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Systematic review of the incidence and clinical risk predictors of atrial fibrillation and permanent pacemaker implantation for bradycardia in Fabry disease

Ravi Vijapurapu,[1,2] Ashwin Roy [ID] ,[1] Polyvios Demetriades,[2] Adrian Warfield,[3] Derralynn A Hughes,[4] James Moon,[5] Peter Woolfson,[6] Joseph de Bono,[2] Tarekegn Geberhiwot,[7,8] Dipak Kotecha [ID] ,[1] Richard Paul Steeds [ID] [1,2]

ABSTRACT

Introduction Fabry disease (FD) is an X-linked lysosomal storage disorder caused by enzyme deficiency, leading to glycosphingolipid accumulation. Cardiac accumulation triggers local tissue injury, electrical instability and arrhythmia. Bradyarrhythmia and atrial fibrillation (AF) incidence are reported in up to 16% and 13%, respectively.

Objective We conducted a systematic review evaluating AF burden and bradycardia requiring permanent pacemaker (PPM) implantation and report any predictive risk factors identified.

Methods We conducted a literature search on studies in adults with FD published from inception to July 2019. Study outcomes included AF or bradycardia requiring therapy. Databases included Embase, Medline, PubMed, Web of Science, CINAHL and Cochrane. The Risk of Bias Agreement tool for Non-Randomised Studies (RoBANS) was utilised to assess bias across key areas.

Results 11 studies were included, eight providing data on AF incidence or PPM implantation. Weighted estimate of event rates for AF were 12.2% and 10% for PPM. Age was associated with AF (OR 1.05–1.20 per 1-year increase in age) and a risk factor for PPM implantation (composite OR 1.03). Left ventricular hypertrophy (LVH) was associated with AF and PPM implantation.

Conclusion Evidence supporting AF and bradycardia requiring pacemaker implantation is limited to single-centre studies. Incidence is variable and choice of diagnostic modality plays a role in detection rate. Predictors for AF (age, LVH and atrial dilatation) and PPM (age, LVH and PR/QRS interval) were identified but strength of association was low. Incidence of AF and PPM implantation in FD are variably reported with arrhythmia burden likely much higher than previously thought.

PROSPERO database CRD42019132045.

For numbered affiliations see end of article.

Correspondence to
Dr Richard Paul Steeds; rick.steeds@uhb.nhs.uk

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Stroke prevalence in Fabry disease is high and is likely due to cerebral sphingolipid accumulation and cardio-embolic disease from undiagnosed atrial fibrillation (AF).
⇒ Single-centre studies demonstrate high prevalence of AF and pacemaker implantation for bradycardia.

WHAT THIS STUDY ADDS

⇒ Incidence of AF and PPM implantation are likely to be much higher than previously understood.
⇒ Device-detected AF was frequent and likely contributing to high stroke prevalence and subsequent mortality in Fabry disease.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review alerts clinicians of the importance of screening for AF early in patients with Fabry disease.
⇒ Once diagnosis is confirmed, early initiation of therapy is imperative in order to reduce cardiac complications related to Fabry disease.

progressive accumulation of glycosphingolipids, predominantly globotriacylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) in various tissues.[2] Deposition of these complex sphingolipids leads to cellular dysfunction and subsequently life-threatening cardiovascular, renal and neurological complications.[3] Cardiovascular involvement includes progressive left ventricular hypertrophy (LVH), myocardial inflammation, fibrosis, congestive cardiac failure, arrhythmia and sudden death.[4] Gb3 and lysoGb3 accumulate in all cardiac cells including the conduction system,[5] triggering a cascade of cellular reactions leading to a pro-inflammatory microenvironment with local tissue injury and apoptosis.[6] The ensuing

INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by a deficiency in the enzyme α-galactosidase A,[1] leading to

damage to conductive tissue contributes to electrical instability and subsequent development of arrhythmia.

