	>22	>140
Subclinical hyperthyroidism	<0.2	9–22	60–140
TSH level dependent thyroid dysfunction			
Euthyroidism	0.4–5.0	9–22	60–140
High-normal euthyroidism	0.2–0.4	9–22	60–140
Subclinical hyperthyroidism (reduced TSH)	0.1–0.2	9–22	60–140
Subclinical hyperthyroidism (suppressed TSH)	<0.1	9–22	60–140

TSH, thyroid stimulating hormone.

Thyroid dysfunction

Thyroid dysfunction is associated with atrial and ventricular tachyarrhythmias, as well as bradyarrhythmias. Hyperthyroidism is accompanied by increased automaticity and triggered activity in the atria and pulmonary veins (PVs), while in hypothyroidism effective refractory periods of the atria, atrioventricular (AV) node, bypass tracts and His-Purkinje system are prolonged.[75–77] Genetic mechanisms involving ion channels, and autoimmune mechanisms involving muscarinic and beta-adrenoreceptors, that are also linked to long-QT syndrome, may contribute to ventricular and atrial arrhythmias in thyroid dysfunction.[78,79] Tachy- and bradyarrhythmia occurrence is different in hyperthyroidism and hypothyroidism, and the evidence on treatment is limited (*Table 3–5*).

Hyperthyroidism

Hyperthyroidism, overt or subclinical [i.e. reduced serum thyroid stimulating hormone (TSH) concentration but free thyroxine levels within reference ranges] (*Table 3*) is associated with increased risk of AF[80–90]; before and after establishment of the diagnosis, it is associated with increased risk of cardiovascular disease development.[91] Hypothyroidism, either overt or subclinical has been shown by several studies confer no AF risk,[80,89,90] though lack of association is not well-established.[92–97]

Atrial fibrillation

Antithyroid treatment and attainment of euthyroid state should be the first line in management of AF in the setting of hyperthyroidism, as in most cases AF reverses spontaneously to sinus rhythm once euthyroid state is achieved, usually after 13–15 weeks of therapy.[98–101] Treatment using antithyriod agents, radioiodine therapy, or thyroidectomy is accompanied by conversion to sinus rhythm in 75–100% of cases, but predictors of persistent arrhythmia are increased age, longer pre-treatment duration of AF and hyperthyroidism.[99,100] For rate control of AF and as an adjunct to antithyriod therapy, non-selective beta-blockers like propranolol may be used, as they exert not only antisympathetic effects slowing heart rate but also reduce metabolic rate and affect triiodthyronine levels; in case of low-output heart failure they should be used cautiously or other short-acting beta-blockers without intrinsic sympathomimetic activity should be considered.[102–104] It is reasonable to recommend cardioversion in patients with persistent AF after establishment of euthyroid state, and in case of recurrent AF when the patient is euthyroid, ablation should be considered.[101,105–110] In patients with persistent AF related to hyperthyroidism, cardioversion results in restoration of sinus rhythm in 88–92.4%; in patients without accompanying structural heart disease, 86% and 67% of them were arrhythmia-free at 3 years and 6.7 years of follow-up, respectively.[105,106]

Hyperthyroidism-related AF usually has a lower recurrence rate than non-hyperthyroidism-related AF. In one study, where only electrical cardioversion was used, the risk of AF recurrence was 36% lower in hyperthyroidism than in non-hyperthyroidism AF ($P = 0.004$) and the only predictor of AF recurrence was the longer duration of arrhythmia ($P < 0.01$).[107] Few studies have reported outcomes of AF ablation,[108–110] with no difference in long-term (4 years) recurrence rate between hyperthyroidism and non-hyperthyroidism-related AF after PV isolation,[109] while in another study recurrence was two-fold higher in hyperthyroid than in non-hyperthyroid patients after single procedure of PV isolation or substrate ablation, while after multiple procedures there was no difference.[110]

Hyperthyroidism does not independently confer higher risk for stroke/systemic embolic events as compared to non-hyperthyroid patients,[111–113] and annual risk of stroke in hyperthyroid patients with AF is lower than in non-hyperthyroid patients.[114] Warfarin reduced the risk of ischaemic stroke in non-self-limiting AF patients with hyperthyroidism and $CHA_2DS_2VASc \geq 1$.[114]

Ventricular arrhythmias

While ventricular arrhythmias are rare in hyperthyroid patients; one of the earliest Holter monitoring studies did not demonstrate reduction of ventricular ectopy with antithyroid therapy.[115] However, QT prolongation is described in Graves disease with thyrotoxicosis.[116] Few cases of isolated VF without structural heart disease and electrolyte imbalance in hyperthyroidism have been reported,[117] among them coronary vasospasm was confirmed in two, one case was due

Table 4 Evidence summary for arrhythmias associated with thyroid dysfunction

Study	Design	Subjects	Follow-up	Thyroid dysfunction	Arrhythmia	Risk (95%CI)
Selmer *et al.*[80]	Cohort	586 460	5.5 years	Euthyroidism	AF	Reference
				Overt hyperthyroidism	2.9%	IRR 1.42 (1.22–1.63)
				Subclinical hyperthyroidism	4.6%	IRR 1.31 (1.19–1.44)
				Overt hypothyroidism	2.5%	IRR 0.67 (0.5–0.9)
				Subclinical hypothyroidism		IRR 0.87 (0.7–0.97)
				TSH levels		IRR 1.16 (0.99–1.36)
				Reduced TSH		IRR 1.41 (1.35–1.89)
				Suppressed TSH		IRR 1.12 (1.03–1.21)
				High-normal euthyroidism		
Colett *et al.*[86] Thyroid studies collaborators	Meta-analysis	52 674	8.8 years	Subclinical hyperthyroidism	AF	HR 1.68 (1.16–2.43)
				Reduced TSH		HR 1.63 (1.1–2.4)
				Suppressed TSH		HR 2.54 (1.08–5.99)
Kim *et al.*[90] Framingham Heart study	Cohort	5055	10 years	TSH 0.45–4.5 μU/L–5.4	AF	Reference
				TSH 4.5–10.0 μU/L–7.0		HR 1.23 (0.77–1.97)
				TSH 10.0–19.9 μU/L–4.0		HR 0.57 (0.21–1.54)
Brandt *et al.*[91]	Observational cohort	2631 pts with hyperthyroidism 10 524 controls 67 years 81% female	6 years	HyperthyroidismControls	CVD + arrhythmia 26% 19%, $P < 0.001$	HR 1.34 (1.15–1.56)
Kobayashi *et al.*[117]	Summary of cases	10 pts w/o CVD and hypokalaemia	–	Hyperthyroidism 1 patient with amiodarone-induced thyroid dysfunction 1 early repolarization 2 cases coronary vasospasm	VF isolated	

AF, atrial fibrillation; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IRR, incidence rate ratio; pts, patients; TSH, thyroid stimulating hormone; VF, ventricular fibrillation.

to amiodarone-induced toxicity and one case was accompanied by early repolarization. All cases were treated with antithyroid therapy, prednisolone, beta-blockers and in some cases an implantable cardioverter-defibrillator (ICD) was used.[117] It should be noted also that antithyroid therapy might worsen early repolarization and arrhythmia.[117]

Bradyarrhythmias

Bradyarrhythmias, AV block and sick sinus syndrome (SSS), are rare entities in hyperthyroid patients;[118,119] one study reported that only 3% of AV block cases with pacemaker implantation were due to primary hyperthyroidism.[118]

Hypothyroidism

Hypothyroidism is accompanied by ventricular arrhythmias and conduction disturbances. One case-control study of 152 hypothyroid and 152 euthyroid patients, revealed higher prevalence of VT ($P = 0.04$) and ventricular arrhythmias ($P = 0.007$) in hypothyroid patients[120] and *Torsades de Pointes* with prolongation of QT interval and bradycardia may develop in hypothyroidism.[121–127] It is advised to consider hypothyroidism in differential diagnosis of polymorphic VT. The VT/VF, accompanying hypothyroidism requires correction with thyroid hormones, DC shock in urgent cases, correction of electrolyte balance, and bradycardia if QT prolongation and Torsades de Pointes arrhythmia. If arrhythmia is sustained or recurs, the implantation of ICD could be considered.[128]

