



# 2013 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy: Addenda

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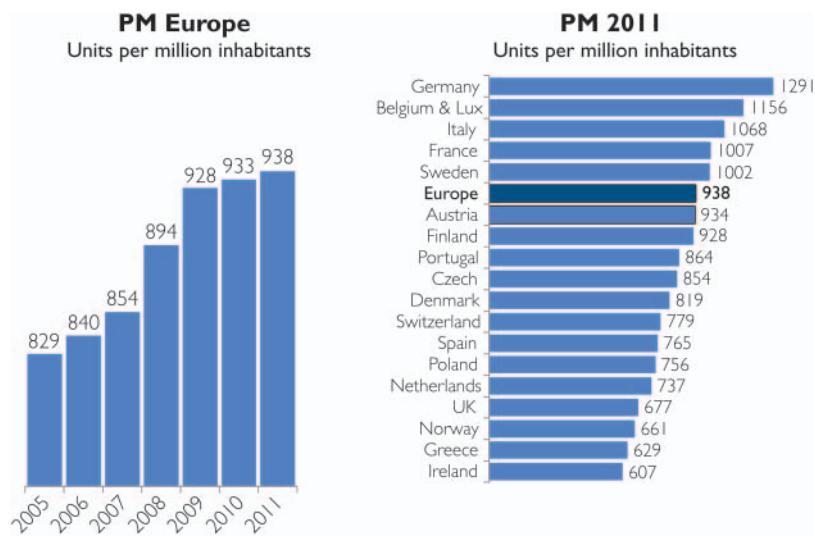
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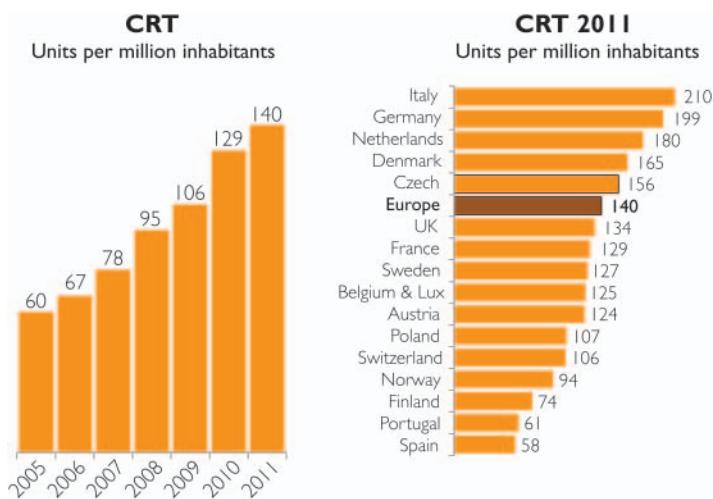
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**Keywords**

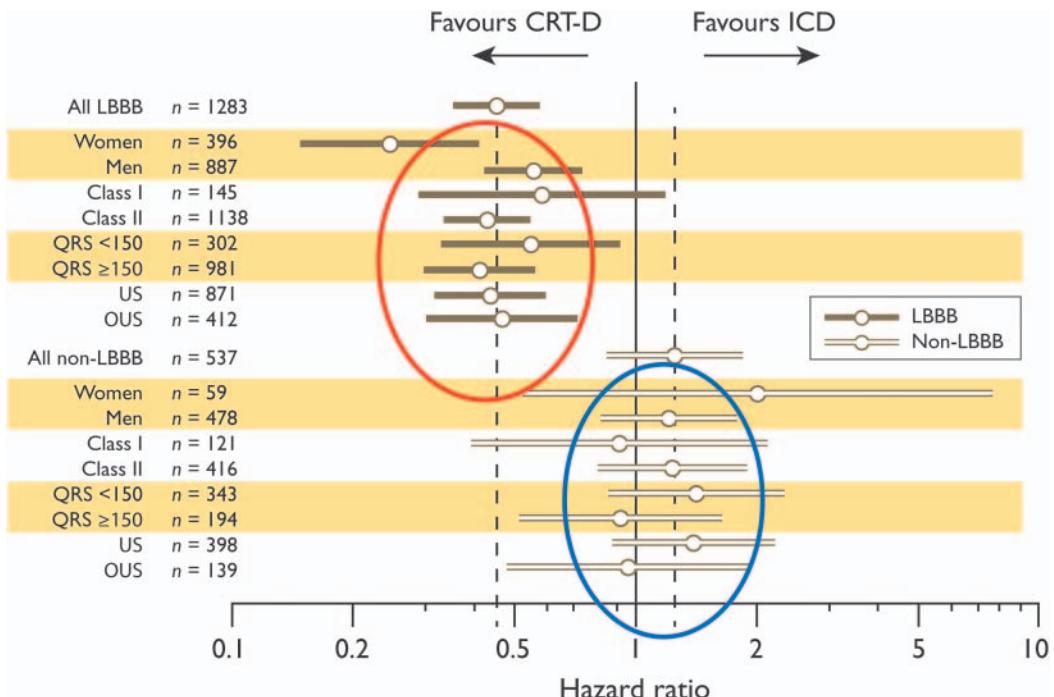
Cardiac pacing • Cardiac resynchronization therapy • Pacemaker • Heart failure • Syncope • Atrial fibrillation



