Predicting Arrhythmic Risk in Arrhythmogenic Right Ventricular Cardiomyopathy: A Systematic Review and Meta-Analysis

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Abstract

While many studies evaluate predictors for ventricular arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), a systematic review consolidating this evidence is currently lacking. Therefore, we searched MEDLINE and Embase for studies analyzing predictors for ventricular arrhythmias (sustained ventricular tachycardia/fibrillation (VT/VF), appropriate implantable cardioverter-defibrillator therapy, or sudden cardiac death) in definite ARVC patients, borderline ARVC patients, and ARVC-associated mutation carriers. In case of multiple publications on the same cohort, the study with the largest population was included. This yielded 45 studies with a median cohort size of 70 (IQR 60) patients and 5.0 (IQR 3.5) years follow-up. The arrhythmic outcome was observed in 10.6%/year in definite ARVC patients, 10.0%/year in borderline ARVC patients, and 3.7%/year in mutation carriers. Predictors for ventricular arrhythmias were population-dependent: consistently predictive risk factors in definite ARVC patients were male sex, syncope, T-wave inversion >V3, right ventricular (RV) dysfunction, and prior (non)sustained VT/VF; in borderline ARVC patients, two additional predictors (inducibility at electrophysiology study and strenuous exercise) were identified; and in mutation carriers, all aforementioned predictors as well as ventricular ectopy, multiple ARVC-related pathogenic mutations, left ventricular dysfunction, and palpitations/pre-syncope determined arrhythmic risk. Most evidence originated from small observational cohort studies, with a moderate quality of evidence. In conclusion, the average risk of ventricular arrhythmia ranged from 3.7% to 10.6%/year depending on the ARVC population. Male sex, syncope, T-wave inversion >V3, RV dysfunction, and prior (non)sustained VT/VF consistently predict ventricular arrhythmias in all ARVC populations.

Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is an inherited cardiomyopathy with a high risk of ventricular arrhythmias, most notably in young individuals and athletes.[1] Identifying individuals at highest risk of arrhythmias is crucial to prevent sudden cardiac death (SCD) using an implantable cardioverter-defibrillator (ICD). Conversely, recognizing subjects at low arrhythmic risk is important since ICD placement bears a considerable risk of complications and inappropriate interventions.[2,3] Since the clinical expression of ARVC is variable, reliable risk prediction is difficult, which presents a challenge to physicians and patients alike.

Over the years, many studies have described risk factors for ventricular arrhythmias in ARVC, including a consensus statement on ARVC treatment.[4] Despite the wealth of data in the literature, most studies were non-randomized, included relatively small patient numbers, and did not account for differences in patient subgroups, leading to high variation in the reported associations. Indeed, while previous sustained ventricular arrhythmias and ventricular dysfunction are generally recognized as important predictors of arrhythmic events, the prognostic value of other risk factors remains unclear. To the best of our knowledge, a systematic review and meta-analysis summarizing the available evidence is currently lacking.

In light of these shortcomings, we systematically reviewed observational studies that assessed predictors for ventricular arrhythmias in ARVC. We evaluated the quality of evidence, quantified them using pooled analyses when appropriate, and performed sub-analyses on patient subgroups to obtain subgroup-specific risk estimates. The results of these analyses may aid clinical decision-making, counseling, and expectation management in this high-risk population.

Methods

This study was performed in accordance with the guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[5] and Meta-analysis of Observational Studies in Epidemiology (MOOSE)[6]. We performed a systematic search of MEDLINE and Embase in January 2017 for clinical studies on risk factors for ventricular arrhythmias in patients with ARVC. A detailed description of our search strategy, selection and data extraction can be found in the Supplementary Methods.

Study Eligibility and Definitions

Any original study involving an ARVC population that investigated an association between ≥1 risk factor(s) and a predefined arrhythmic outcome was considered eligible for inclusion in this review.

The *study population of interest* included patients fulfilling diagnostic Task Force Criteria (TFC) for ARVC. Of note, these criteria were first described in 1994 and revised in 2010[7]. Since restricting the patient population to either one of these criteria would inevitably lead to selection bias, both were considered eligible for inclusion. The included studies were classified in three categories (i.e. patient domains) based on their inclusion criteria: (1) "definite ARVC" refers to cohorts in which all patients fulfilled diagnostic TFC, (2) "borderline ARVC" refers to cohorts in which patients had at least a borderline ARVC diagnosis (TFC score ≥3, thus including definite ARVC patients), and (3) "mutation carriers" refers to cohorts of ARVC-associated mutation carriers regardless of phenotypic expression, thereby including both asymptomatic mutation-carrying relatives and a (small) proportion of definite ARVC patients. Since all three subgroups include definite ARVC patients, all were considered relevant for the purpose of our analyses. However, the patient domains were separately analyzed in this manuscript, since these differences in inclusion criteria is likely to affect the reported results.

The *outcome of interest* was potentially lethal ventricular arrhythmias. All studies that included spontaneous ventricular tachycardia (VT) or ventricular fibrillation (VF), sudden cardiac arrest, SCD, or appropriate ICD intervention for a ventricular arrhythmia were considered eligible for inclusion in this study. Non-sustained VT was excluded as an outcome in our analyses. Since almost all studies exclusively reported risk estimates for a combined arrhythmic outcome, we were obliged to consider all arrhythmic outcomes as equal, although we report outcome-specific risk estimates if available. Studies that included non-arrhythmic outcomes, such as heart failure, heart transplantation or overall mortality, were excluded unless subgroup analysis for arrhythmic outcome was provided or could be reconstructed.

Quality Assessment

To assess the individual study quality and risk of bias, we used the Quality In Prognostic Studies (QUIPS) tool developed by the Cochrane Collaboration.[8] Details can be found in the Supplementary Methods. Study quality was assessed independently by two investigators (LPB and AZS); and a third (ASJMTR) in case of disagreement.

Statistical Analysis

Our analyses were divided in two components: (1) we presented a description of all studies that provided OR, risk ratios (RR), Kaplan Meier (KM) or Receiver Operator Characteristic (ROC), for every risk factor separately; (2) we pooled all studies that reported HRs in a meta-analysis, provided that the variable definitions were uniform. Only studies reporting HRs were considered for meta-analysis, as ORs can only reliably be pooled when follow-up time is equal. Furthermore, meta-analyses were only performed on crude (i.e. unadjusted) HRs within the same patient domain; studies selecting participants based on genotype were not pooled due to the expected high variation in phenotypic expression. All meta-analyses were conducted in Review Manager (RevMan 5.3, Copenhagen: The Cochrane Collaboration, 2014). Statistical heterogeneity between studies was assessed using the Chi-square homogeneity test, expressed by the I^2 index, where I^2 values indicated low(<25%), moderate(25-75%) and high(>75%) degree of heterogeneity. Study-specific crude HRs were combined using inverse variance-weighted averages of a random effects model. Sensitivity analyses were performed to assess the contribution of selection differences based on (1) TFC version and (2) primary prevention populations.

Results

Search Results

Our search results and selection process is shown in Figure 1. Our literature search yielded 712 unique records, which were carefully screened based on title and abstract. Records (n=617) that did not report on prognostic factors for arrhythmic outcomes in the appropriate population were excluded. The remaining 95 candidate publications received a thorough full-text assessment, resulting in a total of 45 studies that met the inclusion criteria, see Supplementary Reference for a full reference list of the included studies. An overview of the excluded studies with reasons for exclusion can be found in Supplementary Table 1. Potential cohort overlap was excluded at the level of the individual risk factors by maintaining only the study with the largest population as disclosed in Figure 2.