Although symptoms such as palpitations and syncope are common in FD, occurring in up to 50% of women and 75% of men on enzyme replacement therapy (ERT),[4 7] little is known regarding the true frequency of arrhythmia.[7] Our previous systematic review identified a prevalence of ventricular tachycardia of 15.3% and a rate of sudden cardiac death similar to studies in sarcomeric hypertrophic cardiomyopathy.[8] Consensus statements suggest that symptomatic bradycardia caused by sinus node dysfunction and atrioventricular block (AV) block are common in Fabry disease (FD).[9] The reported incidence of symptomatic bradycardia varies between 1% and 16%,[10–13] with atrial arrhythmias such as atrial fibrillation (AF) in 13%.[14] Conventional risk predictors for both bradyarrhythmias and tachyarrhythmias are commonplace in patients with FD but may not be discriminatory in this population. The aim of this systematic review was to evaluate the burden of AF and symptomatic bradycardia needing pacemaker implantation within existing literature and to define potential risk factors that may assist clinicians in preventing adverse cardiovascular events.

METHODS

This systematic review was prospectively registered on the PROSPERO database (CRD42019132045) and was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Search strategy

The literature search was performed by two researchers (RV and PD) independently and all studies referring to FD, AF and bradycardia requiring pacemaker were included. All articles with English abstracts published from inception to July 2019 were included. Databases used included: Embase, Medline, PubMed, Web of Science, CINAHL and Cochrane. Due to the rare nature of FD, a broad search strategy was used to ensure a high sensitivity. Examples of Medical Subject Headings and keywords are below, with each search strand combined using 'AND' to identify the initial study list.

► Fabry 'OR' AFD 'OR' Anderson-Fabry 'OR' FD
► Bradycardia 'OR' conduction disease 'OR' AV block 'OR' pacemaker
► Atrial fibrillation 'OR' AF 'OR' tachyarrhythmia 'OR' flutter

Inclusion and exclusion criteria

The study inclusion criteria included the following:

► Gene-positive Fabry disease
► Adults >16 years
► English language or fully translated copy available
► Study outcome included AF or bradycardia requiring therapy
► Evaluation of risk factors
  Exclusion criteria were:

► Review articles/single person case reports/abstracts/animal studies
► No English translation of full manuscript available

Study selection

Initial abstract screening was performed by the same two researchers and included removal of: single-person case studies, duplicate abstracts, reviews, conference abstracts and animal studies. All abstracts were assessed against the inclusion and exclusion criteria listed and any additional relevant studies identified through review articles and reference lists that were not captured through the initial search strategy, were also included in the shortlist. Disagreement between researchers was resolved by consensus review and further discussion with independent specialists where required.

Quality assessment and data extraction

Each study included was evaluated in detail by two independent reviewers (JdB and RS). Initial review included confirmation of eligibility and relevance of content. The Risk of Bias Agreement Tool for Non-Randomised Studies (RoBANS) was utilised to assess bias across several key areas. Any variations in reviewer ratings were resolved by discussion and reviewer consensus.

Data were independently extracted by two researchers (RV and PD) on a standardised worksheet, which included: study design, inclusion and exclusion criteria, diagnostic tests performed, primary and secondary endpoints, patients characteristics (age, gender, therapy, risk factors), duration of follow-up and any statistical association (eg, hazards/ORs from regression modelling). Outcomes without sufficient information for conducting meta-analyses were described in a narrative fashion.

Statistical analysis

Statistical analyses were performed where quantitative data on arrhythmia incidence and risk factors were available, with ORs and mean differences, respectively, used as the effect measure for binary and continuous outcomes. Pooled estimates from individual studies were identified using a meta-analysis of proportions, using generalised linear mixed models with the logit transformation. All meta-analyses and forest plots were performed using Cochrane Review Manager 5.4 and pooled estimate event rate analysis was performed using R package 1.2. Small study effects and publication bias were estimated using the Risk of Bias Assessment tool for Non-randomised Studies (RoBANS).[15] A two-tailed p value of 0.05 was considered as statistically significant.

RESULTS

After removing duplicates, the literature search identified 1138 studies of which 11 studies were included in the systematic review (see figure 1).