**Web Figure 1** Average implantation rate of pacemaker (PM) in the 16 western European countries, Poland and Czech Republic (units per million inhabitants) based on reports from major manufacturers. The figures include first implantations and replacements  
Source: Eucomed ([www.eucomed.org/medical-technology/facts-figures](http://www.eucomed.org/medical-technology/facts-figures)).<sup>w2</sup>

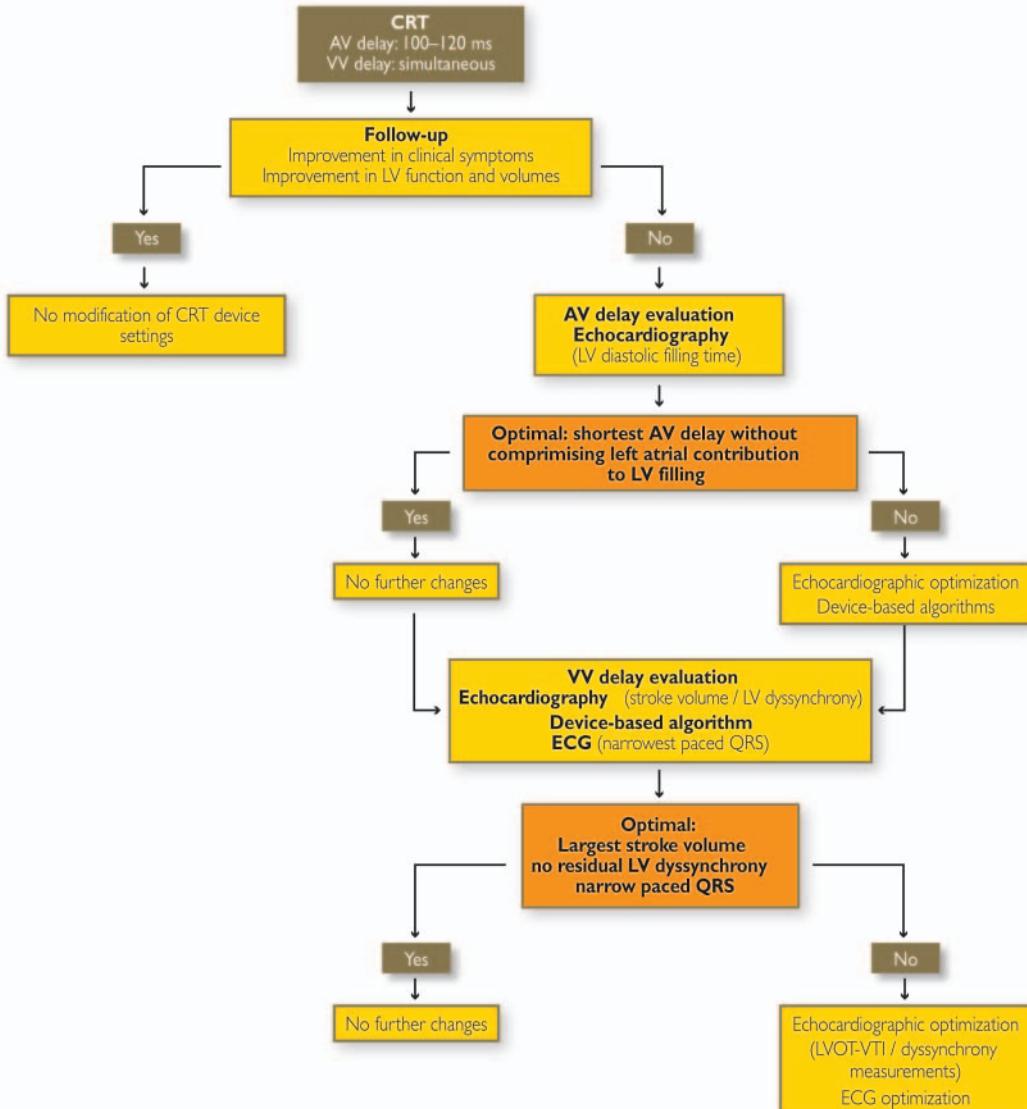


**Web Figure 6** Average implantation rate of devices for cardiac resynchronization therapy (CRT) in the 16 European countries (units per million inhabitants) based on reports from major manufacturers. The figures include first implantations and replacements  
Source: Eucomed ([www.eucomed.org/medical-technology/facts-figures](http://www.eucomed.org/medical-technology/facts-figures)).<sup>w2</sup>