Study Characteristics

The 45 included studies were published between 1999 and 2017 and had a median cohort

size of 70 patients (IQR 60; range 24-541), among whom a median of 31 patients (IQR 30; range 5-301) experienced arrhythmic events during a median follow-up of 5.0 years (IQR 3.5; range 3.2-7.6). The study population included definite ARVC patients in 28 studies, definite or borderline ARVC patients in 9 studies (median 76% fulfilling definite diagnosis [IQR 12; range 68-87%]), and ARVC-associated mutation carriers independent of phenotypic expression in the remaining 8 studies (median 60% fulfilling definite diagnosis [IQR 4; range 34-71%]). ARVC diagnosis was based on the original 1994 TFC in 15 (33.3%) studies and the modified 2010 TFC in 30 (66.7%) studies. While most studies did not differentiate between primary or secondary prevention, ten studies excluded patients who experienced a sustained arrhythmic event prior to inclusion, and three studies included only secondary prevention patients. Figure 2 summarizes the study characteristics.

Quality Assessment

Using the QUIPS tool[8], the risk of bias was evaluated for six pre-defined areas important in observational prognostic research; (1) study participation, (2) study attrition, (3) prognostic factor measurement, (4) outcome measurement, (5) study confounding, and (6) statistical analysis and reporting. As shown in Figure 3, the highest potential for bias was introduced by limited or absent adjustment for confounders using multivariable analysis ("study confounding") and the use of statistical models not correcting for individual and group differences in follow-up time ("statistical analysis and reporting"). Additionally, bias due to selective loss to follow-up ("study attrition") could not be ruled out for most studies as loss to follow-up was rarely addressed. Only studies that reported HRs were used in the meta-analysis, this subgroup of studies had a lower risk of bias given their use of the recommended statistical methods.

Arrhythmic Outcome

The proportion of patients in which the primary arrhythmic outcome was observed during follow-up ranged widely among studies; from 1.0%/year in a cohort of predominantly asymptomatic ARVC-associated mutation carriers, to 30.1%/year in a cohort of severely affected definite ARVC patients. The average proportion of arrhythmic events in studies with definite ARVC patients was 10.6%/year (range 3.0-30.1%), in studies with borderline ARVC patients 10.0%/year (range 6.3-13.1%), and in studies with pathogenic mutation carriers 3.7%/year (range 1.0-6.4%).

Risk Factors for Ventricular Arrhythmia

The main risk factor associations are reported by category below; all extracted results are presented in Supplementary Tables 2A-I. The pooled HRs from all meta-analyses are summarized in Figure 4; the corresponding forest plots can be found in Supplementary Figure 1.

Demographics

Age · was investigated as a predictor of arrhythmic events by 23 studies. The vast majority (n=21/23) of these studies reported non-significant results. Only two studies, both with definite ARVC patients, reported a higher arrhythmic risk in younger patients: below 40 years (HR 2.90, 95%CI 1.51-5.58), or per year increase in age (OR 0.95, 95%CI 0.89-0.99)(Supplementary Table 2A). Meta-analysis of five studies using age as a continuous variable and three studies that used a cut-off value of 35 years did not yield significant results among definite and borderline ARVC subjects (Figure 4).

Male sex · was directed towards an increased risk of ventricular arrhythmias in 22 of 28 studies, although statistical significance was only reached in 6/16 studies with definite and 1/6 studies with borderline ARVC patients. In contrast, significant results were obtained in all six studies with mutation carriers (Supplementary Table 2A). Meta-analysis of seven studies with definite ARVC patients confirmed a higher risk in males, pooled HR 1.83 (95%CI 1.41-2.37). The pooled result from four studies with borderline patients was similar in direction, but did not reach statistical significance, pooled HR 1.42 (95%CI 0.91-2.23)(Figure 4).

Other · demographic and comorbidity risk factors were reported with no statistically significant results (Supplementary Table 2A).

Symptoms

Symptoms · including palpitations, chest pain, pre-syncope, and syncope were studied as predictors of arrhythmic events in 23 studies. Symptomatic participants (i.e. having any one of the abovementioned symptoms) were compared to asymptomatic participants in three studies (one with definite ARVC patients and two with mutation carriers), all reporting a significantly higher risk in the symptomatic group (Supplementary Table 2B).

Unexplained syncope · was investigated as risk factor for arrhythmic events in 19 studies.

While most (n=15/19) studies were uniform in direction towards increased arrhythmic risk, statistical significance was only reached in 6/11 studies with definite ARVC patients, 1/5 studies with borderline ARVC patients, and 1/3 studies with mutation carriers (Supplementary Table 2B). Meta-analysis was feasible for five studies with definite ARVC patients and two studies with borderline ARVC patients: pooled HR 3.67 (95%CI 2.75-4.90) and pooled HR 2.04 (95%CI 0.39-10.74), respectively (Figure 4).

Other · symptoms were also analyzed, for which results can be found in Supplementary Table 2B.

Physical Exercise

Physical exercise · has frequently been associated with ARVC, although it was analyzed as a risk factor for arrhythmic events by only three studies that used non-uniform definitions (Supplementary Table 2C). Regardless, exercise was significantly associated with arrhythmic risk in all three studies. One study with definite ARVC patients reported a HR of 2.90 (95%CI 1.14-7.38) comparing patients participating in strenuous exercise to inactive patients. Similar results were found in borderline ARVC patients, comparing competitive to recreational athletes (HR 1.99 [95%CI 1.21-3.28]). Likewise, a dose-related effect was found in mutation carriers who were endurance athletes, in whom reducing the level of exercise after presentation was protective of ventricular arrhythmias (OR 0.05 [95%CI 0.003-0.67]). Meta-analysis was not performed given the heterogeneity in patient domain and utilized statistics.

Family History and Genotype

Proband status · was analyzed as a risk factor by three studies, comparing the arrhythmic risk of the proband (i.e. first patient diagnosed with ARVC in a family) to family members. Although proband status was found to be associated with arrhythmic events in two of three studies in univariable analysis, this effect was lost after correcting for confounders (Supplementary Table 2D). Meta-analysis of three studies with definite ARVC patients yielded a non-significant result (pooled HR 2.01 [95%CI 0.39-10.74]) with large heterogeneity (I^2 82.4%, p 0.017)(Figure 4).

Family history · positive for premature SCD (defined as <35 years as per diagnostic TFC) was investigated as a risk factor by ten studies, most (n=9/10) of which reported non-significant results (Supplementary Table 2D). This non-significant predictive effect was confirmed in meta-analysis in

definite ARVC patients (four studies, pooled HR 1.25 [95%CI 0.86-1.8]), and borderline ARVC patients (two studies, pooled HR 1.21 [95%CI 0.39-3.80]; Figure 4).

Pathogenic mutation · carriers were compared to patients without mutations by four studies. While two studies found that arrhythmias occurred at a younger age in mutation carriers, three studies compared the risk of arrhythmias from the age of presentation and reported no significant difference (Supplementary Table 2D). Meta-analysis was not performed given the heterogeneity in patient domain and utilized statistics.

Multiple mutations · including compound heterogeneity and mutations in ≥1 ARVC-associated gene was investigated as a risk factor by two studies of which one reported an increased arrhythmic risk (HR 3.01 [95%CI 1.42-6.37]), and the other found a significantly younger age at time of the arrhythmic event (Supplementary Table 2D).

