TITLE: Ventricular arrhythmia and sudden cardiac death in Fabry disease: A systematic review of risk factors in clinical practice

Short title: Arrhythmia and sudden death in Fabry disease

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ABSTRACT

Aims

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of α-galactosidase-A enzyme. Heart disease is a common cause of mortality in FD, in particular heart failure, arrhythmia and sudden death. There are no clear models for risk prediction in FD. This systematic review aims to identify risk factors for ventricular arrhythmia and sudden cardiac death in FD.

Methods

A systematic search was performed following PRISMA guidelines of EMBASE, Medline, PubMed, Web of Science, and the Cochrane Collaboration from inception to August 2016, focusing on identification of risk factors for the development of ventricular arrhythmia or SCD regardless of study type. Registration: PROSPERO-CRD42016042326.

Results

Thirteen studies were included in the systematic review from 1188 articles (n=4146 patients), including one interventional trial and 12 observational studies with an average follow-up of 1.2 to 10 years. Weighted average age was 37.6 years and 2064/2002 was male/female. Death from any cause was reported in 8.3%, death from cardiac causes in 6.2% and SCD in 5.2%. Ventricular tachycardia was reported in 7 studies, with an average prevalence of 15.3%. Risk factors associated with SCD were age, male gender, left ventricular hypertrophy, late gadolinium enhancement on cardiovascular magnetic resonance imaging and non-sustained ventricular tachycardia. Risk of bias was high for selection of participants and for inadequate consideration of confounding variables.

Conclusion

Ventricular arrhythmia and SCD are common in FD. Limited evidence highlights the importance of clinical and imaging risk factors that could contribute to improved decision-making in the management of FD.

KEYWORDS (three to six keywords)

Fabry Disease

Systematic Review

Sudden cardiac death

Ventricular tachycardia

Risk factors

Arrhythmia

CONDENSED ABSTRACT

In a systematic review of ventricular arrhythmia and sudden cardiac death in Fabry disease, a high risk of adverse outcomes was found. Limited evidence suggests that older age, male gender, left ventricular hypertrophy, late-gadolinium enhancement and non-sustained ventricular tachycardia may be important indicators of long-term risk.

ABBREVIATIONS LIST

Abbreviation	**Meaning**
FD	fabry disease
SCD	sudden cardiac death
VA	ventricular arrhythmia
VT	ventricular tachycardia
NSVT	non sustained ventricular tachycardia
LV	left ventricle
LVH	left ventricular hypertrophy
α-gal-A	α galactosidase-A
LGE	late-gadolinium enhancement on cardiac magnetic resonance
CV	cardiovascular
HCM	hypertrophic cardiomyopathy
MSSI	Mainz severity score index
LysoGb3	globotriaosylsphingosine
Gb3	globotriaosylceramide
CMR	cardiovascular magnetic resonance imaging

INTRODUCTION

Fabry disease (FD) is an X-linked lysosomal storage disorder caused by deficiency of α galactosidase-A (α-gal-A) enzyme.[1] This leads to failure to degrade glycosphingolipids and its consequent lysosomal accumulation, in particular globotriaosylceramide (Gb3) and globotriaosylsphingosine (lysoGb3), resulting in multi-system disease including progressive renal impairment, cardiomyopathy and cerebrovascular events. The spectrum of clinical involvement is variable from severe disease in 'classical' males, predominant cardiac involvement in 'cardiac variants', to varying phenotypes in females.[2] Despite being X linked, heterozygous females present with a range of clinical involvement through poorly understood mechanisms.[3,4]

Characteristic cardiovascular (CV) features include left ventricular hypertrophy (LVH), congestive heart failure, and arrhythmia. Symptoms of palpitations and syncope are common and have been reported in up to 30% of patients [5]. Registry data have indicated that CV disease is the most common cause of death in FD, although detail on causation is limited.[6,7] Gb3 and lysoGb3 accumulates in various cardiac cell types, including microvascular endothelium, smooth muscle cells, fibroblasts, conduction tissue and cardiomyocytes leading to a clinical picture that may mimic sarcomeric hypertrophic cardiomyopathy. In addition to the risks posed by myocardial cell hypertrophy, ischaemia and fibrosis, glycolipid accumulation affects conduction tissue contributing to electrical instability (figure 1).[8] There are however, no clear models for risk prediction in FD, and it is specifically excluded from calculators of arrhythmic risk in hypertrophic cardiomyopathy.[9] The purpose of this systematic review is to define the risk of ventricular arrhythmia (VA) and sudden cardiac

death (SCD) in patients with FD, and to identify risk factors for these adverse clinical outcomes.

METHODS

This systematic review was prospectively registered on PROSPERO database (CRD42016042326) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[10]

Literature Search

Two researchers (SB and BL) performed the search independently. All studies that referenced to FD, VA and SCD published from inception to August 2016 and available with an English Language abstract were identified. Electronic search engines used included: Embase, Medline, PubMed, Web of Science, and Cochrane. Relevant Medical Subject Headings (MeSH) and keywords were employed, although due to the rare nature of FD, the search strategy was kept broad to ensure high recall (Supplementary Table 1). There was no restriction on the type of study design. The following is an example of search keywords used:

- Ventricular OR arrhythmia AND (FD OR FD OR Anderson Fabry disease OR Fabry disease OR Fabry)
- Sudden cardiac death OR death AND (FD or FD or Anderson Fabry disease or Fabry disease OR Fabry).

Study Selection and Eligibility Criteria

The first level of filtration included screening of titles, authors and abstracts and was completed independently by the same two reviewers (SB, BL). Where relevant articles were identified, these were read in full by the reviewers and the references checked manually to ensure all relevant articles were shortlisted. Initial filtration removed single person case studies, duplications of datasets and publications, reviews, and animal studies. In addition,

abstracts were compared against the following inclusion criteria; (1) genotype-positive FD patients, (2) adult age range >16 years, (3) predominantly English language although other language articles were considered where available as English translations, (4) arrhythmia and/or SCD. No risk factors were required for inclusion, although risk factors were identified where possible to inform the second part of the systematic review. This resulted in a shortlist of articles which made some reference to VA or SCD and included studies, multiple person case series, and case reports.

Quality Assessment

Each paper within the final shortlist was then subjected to full evaluation of their quality by two independent reviewers (NE; RS). The papers were first reviewed to confirm eligibility and relevance of content. The Risk of Bias Assessment Tool for Non-Randomized Studies (RoBANS) was then used to assess the quality of studies in key areas including selection, performance, detection, attrition and reporting bias (supplementary table 2). Any differences in ROBANS rating were resolved with mutual discussion and consensus among reviewers.