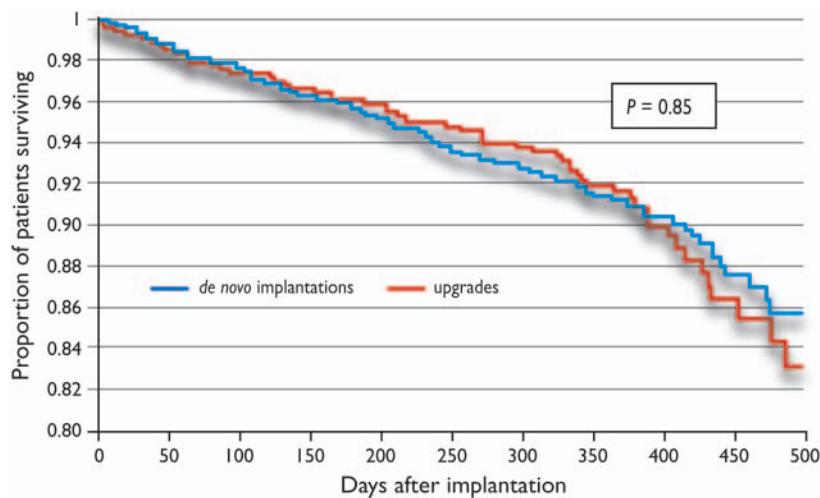
Class I refers to New York Heart Association classification; US = United States patients; OUS = outside United States patients.

**Web Figure 7** Relative risk of primary end-point (heart failure or death) by treatment (cardiac resynchronization therapy and defibrillator (CRT-D) versus implantable cardioverter defibrillator (ICD) only according to selected clinical characteristics in patients with left bundle branch block (LBBB; top) and non-LBBB patients (bottom) in the MADIT-CRT study (adapted from Zareba et al<sup>354</sup>). Class I refers to New York Heart Association classification; US=United States patients; OUS=outside United States patients