Other · reported risk factors defined by family history and genotype, including combinations of the two, can be found in Supplementary Table 2D.

Electrocardiography

T-wave inversion (TWI)· on a standard 12-lead ECG was investigated as a risk factor by 21 studies. Fulfilling a minor repolarization criterion (i.e. TWI in leads V1-2; V4, V5, V6; or V1-4 in presence of complete right bundle branch block) was not associated with arrhythmic events in most (n=3/4) studies regardless of patient domain. Fulfilling a major repolarization criterion (i.e. TWI in V1-3) had no predictive value in definite ARVC patients (five studies), while the results in borderline patients were conflicting (i.e. both significantly predictive and protective effects were reported; two studies), and analyses in mutation carriers reported a significant association with arrhythmic events (two studies). The remaining eight studies showed that a greater extent of TWI (i.e. >V3 or in inferior leads) is a significant risk factor in all patient domains (Supplementary Table 2E). Meta-analysis was only feasible for four studies reporting TWI V1-3 in definite ARVC patients; pooled HR 1.18 (95%CI 0.86-1.62)(Figure 4).

Epsilon waves · are defined as reproducible low-amplitude signals between the end of the QRS and the T-wave, separated from the QRS complex. Epsilon waves were investigated as a risk factor by ten studies, of which 4/10 reported a significantly predictive effect. Meta-analysis was feasible for two studies with definite ARVC patients (pooled HR 1.17 [95%CI 0.34-4.01]) and two

studies with borderline ARVC patients (pooled HR 1.58 [95%CI 0.90-2.77]), both directed towards increased arrhythmic risk, although statistical significance was not reached (Figure 4).

Prolonged terminal activation duration (TAD) · is measured from the S-nadir to the end of all depolarization deflections, and defined as prolonged if ≥55 milliseconds in any of the leads V1-3. Prolonged TAD was investigated as a risk factor by four studies with non-consistent results: an association with ventricular arrhythmias was noted in 1/1 study with definite ARVC patients, 0/1 study with borderline ARVC patients, and 1/2 studies with mutation carriers (Supplementary Table 2E). Meta-analysis was not feasible due to heterogeneity in patient domain and utilized statistics.

Late potentials · are defined as the presence of filtered QRS duration ≥114ms, low-amplitude signal duration ≥38ms, or root-mean square of terminal QRS ≤20uV measured by signal-averaged ECG (SAECG). Late potentials were investigated as a risk factor by nine studies, which predominantly reported non-significant results (Supplementary Table 2E). Meta-analyses confirmed no predictive value of ≥1 late potential criterion in definite ARVC patients (six studies, pooled HR 1.03 [95%CI 0.61-1.72]), and borderline ARVC patients (three studies, pooled HR 1.4 [95%CI 0.86-2.3]; Figure 4).

QRS-fragmentation · is defined as additional deflections/notching at the beginning of QRS, on top of the R-wave, or in the nadir of the S-wave in either ≥1 right precordial lead or in >1 other leads. QRS-fragmentation was reported as a risk factor in three studies, which all reported significant results: HR 8.54 (95%CI 3.65-15.42) and OR 11.64 (95%CI 5.1-16.41) in definite ARVC patients, and HR 1.76 (95%CI 1.01-3.06) in borderline ARVC patients. Meta-analysis was not feasible due to heterogeneity in patient domain and utilized statistics.

Other · potential ECG-derived predictor variables were investigated for which the results can be found in Supplementary Table 2E.

Arrhythmias

Premature Ventricular Complexes (PVCs) · on continuous ECG monitoring were analyzed as a risk factor by 11 studies. Variability in definitions (e.g. total 24-hour PVC count vs. various cut-offs) limits comparability of results. Three studies, two with definite ARVC patients and one with mutation carriers, found an increased arrhythmic risk in patients with >500 PVCs/24hrs, whereas results in borderline ARVC patients were non-significant (Supplementary Table 2F). Meta-analysis was solely feasible for two studies analyzing >1000 PVCs/24hrs in definite ARVC patients: pooled HR 0.86

293 (95%CI 0.45-1.64)(Figure 4).

294 *Non-sustained VT* · is defined as ≥3 ventricular complexes at ≥100beats/minute, and was
295 analyzed as a predictor of sustained ventricular events in 11 studies. A significant association was
296 reported in 1/5 studies with definite ARVC patients, 1/3 studies with borderline ARVC patients, and
297 2/3 studies in mutation carriers (Supplementary Table 2F). Meta-analysis was feasible for three
298 studies with definite ARVC patients, yielding a significantly increased risk for patients who
299 experienced non-sustained VT (pooled HR 1.43 [95%CI 1.10-2.15]; Figure 4).

300 *Sustained VT/VF* · is defined as a documented ventricular arrhythmia at ≥100 beats/minute,
301 lasting ≥30 seconds or with hemodynamic compromise requiring termination. Prior sustained VT/VF
302 was analyzed as a risk factor for recurring sustained ventricular arrhythmias by 17 studies. The
303 majority of studies reported an increased risk of recurring events in definite (n=8/13 studies) and
304 borderline (n=3/4 studies) patients (Supplementary Table 2F). Meta-analysis was feasible for three
305 studies with definite ARVC patients, resulting in a significantly higher risk for patients with a prior
306 sustained VT/VF (pooled HR 2.05 [95%CI 1.08-3.88]; Figure 4).

307 *Other* · reported risk factors are available in Supplementary Table 2F.

308

309 Electrophysiology Study

310 *Inducibility of sustained ventricular arrhythmias* · during EPS was evaluated as a predictor for
311 spontaneous sustained ventricular arrhythmias by 15 studies. Despite the heterogeneity of stimulation
312 protocols between studies, all (n=5/5) studies with borderline ARVC patients reported a significant
313 association between inducibility and future arrhythmic events, whereas 9/10 studies with definite
314 ARVC patients reported non-significant results (Supplementary Table 2G). The same trend was
315 observed in meta-analysis of three studies with borderline ARVC patients (pooled HR 3.24 [95%CI
316 1.95-5.39]) and two studies with definite ARVC patients (pooled HR 1.02 [95%CI 0.39-2.64]; Figure
317 4).

318 *Other* · variables derived from EPS include low-voltage zones, epicardial voltage mapping,
319 sub-specification of inducible ventricular arrhythmias, and fragmented electrograms, for which results
320 are presented in Supplementary Table 2G.

321

322 Structural/Functional imaging

Reduced RV ejection fraction (RVEF) · was analyzed as a risk factor by 11 studies. While most (n=8/11) studies were directed towards increased arrhythmic risk with decreasing RVEF, statistical significance was only reached in 2/8 studies with definite ARVC patients, 0/2 studies with borderline ARVC patients, and 1/1 studies with mutation carriers (Supplementary Table 2H). Meta-analysis was feasible for four studies with definite ARVC patients resulting in a borderline significant increased risk per 5% RVEF reduction, pooled HR of 1.89 (95%CI 0.90-3.99)(Figure 4).

Reduced RV fractional area change (RVFAC) · was analyzed as a risk factor by five studies, most (n=3/5) of which reported a significantly increased arrhythmic risk with decreasing RVFAC: a significant association was observed in 1/3 studies with definite ARVC patients and 2/2 studies with borderline ARVC patients (Supplementary Table 2H). Meta-analysis was feasible for two studies with definite ARVC patients, resulting in a borderline significant increased risk per 5% RVFAC reduction, pooled HR 1.25 (95%CI 0.89-1.15)(Figure 4).