Data Collection and Analysis

Data were extracted on a standardized spreadsheet, including inclusion and exclusion criteria, patient characteristics (age, gender, risk factors), study design (prospective or retrospective), duration of follow-up, any statistical association (e.g. univariate and/or multivariate, Cox regression analysis, hazard ratios, etc), and endpoints (VA and SCD). Case reports were not included in data extraction or analysis but a brief descriptive comment has been included (supplementary Table 4).

Data Analysis

There were significant differences among the included studies in design and presentation, preventing any statistical analysis for meta-analysis. Therefore, the data are presented qualitatively.

RESULTS

Study Selection and Study Characteristics

The initial search resulted in 1188 articles with 845 remaining after removal of duplicates. After abstract and title analysis, 792 articles were excluded. From the 53 papers remaining, 7 were excluded due to incomplete data sets, 8 did not meet the inclusion/exclusion criteria of this systematic review, 7 were removed because of duplication of data within the same cohort, 1 was excluded due to inclusion of paediatric patients and 17 were categorised as case reports (supplementary table 3 and 4).

The remaining 13 papers were subject to full data extraction. The overall filtration process is detailed in Figure 2. Average hazard ratios could not be calculated for the possible risk factors because only two studies reported a hazard ratio. There was considerable variation in study type and outcomes. Twelve studies included were observational in nature with only one being designed as an interventional trial. Only 3 studies [11–13] had VA or SCD as a primary end point, in the other 10 studies, these were combined with other outcomes to form composite endpoints.

The average follow-up ranged from 1.2 to 10 years. Weighted average age was 37.6 years with male/female ratio of 0.99 (2084/2101). Among studies which reported on mortality, death from any cause was reported in 7.8%, death from cardiac causes in 5.9 % and SCD in 4.9%. Ventricular tachycardia was reported in 7 studies, with an average prevalence of 15.3%. Patient and study characteristics are summarised in Tables 1 & 2.

Incidence and Prevalence of SCD and VA

No studies have focussed on SCD as an independent primary end-point. The major FD registries (Fabry Registry and Fabry Outcome Survey) do not collect specific information about SCD. From sparse single centre data, the incidence of SCD ranges from 0.34 to 1.4 % per annum [11,12,14] which is similar to that of hypertrophic cardiomyopathy, although these data were focussed on the young and there may be a risk of ascertainment bias.[15] This rate is higher than that in the non-selected general population of 0.05 to 0.1 % per annum. [16] The frequency of malignant VA varies widely from 5 % [13] to 30 % [17,18].

Risk Factors for SCD and VA

Gender

FD registry data suggest that males have a reduced life expectancy compared to females (58.2 years vs. 75.5 years), with death from any cause increasing in males $\geq$40 years and females $\geq$ 60 years.[7] Fabry registry data suggest that cardiovascular death is the main cause of mortality in both sexes (30/56 males and 5/10 females who died).[7] Two studies have identified male gender as a risk factor for SCD (11/14 deaths).[14,18] but only one of these studies identified it as an independent risk factor for SCD.[14]

No studies have looked specifically at the relationship between gender and VA in FD but 2 studies found these to occur more commonly in males. In a single centre study of 78 consecutive patients (55% male) with a mean follow-up of 1.9 years, Non sustained ventricular tachycardia (NSVT) was reported on 24 hour ambulatory electrocardiographic monitoring in 5/60 patients all of whom were male, with one subject dying of SCD.[11] In a single centre study of the effects of enzyme replacement therapy on complications of FD in

40 patients treated for 6 years, all 6 patients who experienced SCD were male and had evidence of VA on ambulatory ECG monitoring.[18] These studies did not include multivariate analysis to take account of potential confounding factors, such as degree of LVH.

Age

There were no studies looking at age and SCD but three studies have specifically looked at age and all cardiovascular deaths, with SCD being the predominant cause identified in both studies. In a single centre study of 207 patients with 7 years follow-up, cardiovascular deaths occurred in 7 males aged over 40 years (41-85yrs), of which 5/7 were classified as SCD. Age was a univariate predictor of cardiovascular death.[14] The second single centre study of FD enrolled 33 male patients at a mean age 39.2±12.3 years with median 7.3 years follow-up. Cardiovascular death occurred in 7 patients, of which 5 were classified as due to VA or SCD.[19] In univariate analysis in this study, the odds ratio for cardiovascular death in those aged >50 years was 10.2 (1.50–69.8)), compared to those <50 years. In a further study limited to 25 male FD patients with mean age 37.7 $\pm$ 10.9 years on enzyme replacement therapy followed up over 10 years, 8 cardiovascular deaths occurred of which 6 were SCD and all of which occurred in patients age > 40 years (43-49).[20]

None of the studies specifically attributed a statistical risk of VA to age, although in one single centre study (n=60) with a mean follow-up of 1.9 years, all 5/60 patients with VA were aged > 40 years (46 to 83).[11]

Left Ventricular Hypertrophy

Three studies have looked at the association between LVH and outcomes in FD.[14,18,21] In a prospective study of 207 patients from a single centre with a mean follow-up of 7.1 years investigating the clinical and genetic predictors of major CV events, total CV mortality was associated with echocardiographic LVH indexed to body surface area on multivariate analysis (HR 1.05 (CI 1.02 to 1.09)).[14] In a retrospective single centre cohort study of 25 patients, all 6 who experienced SCD had LVH, with LV mass (calculated using the Deveraux formula by M-mode) showing a univariate association with a combined end point of stroke, end-stage renal disease and death (HR 1.12, CI 1.03-1.23).[18] In a third single-centre study of mortality in 80 patients on enzyme replacement therapy there were a total of 7 deaths over a median follow up of 8 years. Three deaths were from SCD. and a higher LV mass index measured on echocardiography (202± 86 vs. 107± 40 g/m2; $p<0.01$) was associated with reduced survival on bivariate analysis.[21]

Only one study commented on any association between LVH and VA specifically. In a prospective single centre study of 78 patients, a maximal wall thickness > 20 mm and mean mass index 243.6±102 g/m2 measured on echocardiography were present in all 5 patients with VA.[11]

Late Gadolinium Enhancement

Late gadolinium enhancement (LGE) on cardiovascular magnetic resonance imaging (CMR) is used to characterize myocardial involvement in FD which, on histology, has been attributed to myocardial fibrosis [22]. LGE on CMR imaging corresponded to histological evidence of fibrosis in a post-mortem study of 7 patients with advanced cardiomyopathy; all had evidence of marked fibrosis on histology with ambulatory ECG monitoring confirming

VA [23]. In addition, 6/7 patients had evidence of inferolateral wall thinning, a common site for late enhancement on cCMR imaging in FD.