Rarely, in patients with implanted pacemakers and ICDs, overt or subclinical hypothyroidism due to functional changes in tissue might increase pacing threshold or create exit block in atrial and ventricular pacing leads that usually are reversible by correction of thyroid status.[129–132]

Conduction abnormalities in the setting of hypothyroidism are represented by fascicular blocks (14.2%), 1st degree AV block (11.9%),[133] advanced AV block, and sinus node dysfunction.[118,134,135] There are also case reports on advanced AV block of 2nd and 3rd degree reversed by thyroid replacement therapy and temporary pacemaker implantation in overt and subclinical hypothyroidism.[136–140] Several reports describe underlying hypothyroidism playing a role in development of lithium-induced sinus node dysfunction, reversed after treatment of hypothyroidism.[134,135] Treatment of subclinical hypothyroidism should follow the recent update on thyroid disease management.[88]

Table 5 Evidence summary for treatment of arrhythmias associated with thyroid dysfunction

Study	Design	Subjects	Treatment	Follow-up	Arrhythmia after treatment	Comment
Effect of antithyroid treatment on arrhythmia						
Nakazawa *et al.*[98]	Prospective	163 pts hyperthyroidism and AF 46.7 years	Antithyroid therapy - 9% RIT+ antithyroid therapy -87% Thyroidectomy 3%	34 months	101 pts with spontaneous AF conversion to sinus rhythm upon attainment of euthyroidism 63 pts persistent AF	Intervals between return to euthyroidism and spontaneous AF conversion to sinus rhythm <1 week 43% 1–3 weeks 75.2% 4–6 weeks – 87.1% 7–9 weeks – 93.1% 10–12 weeks – 97% 13–15 weeks 100% >16 weeks -100%
Zhou *et al.*[99]	Prospective	94 pts hyperthyroidism 41.2 years PAF: 38 pts Pers. AF: 45 pts	Radioiodine therapy	1.6 years	PAF: 0% Pers. AF: 60%	Predictors of pers. AF Age >55 years RR 2.76, 1.16–8.79, $P < 0.01$ Duration of hyperthyroidism RR 3.08, 1.22–11.41, $P < 0.01$ Duration of pre-treatment AF RR 2.96, 1.31–7.68, $P < 0.01$
Tsymbaluk *et al.*[100]	Prospective	61 pts hyperthyroidism due to Graves disease	Antithyroid therapy	Euthyroid state	AF: 25% PAC: 7%	AF rate before and after antithyroid therapy 72% to 25%, $P < 0.001$ PAC: 71–7%, $P < 0.001$
Gauthier *et al.*[101]	Retrospective	40 pts with hyperthyroidism due to GD and 40 euthyroidism multinodular goiter	Thyroidectomy	Before and after operation	AF: 0 (sinus rhythm in 100%) Sinus tachycardia -68.8%	–
Treatment of persistent AF after antithyroid treatment						
Nakazawa *et al.*[105]	Prospective	33 pts with persistent AF	Cardioversion after Antithyroid treatment for hyperthyroidism	35 months	AF—12% SR—88%	AF free survival—86%
Nakazawa *et al.*[106]	Retrospective	106 pts with persistent AF w/o SHD 47.6 years	Cardioversion after Antithyroid treatment for 3 months for hyperthyroidism	6.7 years	AF—7.6% SR—92.4%	Predictor of AF recurrence Duration of AF HR 1.6 (1.14–2.26), $P = 0.005$ Late follow-up: SR—67%
Siu *et al.*[107]	Prospective case-controlled	116 pts 58 hyperthyroidism-related persistent AF 58 non-hyperthyoidism AF	ECV after Antithyroid treatment for 3 months for hyperthyroidism	24 months	–	AF recurrence Hyperthyroidism—59% Non-hyperthyroidism—83% Risk of AF recurrence hyperthyroidism vs non-hyperthyroidism HR 0.64 (0.39–0.97), $P = 0.004$ Predictor of AF recurrence Longer duration of AF HR 1.01 (1.0–1.01), $P < 0.01$

Continued

Table 5 *Continued*

Study	Design	Subjects	Treatment	Follow-up	Arrhythmia after treatment	Comment
Machino *et al.*[109]	Prospective	337 pts Persistent AF with history of hyperthyroidism 4.7% (16) w/o hyperthyroidism 95.3% (321)	First AF ablation (PVI) after 3 months of antithyroid therapy for hyperthyroidism	4 years	–	AF recurrence hyperthyroidism—44% no hyperthyroidism—43% Predictors of AF recurrence hyperthyroidism HR 0.87 (0.40–1.88), $P = 0.73$
Wongcharoen *et al.*[110]	Prospective	717 pts	First AF ablation (PVI and substrate modification 12%) >3 month treatment of hyperthyroidism before ablation	–	AF	Predictor of AF recurrence after single procedure: History of hyperthyroidism OR 2.07 (1.27–3.38) AF recurrence did not differ after multiple procedures
Stroke risk in hyperthyroidism-related AF						
Chan *et al.*[111]	Observational cohort AntiT and risk of ischemic stroke in hyperthyroidism-related AF	Of 9727 pts with non-valvular AF 642 (6.6%) pts with hyperthyroidism 136 pts—warfarin 243—aspirin 263—no AntiT 71.9 years 67.8% female	Hyperthyroidism vs non-hyperthyroidism	2 years	Non-valvular AF	Warfarin Reduced risk of stroke by 67% HR 0.33 (0.12–0.91) Annual risk of stroke by CHA_2DS_2Vas score hyperthyroidism-AF vs non-hyperthyroid-AF 0—0 vs. 2.56 1—2–3.17 vs. 7.02 ≥3—8.11 vs. 10.54 Ischaemic stroke 7.8% Warfarin reduced risk of stroke in non-self-limiting AF $CHA_2DS_2Vasc \geq 1$—$P = 0.04$ But not in self-limiting AF
Bruere *et al.*[114]	Prospective	8962 pts with AF	141 hyperthyroidism history 510 hypothyroidism history 8271 euthyroidism	929 days	AF	Stroke SE hyperthyroidism HR 0.85 (0.41–1.76) hypothyroidism HR 0.98 (0.73–1.34) Bleeding hypothyroidism HR 1.3 (1.02–1.79)
Friberg *et al.*[112]	Swedish Atrial Fibrillation Cohort Study	90 490 patients No anticoagulation at baseline	Thyroid disease 84 Thyrotoxicosis 553 pts	1.5 years	AF	Ischemic stroke Thyroid disease HR 0.95 0.70–1.19 Thyrotoxicosis HR 0.92 (0.85–1.05) Stroke/TIA/systemic emboli Thyroid disease HR 1.00 (0.92–1.09) Thyrotoxicosis HR 1.03 (0.83–1.28)
Petersen *et al.*[113]	Retrospective	610 patients	Hyperthyroidism	Stroke Within 1 year after 1 year	AF - 91 (14.9%)	Stroke, n 1st year after 1st year Sinus rhythm 8 7 AF 5 7

AF, atrial fibrillation; AIT, amiodarone-induced toxicity; AntiT, antithrombotic therapy; CA, catheter ablation; CI, confidence interval; CVD, cardiovascular disease; ECV, electrical cardioversion; HR, hazard ratio; IRR, incidence rate ratio; OR, odds ratio; pts, patients; RIT, radioiodine therapy; RR, relative risk; TIA, transient ischaemic attack; TSH, thyroid stimulating hormone; VT, ventricular tachycardia; VF, ventricular fibrillation.