RV wall motion abnormalities · by qualitative assessment was analyzed as a risk factor by four studies. All studies in definite (n=2) and borderline (n=1) ARVC patients reported non-significant results (Supplementary Table 2H), whereas one study with mutation carriers found a significant association with arrhythmic risk (OR 70.59 [3.91-1273.69]). Of note, quantitative wall motion assessment using echocardiography-derived strain was associated with arrhythmic events in patients with definite or borderline ARVC (OR 1.25 [95%CI 1.08-1.44] per % strain reduction; Supplementary Table 2H). Meta-analysis for either qualitative or quantitative RV wall motion assessment was not feasible due to heterogeneity in patient domain, variable definitions, and utilized statistics.

Fulfillment of RV imaging criteria · as defined by the 2010 TFC was evaluated as a risk factor by ten studies. While studies in definite (n=5) and borderline (n=2) ARVC patients found no difference in arrhythmic risk, three studies with mutation carriers reported a higher arrhythmic risk for those fulfilling major imaging criteria (Supplementary Table 2H). Meta-analysis was feasible for four studies with definite ARVC patients, yielding non-significant results for fulfillment of any RV imaging criterion: pooled HR 1.09 (95%CI 0.65-1.84)(Figure 4).

Reduced LV ejection fraction (LVEF) · was analyzed as a risk factor by 17 studies. The majority of studies in definite ARVC patients (n=9/10) and borderline ARVC patients (n=4/5) reported no effect on arrhythmic risk, whereas all two studies in mutation carriers reported a significant association between reduced LVEF and arrhythmic events (Supplementary Table 2H). Meta-analysis

in four studies with definite ARVC patients and two studies with borderline ARVC patients yielded non-significant results: pooled HR 1.16 (95%CI 0.87-1.54) and pooled HR 1.05 (95%CI 0.93-1.19), respectively, per 5% LVEF reduction (Figure 4).

Other · imaging parameters are reported in Supplementary Table 2H.

Sensitivity Analyses

Of the 18 studies included in our meta-analysis, two used the original 1994 TFC as opposed to the modified 2010 TFC, which remain the current gold standard for ARVC diagnosis. Furthermore, four studies reported on primary prevention patients only, while others included patients with prior sustained events. To analyze the effect of these selection differences, all analyses were repeated by excluding studies that (1) used the 1994 TFC, and (2) included secondary prevention patients. As shown in Supplementary Table 3, pooled estimates remained similar for all risk factors, except for prior non-sustained VT (in both analyses), and male sex (in primary prevention studies) which lost their statistical significance.

Discussion

This manuscript aimed to systematically review predictors for ventricular arrhythmias in ARVC, highlight the quality of evidence as well as its shortcomings, and determine promising risk factors per patient subgroup (i.e. definite ARVC patients, borderline ARVC patients, and mutation carriers). We have summarized our key findings and clinical recommendations in Figure 5.

Quality of Evidence

Although a relatively large number of studies investigated potential risk factors for ventricular arrhythmias in ARVC, the majority (n=43/45) of studies were conducted in observational cohorts (n=14 prospective, n=17 retrospective, n=12 pro- and retrospective), which are inherently (but not necessarily) limited in quality of evidence. Important sources of bias were differences in follow-up time, selective loss to follow-up, and selection towards patients presenting alive (left truncation bias). Correcting for these factors is essential for accuracy and generalizability of results, and fortunately many authors performed at least some level of adjustment. However, as ARVC studies are typically small, the potential for adequate adjustment is often limited by insufficient statistical power. This

resulted in a variable risk of bias which is partly reflected by the inconsistency of reported results.

To compensate for the relatively small study populations, we attempted to pool results into a quantitative meta-analysis to obtain more evidence for the most commonly reported risk factors. Of note, pooling of results is only appropriate in the setting of uniform definitions. Since individual studies used variable predictor definitions and risk estimates, the number of studies satisfying this prerequisite was unfortunately limited.

Given both the limitations in individual study quality (as highlighted by the variable risk of bias) and our inability to pool all available results, we deem the overall quality of available evidence to be moderate. While this opens the path for future studies to specifically address these shortcomings, this should be taken into account when interpreting the main findings of this manuscript.

Main Findings

Overall Risk of Ventricular Arrhythmias in ARVC

We found that the proportion of patients experiencing sustained ventricular arrhythmias in ARVC was relatively high (up to 30.1%/year). It is important to note that the highest of these proportions were observed in cohorts with a high a priori risk (e.g. severely affected definite ARVC patients). Indeed, the proportion of arrhythmic events was strongly associated with overt disease expression and ranged from 10.6%/year in definite patients, to 10.0%/year in borderline patients, to 3.7%/year in mutation carriers.

Risk Factors for Ventricular Arrhythmias are Domain-Dependent

The patient domain (i.e. study population) is a fundamental principle of clinical research and dictates to whom the reported results apply. Given the variability in patient domain across studies, we classified the included studies in three pre-specified domains: studies with definite ARVC patients only, studies with at least borderline ARVC patients (among whom a proportion had definite ARVC), and studies with ARVC-associated mutation carriers (among whom a [smaller] proportion had definite ARVC). Our separate analyses in these domains highlighted a pattern in the predictive value of risk factors based on the population. This is easily understandable in the context of their acquisition: most risk factors are related to disease expression, and therefore they typically overlap with diagnostic criteria. This is also in line with a recent publication suggesting that phenotypic expression is a

prerequisite for arrhythmic events in desmosomal mutation carriers.[9] As such, these risk factors correlate well with arrhythmic events when studied in a cohort of mutation carriers, but their potential to risk stratify patients with an established ARVC diagnosis is limited since the risk factor is present in most subjects. For example, T-wave inversions in V1-3 remained non-significant in definite patients, while conflicting results were obtained in borderline patients, and a strong association was reported among mutation carriers. We believe that the variability in patient domains explains at least some of the conflicting results that were pointed out by previous reviews and guidelines.[4,10]

Main Risk Factors for Ventricular Arrhythmias in ARVC

Figure 6 provides an overview of risk factors and their predictive potential specified by patient domain. In *definite ARVC patients*, consistently predictive risk factors included unexplained syncope, TWI extent, RV dysfunction, and previously registered (non-)sustained VT/VF. In addition, males were found to be at higher risk of ventricular arrhythmia than females. This is in line with a recently published study that reported an association between elevated testosterone levels and arrhythmic events in ARVC.[11]

In *borderline ARVC patients*, additional risk factors were found to be significant. In addition to the risk factors observed in definite ARVC patients, substantial evidence indicated a predictive effect of strenuous exercise and inducibility at EPS.

In *ARVC-associated mutation carriers* (including asymptomatic patients), the list of predictors expanded even further, and also included the presence of symptoms (palpitations, pre-syncope and/or syncope), harboring multiple mutations, LV dysfunction, and ventricular ectopy.

