The Utility of Drug Challenge Testing in Brugada Syndrome: a Systematic Review and Meta-analysis

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Abstract

Introduction: Brugada syndrome is associated with ventricular arrhythmia leading to sudden cardiac death. Risk stratification is challenging, as major arrhythmic events (MAE) are rare. We assessed the utility of drug challenge testing in Brugada syndrome by a systematic review and meta-analysis. Methods and results: We comprehensively searched the databases of MEDLINE and EMBASE from inception to May 2019. Included studies compared the incidence of MAE between spontaneous and drug challenge induced Type-1. Data were combined using the random-effects, generic inverse variance method, to calculate pooled incidence and odds ratio (OR). Mixed-effects Poisson regression was used to calculated incidence rate ratio (IRR). Eighteen studies from 2006 to 2018 were included (4,099 patients, mean follow-up 4.5 years). Pooled annual incidences of MAE in spontaneous, drug challenge induced (regardless of symptoms), asymptomatic drug challenge induced, and symptomatic drug challenge induced Type-1 were 23.8 (95% confidence interval [CI]: 19.8-27.8), 6.5 (95% CI: 3.9-9.1), 2.1 (95% CI: -0.3-4.4), and 19.6 (95% CI: 9.9-29.3) per 1,000 person-years respectively. The incidence of MAE between symptomatic drug challenge induced and asymptomatic spontaneous Type-1 was not statistically different (IRR=1.0, 95%CI: 0.6-1.7). The presence of ventricular tachyarrhythmia during drug challenge testing was a predictor of MAE (OR=3.73, 95% CI: 1.77-7.86, p=0.001). Conclusions: The incidence of MAE in drug challenge induced Type-1 in asymptomatic patients is low. The incidence of MAE between symptomatic drug challenge induced and asymptomatic spontaneous Type-1 was similar. Ventricular tachyarrhythmia during drug challenge testing could be a useful risk marker for MAE in Brugada syndrome.

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Conclusions: The incidence of MAE in drug challenge induced Type-1 in asymptomatic patients is low. The incidence of MAE between symptomatic drug challenge induced and asymptomatic spontaneous Type-1 was similar. Ventricular tachyarrhythmia during drug challenge testing could be a useful risk marker for MAE in Brugada syndrome.

Keywords: Drug challenge testing, Brugada syndrome, Sodium channel blocker

Abbreviations

BrS Brugada syndrome

VF ventricular fibrillation

SCD sudden cardiac death

MAE major arrhythmic events

SCB sodium channel blocker

ECG electrocardiogram

NOS Newcastle-Ottawa quality assessment scale

OR odds ratio

IRR Incidence rate ratio

CI confidence interval

ICD implantable cardioverter defibrillator

1. Introduction

Brugada syndrome (BrS) was first described as a clinical syndrome in 1992 and predisposes patients to ventricular fibrillation (VF), premature sudden arrhythmic death syndrome, and aborted sudden cardiac death (SCD). Typically, patients present in the third or fourth decade of life. Even though most patients are asymptomatic at the time of diagnosis (approximately 63%), major arrhythmic events (MAE) can develop at a rate of 12% over 10 years (1-3). The disease is most prevalent in Southeast Asia where the prevalence has been reported as 3.7 per 1,000 and up to 17.7 per 1,000 in Thailand (4, 5).

Drug challenge testing is a common provocation test performed to unmask Type-1 Brugada pattern in patients with suspected BrS. In the past, a drug challenge induced Type-1 Brugada pattern was considered diagnostic of BrS (6). However, the "Shanghai Score System" was recently proposed, and in that, a drug challenge induced Type-1 Brugada pattern is less emphasized and scores as one component of the diagnostic criteria for BrS (1). That said, previous studies have suggested that positive drug challenge testing is associated with MAE (6). There are conflicting data on the incidence of MAE after drug challenge testing and the utilization of drug challenge testing. We sought to systematically review the incidence and the utility of drug challenge testing in the management of patients with possible BrS.

2. Methods

2.1 Search strategy

Two investigators (WV and PP) independently searched for published studies indexed in MEDLINE and EMBASE databases from inception to August 2019 using a search strategy that including the terms "sodium channel blocker", "ajmaline", "pilsicainide", "flecainide", "procainamide", and "Brugada syndrome" as described in supplementary file 1. Only full articles in English and studies conducted in cohorts were included. A manual search for additional pertinent studies and review articles using references from retrieved articles was also completed.