Recommendations on management of tachy- and bradyarrhythmias associated with thyroid dysfunction	Consensus statement instruction	Level of evidence	References
Correction of thyroid dysfunction with restoration of euthyroid state is one of the primary goals in the treatment of tachy- and bradyarrhythmias associated with hyperthyroidism or hypothyroidism	'Should do this'		98–101
Correction of subclinical forms of thyroid dysfunction associated with tachy- and bradyarrhythmias may be required	'May do this'		88,91
Referral to endocrinologists should be considered for selection of appropriate thyroid function therapy (thyrosuppressive therapy, radioiodine therapy, and thyroidectomy)	'Should do this'		99–101
Hyperthyroidism-related AF that persists after euthyroid condition has been achieved (>3 months of thyrosuppressive therapy) should be managed using cardioversion or ablation for rhythm control. Antithrombotic therapy should be applied as for non-hyperthyroid-AF	'Should do this'		26,105–114
Rare cases of VT/VF in the setting of hyperthyroidism should be managed using antiarrhythmics (caution with amiodarone—see below), DC shock in cases of hemodynamic compromise and therapy with an ICD if indicated. Associated conditions—coronary vasospasm, early repolarisation, amiodarone toxicity should be taken in account	'Should do this'		95,117,128
Severe bradyarrhythmias accompanying hyperthyroidism and hypothyroidism might require use of temporary pacemaker; in persistent cases, after restoration of euthyroid condition, bradyarrthythmias should be managed according to the current guidelines	'Should do this'		118,136–141
VT/VF accompanying hypothyroidism associated with long QT interval should be managed with correction of bradycardia and electrolyte imbalance; avoid antiarrhythmic drugs that prolong the QT interval. In acute cases, DC shock may be necessary. If VT/VF persists, therapy with an ICD should be considered	'Should do this'		95,121–128
Monitoring and correction of thyroid dysfunction may be considered if lead dysfunction/change in atrial or ventricular pacing thresholds appear in patients with implanted pacemakers and ICDs	'May do this'		129–132

Amiodarone-induced thyroid dysfunction

About 10.3–14.7% of patients taking amiodarone for treatment of ventricular and atrial tachyarrhythmias, and 16.7% of patients receiving amiodarone for control of inappropriate ICD shocks develop amiodarone-induced thyroid dysfunction (*Table 6*).

Amiodarone-induced thyroid dysfunction manifests as amiodarone-induced hyperthyroidism with two distinctive types: type 1, which develops in presence of underlying thyroid disease with excessive hormone production in response to iodide load associated with amiodarone leading to true hyperthyroidism and type 2, destructive thyroiditis that develops due to direct toxic effects if iodine associated with amiodarone. Differential diagnosis of two types of hyperthyroidism usually is done using ultrasonography, thyroid I^{131} uptake and thyroid [99m Tc] 2-methoxy-isobutyl-isonitrile (MIBI) scintigraphy.[142,143] Management of amiodarone-induced thyroid dysfunction depends on above-mentioned types of dysfunction, with hormone replacement therapy for amiodarone-induced hypothyroidism, antithyroid medications for amiodarone-induced hyperthyroidism type 1 and steroids for amiodarone-induced hyperthyroidism type 2 (thyroiditis), and use of antithyroid medications and steroids in cases of coexistence of hyperthyroidism and thyroiditis.[142,144] Generally, accepted approaches in prevention and early detection of amiodarone-induced thyroid dysfunction are baseline assessment of thyroid function (thyroxine and TSH levels) before initiation of amiodarone treatment and periodic monitoring of thyroid function (within 3 months after initiation and every 3–6 months thereafter),[145–147] though latest studies demonstrated conflicting results, with no association of amiodarone-induced thyroid dysfunction occurrence and periodic testing of thyroid hormones, it should be mentioned also that 49.5% of patients had detectable abnormalities in thyroid function tests prior to development of amiodarone-induced dysfunction.[148] Thyroid stimulating hormone receptor autoantibody test and ultrasonography may be used for differential diagnosis of type I and type II thyroid dysfunction.[147]

Overt thyroid dysfunction occurs in 3.6–3.7% of patients receiving amiodarone for prevention of SCD and 10.3–14.7% of patients receiving amiodarone for treatment of ventricular arrhythmias and AF[149–153] and 16.7% of patients taking amiodarone for control of inappropriate ICD shocks.[154] Meta-analyses of RCTs on secondary prevention of SCD and adverse effects of amiodarone in patients treated for ventricular arrhythmias reported 4.2–5.7-fold increased risk of thyroid dysfunction and 1.78–2.18 times higher risk for development of bradyarrhythmias[149,150] when compared with placebo groups; about 1/3rd–1/

Table 6 Summary of evidence for amiodarone-induced thyroid dysfunction

Study	Design	Population	Follow-up	Thyroid dysfunction/ toxicity, arrhythmia	Predictors of toxicityOR/ RR/HR (95%CI)
Piccini *et al.*[149]	Met-analysis 15 RCTs of amio vs. placebo efficacy in prevention of SCD, safety	8522 pts 4260 amio arm 4262 placebo arm	12–45.5 months	Thyroid 3.6% vs. 0.4% Pulmonary 2.9% vs. 1.5% Hepatic 1.85% vs. 0.7% Bradyarrhythmias 2.8% vs.1.5%	OR 5.68 (2.94-10.98), $P < 0.0001$ OR 1.97 (1.27-3.04), $P = 0.002$ OR 2.1 (1.15-3.82), $P = 0.015$ OR 1.78 (1.16-2.72), $P = 0.008$ Amio discontinuation rate 31.6%
Vorperian *et al.*[150]	Meta-analysis 4 RCTs amio vs. placebo Adverse effects	738 pts amio arm 727 pts placebo arm low dose amio 100–400 mg maintenance dose	12–45 months	TD 3.7% vs. 0.4% Bradycardia 3.3% vs. 1.4% Discontinuation rate 22.9% vs. 15.4% Skin: 2.3% vs. 0.7% Eye: 1.5% vs. 0.1%	OR 4.23 (2.04–8.74), $P = 0.001$ OR 2.18 (1.11–4.27), $P = 0.024$ OR 1.60 (1.23–2.09), $P < 0.0001$ OR 2.48 (1.05–6.17), $P = 0.05$ OR 3.42 (1.22–3.64), $P = 0.02$
Bathcer *et al.*[151] Substudy of SAFE-T	RCT substudy	612 pts with persistent AF Amio vs Sotalol+ placebo	1–4.5 years	**Hypothyroidism** Subcl.: 25.8% vs 6.6%, $P < 0.0001$, Overt: 5.0% vs. 0.3%, $P < 0.001$ **Hyperthyroidism** Subcl.: 1 case amio, Overt: 5.3% vs. 2.4%, $P = 0.07$	–
Ross *et al.*[152]	Cohort study	163 patients Amio for: SVT: 102 pts, VT: 55 pts, Prevention: 3 pts, Uncertain: 1 pt	679 days	**Hypothyroidism** Subclinical: 7.4% Overt: 8% **Hyperthyroidism** Subcl.: 0.6% Transient hyperthyroidism: 0.6% Overt: 6.7%	–
Kinoshita *et al.*[155]	Retrospective cohort study For overt thyroid dysfunctions Indication for amio VA: 66.7–80% AA: 20–33.3%	317 pts Euthyroid: 256 Subcl. hypothyroid: 52 Subcl. hyperthyroid: 9 58.5 years, 73.5% males	5 years	**Overt hyperthyroidism 9.5%** **Overt hypothyroidism 18.9%**	Predictors of hyperthyroidism : DCM OR 3.3 (1.26-8.9) Sarcoidosis OR 6.47 (1.6–25.77) Predictors of hypothyroidism: Free T4—OR 0.13 (0.03–0.68) TSH—OR 1.47 (1.26–1.74)
Ahmed *et al.*[153]	Prospective	303 pts Amio for: AF-260 pts, VA: 43 pts 63 years, 66% males	3.3 years	**Hyperthyroidism 8%** **Hypothyroidism 6%**	Hyperthyroidism Age <62 years HR 2.4 (1.0–5.7), $P < 0.05$ Hypothyroidism: TSH >1.4 mU/L HR 5.1 (1.1–22.4), $P = 0.03$ LVEF <45% HR 3·8 (1·1-13·3), $P = 0.04$ DM-HR 3·3 (1·1–10·3), $P = 0.04$
Lee *et al.*[154]	Retrospective Amio vs sotalol and beta-	55 pts with ICD Amio: 24 pts Sotalol: 17 pts	4 years	**Hypothyroidism 16.7%** Time to development 16.3(23) months	