The presence of LGE has been associated with an increased risk of cardiovascular mortality in large populations and in several cardiovascular diseases, including hypertrophic cardiomyopathy, there has been interest in defining an associated risk of VA and SCD.[24–26] The evidence for LGE as a risk factor in FD comes from 2 studies from the same centre. In one prospective observational cohort study of 73 patients followed for a median 4.8 + 2.4yrs, 13/73 patients had VA identified on ambulatory ECG monitoring , all of whom had LGE while none of the patients without late gadolinium enhancement had evidence of VA (Kaplan-Meier analysis: log-rank p ¼ 0.017).[12] Furthermore, in 72/73 patients with serial CMR imaging, increase LGE over serial imaging was found to be greater in those with malignant ventricular arrhythmia and this was the only independent predictor of Vas identified (p=0.038). Five patients suffered SCD during follow up, all of whom had late gadolinium enhancement and prior VA. In the second study by this group, 16 patients with known cardiomyopathy on enzyme replacement therapy and evidence of LGE were monitored with implantable loop recorders and followed up for a median 1.2 years (0.3 to 2.0). [17] Five patients had evidence of VA and 4 of these went on to have an implantable cardio-defibrillator.

Non-Sustained Ventricular Tachycardia

Non-Sustained ventricular tachycardia (NSVT) has been widely used as a surrogate end-point for SCD. While NSVT was more frequent in the 3 studies of FD patients who have suffered SCD, a causal link has not been established and a lack of statistical association is complicated by the small numbers of subjects studied.[11,12,18] NSVT has been commonly defined in these 3

studies as an episode of ventricular tachycardia with a heart rate of at least 120 beats per minute, lasting for at least three beats and persisting less than 30 seconds. In the study by Shah et al (n=60), all patients with SCD had previous NSVT.[11] In the study by Krämer et al, 2 of 5 patients with SCD had previously documented NSVT.[12] In another study from the same group, all 6 patients with SCD had evidence of NSVT.[18]

Chronic Kidney Disease

It is widely recognised that SCD is a major cause of death in patients with chronic kidney disease (CKD).[27] While it is acknowledged that FD patients with CKD have an increased risk of cardiovascular events [19–21], none of these studies were designed to establish whether this is heightened compared to the risk that exists in the non-FD CKD population. There are no data on CKD as a risk factor for VA in FD.

Symptoms

Only one study has associated the presence of symptoms in the form of palpitations and syncope with VA [11]. In the single centre study by Shah et al, 5/60 patients with FD followed up for a median 1.9 years (0.3 to 10) had VA detected by ambulatory ECG monitoring. Three of 5 patients had syncope (OR 24.5, 95% CI 2.9-207.3, p=0.006) and 5/5 experienced palpitations (OR 1.4, 95% CI 1.04-1.3, p=0.003).[11]

Miscellaneous

Mainz Severity Score Index score, LA dimension and QRS duration were univariate predictors of cardiac death in a single study, with SCD being the predominant cause.[14] There

is a single case series describing a family with a specific mutation (p.M187R/g7219 T>G) in whom 4/17 members suffered a SCD.[28]

DISCUSSION

This systematic review is the first in FD looking specifically at the risk of SCD and VA. Cardiovascular disease is the leading cause of death in FD despite the availability of specific enzyme replacement therapy. Data remains sparse and is restricted to registries (subject to physician selection bias) and small single centre studies. Risk factors identified for SCD and VA in multiple studies include male gender, older age (> 40 years in males), increasing LV mass index, the presence of LGE on CMR imaging, and prior NSVT. Further research is need to determine the relative importance of each of these factors, with a view to the development of a risk calculator similar to that available for hypertrophic cardiomyopathy and thereby, evidence-based guidelines for the implantation of cardio-defibrillators in FD.

Unlike hypertrophic cardiomyopathy, advancing age appears to be associated with increasing risk of SCD in FD. This is consistent with the current concept of FD-related cardiomyopathy as a progression from early myocardial storage to LVH and myocardial fibrosis to end stage heart failure.[29] While age > 40 years seems to confer increased risk in men, this relationship is less well defined for women and could be 10-15 years later if it is assumed that there is a similar 'threshold' effect to onset of VA and SCD.[6,7] Although women present with cardiomyopathy later, they are also more likely to have evidence of LGE without LVH and the relative significance of these factors is not known.[30] More importantly, few VA and SCD have been reported in women in the existing literature and their representation may simply be a combination of effect of the ages sampled by the studies to-date, and gender bias due to X linked inheritance.[31] As better treatments emerge to treat complications of FD and improve life expectancy, this relationship may change.[32]

There is evidence that LGE on CMR confers increased risk of SCD and VA in a number of CV diseases.[33] The characteristic feature of FD on CMR is the presence of LGE in the basal inferolateral LV, with autopsy series confirming marked fibrosis in this region in advanced disease.[23] Moreover, there is electrophysiological evidence suggesting this region may be a source of VA.[34] Similar to hypertrophic cardiomyopathy, there appears to be increasing risk associated with LVH but the hypertrophy in FD is not simply a quantitative, proportionate consequence of sphingolipid deposition. Recent data have highlighted that other factors may be important in the hypertrophic response and in development of LGE, and that these could prove to be useful biomarkers in future. Firstly, troponin is released in FD and has been proposed to represent myocyte damage and consequent replacement fibrosis.[35] Secondly, multiparametric CMR has revealed that LGE in some patients with FD may not simply be end-stage fibrosis but has characteristics shared with an area of acute inflammation, with disproportionately high T2 values reflecting oedema.[36] It is not yet known whether high-sensitivity troponin, or an imaging biomarker such as T1/T2 mapping could be useful in predicting risk of arrhythmia.

The other risk factors identified by this systematic review are plausible but as yet lack supporting evidence. Palpitations and syncope are likely to be sensitive but are so common in patients with FD that it seems unlikely these will prove useful in a risk calculator without further clarification.[5] Involvement of the conduction system in FD is common, with shortening of the PR or PQ interval an early finding and evidenced both on electrophysiology [37] and pathology.[8] While prolongation of the QRS duration as a risk factor for SCD and VA is widely accepted and is a key element in patient selection for device therapy, evidence in FD is lacking and further evidence is required, particularly in view of the questions raised

regarding efficacy of implantable cardioverter-defibrillators in non-ischaemic cardiomyopathy.[38]

The main limitation of this review is the absence of any randomised trials or large multi-centre collaborative studies. Most evidence comes from retrospective cohort studies without matched controls and with a high risk of bias due to a failure to consider potential confounding variables, including coronary artery disease. Two large prospective FD registries have the potential to deliver data in the volume needed to inform risk stratification but after submitting formal enquiries to both, it was clear that current results are limited by the detail and accuracy of the clinical outcomes recorded. Prospective studies using minimally invasive loop recorders may in future improve recording of arrhythmias and thereby risk stratification. This review also focussed on SCD and VA, so did not investigate risk factors for brady-arrhythmia, which may of course contribute to adverse patient outcomes.[13]

CONCLUSION

This systematic review highlights the potential risk of ventricular arrhythmia and SCD in FD, while outlining factors that can contribute to decision-making for pharmacotherapy and device implantation. These risk factors include older age, male sex, left ventricular hypertrophy and late gadolinium enhancement but further research is needed to support clinicians managing FD in order to improve patient prognosis.