2.2 Inclusion criteria

The eligibility criteria included the following: (1) Cohort studies (prospective or retrospective) or randomized control trials reporting MAE after the diagnosis of BrS including SCD, sudden cardiac arrest, VF, sustained ventricular tachycardia, and appropriate shock in BrS patients diagnosed from drug challenge test by sodium channel blocker (SCB) and spontaneous Type-1 electrocardiogram (ECG).

(2) Adjusted or unadjusted relative risk, Odds ratio (OR), hazard ratio with 95% confidence interval (CI), or sufficient raw data for the calculation were provided. Patients with spontaneous Type-1 ECG were used as controls.

Study eligibility was independently determined by two investigators (CK and NP) and differences were resolved by mutual consensus. The Newcastle-Ottawa quality assessment scale (NOS) was used to assess each study's quality in three domains, recruitment and selection of the participants, similarity and comparability between the groups, and ascertainment of the outcome of interest among cohort and case-control studies (7).

2.3 Data extraction A standardized data collection form was used to obtain the following information from each study: title of study, name of first author, year of publication, study design, country of origin, number,

gender and age of the participants, Brugada ECG pattern, incidence of MAE, available MAE outcome, follow-up duration, and confounders that were adjusted in the multivariable analysis, if available. Two investigators (JK and PM) independently performed this data extraction process to ensure accurate data extraction. Any data discrepancy was resolved by referring back to the original articles.

2.4 Definitions

Brugada syndrome and Drug Challenge Testing

Brugada syndrome was diagnosed in patients with ST-segment elevation with type 1 morphology [?]2 mm in [?]1 lead in the right precordial leads V1, V2, positioned in the 2nd, 3rd, or 4th intercostal space occurring either spontaneously or immediately after drug challenge testing with intravenous administration of SCB class I antiarrhythmic drugs (6). Asymptomatic Brugada syndrome was defined as Brugada syndrome without history of syncope or documented SCD, sudden cardiac arrest, VF, sustained ventricular tachycardia. Symptomatic Brugada syndrome was defined as Brugada syndrome with history of syncope or documented SCD, sudden cardiac arrest, VF, sustained ventricular tachycardia (6).

Major arrhythmic events

MAE were defined as any of the following: SCD, sudden cardiac arrest, VF, sustained ventricular tachycardia, or implantable cardioverter defibrillator (ICD) appropriate shock. SCD was defined as an unexpected, nontraumatic death that occurred within 60 min from the onset of new or worsening symptoms or within 24 hours of last being observed alive and well (8). Sudden cardiac arrest was defined as a sudden cessation of cardiac activity with hemodynamic collapse for which an intervention or spontaneous reversion restored spontaneous circulation.

VF was defined as documented VF rhythm from standard 12-lead ECG or ECG monitoring, or as defined in each study. Sustained ventricular tachycardia was defined as a sustained organized ventricular rhythm, documented from standard 12-lead ECG or ECG monitoring, faster than 100 beats per minute lasting at least 30 seconds or requiring termination earlier due to hemodynamic instability. Only sustained ventricular tachycardia, VF, and appropriate ICD shocks were counted in this study. Non-sustained ventricular tachycardia and inappropriate shock were not considered an outcome of interest. Ventricular tachyarrhythmias are defined as documented VF rhythm or sustained ventricular tachycardia.

2.5 Statistical analysis

We performed a meta-analysis of the included studies using a random-effects model. Studies were excluded if they did not include an outcome in each intervention group, did not have enough information required for continuous data comparison, or shared the same patient population. Incidence rate ratios (IRR) of events were calculated by dividing the number of incident cases of events by the total number of person-years follow-up. IRR were pooled after applying the Freeman-Turkey double arcsine transformation to stabilize the variances (9). We pooled the point estimates of IRR, odds ratio, and incidence rate from each study using the generic inverse-variance method of Der Simonian and Laird (10). If no event was observed, pooled IRR were estimated using Poisson regression with random intervention effects (11). The heterogeneity of effect size estimates across these studies was quantified using the I^2 statistic. The I^2 statistic ranges in value from 0 to 100% ($I^2 < 25\%$, low heterogeneity; $I^2 = 25\%$–50%, moderate heterogeneity; and $I^2 > 50\%$, substantial heterogeneity). A sensitivity analysis was performed to assess the influence of the individual studies on the overall results by omitting one study at a time. Publication bias was assessed using a funnel plot and the Egger's regression test (12). ($p < 0.05$ was considered significant). All data analyses were performed using the STATA SE version 14.2.

2.6 Sensitivity analysis

We used a sequential exclusion strategy, as described by Patsopoulos et al., to examine whether overall estimates were influenced by the substantial heterogeneity observed (13). We sequentially and cumulatively

excluded studies that accounted for the largest share of heterogeneity until I^2 was less than 50%. We then examined whether RR estimates were consistent.