All 11 studies were observational,[10 13 14 16–23] with one designed as a non-randomised interventional trial.[21] Nine studies were longitudinal (six retrospective and
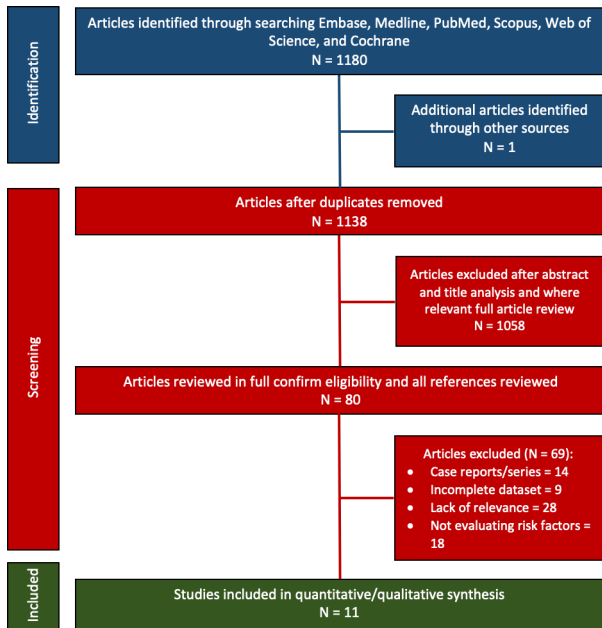
Figure 1 Search strategy.

three prospective), one was a registry data review and one a single timepoint cross-sectional study. Pooled median follow-up time was 4.5 years. Common comorbidities in these patients included chronic kidney disease, hypertension, previous stroke and coronary artery disease. Table 1 shows a summary of study characteristics. Weighted mean age was 39 years, and there was an average male:female ratio of 1.5. The risk of bias was high in 10 studies, most notable in the confounding variables, incomplete dataset and blinding of outcome assessment domains.

Incidence of arrhythmia: AF and bradycardia requiring pacemaker implantation

Eight studies provided data on incidence of AF (n=710) or permanent pacemaker (PPM) implantation (n=651). One registry study provided incidence of composite cardiovascular events, of which AF and PPM implantation were included. The weighted estimates of event rates for AF needing anticoagulation were 12.2% (95% CI 7.2% to 19.7%) and 10.0% for PPM implantation (95% CI 6.6% to 14.8%). Table 2 shows a detailed breakdown of the incidence of each arrhythmia type for each study over the follow-up duration.

Risk factors for AF

Age was significantly but weakly associated with incident AF in three studies (n=328)), with ORs ranging from 1.05 to 1.20 per 1-year increase in age. Increasing LV mass also had limited value, with only two studies (n=285) demonstrating a link with incident AF. A significant but very weak association was seen in one study using echocardiographic left ventricular mass indexed to body surface area (LVMi) (HR 1.02, 95% CI 1.01 to 1.03)[14] and similarly in another study where AF was part of a composite endpoint with stroke (HR 1.02).[17] One further study of 78 patients identified both increasing LVMi and maximum wall

thickness from M-mode echo as independent predictors on univariate analysis.[19] Left atrial (LA) dilatation was weakly associated with the development of AF. A study of 207 patients reported that increasing LA diameter on M-mode echocardiography (single measurement) was associated with AF; however, this was not significant (HR 1.11, 95% CI 0.99 to 1.24).[14] A prospective study of 16 patients found a clinically irrelevant difference in LA size on M-mode echocardiography in those with and without AF (38.4±2.1 mm vs 37.5±3.9 mm).[21] A retrospective study of 43 patients carrying out detailed echocardiography found that LA volume (2D biplane assessment) predisposed to AF and stroke as a composite endpoint (HR 1.023, p=0.070).[17]