Limitations and Future Directives

Given the nature of our study as a systematic review, our analyses are limited by the reported data in the original reports. Since almost all studies used a composite arrhythmic endpoint of sustained ventricular arrhythmias and/or ICD interventions, their outcomes may have included non-life-threatening arrhythmias. Future studies should specifically confirm whether the predictors highlighted in this review also remain significant for truly life-threatening (cycle length <240 milliseconds or VF) arrhythmias. The reported HRs from all 45 studies were cause-specific. As such, the results cannot directly be translated to event rates. Nonetheless, our study results remain

meaningful for characterizing risk factors associated with arrhythmic events. Despite our efforts to analyze the three pre-defined domains separately, some level of heterogeneity in study population remains as some studies employed specific inclusion criteria, e.g. ICD carriers or secondary prevention populations. We accounted for this by fully disclosing the study populations, refraining from using these studies in our pooled analyses, and performing sensitivity analyses. Although meta-analysis potentially increases the power of pooled crude associations, it does not eliminate potential confounding, which is reflected by the severe heterogeneity of some pooled estimates in our study. Some of the included references only report adjusted values when significant in univariable analysis, which results in publication bias that cannot be corrected in our analyses. In addition, the design of this study as a systematic review limited our ability to analyze arrhythmic risk based on number of risk factors. Quantification of cumulative arrhythmic risk based on number of risk factors may help guide risk/benefit considerations of ICD placement in the individual patient. These limitations can only be overcome by developing a comprehensive arrhythmia prediction model that incorporates multiple risk factors. Development of such a prediction model will require a multicenter collaborative effort to obtain survival data on a large group of ARVC patients, so that absolute risk estimations can be made based on individual patient characteristics.

Conclusion

This study aimed to systematically review current evidence on arrhythmic risk stratification in ARVC. The average annual risk of ventricular arrhythmia ranged from 3.7% to 10.6%/year depending on the ARVC population. Since many predictors for ventricular arrhythmias overlap with diagnostic criteria, the potential to risk stratify patients with an established ARVC diagnosis is limited. Regardless, consistently predictive risk factors for ventricular arrhythmias are male sex, unexplained syncope, TWI beyond V3, RV dysfunction and previously registered (non-)sustained VT/VF. Since most evidence originates from observational cohort studies in small patient cohorts, one has to be critical of the quality of evidence. Future studies in collaborative international registries should investigate the incremental value of multiple risk factors so that accurate risk predictions can be made for the individual patient.

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References

1. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, Grosgogeat Y: Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982; 65:384–398.

2. Schinkel AFL: Implantable cardioverter defibrillators in arrhythmogenic right ventricular dysplasia/cardiomyopathy: patient outcomes, incidence of appropriate and inappropriate interventions, and complications. Circ Arrhythm Electrophysiol 2013; 6:562–568.

3. Olde Nordkamp LRA, Postema PG, Knops RE, van Dijk N, Limpens J, Wilde AAM, de Groot JR: Implantable cardioverter-defibrillator harm in young patients with inherited arrhythmia syndromes: A systematic review and meta-analysis of inappropriate shocks and complications. Heart Rhythm 2016; 13:443–454.

4. Corrado D, Wichter T, Link MS, et al.: Treatment of arrhythmogenic right ventricular cardiomyopathy/dysplasia: an international task force consensus statement. Eur Heart J 2015; 36:3227–3237.

5. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009; 339:b2535–b2535.

6. Stroup DF, Berlin J a, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000; 283:2008–2012.

7. Marcus FI, McKenna WJ, Sherrill D, et al.: Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: Proposed Modification of the Task Force Criteria. Eur Heart J 2010; 31:806–814.

8. Hayden J a, van der Windt DA, Cartwright JL, Côté P, Bombardier C: Assessing Bias in Studies of Prognostic Factors. Ann Intern Med 2013; 158:280.

9. Zorzi A, Rigato I, Pilichou K, et al.: Phenotypic expression is a prerequisite for malignant arrhythmic events and sudden cardiac death in arrhythmogenic right ventricular

cardiomyopathy. Europace 2016; 18:1086–1094.

10. Cadrin-Tourigny J, Tadros R, Talajic M, Rivard L, Abadir S, Khairy P: Risk stratification for sudden death in arrhythmogenic right ventricular cardiomyopathy. Expert Rev Cardiovasc Ther 2015; 13:653–664.

11. Akdis D, Saguner AM, Shah K, Wei C, Medeiros-Domingo A, von Eckardstein A, Lüscher TF, Brunckhorst C, Chen HSV, Duru F: Sex hormones affect outcome in arrhythmogenic right ventricular cardiomyopathy/dysplasia: from a stem cell derived cardiomyocyte-based model to clinical biomarkers of disease outcome. Eur Heart J 2017; 38:1498–1508.

Figures

Figure 1. Flowchart of Search Results and Selection Process.

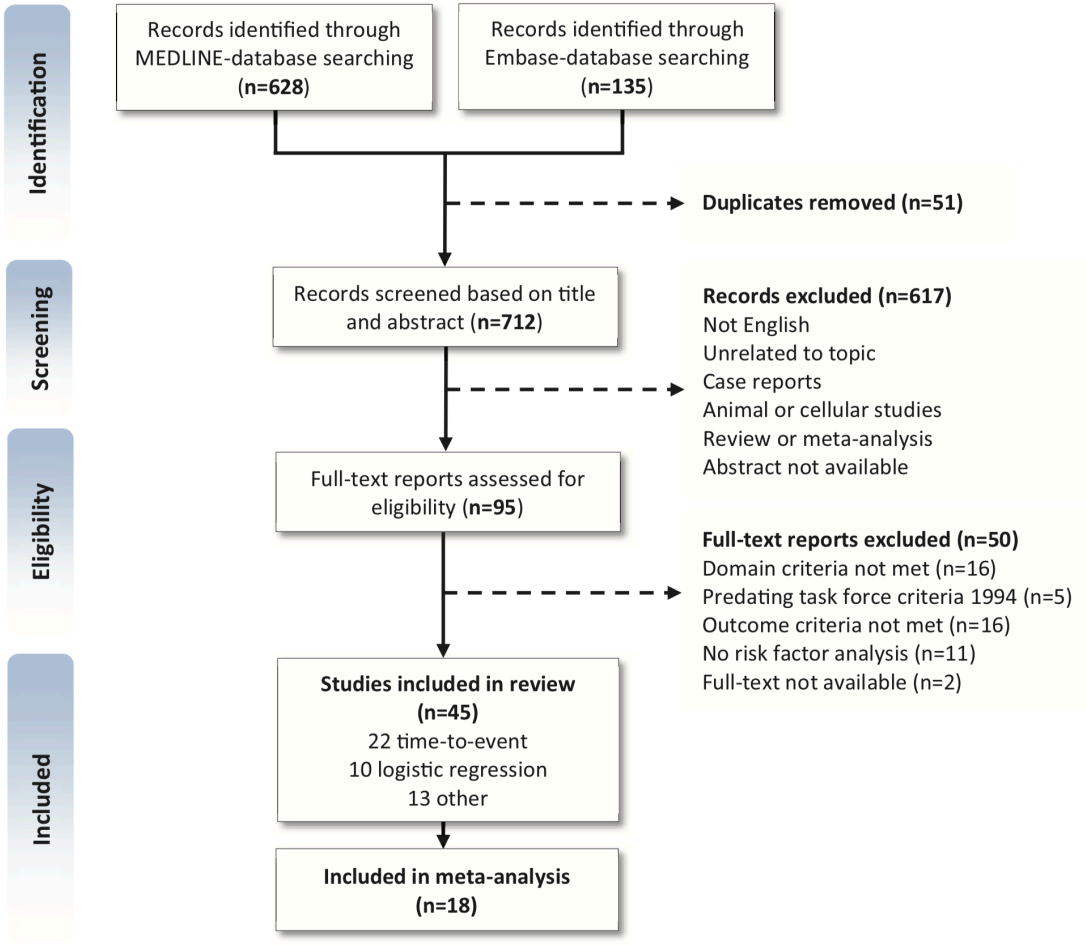


Figure 2. Study Characteristics of 45 Included Studies†.