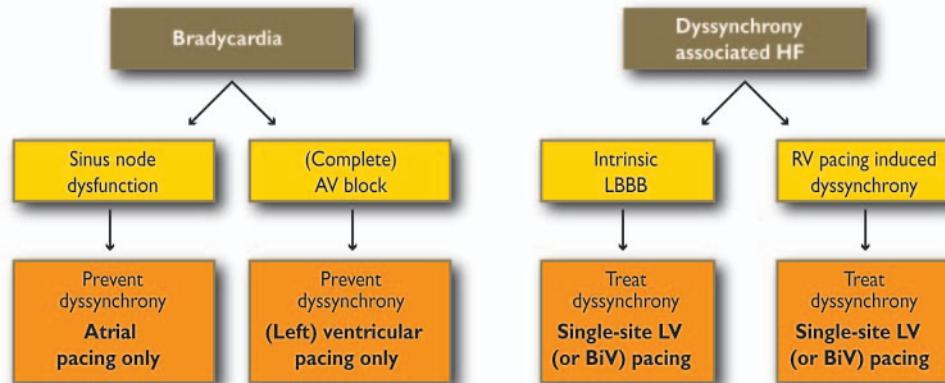


AV = atrioventricular; CRT = cardiac resynchronization therapy; ECG = electrocardiogram; LV = left ventricular.

**Web Figure 9** Algorithm for atrioventricular and interventricular delay optimization. AV=atrioventricular; CRT=cardiac resynchronization therapy; ECG=electrocardiogram; LV=left ventricular



**Web Figure 11** Kaplan-Meier estimates of time to death of any cause during the follow-up period of >1 year (9–15 months) in the European CRT Survey.<sup>w355</sup>



**Web Figure 12** Suggested optimal pacing mode in children (modified from van Geldorp I et al<sup>w204</sup>)

**Web Table 3** Clinical characteristics and pacing modality in patients treated by permanent pacing in the registries of the some European national pacing societies<sup>w3-8</sup>

	Italy year 2007 <i>n</i> = 31 146	Germany year 2008 <i>n</i> = 67 689	France year 2009 <i>n</i> = 64 306	Spain year 2010 <i>n</i> = 11 648	Sweden year 2010 <i>n</i> = 6494	UK year 2010 <i>n</i> = 43 650
Mean age (years), gender	77.6	76m/79f	-	76.8	75m/78f	75m/77f
Indication for implant						
AVB	44.6%	37.4%	-	55.6%	37.7%	42.2%
AF + AVB	18.1%	19.6%	-	16.2%	20.7%	15.9%
SSS	26.8%	36.2%	-	20.2%	33.5%	26.3%
BBB	4.9%	6.8%	-	6.2%	6.5%	8.3%
Others (not classified)	5.5%	0.3%	-	-	1.6%	7.4%
Pacemaker type						
Dual-chamber	66.2%	70.8%	75.4%	75.0%	71.0%	63.8%
Single-chamber, ventricular	32.0%	27.6%	21.4%	24.8%	22.0%	28.2%
Single-chamber, atrial	0.2%	0.6%	-	-	1.3%	0.8%
Biventricular	1.7%	0.7%	3.2%	-	5.7%	7.2%

AVB=atrioventricular block (includes I, II and III degree); AF=atrial fibrillation; SSS=sick sinus syndrome (includes reflex syncope); BBB=bundle branch block.

**Web Table 4** Causes of bradycardia

INTRINSIC
Idiopathic (ageing) degeneration
Ischaemic heart disease
Infiltrative diseases: sarcoidosis, amyloidosis, haemochromatosis
Collagen vascular diseases: systemic lupus erythematosus, rheumatoid arthritis, scleroderma
Congenital diseases, including sinus node and AV node disease
Infective diseases: myocarditis, endocarditis, Chagas disease, diphtheria, Gram-negative sepsis, typhoid fever, Lyme disease
Rare genetic diseases: associated with a cardiomyopathy (laminopathies, myotonic dystrophy, desminopathies, mitochondrial disorders, Danon disease, Anderson–Fabry disease, PRKAG2 mutation) or not (primary conduction defect)
Surgical trauma: valve replacement (including percutaneous aortic replacement), heart transplantation
Intended or unintended AV block due to catheter ablation procedures
EXTRINSIC
Physical training (sports)
Vagal reflex: vasovagal, situational (micturition, defaecation, swallow, gastrointestinal stimulation, cough, post-prandial, etc), carotid sinus syndrome
Idiopathic paroxysmal AV block
Drug effects
Cocaine abuse and other recreational drugs
Electrolyte imbalance: hypokalaemia, hyperkalaemia
Metabolic disorders: hypothyroidism, hypothermia, anorexia nervosa
Neurological disorders: increased intracranial pressure, central nervous system tumours
Obstructive sleep apnoea

AV=atrioventricular.