A study by Pichette et al[17] identified multiple parameters on transthoracic echocardiography predictive of AF and stroke as a composite endpoint. These included impaired (less negative) early diastolic strain (HR 0.777, p=0.006), reduced (less negative) early diastolic strain rate (HR 7.64, p=0.028) and impaired (less negative) left ventricular (LV) global longitudinal strain (GLS) (HR 1.63, p=0.006). Receiver operating characteristics demonstrated an optimal cut-off point of 20.9% for early diastolic strain (area under the curve (AUC) 0.91, sensitivity 88%, specificity 88%, p<0.001) and −18.6% for LV GLS (AUC 0.85, sensitivity 89%, specificity 70%, p=0.002). Although an increasing E/e' ratio (HR 1.32, p=0.014) showed some association with AF and stroke, this was weaker. Advanced severity of cardiac disease signified by extensive fibrosis on cardiac magnetic resonance imaging (CMR, defined by late gadolinium enhancement (LGE) on more than 2 AHA segments of the LV myocardium) as well as general progression of FD signified by an elevated Mainz Severity Score Index (MSSI) were both associated with the development of AF—elevated MSSI: HR 1.07, p=0.004,[14] and LGE on CMR: no AF 19/29 vs AF 10/11, p=0.033.[22]

Risk factors for bradycardia requiring pacemaker implantation

Increasing age was a common risk factor for PPM implantation in FD. Three studies using PPM insertion as a primary endpoint found an increased incidence as patients became older, with a composite OR of 1.03 (1.01–1.04)[10 14 18] (figure 2). Sené et al[18] described a median age of 63 years (range 48–76) in those who underwent device implantation compared with 36 years (17–66) in those not requiring a device (p<0.001). A study by O'Mahony et al[10] also identified a mean age of 54±11 years in those patients requiring a PPM.

A single timepoint study of 53 patients by Di et al[16] evaluated all bradyarrhythmic events (pause >2s, severe sinus bradycardia <40 bpm, or any conduction abnormality requiring a PPM) as a composite outcome and found these to be more common in those who were older (58±13 vs 41±15 years, OR 1.093, p=0.004).

Elevated LV mass was in five studies as a strong predictor of PPM implantation. A retrospective study of 49 patients with a median follow-up of 8 years evaluated cardiac

Table 1 Study characteristics

References	Sample size (n)	Inclusion criteria	Exclusion	Male (n, %)	Enzyme replacement (n, %)	Mean age (years±SD)	Median follow-up in years (IQR)
O'Mahony et al[10]	204	FD confirmed with plasma a-Gal activity+mutation analysis	<16 years old	99 (49)	46 (23)	42±15	4.8 (0.07–18)
Shah et al[19]	78	FD confirmed with plasma a-Gal activity+mutation analysis	Nil	43 (55)	41 (53)	44±15	1.9 (0.3–10)
Patel et al[14]	207	FD confirmed with plasma a-Gal levels+mutation analysis	<16 years old	98 (47)	47 (23)	44±15	7.1 (4.0–9.1)
Weidemann et al[21]	16	1. Genetically proven FD 2. Evidence of LV fibrosis 3. No previously detectable arrhythmia 4. Stable treatment with ERT for 12 months	1. Anticoagulation for AF 2. PPM or ICD implant 3. History of AF or VT	12 (75)	16 (100)	52±11	1.2 (0.3–2.0)
Talbot et al[20]	25	1. Male patients with genetically confirmed FD 2. Stable on ERT with TTE/ECG performed	1. Female patients 2. Not on ERT	25 (100)	25 (100)	38±11	10
Acharya et al[13]	19	FD	Nil	11 (58)	18 (95)	18 to 72	4.4
Hopkin et al[23]	1411	FD registry patients of any age on agalsidase-beta	Not on agalsidase-beta	969 (69)	1411 (100)	Males: 35±14 Females: 44±14	Males: 4.3 (0–11.1) Females: 3.2 (0–10)
Sené et al[18]	49	FD confirmed with plasma a-Gal activity+mutation analysis	<15 years and 3 months	20 (41)	27 (55)	35 (20–50)	8 (2–11)
Di et al[16]	53	FD confirmed with mutation analysis	Nil	22 (42)	28 (53)	45±16	Not stated
Pichette et al[17]	43	FD confirmed with mutation analysis	Poor endocardial definition on TTE	21 (42)	12 (24)	40±15	4.2 (2.5–6.3)
Vijapurapu et al[22]	90	FD confirmed with mutation analysis	<16 years	69 (77)	62 (69)	56±13	4.3 (2.2–7.7)