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Contributions

The study was conceived by SB, NCE, DK, JCM, TG and RPS. SB and BL performed the systematic search and literature review, NCE and RPS performed the quality assessment of the literature, SN and RK contributed to the script. All authors contributed to writing and reviewing of the final manuscript.

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36. Nordin S, Kozor R, Bulluck H, Castelletti S, Rosmini S, Abdel-Gadir A, et al. Cardiac Fabry Disease With Late Gadolinium Enhancement Is a Chronic Inflammatory Cardiomyopathy. J Am Coll Cardiol. 2016 Oct;68(15):1707–8.

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39. Deva DP, Hanneman K, Li Q, Ng MY, Wasim S, Morel C, et al. Cardiovascular magnetic resonance demonstration of the spectrum of morphological phenotypes and patterns of myocardial scarring in Anderson-Fabry disease. J Cardiovasc Magn Reson Off J Soc Cardiovasc Magn Reson. 2016;18:14.

TABLES

Table 1: Study Characteristics

References	Study Type	Inclusion Criteria	Exclusion Criteria
Shah 2005 [11]	Observational, longitudinal, prospective cohort	Diagnosis of FD based on plasma -galactosidase A levels and mutational analysis	None
Patel 2015 [14]	Observational, longitudinal, prospective cohort design with retrospective analysis	Confirmed FD based on plasma and leucocyte α-galactosidase A enzyme activity and sequencing of the GLA gene.	None
Weidemann 2013 [18]	Observational, longitudinal, prospective cohort with controls	Genetically confirmed FD treated for at least 5 years with ERT	None
Krämer 2014 [12]	Observational, longitudinal, prospective cohort	Genetically confirmed FD, no contraindication to CMRI, no ERT before study and no switch during study, minimum follow-up time of 1 year	None
Weidemann 2016 [17]	Non randomised clinical study without controls	Genetically confirmed FD, severe LV fibrosis, no previous clinically relevant arrhythmia on holter ECG, ERT for at least 12months	Anticoagulation treatment due to AF, implanted pacemaker or defibrillator, or AF/VT in the past.
Talbot 2015 [20]	Retrospective chart review	Genetically confirmed FD, male sex, ERT, available cardiac investigations	None
Nicholls 2012 [19]	Prospective cohort observational	Male sex, genetically confirmed FD	None
Waldek 2009[7]	Registry (observational database)	Genetically confirmed FD	None
Linhart 2007 [5]	Registry (observational database)	FD confirmed genetically and /or by enzyme assay.	None
Acharya 2012 [13]	Retrospective Chart review	FD cardiomyopathy	No cardiac involvement
Frustaci 2015 [8]	Cross-sectional study	FD with conduction system tissue included in at least 1 specimen on endomyocardial biopsy	None

Reisin 2016 [21]	Observational, longitudinal, prospective cohort	FD, ERT, at least 1 year follow up	None
Deva 2016[39]	Cross-sectional study	FD confirmed genetically and / or by enzyme assay.	age <18 at CMR acquisition, more than mild aortic stenosis, HCM mutations and LGE due to myocardial infarction

Table 2: Patient Characteristics and Study Outcomes

References	Number of patients	Phenotype	Male (%)	ERT	Mean age in years	Mean follow-up (range)	Ventricular tachycardia	Sudden cardiac death (%)	Death from cardiac cause (%)	Death from any cause (%)
Shah 2005 [11]	78	All	43/78 (55%)	41/78 (52.6%)	43.5 ±15.0	1.9 years (0.3 to 10)	5/60 (8%)	1/66 (1.5%)	1 / 66 (1.5%)	1/66 (1.5%)
Patel 2015 [14]	207	All	98/207 (47.3%)	47/207 (22.7%)	44±14.9	7.1 years (4.0–9.1)	not available	5/207 (2.4 %)	7/207 (3.3%)	13/207 (6.2%)
Weidemann 2013 [18]	40	All	31/40 (77.5%)	40/40 (100%)	40 ±9	6 years (median)	12/40 (30%)	6/40 (15%)	6/40 (15%)	7/40 (17.5%)
Krämer 2014 [12]	73	All	38/73 (48%)	0 / 73 (0 %)(57 received ERT after study started)	39 ±11	4.8±2.4 years	13/73 (17.8%)	5/73 (6.8%)	5/73 (6.8%)	5/73 (6.8%)
Weidemann 2016 [17]	16	All	12/16 (75%)	16/16 (100%)	52 ±11	1.2 years (0.3 to 2.0)	5/16 (31.25%)	0/16 (0 %)	0/16 (0%)	0/16 (0%)
Talbot 2015 [20]	25	All	25/25 (100%)	25/25 (100%)	37.7±10.9	10 years	NR	6 / 25 (24%)	6/25 (24%)	8/25 (32%)
Nicholls 2012 [19]	33	NR	33/33 (100%)	27/33 (81.1%)	39.2±12.3	7.3 years (0.9–9.5)	NR	3 / 33 (9.1 %)	7/33 (21%)	7/33 (21.2%)
Waldek 2009[7]	2848	All	1422/2848 (49.9%)	NR	NR	NR	NR*	NR*	35/2848 (1.2 %)	87/2848 (3%)
Linhart 2007 [5]	714	All	345/714 (48.3 %)	336/714 (47%)	35±17	Cross-sectional study	NR*	NR*	NR	NR
Acharya 2012 [13]	19	All	11/19 (57.89 %)	18/19 (94.7%)	18 to 72	4.4 years	1/19 (5.2%)	1/19 (5.2%)	1/19 (5.2%)	1/19 (5.2%)

Frustaci 2015 [8]	13	All	6 /13 (46.2%)	not available	50.1 ± 13.5	Cross-sectional study	2/13 (15.3%)	0/13 (0 %)	0/13 (0%)	0/13 (0%)
Reisin 2016 [21]	80	All	NR	80/80 (100%)	32±15	8 years	not available	3/80 (3.7 %)	3/80 (3.7%)	6/80 (7.5%)
Deva 2016[39]	39	All	20 (51 %)	27/39 (69%)	45.2 (34.7-55.5)	Cross-sectional study	5 /39 (13 %)	0/39(0%)	0/39 (0%)	0/39 (0%)

NR, not reported; ERT, enzyme replacement therapy

*Registries do not specifically collect information on sudden cardiac death. Reporting of specific ventricular arrhythmias is limited.