**Web Table 5** Typical symptoms of bradycardia (SB and AV block)

Persistent bradycardia	Intermittent bradycardia
Due to cerebral hypoperfusion	
• Easy fatigability	• Syncope, pre-syncope
• Irritability, lassitude, inability to concentrate	• Dizziness, vertigo
• Apathy, forgetfulness, cognitive impairment	• Light-headedness, blurred vision
• Dizziness, vertigo	
Due to other mechanisms	
• Shortness of breath, heart failure	• Sudden dyspnoea and chest pain unrelated to exercise
• Reduced exercise capacity (chronotropic incompetence)	• Palpitation (irregular beats)

AV=atrioventricular; SB=sinus bradycardia.

**Web Table 9** Classification of ECG observations obtained with ILR at the time of spontaneous syncope, with their probable related mechanism (adapted from ISSUE classification<sup>w54</sup>)

Classification	Description	Suggested mechanism
Type 1, asystole	R-R pause $\geq 3$ s	
• Type IA, sinus arrest	Progressive SB or initial sinus tachycardia followed by progressive SB until sinus arrest.	Probably reflex
• Type IB, SB plus AV block	Progressive SB followed by AV block (and ventricular pause/s) with concomitant decrease in sinus rate.	Probably reflex
• Type IC, AV block	Sudden onset AV block (and ventricular pause/s) with concomitant increase in sinus rate.	Probably intrinsic or idiopathic AV block.
Type 2, bradycardia	Progressive decrease of heart rate $>30\%$ or $<40$ b.p.m. for $>10$ s.	Probably reflex
Type 3, no or slight rhythm variations	Variations of heart rate $<30\%$ and heart rate $>40$ b.p.m.	Uncertain
Type 4, tachycardia	Increase of heart rate $>30\%$ of $>120$ b.p.m.	
• Type 4 A	Progressive sinus tachycardia.	Uncertain
• Type 4 B	Atrial fibrillation	Cardiac arrhythmia
• Type 4 C	Supraventricular tachycardia (except sinus).	Cardiac arrhythmia
• Type 4 D	Ventricular tachycardia	Cardiac arrhythmia

AV=atrioventricular; ECG=electrocardiogram; SB=sinus bradycardia.

**Web Table 11** Definition of intraventricular conduction disturbances (adapted from Surawicz et al<sup>w111</sup> and Zareba et al<sup>w354</sup>)

Disturbance	Definition
Complete LBBB	<ul style="list-style-type: none"> <li>• QRS duration <math>\geq 120</math> ms</li> <li>• QS or rS in lead V<sub>1</sub></li> <li>• broad (frequently notched or slurred) R waves in leads I, aVL, V<sub>5</sub>, or V<sub>6</sub></li> <li>• absent Q waves in leads V<sub>5</sub> and V<sub>6</sub></li> </ul>
Complete RBBB	<ul style="list-style-type: none"> <li>• QRS duration <math>\geq 120</math> ms; rSR', rSR', rSR', or qR in leads V<sub>1</sub> or V<sub>2</sub></li> <li>• occasionally, a wide and notched R wave and wide S</li> <li>• waves in leads I, V<sub>5</sub>, and V<sub>6</sub>.</li> </ul>
Non-specific IVCD	QRS $\geq 120$ ms without typical features of LBBB or RBBB
Incomplete LBBB or RBBB	QRS duration between 110 and 119 ms

LBBB=left bundle branch block; IVCD=intraventricular conduction delay; RBBB=right bundle branch block.