AF, atrial fibrillation; a-Gal, alpha-galactosidase; ECG, electrocardiogram; ERT, enzyme replacement therapy; FD, Fabry disease; ICD, implantable cardio-defibrillator; LV, left ventricle; PPM, permanent pacemaker; TTE, transthoracic echocardiogram; VT, ventricular tachycardia.

device implantation as their primary endpoint and found that LVH (defined as a diastolic posterior wall or septal thickness >13 mm) was significantly more common in those who went on to require a PPM (PPM: 8/9 vs no PPM 14/40, p<0.001).[18] LVH was also an independent predictor on univariate regression. This association was confirmed in three other studies with a composite HR 1.01 (95% CI 1.00 to 1.01)[10 14 16] (figure 3). Di et al[16] found that patients with bradyarrhythmic events had a significantly higher LV mass on 2D echocardiography (144±83 vs 83±26 g/m², p=0.026).

In a retrospective chart review evaluating any cardiac device implantation (PPM and internal cardioverter defibrillator) as a composite endpoint, those with devices had a significantly higher indexed LV mass on echo compared with those without (device: 136±40 vs no device: 93±19 g/m², p=0.008).[13]

Three studies identified a prolonged PR interval and QRS duration as clinical predictors of PPM implantation in FD. PQ interval was not evaluated in any studies. The first was a retrospective study of 204 patients over 4.8 years, in which a PR interval >200 ms and a QRS duration >110 ms were both independent predictors on multivariate regression analysis (HR 1.03, 95% CI 1.004 to 1.060 and HR 1.05, 1.02 to 1.09, respectively).[10] A similar association was described in a study by Patel et al,[14] where both were univariate predictors of device implantation (PR: HR 1.02, 1.00 to 1.05 and QRS: HR 1.05, 1.05 to 1.08). A

Table 2 Incidence of bradycardia requiring PPM implantation and AF needing anticoagulation

References	Arrhythmia monitoring method	Definition of AF	Median follow-up (years, IQR)	Bradycardia needing PPM		AF needing anticoagulation	
				No. at end of follow-up duration (n, %)	Rate (n/year)	No. at end of follow-up duration (n, %)	Rate (n/year)
O'Mahony et al[10]	ECG	Any duration	4.8 (0.07–18)	12 (5.9)	1.46*	6 (2.9)	1.25
Shah et al[19]	ECG/Holter	Any duration	1.9 (0.3–10)	6 (7.8)	3.16	15 (19.2)	2.11*
Patel et al[14]	ECG	Any duration	7.1 (4.0–9.1)	13 (6.3)	1.13*	13 (6.3)	1.27*
Weidemann et al[21]	ILR	Episode >3 min	1.2 (0.3–2.0)	5 (31.25)	4.17	5 (31.25)	4.17
Talbot et al[20]	ECG	N/A	10	4 (16)	0.1*	N/A	N/A
Acharya et al[13]	ECG/Holter/cardiac device (retrospective)	No definition	4.4	2 (10.5)	0.45	2 (10.5)	0.45
Hopkin et al[23]	Holter/ECG	N/A	Males: 4.3 (0–11.1) Females: 3.2 (0–10)	N/A	N/A	N/A	N/A
Sené et al[18]	ECG	N/A	8 (2–11)	8 (16.3)	1	N/A	N/A
Di et al[16]	Holter	Episode >30 s	N/A	6 (11.3)	N/A	11 (20.8)	N/A
Pichette et al[17]	Holter	Clinically significant episode >30 s	4.2 (2.5–6.3)*	N/A	N/A	5 (11.6)	0.24*
Vijapurapu et al[22]	Cardiac device	Episode>30 s	4.3 (2.2–7.7)	N/A	N/A	17 (18.9)	3.95
Estimate of event rates (%)*	N/A	N/A	N/A	12.2 (7.2–19.7)		10.0 (6.6–14.8)	