Table 3: Risk Factor Association

Anderson-Fabry disease risk factor	Strong association with VA	Moderate association with VA	Weak association with VA	Not enough evidence to support association with VA	Strong association with SCD	Moderate association with SCD	Weak association with SCD	Not enough evidence to support association with SCD
Male			✓			✓		
Age > 40 (For males > 40, unclear for females)			✓			✓		
LVH		✓				✓		
Late Gadolinium enhancement		✓				✓		
Ventricular Arrhythmias	Not applicable	Not applicable	Not applicable	Not applicable		✓		
Chronic kidney disease				✓			✓	
Palpitations			✓					✓
Syncope			✓					✓
Specific mutations				✓			✓	
QRS duration > 120				✓			✓	
Left atrial diameter > 40 mm				✓			✓	
Mainz severity score index				✓			✓	

Definition of associations: Strong – supported by randomised control trials; Moderate – supported by 2 or more studies (observational or clinical study); Weak – supported by 1 study or registry data only.

FIGURE LEGENDS

Figure 1: Etiopathogenesis of Cardiac Involvement in Fabry disease

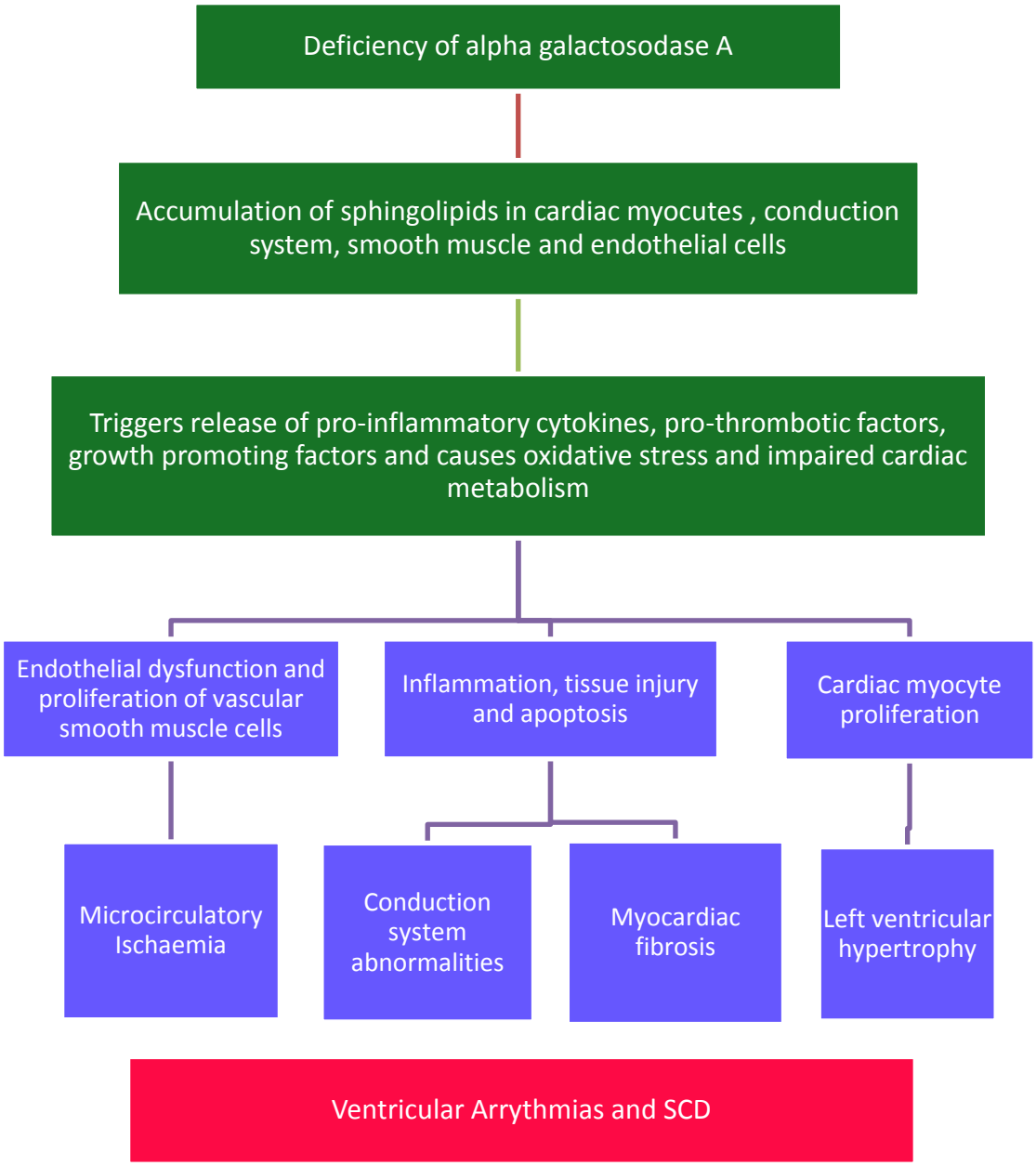
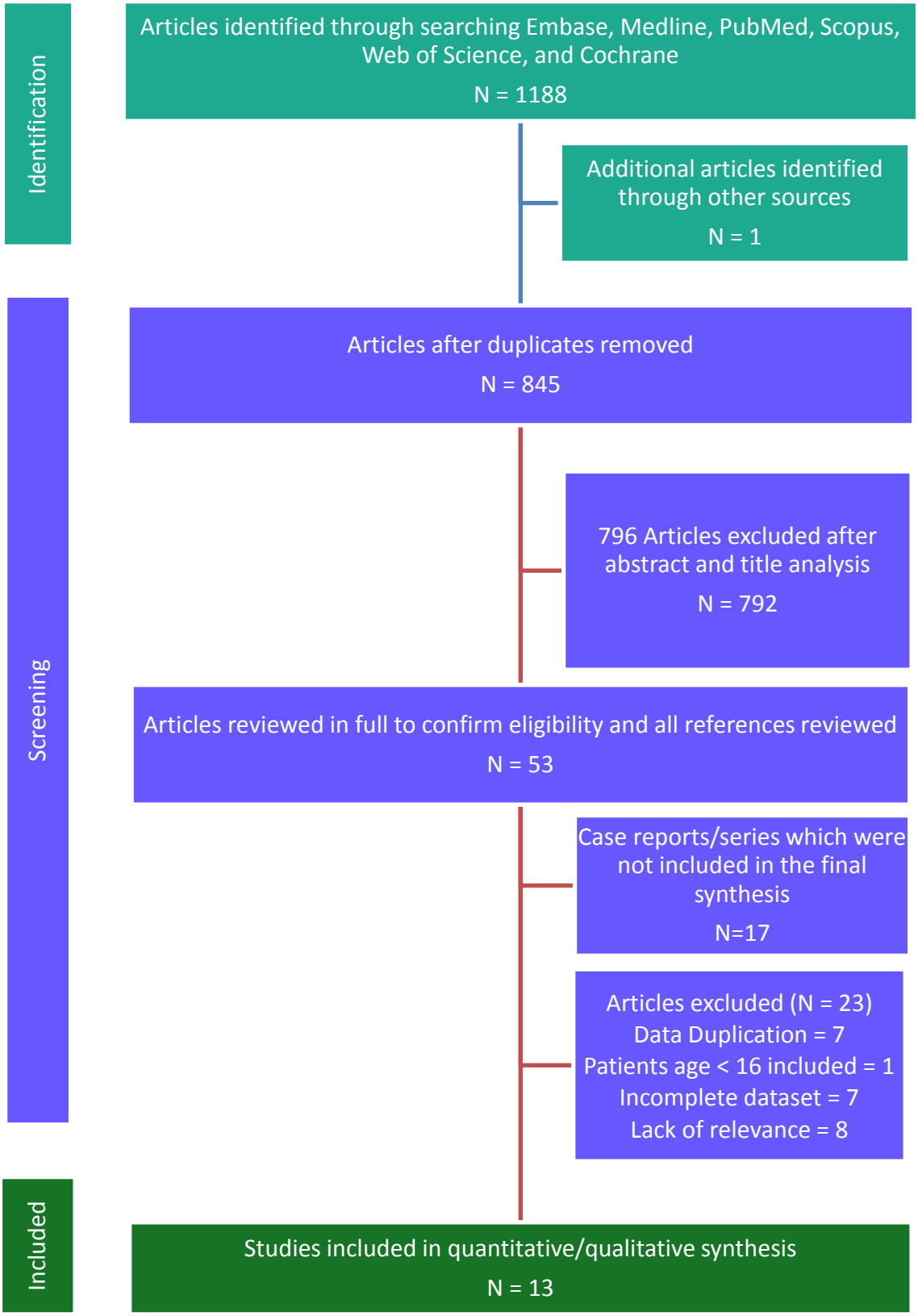