3. Results

*3.1 Search results*Our search strategy yielded 815 potentially relevant articles (465 articles from EMBASE and 350 articles from MEDLINE). After the exclusion of duplicated articles, 732 articles underwent title and abstract review. At this stage, 633 articles were excluded as they were not cohort, case-control, or randomized controlled trials, were not conducted in BrS patients or the titles and abstracts were not relevant. This left 99 articles for full-length review. Another 81 studies were excluded as they did not report data regarding SCB use, outcome of interest, or did not provide sufficient data to calculate OR. Therefore, a total of 18 studies were included in this meta-analysis (3, 14-30). Figure 1 outlines the search and literature review process.

3.2 Description of included studies

Eighteen studies from 2006 to 2018 were included in this meta-analysis involving 4,099 Brugada syndrome patients. Seventeen of 18 studies involving 3,596 Brugada syndrome patients reported the incidences of MAE in spontaneous Type-1 and drug challenge induced Type-1 Brugada pattern (3, 14-26, 28-30). Three of eighteen studies involving 776 Brugada syndrome patients reported MAE during drug challenge testing (16, 27, 30). Six of eighteen studies involving 541 Brugada syndrome patients reported symptomatic versus asymptomatic patients who had undergone drug challenge testing (3, 14, 21, 23, 24, 30). Mean follow-up was 4.5 years and 57.6% of Brugada syndrome patients were diagnosed by drug challenge induced Type-1 Brugada pattern. A summary of study characteristics is shown in Table 1.

*3.3 Quality assessment of included studies*The NOS of included studies are described in Supplement Table. The NOS uses a star system (0 to 9) to evaluate included studies on 3 domains: selection, comparability, and outcomes. Higher scores represent a higher study quality.

3.4 Meta-analysis results

Pooled annual incidences of MAE in spontaneous and drug challenge induced Type-1 Brugada pattern were 23.8 (95% CI: 19.8-27.8) (Figure 2) and 6.5 (95% CI: 3.9-9.1) per 1,000 person-years (Figure 3) respectively. Spontaneous Type-1 Brugada pattern was associated with a higher risk of MAE (OR=3.05, 95%CI: 2.08-4.46, $p<0.001$, $I^2=23.8\%$) than drug challenge induced Type-1 Brugada pattern (Figure 4).

We performed subgroup analysis of symptomatic (with history of syncope or documented SCD, sudden cardiac arrest, VF, sustained ventricular tachycardia) and asymptomatic (without history of syncope or documented SCD, sudden cardiac arrest, VF, sustained ventricular tachycardia) drug challenge induced Type-1 Brugada pattern subjects. In asymptomatic individuals with drug challenge induced Type-1 Brugada pattern, pooled annual incidences of MAE was 2.1 (95% CI: -0.3-4.4) per 1,000. In symptomatic individuals with drug challenge induced Type-1 Brugada pattern, pooled annual incidences of MAE was 19.6 (95% CI: 9.9-29.3) per 1,000. Thus, the combination of symptoms and drug challenge induced Type-1 Brugada pattern was associated with a higher risk of MAE (IRR=9.7, 95%CI: 3.6-25.9, $p<0.001$) than drug challenge induced Type-1 Brugada pattern but no history of symptoms. Drug challenge induced Type-1 Brugada pattern in symptomatic patients has a similar incidence of MAE when compared to asymptomatic spontaneous Type-1 Brugada pattern (IRR=1.0, 95%CI: 0.6-1.7, p=0.861).

The presence of ventricular tachyarrhythmia during drug challenge testing was associated with four-fold increased risk of MAE in drug challenge induced BrS patients (pooled OR=3.73, 95% CI: 1.77-7.86, p=0.001, $I^2=0.0\%$) (Figure 5) and increased to 13-fold in the subgroup of symptomatic patients (pooled OR=12.9, 95% CI: 3.8-43.2, $p<0.001$, $I^2=0.0\%$). In asymptomatic drug challenge induced BrS patients, ventricular tachyarrhythmia during drug challenge testing increased risk of MAE but non-significant (OR=2.78, 95% CI: 0.07-103.83) (data only available from one study)(16).

3.5 Sensitivity analysis

To assess the stability of the results of the meta-analysis, we conducted a sensitivity analysis for each outcome by excluding one study at a time. For every outcome, none of the results were significantly altered, as the results after removing one study at a time were similar to that of the main meta-analysis indicating that our results were robust.