**Web Table I2 Inclusion criteria, design, end-points and main findings of the clinical trials evaluating the effect of atrioventricular and interventricular delay optimization**

Trial (ref. no.)	No.	Design	NYHA	LVEF	QRS	Primary endpoints	Secondary endpoints	Main findings
SMART-AV <sup>w356</sup>	980	Double-blinded, randomized AV delay optimization AV delay settings based on SmartDelay vs. Echo vs. Empiric fixed I20 ms $5.8 \pm 1.6$ months	III–IV	$\leq 35\%$	$\geq 120$	LVESV	NYHA class, QoL, 6MWD, LVEDV, LVEF	AV delay optimization with SmartDelay or echocardiography did not provide incremental benefit over the empiric fixed AV delay at 120 ms
InSync III <sup>w357</sup>	397	Prospective cohort VV delay optimization Sequential BiV pacing (Echo) vs. simultaneous BiV pacing 6 months	III–IV	$\leq 35\%$	$\geq 130$	NYHA class, 6MWD, QoL, LV stroke volume	NA	VV optimization with sequential BiV pacing set with echocardiography methods improved the primary endpoint
RHYTHM II ICD <sup>w358</sup>	121	Single-blinded, randomized, VV delay optimization Sequential BiV pacing (Echo) vs. simultaneous BiV pacing 6 months	III–IV	$\leq 35\%$	$\geq 150$	NYHA class, 6MWD, QoL	All-cause mortality and hospitalizations	VV optimization with sequential BiV pacing set with echocardiography methods did not improve the primary and secondary endpoints
DECREASE-HF <sup>w359</sup>	306	Double-blinded, randomized VV delay optimization (algorithms based on intracardiac ECG) Simultaneous BiV pacing vs. Sequential BiV pacing vs. LV pacing 6 months	III–IV	$\leq 35\%$	$\geq 150$	Peak VO <sub>2</sub> and LVESD	LVEF, LV volumes and MR	Simultaneous BiV pacing was associated with trend toward improvement in LVESD
FREEDOM <sup>w360</sup>	1647	Double-blinded, randomized AV and VV delay optimization QuickOpt vs. standard of care method / intracardiac electrograms	III–IV	NA	NA	Composite heart failure score	Hospitalizations and all-cause mortality	AV and VV optimization did not improve further the primary endpoint
CLEAR <sup>w361</sup>	268	Randomized, multicenter, single-blind AV and VV delay optimization SonR® vs. standard of care	III–IV	$\leq 35\%$	$\geq 120$	Composite heart failure score	Changes in NYHA functional	AV and VV optimization improved the proportion of responders at 1 year (76 vs. 62%, $P = 0.03$ )
Adaptive CRT <sup>w362</sup>	522	Randomized, double-blinded AV and VV delay optimization Ambulatory automatic adaptive vs. echo-optimized CRT	III–IV	$\leq 35\%$	$\geq 120$	Composite heart failure score	aortic velocity time integral concordance	Automatic adaptive optimization non inferior to echocardiographic optimization
Abraham et al. <sup>w363</sup>	238	Randomized, multicenter, double-blind VV delay optimization Sequential BiV pacing (Echo) vs. simultaneous BiV pacing	III–IV	$\leq 35\%$	$\geq 130$	Composite heart failure score	NYHA classification, 6MWD, quality of life, peak VO <sub>2</sub>	Composite score improved in 75% of sequential vs. 65% of simultaneous ( $P = 0.001$ )

AV=atrioventricular; biv.=biventricular; DECREASE-HF=Device Evaluation of CONTAK RENEWAL 2 and EASYTRAK 2: Assessment of Safety and Effectiveness in Heart Failure; FREEDOM=Frequent Optimization Study Using the QuickOpt Method; LV=left ventricular; LVEF=left ventricular ejection fraction; LVESD=left ventricular end-systolic dimension; LVESV=left ventricular end-systolic volume; No.=number of patients; NYHA=New York Heart Association; QoL=quality-of-life score; RHYTHM ICD II=Resynchronization for the Hemodynamic Treatment for Heart Failure Management Implantable Cardioverter Defibrillator II; SMART-AV=SmartDelay Determined AV Optimization: A Comparison to Other AV Delay Methods Used in Cardiac Resynchronization Therapy; VO<sub>2</sub>=volume of oxygen; VV=interventricular; 6MWD=6-min walk distance. CLEAR=Clinical Evaluation on Advanced Resynchronization.