Figure 2: Search strategy



SUPPLEMENTARY DATA

Supplementary table 1: Search Strategy

Fabry registry data analysis request report 2016

A search strategy was formulated using following key search keywords, which were used in various combinations.

1. Ventricular
    - Ventricular Arrhythmia
    - Ventricular Tachycardia
    - Ventricular Flutter
    - Ventricular Fibrillation
    - Ventricle
    - Ventric*
    - Cardiac
    - Cardiac Arrhythmia
2. Arrhythmia
    - Arrhy*
    - Arrhythmia
    - Arrhythmia
    - Tachycardia
    - Fibrillation
3. Death
    - Sudden Cardiac Death
    - Death
    - Mortality

- Cardiopulmonary Arrest
- Heart Arrest
- Mortality

4. Fabry

- Fabry*
- Fabry
- Fabry Anderson Disease
- Anderson-Fabry Disease
- Fabry's Disease
- Fabry Disease
- Fabry Syndrome
- Fabry's Disease
- Fabry Syndrome
- FD

* at the end of a search term is used as a truncation and wildcard symbol

An example of some of the combinations used were

1. Fabry* AND (ventric* OR arrhy* OR death OR tachycardia)
2. Fabry AND (ventricular OR arrhythmia OR death OR tachycardia)
3. Ventricular OR arrhythmia OR death AND (AFD OR FD OR Anderson Fabry disease OR Fabry disease OR Fabry)
4. Sudden cardiac death AND (AFD or FD or Anderson Fabry disease or Fabry disease OR Fabry).

The search strategy was broad to ensure high recall. All references were subsequently imported into a reference manager and any duplicates removed.

Supplementary Table 2: ROBANS Assessment of Included Articles

References	Selection biases caused by the inadequate selection of participants	Selection biases caused by the inadequate confirmation and consideration of confounding variables	Performance biases caused by inadequate measurements of exposure	Detection biases caused by the inadequate blinding of outcome assessments	Attrition biases caused by the inadequate handling of incomplete outcome data	Reporting biases caused by the selective reporting of outcomes
Shah 2005 [11]	High	High	Low	Low	High	Low
Patel 2015 [14]	High	High	Low	Low	Unclear	Low
Weidemann 2013 [18]	Unclear	High	Low	Low	Low	Low
Krämer 2014 [12]	High	High	Low	Low	Unclear	Low
Weidemann 2016 [17]	Unclear	Low	Low	Low	Low	Low
Talbot 2015 [20]	High	High	Low	High	High	High
Nicholls 2012 [19]	High	High	Low	High	Low	Low
Waldek 2009 (14)	High	Unclear	Unclear	Unclear	Unclear	Low
Linhart 2007 [5]	High	High	High	Unclear	Unclear	Low
Acharya 2012 [13]	High	High	Low	Low	High	High
Frustaci 2015 [8]	High	High	Low	Unclear	High	Unclear
Reisin 2016 [21]	Unclear	High	Unclear	Low	Unclear	Unclear
Deva 2016[39]	High	High	Unclear	High	High	High