3.6 Publication bias

To investigate potential publication bias of the association of a spontaneous Type-1 Brugada pattern and increased risk of MAE, we examined the funnel plot of the included studies in assessing change in log OR of MAE (Figure 6). The vertical axis represents study size (standard error) while the horizontal axis represents effect size (log OR). From this plot, no bias was observed because distribution of studies was symmetrical on both sides of the mean. Egger's test showed no small study bias ($p = 0.688$).

Only four studies included in this meta-analysis could be used to assess the association between ventricular tachyarrhythmia during drug challenge testing and increased risk of MAE. Thus, we did not perform a funnel plot or Egger's test (12).

4. Discussion

A main finding from this meta-analysis is that the pooled annual incidences of MAE in subjects with spontaneous Type-1 Brugada pattern was 4-fold higher than the pooled annual incidences of MAE in those with drug challenge induced Type-1 Brugada pattern. Another important finding was that the annual incidences of MAE in drug challenge induced Type-1 Brugada pattern in asymptomatic patients was as low as 2.1 per 1000 person-years. However, drug challenge induced Type-1 Brugada pattern in symptomatic patients has similar incidence of MAE when compared to spontaneous Type-1 Brugada pattern (IRR=1.0). The utilization of drug challenge induced Type-1 Brugada pattern for diagnosing Brugada syndrome in asymptomatic patient is limited. However, the presence of ventricular tachyarrhythmia during drug challenge testing was an independent predictor of MAE in Brugada syndrome patients.

Brugada syndrome has been approximated to be the cause in 4% of all SCD and 20% of SCD in patients with structurally normal hearts (2). Implantable cardioverter defibrillator (ICD) implantation is a class I recommendation in BrS patients with a documented history of MAE (31). However, a majority of newly diagnosed BrS patients, especially those with a drug challenge induced Type-1 Brugada pattern, have no previous history of MAE (32). It thus remains a challenge to identify asymptomatic patients who are at risk for MAE and therefore might benefit from an ICD (31).

Disopyramide and procainamide were the first two SCB reported to transiently slow down conduction and repolarization in BrS(33). Ajmaline (1 mg/kg), procainamide (10 mg/kg), and flecainide (2 mg/kg) were later tested as provocative drugs in BrS evaluation. Their sensitivity for unmasking Type-1 Brugada pattern was found to be at 100% and positive results were 100% in a small study (n=34). Drug challenged test provoked Type-1 Brugada pattern in all patients (n=11) who had sodium channel mutation without baseline ST elevation ECG (34). Positive drug challenge testing is widely used and considered in current guidelines as diagnostic of BrS regardless of symptoms (6). However, drug challenge testing may over-diagnose BrS. Most BrS patients (approximately 70%) in Europe were diagnosed with asymptomatic Brugada syndrome but positive ajmaline test (3). Ajmaline was more likely to provoke Type-1 Brugada pattern than procainamide but the false-positive results of Ajmaline was undetermined (35). A BrS syndrome diagnosis criteria "Shanghai Score System" was proposed in the recent J-Wave Syndrome Expert Consensus Conference Report to assign fewer points to drug challenge induced Type-1 Brugada pattern than spontaneous Type-1 Brugada pattern (2.0 VS 3.5 points respectively) (1).

Our study results are in line with the recent J-Wave Syndrome Expert Consensus Conference in that SCB drug challenge testing may over-diagnose BrS. The pooled annual incidences of MAE in drug challenge induced Type-1 Brugada pattern subjects is only 6.1 per 1000 person-years and only 2.1 per 1000 person-years in asymptomatic patients who had drug challenge induced Type-1 pattern, compared to 23.5 per 1000 person-years in spontaneous Type-1 Brugada pattern. The utilization of drug challenge induced Type-1

Brugada pattern for diagnosing Brugada syndrome in asymptomatic patients is therefore limited. However, drug challenge induced Type-1 Brugada pattern in symptomatic patients has a similar incidence of MAE when compared to asymptomatic spontaneous Type-1 Brugada pattern in our pooled analysis (IRR=1.0). In the FINGER registry, the incidence of MAE in asymptomatic BrS patients was very low at 5 per 1000 person-years as well (3). In 10 years of follow-up in the BrS ICD registry, the incidence of appropriate shock was 48 per 1000 person-years in patients with aborted sudden cardiac arrest, 19 per 1000 person-years for BrS patients with syncope, and only 12 per 1000 person-years for those who were asymptomatic at implantation (36). Recent meta-analysis of clinical outcomes after ICD implantation in BrS showed high incidence of ICD-related complications, including inappropriate shocks 33 per 1000 person-years, lead malfunction 16 per 1000 person-years, lead dislocation, 6 per 1000 person-years lead dislocation 4 per 1000 person-years (37). The lower annual incidence of MAE in drug challenge induced Type-1 Brugada pattern versus the lower incidence of ICD related complications should be taken into account when considering ICD implantation in patients.