*Percentage estimate of event rate with 95% CIs, calculated using generalised linear mixed models with logit transformation.
AF, atrial fibrillation; ILR, implantable loop recorder; PPM, permanent pacemaker.

final study of 53 patients with FD found that QRS prolongation was associated with a composite outcome of all bradyarrhythmic events (HR 1.014, p=0.012).[16]

Increasing MSSI, used as a marker of general progression of FD, was associated with PPM implantation in two studies.[10 14] Female gender was noted to be protective of the need for pacemaker insertion—HR 0.27 (95% CI 0.07 to 0.99) and HR 0.26 (95% CI 0.06 to 0.79).[10 14] A study of 25 patients by Talbot et al[20] found that patients with advanced renal dysfunction (chronic kidney disease stage 5 (CKD5)) had a tendency towards needing cardiac pacing, although this was not significant due to low numbers (CKD 5: 75% vs not CKD5 25%).

DISCUSSION

This systematic review is the first evaluating the incidence of AF and bradycardia requiring pacemaker implantation and the associated predictive factors in FD. First, although the consensus is that AF and symptomatic bradycardia caused by sinus node dysfunction and AV block are common in FD, the evidence in support of this consensus is limited to predominantly small, single-centre retrospective studies. Second, the incidence of these is variable and choice of diagnostic modality appears to play a significant role, with sporadic performance of 12-lead ECG and Holter monitoring showing lower detection rates (2.9%–10% per year) compared with higher rates (19%–31%

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI	Odds Ratio IV, Random, 95% CI
O'Mahoney 2011	0.0253	0.0085	53.9%	1.03 [1.01, 1.04]	
Patel 2015	0.0212	0.0108	41.0%	1.02 [1.00, 1.04]	
Sene 2016	0.0864	0.0375	5.1%	1.09 [1.01, 1.17]	
Total (95% CI)			100.0%	**1.03 [1.01, 1.04]**	

Heterogeneity: Tau² = 0.00; Chi² = 2.80, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 3.07 (P = 0.002)
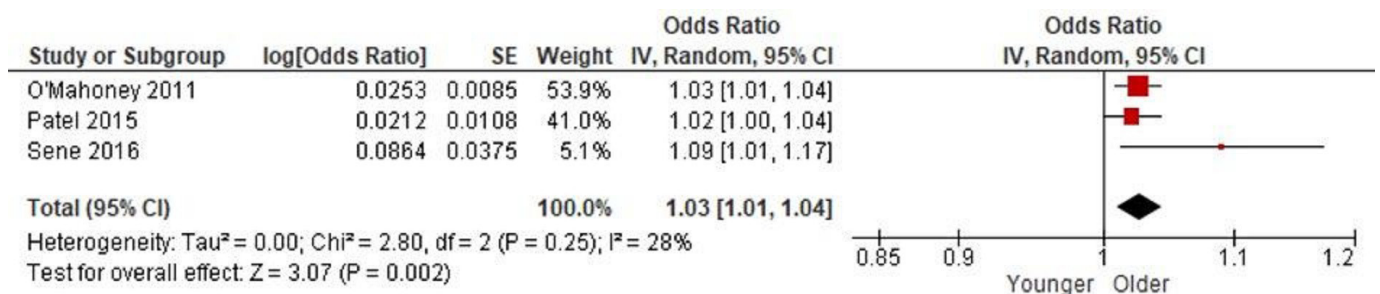
Figure 2 Age as a predictor for bradycardia requiring permanent pacemaker implantation.

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Fixed, 95% CI
Di 2018	0.01114736	0.01098765	1.3%	1.01 [0.99, 1.03]
O'Mahoney 2011	0.0043	0.0015	67.4%	1.00 [1.00, 1.01]
Patel 2015	0.0086	0.0022	31.3%	1.01 [1.00, 1.01]
Sene 2016	0	0		Not estimable
Total (95% CI)			100.0%	1.01 [1.00, 1.01]