Author, year	Design	Study population	Type of prevention	Size/ Events	Follow-up (yrs)	Endpoint	Risk factor type (n)	Statistic	Bias risk
Battipaglia, 2012[S1]	RC	Definite TFC10	P	30/5	1.6±0.6	sVT, ATP/Shock, SCD	Clinical(4), Arrhythmic(13), ECG(5), Imaging(3), EPS(1)	HR	▲
Berruezo, 2016[S2]	PC	Definite TFC10	S	41/11	2.7±1.8	sVT, ATP/Shock	Clinical(1), Arrhythmic(1), Imaging(4), EPS(4)	HR	●
Bhonsale, 2011[S3]	RC/PC	Definite/borderline TFC10, ICD	P	84/40	4.7±3.4	ATP/Shock	Clinical(6), Arrhythmic(3), ECG(3), EPS(1), Imaging(2), Genotype(1)	HR, KM	●
Bhonsale, 2013[S4]	RC/PC	Mutation carriers	P/S	215/86	5[8]	sVT, ATP/Shock, SCD	Clinical(13), Arrhythmic(3), Imaging(1), ECG(2)	HR, KM, OR	▲
Bhonsale, 2015[S5]	RC/PC	Mutation carriers	P/S	541/207	6.0±7.0	sVT, VF, ATP/Shock, SCD	Clinical(1), Genotype(2)	KM	▲
Canpolat, 2013[S6]	RC	Definite TFC10	P/S	78/39	3.2±1.2	VT, VF, SCD	Clinical(8), Arrhythmic(2), ECG(2), Imaging(3)	HR	▲◆
Chan, 2015[S7]	RC	Definite TFC10, RFA	P/S	59/14	2.5±1.7	VT, VF, ATP/Shock, SCD	ECG(1)	KM, OR	▲◆
Choudhary, 2016[S8]	PC	Definite/borderline TFC10, ICD	P/S	101/19	3.0±1.8	ATP/Shock	Clinical(1)	HR, KM	▲
Chung, 2016[S9]	PC	Definite/borderline TFC10	P/S	63/19	2.3±1.3	sVT, VF, SCD	Clinical(4), Arrhythmic(1), Imaging(4), ECG(3), EPS(1)	HR	●
Corrado, 2003[S10]	RC	Definite TFC94, ICD	P/S	132/64	3.3±2.1	ATP/Shock on VF	Clinical(2), Arrhythmic(1), Imaging(2)	OR	▲
Corrado, 2010[S11]	RC	Definite TFC94, ICD	P	106/25	4.8±2.9	ATP/Shock	Clinical(4), Arrhythmic(1), ECG(2), Imaging(2), EPS(1)	HR	●
Dalal, 2006[S12]	RC	Definite TFC94	P/S	48/28	5.0±4.0	ATP/Shock	Genetics(1)	KM	▲
Folino, 2002[S13]	RC	Definite TFC94	P	46/8	10.8±1.9	sVT / VF	Clinical(2), Arrhythmic(6), Imaging(4)	OR, Means	◆
Groeneweg, 2015[S14]	RC	Definite TFC10	P/S	416/301	7[12]	sVT, VF, ATP/Shock	Genotype(1)	KM	▲
Hong, 2012[S15]	RC	Definite TFC94, ICD	P/S	24/n.a.	3.3±1.7	ATP/Shock rate	Clinical(1), Biomarker(1)	OR, ROC	▲◆
James, 2013[S16]	RC	Mutation carriers	P	87/39	8.4±6.7	sVT, VF	Exercise(1)	KM, OR	▲
Kikuchi, 2016[S17]	RC	Definite TFC10	P/S	90/47	10.2±7.1	sVT, VF	TFC2010(12)	HR	▲
Liao, 2014[S18]	PC	Definite TFC10	P/S	24/13	1.8±1.6	sVT, VF	Clinical(4), Imaging(5), ECG(5), Arrhythmic(1), Histology(1)	OR	▲
Lin, 2017[S19]	RC	Definite TFC10, RFA	S	70/38	1.4±1.0	nsVT, sVT, VF	Clinical(5), Arrhythmic(1), ECG(2), Imaging(1), Histology(1), EPS(11)	HR	▲
Link, 2014[S20]	PC	Definite/borderline TFC94, ICD	P/S	108/48	3.3±1.7	ATP/Shock	Clinical(7), Arrhythmic(3), ECG(4), Imaging(2), EPS(1)	HR	●
Marcus, 2009[S21]	PC	Definite TFC94, ICD	P/S	95/32	1.3±1.1	sVT, VF, ATP/Shock	Clinical(7), Arrhythmic(2), ECG(1), Imaging(2)	OR, Means	▲◆
Martin, 2016[S22]	PC	Definite TFC10, ICD	P/S	26/13	6.7[3.3-9.3]	ATP/Shock	Clinical(5), Arrhythmic(1), ECG(2), Imagine(1)	HR	●
Mast, 2015[S23]	PC	Definite TFC10	P/S	38/20	5.9±2.3	sVT, VF, ATP/Shock, SCD	Clinical(3), ECG(2), Arrhythmic(1), Imaging(11)	HR	●
Mazzanti, 2016[S24]	RC/PC	Definite TFC10	P/S	267/47	5.8[1.3-10.6]	sVT, VF, ATP/Shock, SCD	Clinical(6), Arrhythmic(4), Exercise(1), ECG(1)	HR	●
Migliore, 2013[S25]	PC	Definite TFC10	P/S	69/19	3.4[2.3-4.7]	sVT, VF, ATP/Shock, SCD	Clinical(4), Arrhythmic(2), Imaging(4), EPS(4)	HR	●
Peters, 2007[S26]	PC	Definite TFC94	P/S	313/26	8.5±3.9	SCD	Clinical(2), Imaging(1), ECG(5)	OR, PV	▲
Peters, 2012[S27]	RC	Definite TFC94	P/S	305/101	6.3±3.1	sVT, VF, ATP/Shock	Clinical(3), ECG(2), Arrhythmic(1), Imaging(2)	OR	▲
Pezawas, 2006[S28]	PC	Definite TFC94	S	34/12	6.5±2.4	sVT	ECG(1), Arrhythmic(1), Imaging(2), EPS(2)	HR, KM, PV	▲◆
Piccini, 2005[S29]	RC/PC	Definite/borderline TFC94, ICD	P/S	67/44	4.4±2.9	ATP/Shock	Clinical(5), Arrhythmic(4), ECG(3), Imaging(2), EPS(3)	OR, KM	▲
Protonotarios, 2016[S30]	PC	Mutation carriers	P/S	105/43	n.a.	sVT, SCD	Clinical(3), ECG(2), Imaging(2), Genotype(4)	HR, OR	●
Protonotarios, 2015[S31]	PC	Definite TFC10	n.a.	86/53	9.0±7.0	sVT, SCD	ECG(1)	OR	▲◆
Rigato, 2013[S32]	RC/PC	Mutation carriers	P	134/22	n.a.	sVT, VF, ATP/Shock, SCD	Clinical(1), Genotype(5)	HR, KM	▲
Roguin, 2004[S33]	RC/PC	Definite TFC94, ICD	P/S	42/33	3.5±2.2	ATP/Shock	Clinical(6), Arrhythmic(3), ECG(4), Imaging(12), EPS(1)	OR, KM	●
Ruwald, 2015[S34]	RC	Definite/borderline TFC10	P	108/83	3.0±1.7	sVT, VF, SCD	Exercise(1), Histology(3)	HR	▲
Saguner, 2013[S35]	RC	Definite/borderline TFC10	P/S	62/30	9.8[4.4-12.7]	sVT, VF, SCD	Clinical(9), Arrhythmic(3), Imaging(2), EPS(22)	HR, OR, Means	●
Saguner, 2014[S36]	RC	Definite/borderline TFC10	P/S	106/51	4.6[1.9-10.0]	sVT, VF, SCD	ECG(14)	HR	●
Saguner, 2014[S37]	RC	Definite/borderline TFC10	P/S	70/37	5.3[1.8-9.8]	sVT, VF, SCD	Clinical(3), Imaging(19)	HR	●
Santangeli, 2012[S38]	RC	Definite TFC10, ICD	P	32/12	2.1±0.6	ATP/Shock	Clinical(4), Arrhythmic(2), Imaging(4), EPS(5)	HR	●
Sarvari, 2011[S39]	CC	Mutation carriers	n.a.	69/42	n.a.	VT, VF	ECG(6), Imaging(9)	OR, Means	▲
Schuler, 2012[S40]	RC	Definite TFC94, ICD	P/S	26/12	10.0[2.7-37.0]	ATP/Shock	Clinical(7), Arrhythmic(5), ECG(2), Imaging(9)	OR	▲
Te Riele, 201[S41]	PC	Mutation carriers	P	69/11	5.8±4.4	sVT, ATP/Shock, SCD	Clinical(7), Arrhythmic(3), ECG(5), Imaging(16)	OR, KM, Means	▲
Te Riele, 2016[S42]	RC/PC	Definite TFC10, relatives	P/S	96/21	6.7±3.8	sVT, VF	Clinical(8), Arrhythmic(1), Genetics(1), ECG(8), Imaging(3)	OR, Means	▲
Turrini, 1999[S43]	CS	Definite TFC94	P/S	38/15	n.a.	sVT, VF	ECG(2), Imaging(1)	OR	▲
Wichter, 2004[S44]	PC	Definite TFC94, ICD	P/S	60/41	6.7±3.6	ATP/Shock	Imaging(3), EPS(1)	OR	▲
Zorzi, 2016[S45]	PC	Mutation carriers	P	116/10	8.5[5.0-12.0]	sVT, VF, ATP/Shock, SCD	Clinical(5), Arrhythmic(3), ECG(5), Imaging(3)	OR, KM, Means	▲