Continued

Table 6 *Continued*

Study	Design	Population	Follow-up	Thyroid dysfunction/ toxicity, arrhythmia	Predictors of toxicityOR/ RR/HR (95%CI)
	blockers for inappropriate shock reduction in ICD pts	Beta-blockers: 19		**Treatment** Dose reduction in amio hypothyroidism group and discontinuation in pulmonary toxicity group (16.7%) pts	
Shiga *et al.*[156]	Prospective Recurrence of VT/VF during amiodarone induced toxicity as compared to euthyroid state Holter monitoring and plasma amio	232 pts amio therapy	2 years	**Hypothyroidism 10.8**% No change in arrhythmia recurrence and plasma amio **Hyperthyroidism 12.5**% VT/VF recurrence: euthyroid 1 vs. hyperthyroid 9 pts, $P < 0.01$; VPC three-fold increase, $P < 0.05$, No change in plasma amio **Treatment** Hypothyroidism: 12-L-thyroxine, no discontinuation of amio hyperthyroidism: 6 methimizole, 2 prednisolone, 3 amio discontinuation, 18—gradual improvement	
Czarnywojtek *et al.*[161]	Cohort RIT for pts on amio and TD Amio indication: SVT, VT, ICD inappropriate shocks, AF	297 cases amio A 78: euthyroidism on amio B118: hyperthyroidism History amio C 79: hyperthyroidism amio D 22: hypothyroidism	12 months	Recurrence of hypothyroidism after RIT: A: 53.8%, B: 33.9% , C: 34.1% Recurrence of hyperthyroidism after RIT: A: 7.7%, B: 12.5% , C: 11.4% ABC: reinstated amio after 3–6 weeks of RIT D: permanent hypothyroidism–thyroxine replacement therapy	
Diederichsen *et al.*[164]	RCT double-blind placebo-controlled Amio vs place bo for 8 weeks after catheter ablation of AF Endpoint: TD	212 patients after catheter ablation of AF without history of thyroid dysfunction Amio group: 8 weeks amio Placebo group	6 months	Thyroid dysfunction Amio discontinuation Amio group—3 Placebo—1 Amio group significantly higher TSH, fT4 and T4 and lower fT3 and T3 at 1 and 3 months as compared to placebo TD after 1 month of amio treatment	

AA, atrial tachyarrhythmias; AF, atrial fibrillation; Amio, amiodarone; CI, confidence interval; CVD, cardiovascular disease; DM, diabetes mellitus; ECV, electrical cardioversion; HR, hazard ratio; ICD, implantable-cardioverter defibrillator; IRR, incidence rate ratio; LVEF, left ventricular ejection fraction; OR, odds ratio; pts, patients; RCT, randomized controlled trial; RIT, radioiodine therapy; RR, relative risk; subcl., subclinical; SVT, supraventricular tachycardia; TD, thyroid dysfunction; TSH, thyroid stimulating hormone; VA, ventricular arrhythmia; VPC, ventricular premature complexes; VT, ventricular tachycardia; VF, ventricular fibrillation.

4th of patients discontinued amiodarone treatment. Amiodarone-induced thyroid dysfunction includes overt and subclinical hypothyroidism and hyperthyroidism,[151,152] although changes in thyroid hormone levels in euthyroid patients on amiodarone treatment are common without clinical manifestations of amiodarone-induced thyroid dysfunction.[142] In the SAFE-T (Sotalol-Amiodarone Fibrillation Efficacy) trial, overt hypothyroidism developed in 5.0%, subclinical hypothyroidism in 25.8% and overt hyperthyroidism in 5.3% and it's subclinical form only in one patient in amiodarone arm that were significantly higher than in control arm receiving sotalol or placebo for treatment of persistent AF ($P < 0.05$ for all).[151] In another cohort study of patients receiving amiodarone for ventricular and atrial tachyarrhythmias, subclinical and overt hypothyroidism developed in 7.4% and 8% of patients, respectively; and subclinical and overt hyperthyroidism in 0.6% and 6.7%, respectively, after 943 days of treatment.[152] Though the evidence on predictors of amiodarone-induced thyroid dysfunction is limited, two studies[153,155] addressed the issue of identifying patients at risk of thyroid dysfunction: in one study, patients with low thyroxine and high TSH levels were at risk of hypothyroidism development, while patients with dilated cardiomyopathy and sarcoidosis had 3.3 and 6.47-fold increased risk of hyperthyroidism development,[155] it should be noted that patients with subclinical thyroid dysfunction at baseline were also included in the study. In another prospective study of patients with AF and ventricular arrhythmias receiving amiodarone, 8% of patients developed hyperthyroidism and 6% of patients—hypothyroidism during 3.3 years of follow-up, and the only predictor for development of hyperthyroidism was age <62 years, while hypothyroidism risk was associated with TSH levels >1.4 mU/L, low ejection fraction and DM.[153]

In summary, amiodarone-induced overt thyroid dysfunction occurs in approximately 10.3–14.7% of patients with arrhythmias receiving amiodarone and should be suspected if symptoms of toxicity develop, including tachy- and bradyarrhythmias, other organs lesions and change in thyroid tests (*Table 3*).

Of note, amiodarone-induced thyroid dysfunction depends neither on dose,[150] nor on plasma concentration of amiodarone,[156] but tachy- and bradyarrhythmias may occur. Holter monitoring study in patients with VT/VF receiving amiodarone treatment demonstrated statistically significant increase in recurrence of VT and ventricular premature complexes in hyperthyroid state when compared with baseline euthyroid state,[156] and in rare cases of thyroid storm VT/VF may develop.[128] Withdrawal of amiodarone and switching to other antiarrhythmic drugs can be effective in treatment of VT/VF episodes due to amiodarone-induced thyroid dysfunction.[157]

Bradyarrhythmias usually occur in hypothyroidism, AV block tends to develop in presence of pre-existing conduction abnormality.[77]

Recommendations on management of amiodarone-induced thyroid dysfunction	Consensus statement instruction	Level of evidence	References
Before prescribing amiodarone therapy for long-term use it is recommended to weigh risk/benefit of its toxicity and strongly consider catheter ablation to cure or modify the substrate for arrhythmias instead	'Should do this'		145,149–151
It is recommended to carry out baseline thyroid tests (thyroxine and TSH) before initiation of amiodarone treatment); thyroid-directed autoantibodies and ultrasonography should be considered for differential diagnosis of type I and type II amiodarone-induced hyperthyroidism.	'Should do this'		116,117,119,120,142, 143,145–147,163
It is advised to monitor thyroid function tests and ECG for amiodarone-induced thyroid dysfunction screening	'Should do this'		145,147,148
If hyperthyroidism occurs during treatment with amiodarone, its discontinuation MANDATORY. The eventual decision to initiate or continue amiodarone once the euthyroid state is achieved for preventing life-threatening ventricular tachyarrhythmias should be carefully evaluated in each individual case in terms of expected risk and benefits.	'Do not do this'		142,143,145,154,161,165
Hypothyroidism should be treated with thyroid replacement agents, and amiodarone therapy may be continued if necessary.	'Should do this'		145,156,165
In case of VT/VF withdraw amiodarone and treat using antiarrhythmics and DC shock, if hemodynamic compromise.	'Should do this'		128,156
The use of amiodarone in elderly patients increases the risk of bradyarrhythmias, such as advanced AV block or SSS, requiring a permanent pacemaker.	'Should do this'		141,160

Amiodarone-induced thyroid dysfunction may manifest as SSS, constituting 22% of all causes of SSS.[158–160] In some circumstances, correction of thyroid dysfunction in patients with AF and bradycardia developed on amiodarone treatment unmasks underlying tachycardia-bradycardia syndrome.[159]