Supplementary Table 3: Excluded Articles

Articles Excluded	**Reason For Exclusion**
(Niemann et al., 2012) Niemann, M., Hartmann, T., Beer, M., Emmert, A., Breunig, F., Ertl, G., Wanner, C. and Weidemann, F. (2012). P07—Ventricular Arrhythmias are the Major Cause of Death in Patients With the Classical Phenotype of Fabry Disease. *Clinical Therapeutics*, 34(4), p.e21.	Duplication of data
(Mehta et al. 2009) Mehta, A., Clarke, J., Giugliani, R., Elliott, P., Linhart, A., Beck, M. and Sunder-Plassmann, G. (2009). Natural course of Fabry disease: changing pattern of causes of death in FOS - Fabry Outcome Survey. *Journal of Medical Genetics*, 46(8), pp.548-552.	Duplication of data
(Niemann et al., 2012) Niemann, M., Hartmann, T., Namdar, M., Breunig, F., Beer, M., Machann, W., Herrmann, S., Ertl, G., Wanner, C. and Weidemann, F. (2012). Cross-sectional baseline analysis of electrocardiography in a large cohort of patients with untreated Fabry disease. *Journal of Inherited Metabolic Disease*, 36(5), pp.873-879.	Duplication of data, Incomplete dataset to establish any risk association
(Krämer et al., 2015) Krämer, J., Nordbeck, P., Störk, S., Ritter, C., Ertl, G., Wanner, C. and Weidemann, F. (2015). Electrical Changes in Resting, Exercise, and Holter Electrocardiography in Fabry Cardiomyopathy. *JIMD Reports*, pp.19-28.	Duplication of data, Incomplete dataset to establish any risk association
(C. M. Eng et al., 2007) Eng, C., Fletcher, J., Wilcox, W., Waldek, S., Scott, C., Sillence, D., Breunig, F., Charrow, J., Germain, D., Nicholls, K. and Banikazemi, M. (2007). Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *Journal of Inherited Metabolic Disease*, 30(2), pp.184-192.	Duplication of data
(Manesh R. Patel et al, 2010) Patel, M., Cecchi, F., Cizmarik, M., Kantola, I., Linhart, A., Nicholls, K., Strotmann, J., Tallaj, J., Tran, T., West, M. and Abiose, A. (2010). Cardiovascular events in patients with fabry disease: natural history data from the fabry registry. Journal of the American College of Cardiology, 55(10), pp.A30.E291.	Duplication of data, Incomplete dataset to establish any risk association
(L.J. Pinderski, et al, 2006) Pinderski, L. and Strotmann, J. (2016). Congestive heart failure in fabry cardiomyopathy: natural history experience in an international cohort of 1,448 patients. The Journal of Heart and Lung Transplantation. Volume 25, Issue 2, Supplement, February 2006, Pages S70	Duplication of data, Incomplete dataset to establish any risk association
(Waldek et al. 2009) Waldek S.,Molana S.,Woolfson P. (2009). Cardiac arrhythmias due to fabry disease do not respond to enzyme replacement therapy. Molecular Genetics and Metabolism, September;October 2009,	Incomplete dataset to establish any risk association

vol./is. 98/1-2(75), 1096-7192 (September-October 2009)	
(Takenaka et al., 2008) Takenaka, T., Teraguchi, H., Yoshida, A., Taguchi, S., Ninomiya, K., Umekita, Y., Yoshida, H., Horinouchi, M., Tabata, K., Yonezawa, S., Yoshimitsu, M., Higuchi, K., Nakao, S., Anan, R., Minagoe, S. and Tei, C. (2008). Terminal stage cardiac findings in patients with cardiac Fabry disease: An electrocardiographic, echocardiographic, and autopsy study. Journal of Cardiology, 51(1), pp.50-59.	Incomplete dataset to establish any risk association
(San Román-Monserrat et al., 2014) San Román-Monserrat, I., Moreno-Flores, V., López-Cuenca, D., Rodríguez-González-Herrero, E., Guillén-Navarro, E., Rodríguez-González-Herrero, B., Alegría-Fernández, M., Poza-Cisneros, G., Piñero-Fernández, J., Sornichero-Martínez, J. and Gimeno-Blanes, J. (2014). Comprehensive clinical evaluation of a large Spanish family with Anderson-Fabry disease, novel GLA mutation and severe cardiac phenotype. Medicina Clínica, 142(11), pp.497-504.	Incomplete dataset to establish any risk association
(Robertson et al., 2009) Robertson, P., Kay, G., Warnock, D., Jackson, L. and Tallaj, J. (2009). 94: Arrhythmias and Implantable Cardioverter Defibrillators in Fabry Cardiomyopathy. The Journal of Heart and Lung Transplantation, 28(2), p.S98.	Incomplete dataset to establish any risk association
(Teraguchi H et al, 2004) Teraguchi H, Takenaka T, Yoshida A, Taguchi S, Ninomiya K, Yoshida H, Horinouchi M, Yonezawa S, Nakao S, Minagoe S, Tei S.(2004). End-stage cardiac manifestations and autopsy findings in patients with cardiac fabry disease. J Cardiol. 2004 Feb;43(2):98-9.	Incomplete dataset to establish any risk association.
(Fabry registry data analysis request report 2016)	Incomplete dataset to establish any risk association
(Schiffmann et al. 2009) Schiffmann, R., Warnock, D., Banikazemi, M., Bultas, J., Linthorst, G., Packman, S., Sorensen, S., Wilcox, W. and Desnick, R. (2009). Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. Nephrology Dialysis Transplantation, 24(7), pp.2102-2111.	Incomplete dataset to establish any risk association
(MacDermot, 2001) MacDermot, K. (2001). Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. Journal of Medical Genetics, 38(11), pp.769-775.	Lack of relevance
(MacDermot, 2001) MacDermot, K. (2001). Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. Journal of Medical Genetics, 38(11), pp.750-760.	Lack of relevance
(Kawano et al., 2007) Kawano, M., Takenaka, T., Otsuji, Y., Teraguchi, H., Yoshifuku, S., Yuasa, T., Yu, B., Miyata, M., Hamasaki, S., Minagoe, S., Kanmura, Y. and Tei, C. (2007). Significance of Asymmetric Basal Posterior Wall Thinning in Patients With Cardiac Fabry's Disease. *The*	Lack of relevance