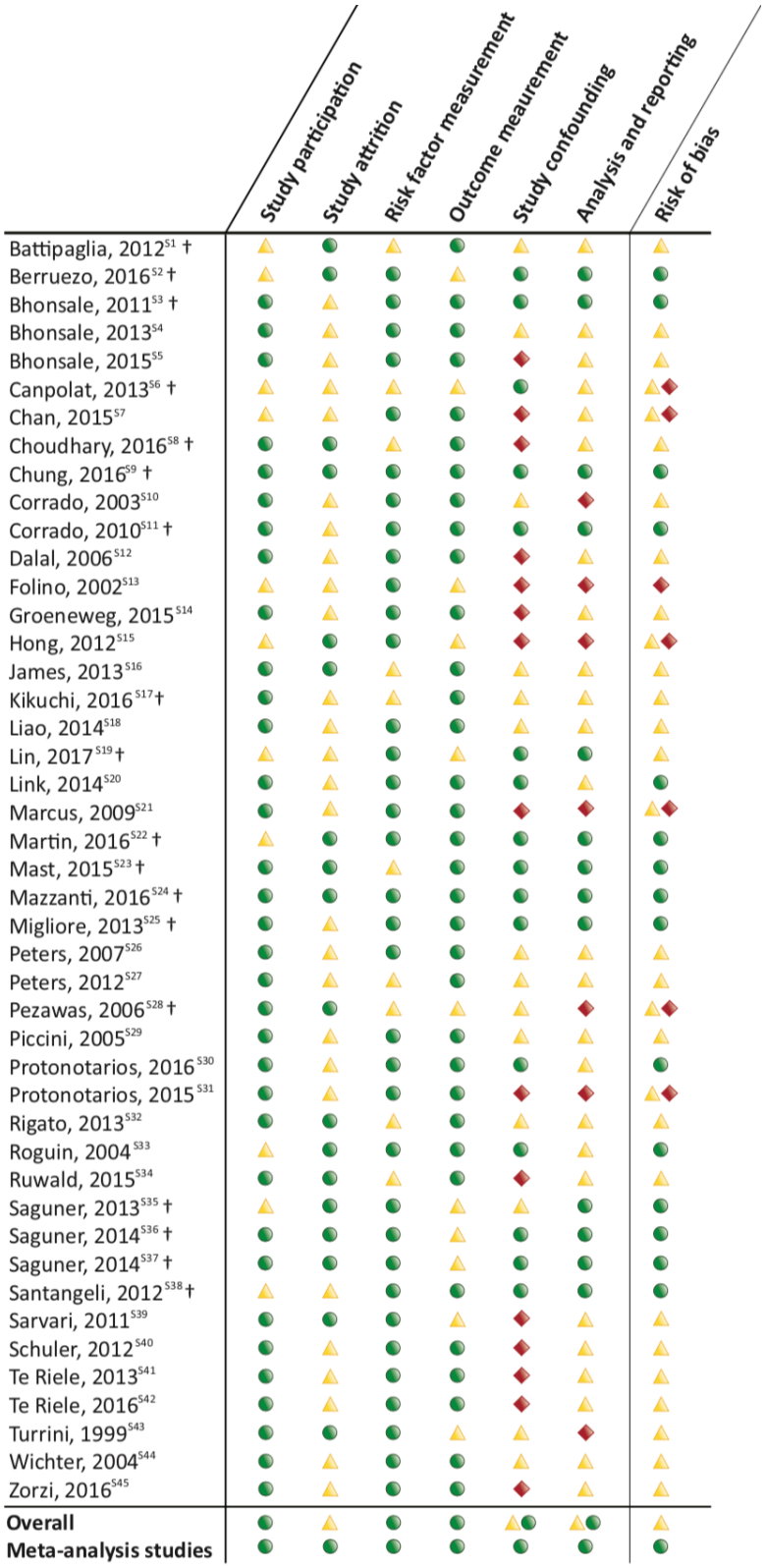
● = low, ▲ = moderate, ◆ = high

For full references see supplementary material. Follow-up is in average±SD or median[IQR]. Abbreviations: ATP=anti-tachycardia pacing; CC=case-control study; CS=cross-sectional study; P=primary prevention; PC=prospective cohort; PV=predictive value; RC=retrospective cohort; RFA=radiofrequency ablation; S=secondary prevention; others: see text.

† There was potential overlap in 41 studies, in case of overlap, only results from the largest population were incorporated.

525 **Figure 3. Quality Assessment of 45 Included Studies using the QUIPS tool**.