Withdrawal of amiodarone therapy should be strongly considered in cases of hyperthyroidism; proper management of VT/VF, AV block and SSS is required. In a study of amiodarone-induced thyroid dysfunction in patients receiving amiodarone for prevention of inappropriate shocks, dose reduction of amiodarone was adequate to reduce signs of amiodarone-induced thyroid dysfunction.[154] Latest studies on use of antithyroid therapy in patients requiring long-term amiodarone treatment (ventricular/atrial arrhythmias or inappropriate shock reduction in ICD patients) demonstrated that application of antithyroid radioiodine therapy might be an option to reinstitute amiodarone treatment[161]; radioiodine ablation of thyroid is also an option in amiodarone-induced thyroid dysfunction with resistant tachyarrhythmias.[162]

It is recommended also to weigh the risk of amiodarone-induced thyroid dysfunction before considering the long-term treatment or prefer treatment like catheter ablation. Monitoring of thyroid function every 6 months and electrocardiogram follow-up in patients on amiodarone therapy should be considered.[145,148,163]

Pheochromocytoma

The prevalence of pheochromocytoma (PCC) discovered during life is 0.15–0.4%; however, many cases remain undiscovered as the prevalence noted in autopsy studies is higher.[166] The clinical picture ranges from totally asymptomatic patients to life-threatening complications including MI, severe heart failure, Tako-tsubo cardiomyopathy, and arrhythmias. Typically, additional release of catecholamines by PCC is accompanied by paroxysmal headache, sweating, hypertension, and palpitations. Therefore, recurrent arrhythmias in such clinical context should raise the suspicion of PCC. Palpitations are present in one-half to 70% of patients.[167]

Arrhythmia mechanisms include beta-adrenergic stimulation of the heart, alpha1-adrenergic stimulation (especially during myocardial ischemia and reperfusion),[168] desensitization of adrenergic cardiovascular receptors due to prolonged adrenergic stimulation and reflex increase in vagal tone. Most often sinus tachycardia is encountered. However, a large spectrum of arrhythmias could be part or the first clinical manifestation of PCC, before typical signs are present. It includes mostly supraventricular arrhythmias and AF but also malignant and bidirectional VT.[169] Some PCC patients manifest with reflex bradycardia, asystole, AV dissociation, Wolf-Parkinson-White syndrome or SSS.[170] Patients with PCC may present with repolarization abnormalities consisting of marked QT prolongation and deep, wide inverted T wave[171] with subsequent risk for Torsades des Pointes.

Esmolol, a beta1-adrenergic cardioselective blocker with rapid onset of action can be used to control fast rate due to AF or atrial flutter (0.5 mg/kg iv followed by continuous infusion of 0.1–0.3 mg/kg/min).[170] Associated alpha-blockade (i.e. phenoxybenzamine 10 mg once to 10–30 mg twice or α1 blockade with prazosin—starting with 1 mg and increasing to 1 or 2 mg two or three times daily) may be used to prevent the incidence of hypertensive crisis during beta blockade. There is no specific treatment for other arrhythmias and VT could respond to lidocaine.[172]

Recommendations on management of PCC	Consensus statement instruction	Level of evidence	References
Pheochromocytoma should be considered as possible diagnosis in patients with paroxysmal headache, hypertension, palpitations, and recurrent arrhythmia	'Should do this'		167
Esmolol should be used to control rapid rate in AF and flutter. Associated alpha blockade is mandatory to prevent hypertensive crisis	'Should do this'		170
Lidocaine may be used to treat sustained VT	'May do this'		169,172,173
As PCC can prolong QTc interval, antiarrhythmic drugs prolonging the QTc should be used with caution and only after QTc monitoring	'Should do this'		171

Growth hormone dysfunction

Acromegaly

Acromegaly is a rare and debilitating disease with a prevalence of 40 per million, characterized by increased growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Early clinical trials have demonstrated a two-fold increase in overall mortality in patients with acromegaly when compared with general population, with cardiovascular causes accounting for 40–60% of all deaths.[174–176] Acromegalic cardiomyopathy is characterized by biventricular hypertrophy progressing to diastolic and systolic dysfunction culminating in heart failure in 10% of patients.[177–179] Recent cohorts, with patients treated early in the disease course, suggest lower rates of cardiovascular involvement.[180,181] Classically, mononuclear cell infiltration,[182] apoptosis,[183] myofibrillary abnormalities,[184] interstitial fibrosis, oedema, and cardiomyocyte hypertrophy are characteristic of acromegalic cardiomyopathy and may represent the histological substrate for arrhythmias.[184,185]

Cardiac arrhythmias in acromegaly

There is paucity of data on the prevalence and severity of cardiac arrhythmias in acromegaly.[186–188] Supraventricular arrhythmias are uncommon in patients with acromegaly with one study reporting supraventricular arrhythmias in 6/27 patients while two other show absence of any increase.[188–190] Asymptomatic sinus node disease has also been described in a small proportion of patients in another study.[191] However, complex ventricular ectopy is common, occurring in 40–48% of acromegalic patients[188,189,192] and increasing with exercise.[188] The ventricular ectopy increased with duration of acromegaly and severity of ectopy correlated with left ventricular mass but not GH levels.[188] Sustained VT and sudden death has been reported in patients with acromegaly with severe cardiomyopathy.[193–195] Late potentials are common in acromegalic cardiomyopathy and correlate with frequency of ventricular ectopy.[181,192] Similarly, greater QT dispersion (dQT) and prolonged QTc interval are seen in active acromegaly and may predispose to ventricular tachyarrhythmia.[196,197]

Impact of acromegaly specific treatment on cardiac arrhythmias

There is lack of longitudinal studies evaluating the impact of treatment of acromegaly on associated cardiac arrhythmia. However, there is indirect evidence to suggest that control of acromegaly in early stages may decrease cardiac remodelling,[180] development of late potentials,[181] ventricular arrhythmia,[198–200] and cardiac mortality.[201]

Growth hormone deficiency

Growth hormone deficiency is diagnosed in 0.1% of the population in general clinical practice and is characterized by the short stature, frontal bossing, central obesity, and high-pitched voice.[202] Growth hormone deficiency usually manifests early in childhood, while in adults it may be accompanied by increased sensitivity to insulin in patients with diabetes and manifests with fine wrinkling around eyes and mouth. Deficiency of GH, adrenocorticotropic hormone and gonadotropin, and hypothyroidism are common in hypopituitarism.[203] Though rarely, tachy- and bradyarrhythmias may accompany GH deficiency.[204,205] In one prospective study of pituitary hormone levels in patients who underwent