**Web Table 19 Examples of rare inherited disorders associated with clinically significant cardiac disease**

Inherited primary arrhythmias	Gene and gene symbol or proteins	Cardiac phenotype
Familial long QT syndrome	KCNQ1, KCNH2, SCN5A	Brady-dependent VA
Progressive familiar AV block, autosomal dominant sick sinus syndrome.	HCN4, SCN5A, TRPM4, GJA5 genes	Bradycardia, nodal rhythm, PAF, AV block
Neuromuscular disorders		
Myotonic dystrophy type 1 (Steinert's disease).	Myotonin kinase DMPK	AV block, fascicular block, bundle branch block, atrial flutter and fibrillation, VA, DCM.
Myotonic dystrophy type 2 (proximal myotonic myopathy: PROMM).	Zinc finger protein 9 ZNF9	PAF, AV block, VA.
X-linked Emery Dreifuss muscular dystrophy (EDMD).	Emerin EMD or STA	AV block; atrial paralysis; VA; atrial flutter and fibrillation, DCM.
Laminopathies (including autosomal EDMD, limb girdle muscular dystrophy type 1B (LGMDIB) and lamin associated protein defects.	Lamin AC (LMNA) FHL1	AV block, atrial arrhythmia, VA, DCM, ARVC, SCD.
Desminopathies	Mutated desmin (DES)	Conduction defects, arrhythmias, sudden death.
Metabolic disorders		
Anderson–Fabry disease (alpha-galactosidase A deficiency).	Alpha-galactosidase A GLA	Progressive AV block, sinus node dysfunction, HCM.
Familial amyloidosis	Transthyretin TTR	Varies with mutation: AV block, cardiomyopathy.
Mutations in AMP kinase	PRKAG2	HCM, AV block, WPW
Mitochondrial cytopathies (including Kearns–Sayre disease).	mitochondrial DNA (mtDNA) deletions	AV block, atrial and ventricular arrhythmia, ventricular preexcitation, cardiomyopathy (HCM, DCM).
Danon disease	LAMP2	
Developmental disorders		
ASD with conduction disease, tetralogy of Fallot.	NK2 homeobox 5 gene NKX2.5	ASD, VSD, tetralogy of Fallot, AV conduction.
Holt Oram syndrome	TBX5	Congenital heart defects; AV block; sinoatrial disease; WPW.

ARVC=arrhythmogenic right ventricular cardiomyopathy; ASD=atrioseptal defect; AV=atrioventricular; DCM=dilated cardiomyopathy; HCM=hypertrophic cardiomyopathy; PAF=paroxysmal atrial fibrillation; VA=ventricular arrhythmia; VSD=ventriculoseptal defect; WPW=Wolff-Parkinson-White syndrome.

**Web Table 21** Most frequent/important complications of PM and CRT implantation

Related to venous access:	<ul style="list-style-type: none"> <li>• Pneumothorax</li> <li>• Haemothorax</li> </ul>
Lead-related:	<ul style="list-style-type: none"> <li>• Brady/tachyarrhythmias</li> <li>• Cardiac perforation</li> <li>• Cardiac tamponade</li> <li>• Coronary sinus dissection/perforation</li> <li>• Dislodgement</li> <li>• Diaphragmatic stimulation</li> <li>• Lead malposition</li> <li>• Venous thrombosis</li> </ul>
	<ul style="list-style-type: none"> <li>• Haematoma</li> <li>• Wound pain</li> </ul>
	<ul style="list-style-type: none"> <li>• Pocket infection without bloodstream infection</li> <li>• Pocket infection with bloodstream infection</li> <li>• Device-related endocarditis</li> </ul>

CRT=cardiac resynchronisation therapy; PM=pacemaker.