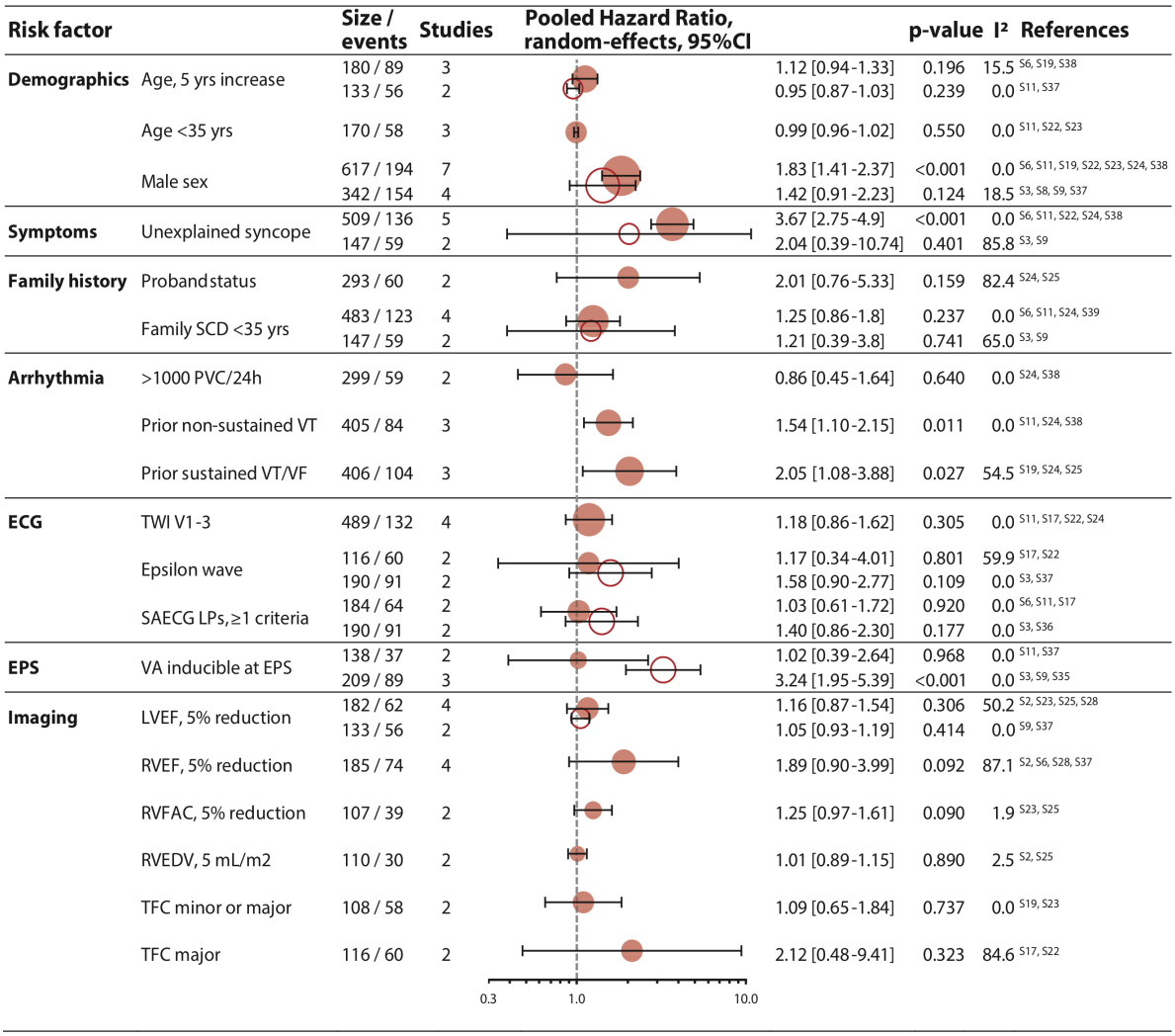
526



† = selected for meta-analysis

527 Risk of bias: = low, = moderate, = high

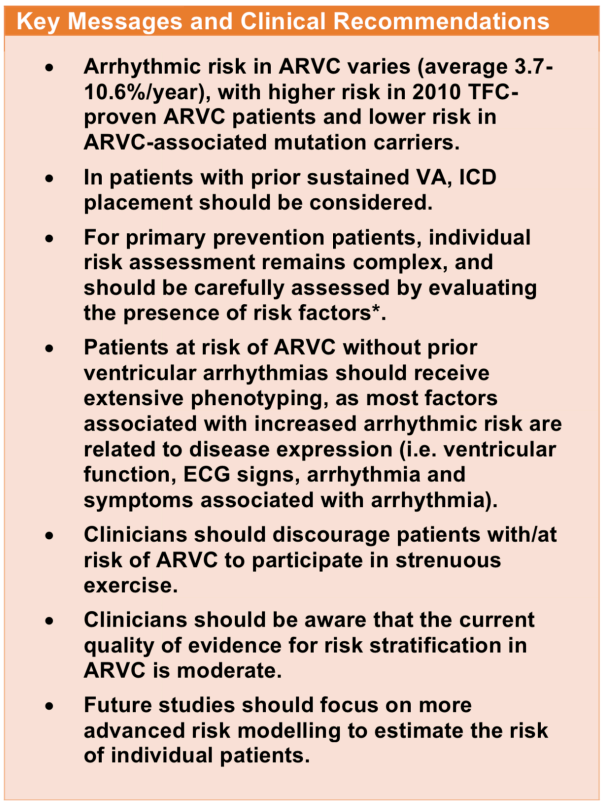
Figure 4.



= cohort with definite ARVC patients only (TFC ≥4) = cohort with at least borderline ARVC patients (TFC ≥3)

Summary of Meta-Analysis Results. Pooled HR with 95%CI are plotted. Filled circles correspond to studies with definite ARVC patients, empty circles to studies with (at least) borderline ARVC subjects. Circles size is scaled to the number of events. I^2=Chi-square test of heterogeneity(%). Abbreviations: see text.

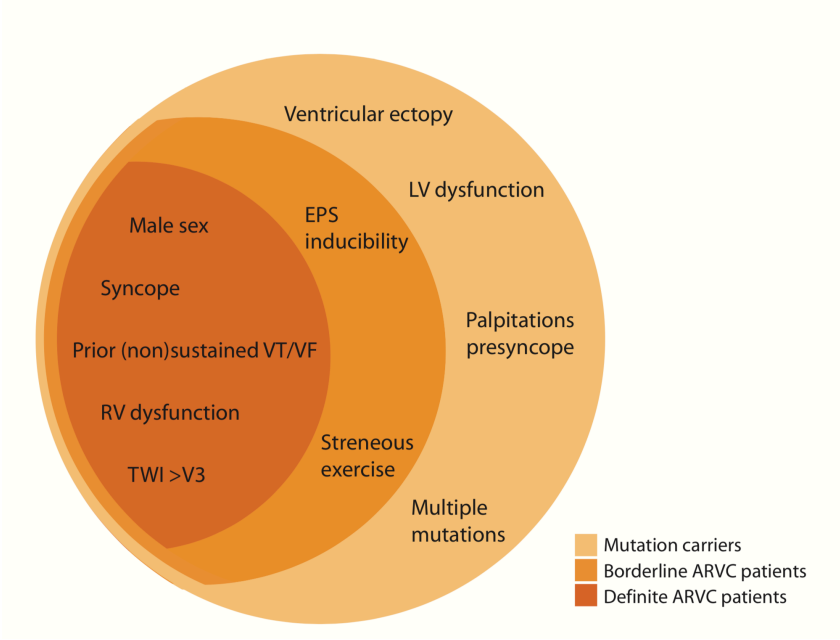
535 **Figure 5.** Key Messages and Clinical Recommendations.



536
537 *Risk factors per patient population as shown in Figure 6. Abbreviations: see text.

538

Figure 6.



Predictors for Sustained VA Are Population-Dependent. Predictors are plotted by patient domain. The dark region (small circle) applies to definite ARVC patients; dark region plus lighter region (intermediate circle) applies to at least borderline ARVC patients; the full ellipse applies to mutation carriers. Abbreviations: see text.