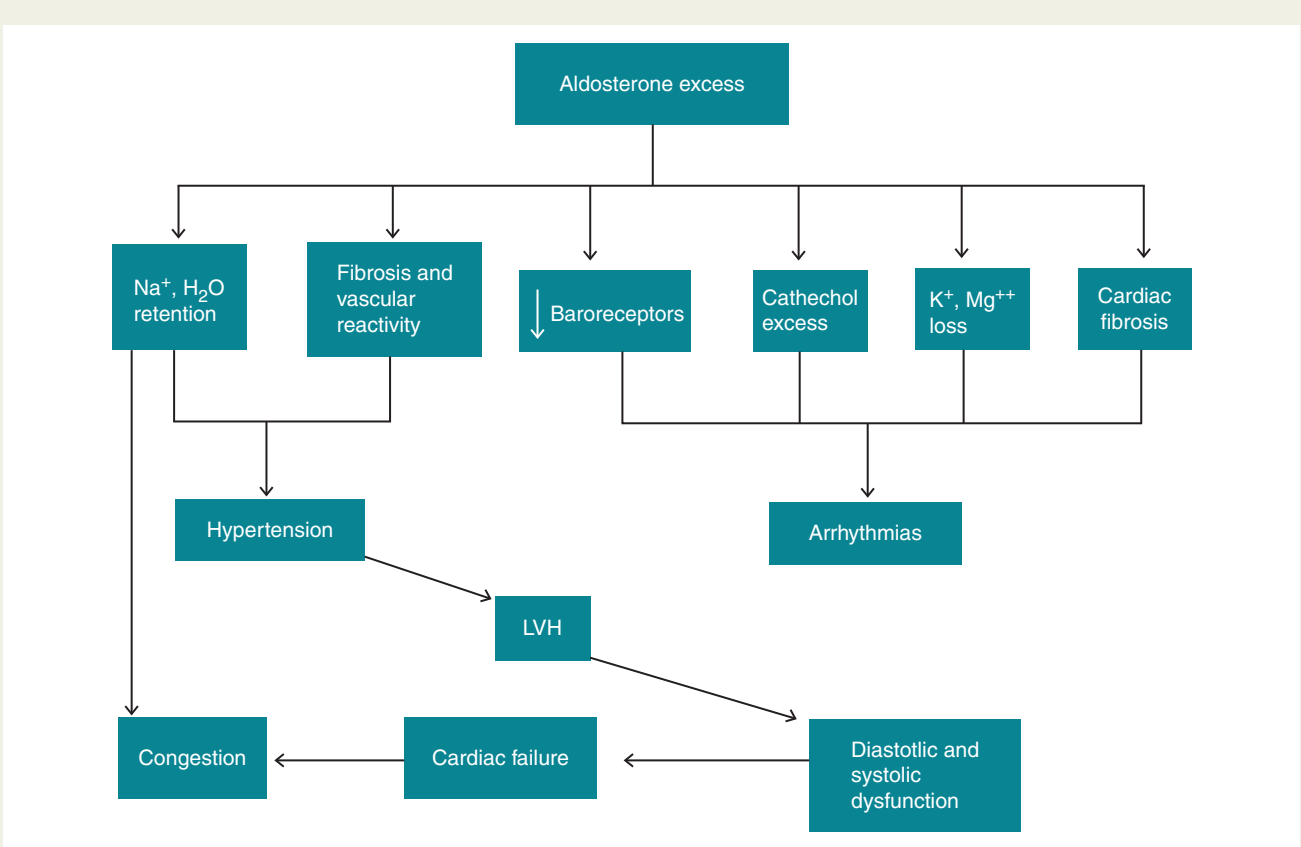

Figure 4 Effect of aldosterone on the cardiovascular system.[215] Cathechol., cathecholamine; LVH, left ventricular hypertrophy.

cardiopulmonary resuscitation due to VT/VF, GH deficiency was present in 27.5% of them,[204] with (GH)-IGF-1 being significantly lower in a group of patients with GH deficiency when compared with group of patients with normal GH values. There are also reports on increased cardiovascular morbidity in children with GH deficiency treated with GH, due to cardiomegaly.[205] A complete AV block was described in a child with GH deficiency during therapy with hGH, treated successfully by pacemaker implantation.[205]

Thus, cardiac evaluation and monitoring is reasonable in patients with GH deficiency and during its therapy.

Diseases of adrenal cortex

Hyperaldosteronism

Primary hyperaldosteronism (PH) also known as Conn's disease, is an endocrine disorder caused by an adrenal adenoma (uni- or bilateral). It causes hypertension, hypokalaemia, metabolic alkalosis, and renin suppression.[206–208] Long-standing PH has been associated with myocardial injury, leading to heart failure and either atrial or ventricular arrhythmias.[209–214] *Figure 4* summarizes the effect of aldosterone on the cardiovascular system.[215]

Management of PH associated arrhythmias focuses on controlling metabolic and electrolyte disturbances.[216] Deleterious cardiovascular effects can be controlled by either performing aldosterone receptor blockade or adrenalectomy.[217] *Tables 7* and *8* summarize PH related arrhythmias.

Specific data on indications for device implantation in PH patients is very limited and general guideline recommendations apply for this population. The main treatment approach for this condition is either surgical resection of the adrenal adenoma or pharmacological therapy targeting adrenal hyperplasia.[207–210]

Table 7 Electrocardiographic disorders associated with PH

Prolonged QT-interval[218]
Atrial fibrillation[219,220]
Atrial flutter[221]
Ventricular tachycardia[222]
Polymorphic ventricular tachycardia[223,224]
Ventricular fibrillation[225–227]

PH, primary hyperaldosteronism

Adrenal insufficiency

Primary adrenal insufficiency (PAI), also known as Addison's disease, it is characterized by corticosteroid and mineralocorticoid deficiency.[230,231] Patients with PAI typically present with hyponatraemia, hyperkalaemia, hypoglycaemia, and hyperpigmentation. Cardiac manifestations include hypotension, syncope, arrhythmias, and cardiomyopathy. Acute exacerbations are called Addisonian crises.[232] *Table 9* summarizes the most common cardiac abnormalities and ECG findings, which are usually reversible with definitive treatment of the underlying cause.[231,233]

Table 8 Description of the most important studies on PH

Study	Type of study	Number of patients (*n*)	AF (%)	VT (%)	Sustained arrhythmias (%)
Milliez *et al.*[212]	Case control	124	7.3	NA	NA
Catena *et al.*[228]	Prospective cohort	54	NA	NA	15
Born *et al.*[222]	Retrospective cohort	640	7.1	NA	NA
Mulatero *et al.*[221]	Case control	270	NA	NA	7.8
Savard *et al.*[229]	Case control	459	3.9	NA	NA

AF, atrial fibrillation; NA, data not available; PH: primary hyperaldosteronism; VT, ventricular tachycardia.

Recommendations	Consensus statement instruction	Level of evidence	References
Primary hyperaldosteronism patients with atrial or ventricular arrhythmias should receive treatment for stabilization of their electrolyte and metabolic disturbances	'Should do this'		216,217
In PH patients with persistent rhythm abnormalities or myocardial damage, pacemakers or high voltage devices may be used according to life expectancy and response to optimal medical therapy	'May do this'		218,225,226

Table 9 Cardiac abnormalities associated with PAI

Idiopathic dilated cardiomyopathy[234]
Tako-tsubo cardiomyopathy[235]
ECG:
Low voltage[236]
Sinus bradycardia[237]
Prolonged PR-interval[237]
Prolonged QT-interval[238]
T-wave inversion[239]
Brugada like-pattern[240]
Polymorphic ventricular tachycardia[241]
Ventricular fibrillation[237]

ECG, electrocardiogram; PAI, primary adrenal insufficiency.

Recommendations	Consensus statement instruction	Level of evidence	References
Patients with PAI and ECG changes should be treated for electrolyte and metabolic disturbances	'Should do this'		230
Patients with PAI in the setting of dilated cardiomyopathy and/or heart failure who receive optimal medical therapy should be started on hydrocortisone and fludrocortisone. Fludrocortisone should be used with caution because; excessive fluid retention may lead to, or worsen heart failure symptoms	'Should do this'		231,232
Patients with PAI and persistent rhythm abnormalities or myocardial damage may be candidates for pacemakers or high voltage device therapy based on life expectancy and response to optimal medical therapy	'May do this'		233

Parathyroid disease

Hypoparathyroidism and hyperparathyroidism are rare hormone disorders characterized by abnormally low or high levels of the parathyroid hormone (PTH). Physiologically, PTH plays a critical role in the regulation of calcium homeostasis through several mechanisms. The consequence of PTH deficiency is hypocalcaemia, which can cause QT interval prolongation and arrhythmias. In clinical practice, however, torsades de pointes or other life-threatening tachyarrhythmias are infrequent in patients with hypoparathyroidism, despite extreme QT prolongation.[242] In the literature, there is only one case report of a patients with hypoparathyroidism who suffered VF probably due to heart failure and severe hypocalcaemia.[243] Severe hypocalcaemia requires treatment as soon as possible with intravenous calcium. Long-term treatment of hypoparathyroidism includes calcium and Vitamin D supplementation for the stable control of plasma calcium levels.[243]