**Web Table 22** Suggested strategy for management of antiplatelet and anticoagulant therapy in the peri-implantation period of PM/CRT

Antiplatelet therapy	Suggested strategy	References
Primary prevention	Withhold antiplatelet therapy for 3–7 days before implant, depending on the drug.	Non-randomized large observational studies.
Dual antiplatelet therapy after stent placement and acute coronary syndromes.	Continue aspirin (low increase in bleeding risk).	Non-randomized large observational studies; expert consensus.
Non-high risk period		
High risk period <sup>a</sup>	Continue dual antiplatelet therapy (high increase in bleeding risk).	
Warfarin therapy		
	Withhold warfarin 3–5 days before implant or continue warfarin (lower end of the recommended INR) according to a risk evaluation <sup>b</sup> performed by the physician.	International expert consensus
Novel oral anticoagulant		
	Withhold anticoagulant 1–3 day before implant or continue according to a risk evaluation <sup>b</sup> performed by the physician and restart as soon as effective haemostasis has been achieved.	Expert consensus

<sup>a</sup>During the minimum recommended duration of dual platelet therapy

<sup>b</sup>High risk typical setting: prosthetic valves, AF and history of stroke, intracardiac thrombus or other acute thromboembolic event, etc.

AF=atrial fibrillation; CRT=cardiac resynchronisation therapy; INR=international normalized ratio; PM=pacemaker.

**Web Table 23** Summary of randomized studies on pacing from alternative right ventricular sites

Trial	Study design	Patients	Length of follow-up	Main results
Barin et al. <sup>w310</sup>	RVOT vs. RVA parallel	33	73 months	Similar electrical performances and complications.
Tse et al. <sup>w326</sup>	RVOT vs. RVA parallel	24	18 months	No difference at 6 months. RVOT: better EF at 18 months, fewer perfusion defects and wall motion abnormalities.
Lewicka-Nowak et al. <sup>w319</sup>	RVOT vs. RVA parallel	27	7 years	EF deterioration in RVA but not in RVOT group.
Leong et al. <sup>w318</sup>	RVOT vs. RVA parallel	58	11–53 months	EF deterioration in RVA but not in RVOT group. Less dyssynchrony with RVOT
Stambler et al. <sup>w323</sup>	RVOT vs. RVA RVOT + RVA vs. RVA Cross-over	103	9 months	RVA higher LVEF. QoL no difference.
Gong et al. <sup>w315</sup>	RVOT vs. RVA parallel	96	12 months	Less dyssynchrony with RVOT. No difference in cardiac remodelling and LV systolic function.
Occhetta et al. <sup>w321</sup>	Para-Hisian vs. RVA pacing cross-over	16	6 months	Para-Hisian: improvement in functional and haemodynamic parameters.
Mera et al. <sup>w320</sup>	RVS vs. RVA cross-over	12	2 months	High RVS: greater FS and resting EF, no difference in exercise capacity.
Victor et al. <sup>w324</sup>	RVOT vs. RVA cross-over	16	4 months	No difference whatever the EF.
Flevari et al. <sup>w314</sup>	RVS vs. RVA parallel	31	12 months	EF deterioration in RVA but not in RVS group.
Kypta et al. <sup>w317</sup>	RVS vs. RVA parallel	98	18 months	Similar HF rate during follow-up, no difference in EF and in exercise capacity.
Cano et al. <sup>w311</sup>	RVS vs. RVA parallel	93	12 months	Less dyssynchrony with RVS. No difference in cardiac function, exercise capacity, NYHA class and QoL.
Domenichini et al. <sup>w313</sup>	RVS vs. RVA parallel	59	1 and 4 years	RVS: no advantage on LVEF. May be deleterious when the RVS lead is inadvertently positioned anterior.
Wang et al. <sup>w325</sup>	RVOT vs. RVA parallel	60	12 months	RVA: more dyssynchrony and LV wall motion abnormalities. No difference observed between the groups with respect to LVEF.
Kristiansen <sup>w316</sup>	CRT with RVS vs. RVA, parallel	85	6 months	No difference in LV reverse remodelling and dyssynchrony.

EF=ejection fraction; FS=fractional shortening; HF=heart failure; LV=left ventricular; NYHA=New York Heart Association; QoL=quality of life; RVOT=right ventricle outflow tract pacing; RVA=right ventricle apical pacing; RVS=right ventricle septal pacing.

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