The presence of ventricular tachyarrhythmia during drug challenge testing was an independent predictor of MAE in BrS patients. There has been disagreement between studies regarding the association between ventricular tachyarrhythmia during drug challenge testing and risk of MAE in BrS patients. However, our pooled OR from 4 studies suggested that ventricular tachyarrhythmia during drug challenge testing could be a useful marker of increased risk of MAE in patients with BrS, especially in asymptomatic patients. We also demonstrated that spontaneous Type-1 Brugada pattern was associated with a higher risk of MAE than drug challenge induced Type-1 Brugada pattern, similar to previous studies.

5. Limitations

Our study is not without limitations. First, we were not able to address sensitivity and specificity of drug challenge testing by meta-analysis because of insufficient data provided in included articles. Secondly, four different SCB were used across the studies- likely the main source of cause heterogeneity in our results (SCB and doses are shown in Table 1). Moreover, for the pooled OR of ventricular tachyarrhythmia during drug challenge testing, extracted data from the included studies were not all adjusted for other variables and may be influenced by other confounders.

6. Conclusions and Clinical Implications

Drug challenge induced Type-1 Brugada pattern in symptomatic patients has similar incidence of MAE when compared to spontaneous Type-1 Brugada pattern. However, the incidence of MAE in drug challenge induced Type-1 Brugada pattern in asymptomatic patients is very low. A positive drug challenge testing is not a good predictor of MAE in asymptomatic patient. Ventricular tachyarrhythmia during drug challenge testing could be a useful marker of risk for MAE in patients with Brugada syndrome.

Table and figure legends

Figure 1 : Search methodology and selection process.

Figure 2: Forest plot of the pooled incidence of MAE in spontaneous Type-1 BrS patients.

Figure 3: Forest plot of the pooled incidence of MAE in drug challenge induced Type-1 BrS patients.

Figure 4: Forest plot demonstrating the association of a spontaneous Type-1 Brugada pattern and increased risk of MAE when compared to drug challenge induced Type-1 Brugada pattern.

Figure 5: Forest plot demonstrating the association of ventricular tachyarrhythmia during drug challenge testing and increased risk of MAE in drug challenge induced Type-1 BrS patients.

Figure 6: Funnel plot of meta-analyis of demonstrating the association of a spontaneous Type-1 Brugada pattern and increased risk of MAE when compared to drug challenge induced Type-1 Brugada pattern.

Table 1: Summary characteristics of individual included studies of patients with a Brugada syndrome .

Supplementary file 1 : Search strategy

Supplementary file 2: Supplement Table (Newcastle-Ottawa quality assessment scale of included studies in meta-analysis).

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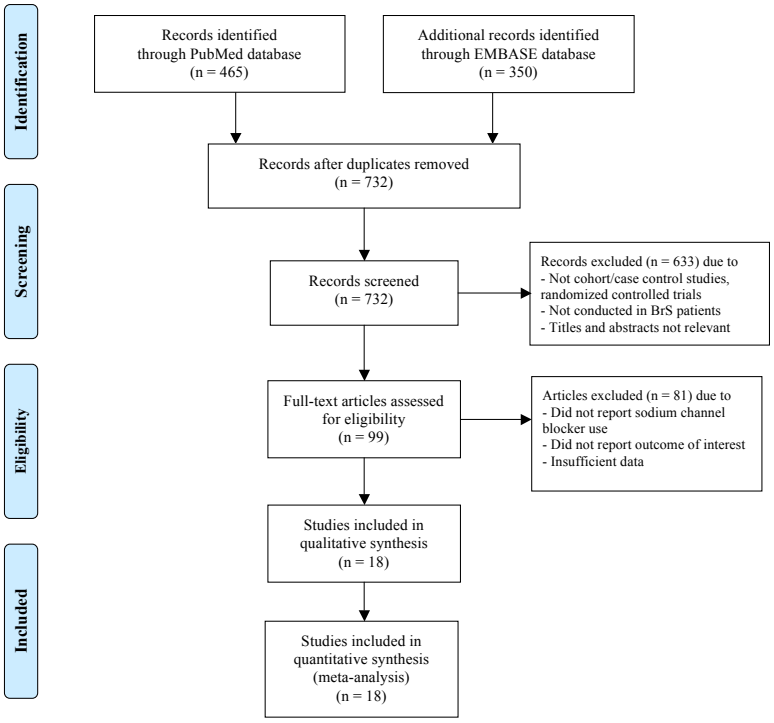

Figure 1 Search methodology and selection process