Heterogeneity: Chi² = 2.85, df = 2 (P = 0.24); I² = 30%
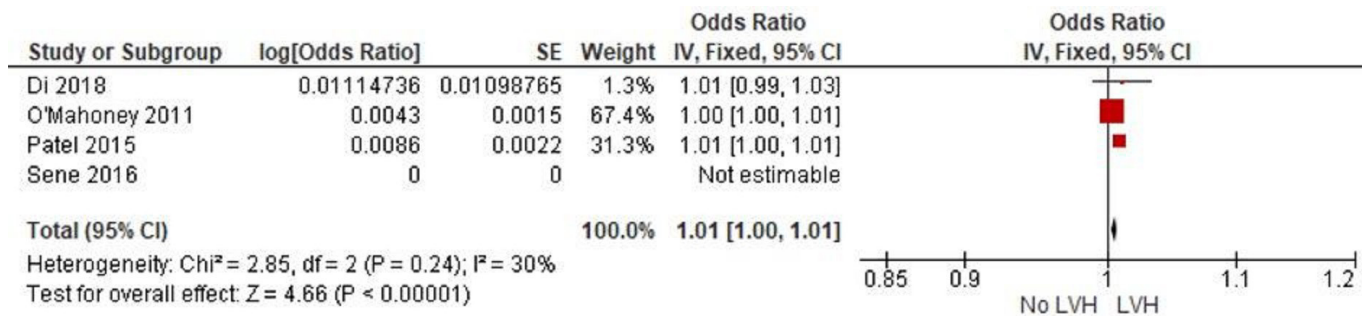Test for overall effect: Z = 4.66 (P < 0.00001)

Figure 3 LVH as a predictor for bradycardia requiring permanent pacemaker implantation. LVH, left ventricular hypertrophy.

per year) on continuous rhythm monitoring.[21 22] This suggests that both AF and bradycardia may be underdiagnosed in FD, particularly in those patients with advanced FD cardiomyopathy, in whom the event rate requiring therapy may be as high as 31% per year.[21] However, it is currently not known whether the benefits of anticoagulation seen in AF detected on ECG or Holter are seen in AF episodes (or atrial high rate episodes) detected on implantable devices or novel technology.[24] Third, predictive risk factors for AF and symptomatic bradycardia requiring PPM implantation are poorly defined in FD. Although several clinical predictors for AF (age, LVH and LA dilatation) and PPM implantation (age, LVH, prolonged PR/QRS and beta-blocker therapy) were identified, the strength of association was low with HRs between 1 and 1.2 for most.

The worldwide incidence and prevalence of AF is increasing in the general population,[25] due to advancing age, improved survival from co-existing disease and increasing co-morbidity. These drivers are shared in those who have FD, including increasing age, improving survival, for example, with renal replacement therapy, but also increasing co-morbidity.[9] In all populations, AF is associated with greater morbidity, including stroke and heart failure, and increased mortality, particularly cardiovascular-related.[26 27] Ischaemic stroke, in particular, is a common and serious clinical event in both early and advanced FD, with vascular endothelial sphingolipid accumulation presumed to play a predominant role in its aetiology.[28] The higher rates of asymptomatic AF identified in this systematic review suggest however that thromboembolic disease may have a more significant role in the aetiology of ischaemic stroke in FD. Being able to determine those patients with FD most at risk of AF or those most likely to progress from paroxysmal to sustained AF is critical to devising treatment strategies or implementing targeted preventative measures. Two issues arise from the data in this systematic review. First, the risk factors hitherto identified are limited to age, LVH and atrial dilatation, yet current predictive models in the general population are much more detailed and more accurate, incorporating clinical risk factors (sex and body mass index) and biomarkers (N-terminal pro-B-natriuretic peptide and fibroblast growth factor) that have not been explored in FD.[29] Further prospective research is needed to explore the interaction of more clinical, imaging and biomarkers in