American Journal of Cardiology, 99(2), pp.261-263.	
(Niemann et al., 2011) Niemann, M., Herrmann, S., Hu, K., Breunig, F., Strotmann, J., Beer, M., Machann, W., Voelker, W., Ertl, G., Wanner, C. and Weidemann, F. (2011). Differences in Fabry Cardiomyopathy Between Female and Male Patients. JACC: Cardiovascular Imaging, 4(6), pp.592-601.	Lack of relevance
(O'Mahony et al., 2011) O'Mahony, C., Coats, C., Cardona, M., Garcia, A., Calcagnino, M., Murphy, E., Lachmann, R., Mehta, A., Hughes, D. and Elliott, P. (2011). Incidence and predictors of anti-bradycardia pacing in patients with Anderson-Fabry disease. Europace, 13(12), pp.1781-1788.	Lack of relevance
(Blagova et al., 2011) Blagova O.V.,Nedostup A.V.,Kogan E.A.,Sulimov V.A.,Abugov S.A.,Kupryanova A.G.,Zaidenov V.A.,Donnikov A.E.(November 2011). What is behind "Idiopathic arrhythmia": Endomyocardial biopsy as a clue to the precise diagnosis. Pacing and Clinical Electrophysiology, November 2011, vol./is. 34/11(1450-1451), 0147-8389	Lack of relevance
(PazarinVillasenor et al., 2012) PazarinVillasenor, L.,ValadezJuvera, G.,FigueroaSauceda, S.,NavarroCruz, D.,RadilloDiaz, P.,LopezSantiago, M.A.,CerrillosGutierrez, I.,Aragaki Y.,Medina O. (April 2012). Cardiovascular manifestations of fabry disease in Mexico. Clinical Therapeutics, April 2012, vol./is. 34/4 SUPPL. 1(e24), 01492918.	Lack of relevance
(Schiffmann et al., 2014) Schiffmann, R., Forni, S., Swift, C., Brignol, N., Wu, X., Lockhart, D., Blankenship, D., Wang, X., Grayburn, P., Taylor, M., Lowes, B., Fuller, M., Benjamin, E. and Sweetman, L. (2014). Risk of Death in Heart Disease is Associated With Elevated Urinary Globotriaosylceramide. Journal of the American Heart Association, 3(1), pp.e000394-e000394.	Lack of relevance
(Kim JH et al, 2016) Kim, J., Lee, B., Hyang Cho, J., Kang, E., Choi, J., Kim, G. and Yoo, H. (2016). Long-term enzyme replacement therapy for Fabry disease: efficacy and unmet needs in cardiac and renal outcomes. Journal of Human Genetics.	Paediatric and adults combined

Supplementary Table 4: Case Reports Excluded

Case Reports	No of cases
(Efthimiou et al. 1986) Efthimiou, J., McLelland, J. and Betteridge, D. (1986). Short PR intervals and tachyarrhythmias in Fabry's disease. Postgraduate Medical Journal, 62(726), pp.285-287.	3
Ikari et al. 1992 (Ikari, Y., Kuwako, K. and Yamaguchi, T. (1992). Fabry's disease with complete atrioventricular block: histological evidence of involvement of the conduction system. Heart, 68(9), pp.323-325.)	1
(Sivaloganathan 1992) Sivaloganathan, S. (1992). 3. Fabry's Disease – A Rare Cause of Sudden Death. Medicine, Science and the Law, 32(3), pp.263-266.	1
(Carter et al. 1995) Carter, N., Milroy, C. and Shepherd, R. (1995). Sudden Death in Elderly Women with Fabry's Disease. The American Journal of Forensic Medicine and Pathology, 16(1), pp.21-26.	2
(Eckart et al. 2000) Eckart, R., Kinney, K., Belnap, C. and Le, T. (2001). Ventricular Fibrillation Refractory to Automatic Internal Cardiac Defibrillator in Fabry's Disease. Cardiology, 94(3), pp.208-212.	1
(Igawa et al. 2005) (Igawa, O., Miake, J. and Hisatome, I. (2005). Ventricular Tachycardias and Dilated Cardiomyopathy Caused by Fabry Disease. Pacing and Clinical Electrophysiology, 28(10), pp.1142-1143.)	1
(Frustaci and Chimenti, 2007) Frustaci, A. and Chimenti, C. (2007). Cryptogenic Ventricular Arrhythmias and Sudden Death by Fabry Disease: Prominent Infiltration of Cardiac Conduction Tissue. Circulation, 116(12), pp.e350-e351.	1
(Joshi et al. 2008) (Joshi, S., Ahmar, W., Lee, G. and Aggarwal, A. (2008). Fabry's disease presenting as ventricular tachycardia and Left Ventricular 'Hypertrophy'. European Journal of Echocardiography, 9(5), pp.697-699.)	1
(Mougenot et al. 2008) Mougenot, P., Lidove, O., Caillaud, C., Arnaud, P. and Papo, T. (2008). Fabry disease and treatment with agalsidase alpha: unsuspected cardiac arrhythmia in two heterozygous women. European Journal of Clinical Pharmacology, 64(6), pp.635-639.	2
(Fukuzawa et al. 2009) Fukuzawa, K., Yoshida, A., Onishi, T., Suzuki, A., Kanda, G., Takami, K., Kumagai, H., Torii, S., Takami, M., Fukuda, Y., Kawai, H. and Hirata, K. (2009). Dilated phase of hypertrophic cardiomyopathy caused by Fabry disease with atrial flutter and ventricular tachycardia. Journal of Cardiology, 54(1), pp.139-143.	1
(Nakano et al. 2010)	1

Nakano, E., Harada, T., Soejima, K., Sasaki, T., Mizuno, K. and Miyake, F. (2010). Catheter Ablation of Reentrant Left Ventricular Tachycardia Associated with Fabry disease: A Case Report. Journal of Arrhythmia, 26(3), pp.209-215.	
(Li et al. 2012) Li J, Warth A, Schnabel P, Schweizer PA, Buss SJ, Steen H, et al. Electrophysiological findings in Fabry cardiomyopathy: mapping the maze of risk stratification. Acta Cardiol. 2012 Aug;67(4):481–5.	1
(Poulin et al. 2015) Poulin M-F, Shah A, Trohman RG, Madias C. Advanced Anderson-Fabry disease presenting with left ventricular apical aneurysm and ventricular tachycardia. World J Clin Cases. 2015 Jun 16;3(6):519–24.	1
(Kanda et al. 2015) Kanda, T., Masuda, M., Sunaga, A., Fujita, M., Iida, O., Okamoto, S., Ishihara, T., Nanto, K., Shiraki, T., Sera, F. and Uematsu, M. (2015). Fabry cardiomyopathy presenting with a high defibrillation threshold: A short case report. Journal of Arrhythmia, 31(3), pp.170-171.	1
(Nakano et al. 2015) Nakano, M., Fukuda, K., Kondo, M., Segawa, M., Hirano, M., Chiba, T., Fukazawa, K., Miki, K., Morosawa, S. and Shimokawa, H. (2015). Implantable Cardioverter Defibrillator for Primary Prevention Properly Terminated Ventricular Tachycardia in Patient with Cardiac Fabry Disease. Journal of Cardiac Failure, 21(10), p.S188.	1
(Rodda et al. 2016) Rodda, O., Lynch, M. and Parsons, S. (2016). Sudden death following AV node ablation in a man with Fabry disease mimicking hypertrophic cardiomyopathy. Journal of Forensic and Legal Medicine, 42, pp.8-10.	1
(Higashi et al. 2011) Higashi, H., Yamagata, K., Noda, T. and Satomi, K. (2011). Endocardial and epicardial substrates of ventricular tachycardia in a patient with Fabry disease. Heart Rhythm, 8(1), pp.133-136.	1