The main biochemical feature of primary hyperparathyroidism is hypercalcaemia. Hypercalcaemia may induce arrhythmias through both early and delayed ventricular after depolarization. Previous studies have shown that primary hyperparathyroidism and hypercalcaemia are directly related to electrocardiographic abnormalities, such as high-amplitude QRS complex, short ST segment and QT interval, and T wave extension.[244] A variety of arrhythmias, such as sinus arrest, supraVT and AF has been documented in patients with primary hyperparathyroidism.[245] Furthermore, ventricular arrhythmias in association with hyperparathyroidism have been reported, including ventricular bigeminy, VT, and VF.[246–248] Although patients with hyperparathyroidism have an increased risk of death, it is not known if arrhythmias play any role in increased cardiovascular mortality. The most effective method for the treatment of primary hyperparathyroidism is parathyroidectomy. However, the role of surgery regarding the effect on cardiac arrhythmia risk is controversial. Some studies did not report a reduced incidence of mortality in hyperparathyroidism after parathyroidectomy, while the other showed that parathyroidectomy reduced the occurrence of ventricular arrhythmias and restored the QTc adaptation during exercise test.[249–251] A series of case reports indicate that in rare cases ventricular storm induced by hyperparathyroidism may be controlled only after parathyroid surgery.[247,248,252,253]

Sex hormones-related differences in the risk of arrhythmias

It is well recognized that men and women differ with respect to the risk of developing arrhythmias.[3,254–256] The mechanisms involved in these differences have not been fully elucidated, but may be related to the electrophysiological effects of sex hormones. In experimental studies,[257,258] 17β-oestradiol has protective effects on ischemia-induced arrhythmias and reduces L-type $Ca2^{+}$ current (ICaL). Nevertheless, estrogens may partially suppress the delayed rectifier K^{+} current (IKr), thus enhancing drug-induced APD and QTc prolongation. Progesterone increases slow activating delayed rectifier K^{+} current (IKs) and modulates ICaL, therefore promoting APD shortening. Testosterone also regulates both IKs and ICaL in a dose-dependent manner and results in shortening of APD.[257,258]

Women have higher resting heart rate, shorter PR and QRS intervals, and longer QTc intervals, whereas men more frequently exhibit early repolarization.[3,254–256] Notably, repolarization differences between men and women do not occur in prepubertal children.[259] Repolarization is also affected by the ovarian cycle: since repolarizing currents are increased by progesterone and decreased by oestrogen,

QTc is longer in the follicular phase when compared with the luteal phase.[255,258] The longer repolarization renders women more susceptible to drug-induced Torsades de Pointes.[260] Therefore, QT prolonging drugs should be used carefully in females, particularly in those with other abnormalities, such as electrolyte imbalance. Accordingly, progesterone may attenuate drug-induced QTc lengthening.[261] Also, women have greater arrhythmic risk than men in congenital LQTS, especially after puberty.[262] Further emphasizing the role of hormonal modulation in arrhythmia development, in congenital LQTS, the risk of life-threatening events is reduced during pregnancy but increased in the postpartum period.[263] On the other hand, Brugada syndrome and AF predominate in men.[254–256] It is well known that women have a higher incidence of AV nodal re-entry tachycardia and inappropriate sinus tachycardia.[264] Exacerbation of supraventricular tachycardias may occur during pregnancy, likely due to hormonal and autonomic tone changes.[265]

Recommendations	Consensus statement instruction	Level of evidence	References
QT prolonging drugs (www.crediblemeds.org) should always be used carefully in both women and men. However, due to an increased risk of drug-induced Torsades de Pointes, this recommendation should be further emphasized for women, particularly in the presence of electrolyte imbalance	'Should do this'		[260,261]

Stroke risk assessment and prevention in arrhythmias associated with endocrine disorders

As described in previous sections, the presence of various endocrine disorders can be associated with AF, which is the arrhythmia most commonly associated with increased risk of stroke and thromboembolism.

Older small studies[113] have suggested an association between thyroid disease and an increased risk of stroke in AF. In the largest analysis from the Swedish AF cohort study,[112] a nationwide cohort of 182 678 subjects with AF, thyroid disease (HR 0.95, 95% CI 0.85–1.05) or thyrotoxicosis (HR 0.92, 95% CI 0.70–1.19) were not independent predictors of ischaemic stroke in multivariate analysis. Similarly, either thyroid disease or thyrotoxicosis were not independent predictors of major bleeding or intracranial haemorrhage. Similar observations were noted in the Loire Valley AF project, where history of hyperthyroidism was not an independent risk factor for stroke/systemic embolism, whereas hypothyroidism was associated with a higher risk of bleeding events.[114] Thus, AF patients with thyroid disease are associated with stroke or thromboembolism only in association with other established stroke risk factors, the most common of them are included within the CHA_2DS_2-VASc score.[266] Similar for stroke or thromboembolism, risk assessment should be used to identify patients at risk for bleeding, and to address the potentially reversible bleeding risk factors, as advocated by validated practical bleeding risk scores such as the HAS-BLED score.[267]

Diabetes mellitus is well established as a clinical stroke risk factor in AF and is incorporated into the CHA_2DS_2-VASc score.[266,268] Duration of diabetes may accentuate stroke risk, but not bleeding risk.[269] Indeed, duration of diabetes may be a more important predictor of ischaemic stroke than glycaemic control in such patients.[270]

Whilst diabetic complications such as diabetic retinopathy are associated with higher risks, such evidence of 'diabetic target organ damage' does not independently add to stroke or bleeding risk prediction.[271]

With regard to prevention of stroke, the most important measure is oral anticoagulation (OAC) whether given as a Vitamin K antagonist (VKA, e.g. warfarin) with good quality anticoagulation control (with "time in therapeutic range" or TTR >70%) or a non-VKA oral anticoagulant (NOAC, e.g. dabigatran, rivaroxaban, apixaban, or edoxaban). The NOACs are the preferred option in most patients starting anicoagulation, but given the heterogeneity of AF patients and the availability of different OAC options, we should fit the drug to the patient profile. In general, NOACs appear relatively more effective and safer than VKA in reducing stroke/systemic embolism and major bleeding irrespective of patient comorbidities.[272]

In summary, AF stroke risk stratification even with concomitant endocrine disorders should use the established CHA_2DS_2-VASc score[266] to initially identify 'low risk' patients (CHA_2DS_2-VASc 0 in males or 1 in females) who do not need any antithrombotic therapy, followed by prevention of stroke (i.e. OAC) in patients with >1 risk factor.

As OAC is being initiated, a clinical bleeding risk score such as HAS-BLED score (see above) should be used to identify patients at risk for bleeding, and importantly, to address the potentially reversible bleeding risk factors (that should be considered in all patients, irrespective of HAS-BLED score value). The next step is to consider choice of OAC, and the SAMe-TT_2R_2 score[273] can be used to aid decision making between a VKA with likelihood of a good TTR (score 0–2) or those less likely to achieve it, thus requiring more regular INR checks, or as a better option, use of a NOAC.[274] This simple three-step pathway has been advocated to help streamline decision making for stroke prevention in AF.[274]

Recommendations	Consensus statement instruction	Level of evidence	References
Irrespective of underlying endocrine abnormalities (which should be concurrently managed), the CHA_2DS_2-VASc score should be used to initially identify 'low risk' patients (CHA_2DS_2-VASc 0 in males or 1 in females) who do not need any antithrombotic therapy, followed by prevention of stroke (ie, OAC) in patients with >1 risk factor	'Should do this'		266,274
As OAC is being initiated, a clinical bleeding risk score such as HAS-BLED score should be used to identify patients at risk for bleeding (HAS-BLED ≥3) Importantly, potentially reversible bleeding risk factors should be considered in all patients, irrespective of HAS-BLED score value	'Should do this'		266,267,274
The SAMe-TT_2R_2 score may be used to aid decision making between a VKA with likelihood of a good TTR (score 0–2) or those less likely to do so, thus requiring more regular INR checks, or as a better option, use of a NOAC	'May do this'		273,274

Catheter ablation of arrhythmias associated with endocrine disorders

Catheter ablation for atrial or ventricular arrhythmia is optimally performed in as much as possible stable electrolytic and metabolic conditions, in order to avoid transient arrhythmias. Arrhythmias associated with endocrine disorders would theoretically need no ablation since they are supposed to spontaneously disappear once return to steady state is obtained. They may also alter the analysis of targets to be ablated and interpretation of results for complex procedures. However, ablation sometimes needs to be performed in patients with acute or subacute endocrine disorders. This may apply to patients with severe ventricular tachyarrhythmia and electrical storm, or atrial tachyarrhythmia with haemodynamic compromise not efficiently treated with other methods.