predicting risk of AF in FD, not only limited to those risk factors detected in the general population but also potential incremental FD-related factors such as type of mutation, enzyme activity and levels of lyso-Gb3. Second, the European Society of Cardiology state that a definitive diagnosis of AF can be made from either a 12-lead ECG or a single-lead ECG tracing with ≥30s showing a heart rhythm with no discernible p waves and irregular RR intervals.[30] Annual performance of Holter monitoring of patients with FD as recommended in consensus guidelines is likely to significantly underestimate the burden of AF compared with continuous monitoring.[31] Alternative strategies that employ novel digital technology need to be explored in FD, not only because these modalities engage patients in their care but also since these are likely to lead to optimisation of pharmacological and interventional therapy in AF.[32] The European Society of Cardiology recently accepted wearable device readings, interpreted by a physician as a validated method of diagnosing AF over a 30s period. This shows a drive for use of novel digital technology in combination with good clinical judgement as to whether the ECG waveforms represent true AF or not.[30 33] The outstanding question is then when and in whom to commence anticoagulation since common calculators such as the CHA_2DS_2-VASc score are not applicable for use in FD.[34 35] Other Fabry-specific risk scores have been suggested[36] but further validation is needed.

The weighted estimate of event rate for symptomatic bradycardia and AV block requiring PPM implantation was 12.2% (95% CI 7.2 to 19.7). Although a few clinical predictors were identified in the systematic review (age, LVH, prolonged PR/QRS and beta-blocker therapy), the strength of association was again low with HRs between 1 and 1.2 for most. Chronic beta-blocker therapy alone, however, was a strong predictor of a bradycardic event necessitating PPM implantation (HR 7.333, p=0.024). Beta-blockers are often used to treat ventricular arrhythmia occurring in FD, but this suggests that greater caution should be taken. Risks are not limited to beta-blocker therapy but likely extend to other bradycardia-inducing drugs, such as amiodarone,[37] due to potential interaction with lysosomal activity. The additional concern is that, once the conduction system is affected in FD sufficient to stimulate tachyarrhythmias, the same disease processes may simultaneously increase susceptibility to symptomatic bradycardia and AV block.

The limitation of this systematic review is the absence of large prospective or multicentre trials. Most of the data described in this review are from retrospective cohort studies without the presence of detailed matched control cohorts. Thus, there is a high risk of bias due to a failure to consider potential confounding factors. Future prospective studies characterising risk predictors of both atrial and ventricular arrhythmias will hopefully provide further insight into this area in FD.[38]

CONCLUSION

This review has demonstrated that the incidence of AF and PPM implantation is variably reported, and the burden of arrhythmia may be much higher than previously believed. Diagnosis of asymptomatic atrial high rate episodes from a cardiac device was frequent, and it is possible that these may represent AF and contribute to the increased risk of ischaemic stroke, the second highest cause of mortality in patients with FD. Early diagnosis and initiation of therapy are crucial in preventing adverse cardiovascular outcomes. Understanding the precise mechanisms involved and thus clinical predictors of arrhythmia are essential in establishing therapy promptly.

Author affiliations
[1]Institute of Cardiovascular Sciences, University of Birmingham, Birmingham, UK
[2]Department of Cardiology, Queen Elizabeth Hospital, Birmingham, UK
[3]Department of Histopathology, Queen Elizabeth Hospital, Birmingham, UK
[4]University College London, London, UK
[5]Department of Cardiology, Saint Bartholomew's Hospital Barts Heart Centre, London, UK
[6]Department of Cardiology, Salford Royal Hospital, Salford, UK
[7]Department of Metabolic Medicine, Queen Elizabeth Hospital, Birmingham, UK
[8]University of Birmingham, Birmingham, UK

Twitter Ashwin Roy @ashwinroy90 and Richard Paul Steeds @Richard.Steeds

Contributors RV and PD conducted the literature search and identified eligible studies. Included studies were evaluated by JdB and RPS with support from DAH, PW, AW and JM. Data was extracted by RV, PD and AR. Statistical analysis was conducted by RV and AR. The manuscript was written by RV with support from AR, RPS, AW, DAH, JM and PW. The manuscript was reviewed by all authors prior to submission. RPS is responsible for the overall content as guarantor.

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ORCID iDs
Ashwin Roy http://orcid.org/0000-0003-4600-2733
Dipak Kotecha http://orcid.org/0000-0002-2570-9812
Richard Paul Steeds http://orcid.org/0000-0001-5687-2535

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