Diabetes

A meta-analysis of 15 studies and 1464 patients indicated that catheter ablation of AF in patients with diabetes had similar safety and efficacy than that in the general population, especially when performed in younger patients with satisfactory glycaemic control.[29] Catheter ablation of AF reduces the amount of patients requiring antiarrhythmic drugs, an additional benefit in a population commonly exposed to adverse effects of AF pharmacological treatments.

Thyroid disorders

FT4 levels may influence the success rate of AF ablation procedures, even within the normal range.[275,276] It has been found that right atrial non-PVs triggers were more prevalent in AF patients treated with thyroid hormone replacement. After elimination of non-PV triggers, there was still a worse arrhythmia-free survival in these patients.[277] Patients with hyperthyroid history have a higher number of PV ectopic beats and higher prevalence of non-PV ectopic foci compared with euthyroid patients, which may result in a higher AF recurrence rate after ablation procedure.[110] Catheter ablation for paroxysmal AF in patients with amiodarone-induced hyperthyroidism is usually safe and effective albeit with higher rate of early AF recurrences up to 3 months after PV isolation relative to controls, but not beyond 12 months.[278] Pulmonary vein isolation alone may have a lower efficacy for preventing recurrence in paroxysmal AF in these patients with amiodarone-induced hyperthyroidism, which may need repeat ablations.[279]

Device-based therapy of arrhythmias in patients with endocrine disorders

Diabetes and long-term treatment with chronic corticosteroids (frequently prescribed in endocrine disorders) are important factors associated with an increased risk of infections of cardiac electrical implanted devices (CIEDs), as shown in *Table 8*.[280–284] Pacemaker- and ICD-related infections represent one of the most difficult complications that may occur in a patient implanted with a CIED. There is increasing concern on the important clinical and economic consequences of the rise in the incidence of CIEDs-related infections that have occurred in the last 10 years.[280–284] The incidence of pacemaker- and ICD-related infections has been reported to range between 0.1% and 19.9%, for pacemakers, and between 0.8% and 9.5% for ICDs, including biventricular devices, in observational studies with different follow-up durations.[280–284] Cardiac electrical implanted devices infections usually appear as infections limited to the device pocket, often with fistulas and skin erosion, but lead endocarditis may be detected in around one out of 10 cases, with an incidence of 0.06–0.6%.[280–284] The outcome of CIED infections is characterized by serious events including a high risk of death, so preventive measures are mandatory, on the basis of appropriate identification of risk factors (*Table 10*).

In patients with an ICD or a device for cardiac resynchronization therapy (CRT) implanted, diabetes influences outcome, similarly to other comorbidities included in the Charlson comorbidity score.[285] The comorbidities that are represented in the Charlson comorbidity

Table 10 Risk of CIED infection according to a series of risk factors, as reported in literature[280–284]

	Odds ratio for the risk of CIED infection
Patient factors	
Male gender	1.5
Younger age	1.4–4.5
Diabetes	2.3–3.5
Chronic kidney disease	4.6–6.3
Haemodialysis	8.6
Treatment with anticoagulants	2.6–3.4
Chronic corticosteroid use	9.1
History of malignancy	4.0
Underlying heart disease	3.1
High Charlson co-morbidity index	2.7–3.0
Fever, systemic infection	5.8
Device or procedure-related factors	
Prior CIED infection	11.3
≥3 implanted leads	4.0–5.4
Device replacement, device upgrades or implant revision	1.7–3.1
Early reinterventions	2.7–15
Temporary pacing prior to implantation	2.5
Post-operative haematoma at pocket site	4.0–6.7
Physician experience	2.5

CIED, cardiac electrical implanted device.

score are independent predictors of death, all-cause, and cardiovascular hospitalizations, as well as of days spent alive and out of hospital.[286] In a report from the United States on more than 18 000 patients with a cardiac resynchronization therapy-defibrillator (CRT-D) device implanted, patients with diabetes had a higher mortality than those without diabetes, both at 1 and 3 years,[287] in agreement with a meta-analysis based on five studies on cardiac resynchronization in heart failure.[288,289] However, these findings have to be analysed in combination with the evidence derived from randomized studies that CRT is equally effective in reducing mortality vs. control in diabetic as compared to non-diabetic patients.[288,290]

The effectiveness of ICDs for primary prevention of SCD in patients with diabetes has raised great interest since diabetes, as well as other comorbidities, may be also associated with a high risk of non-arrhythmic cardiac and non-cardiac death. This complex topic has been studied through subanalysis of randomized trials, systematic reviews, and meta-analysis.[291] The subanalysis of diabetic patients in randomized clinical trials provides reassurance, since the beneficial effect of ICD on survival is confirmed both in patients with and without diabetes.[291–293] The frequent association between diabetes and chronic kidney disease (CKD) is of great relevance, since CKD *per se* may condition the outcome and the benefits after implant of a ICD or a CRT device.[294]

In patients implanted with a defibrillator the occurrence of AF due to hyperthyroidism may induce inappropriate shocks and requires proper management.[258] Hyperthyroidism, either due to primary thyroid disease or secondary to amiodarone treatment, should be excluded in any case of new-onset of atrial tachyarrhythmias.[295,296]

Hypothyroidism has been associated with poor outcomes in patients with heart failure and therefore it is of interest to assess the outcome of patients with previous diagnosis of hypothyroidism after CRT device implantation. In a case series of heart failure patients implanted with CRT a history of hypothyroidism was present in 16.4% and was an independent predictor of poor outcome (cardiac death heart failure hospitalization or need for heart transplant).[297,298]

Current research gaps, ongoing trials and future directions

Most of the information present in the literature is based on registries and the communication of some exceptional cases. Mostly, there are no data on the specific effect of hormones on heart rate disturbances, and their effects are estimated based on structural remodelling and associated comorbidities (i.e. changes in blood pressure, obesity, sleep disorders, or increased catecholamine levels). Importantly, there is scarce evidence of the real incidence of arrhythmias in endocrine diseases. Indeed, the lack of clinical trials with specific attention to the effect on arrhythmias is general. Specific randomized trials are needed beyond drug safety, where only the effect on heart rhythm disturbances is very marginal.

Different trials are searching for the biological effect of antidiabetic drugs on heart rhythm. For example, it has led to study the effects of intravenous exenatide on cardiac repolarisation,[299] exploring changes to QTc interval changes. In the same line, Addhope 2 trial[300] studies the heart rate variability modifications with liraglutide in patients with ischaemic heart disease and newly diagnosed DM type 2.

An interesting field is the diagnosis of AF in patients treated for hyperthyroidism. In this setting, there is a thumb-ECG ambulant screening for AF in this type of patients,[301] though in clinical setting other monitoring methods can be used. Whereas TABLAS study explores the influence of subclinical hyperthyroidism on the results of AF ablation.[302]

Regarding PCC, the PRESCRIPT trial compares phenoxybenzamine vs. doxazosin, and assesses the differences in high blood pressure and tachycardia episodes.[303] There is also an ongoing study in acromegaly patients; it is exploring the effects of repeated subcutaneous injection with BIM23B065—a somatostatin 2 receptor agonist-in acromegalic patients[304] on blood pressure, heart rate, and QT interval.

Cardiac arrhythmias in endocrine disorders are frequent and modify the natural history of the disease. These facts invite cardiologists to participate in future research and trials to explore pathophysiologic pathways, diagnosis and therapeutic approach in endocrine disorders.

Supplementary material

Supplementary material is available at *Europace* online.

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