# IBRUTINIB AND THE UNDERRECOGNIZED RISK OF VENTRICULAR TACHYCARDIA: A METANALYSIS AND METAREGRESSION

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## INTRODUCTION

- Atrial fibrillation following initiation of Ibrutinib is an increasingly recognized phenomenon.
- Ibrutinib has emerged as a widely used treatment option for patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma, and Waldenstrom's macroglobulinemia, especially as salvage therapy for refractory disease.
- Although the clinical relationship between atrial fibrillation and Ibrutinib is well known, there is very little investigation of the relationship between ventricular arrhythmias and initiation of Ibrutinib.
- Atrial fibrillation often requires treatment without discontinuation of Ibrutinib, but in many cases ventricular arrhythmias can be fatal.
- Data comparison between ventricular arrhythmias and Ibrutinib has shown inconsistent results in terms of both incidence and mortality.
- Our clinical hypothesis is that Ibrutinib is associated with a much higher incidence of ventricular arrhythmias than patients not treated with Ibrutinib and the incidence will increase with longer duration of treatment with Ibrutinib.

## METHODOLOGY

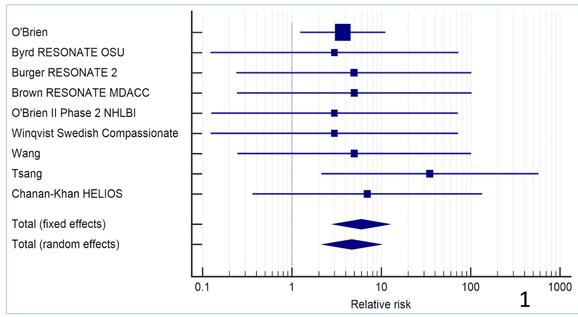
- An aggregate data meta-analyses was performed on 9 studies with 3,809 patients being treated with Ibrutinib to examine the incidence of ventricular arrhythmias.
- A meta-regression analysis was also performed to evaluate the effect of duration of therapy on incidence of ventricular arrhythmias.
- Summary relative risk (RR) and 95% confidence intervals (CI) were estimated using a random-effects model.
- An electronic database search was performed through **MEDLINE/PUBMED, EBSCO, EMBASE, Thomson Reuters' Web of Science, the Cochrane Library, Google Scholar, and Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov**
- Using standardized methods the following keywords were searched: "Ventricular Arrhythmia, Ventricular Tachycardia, Ibrutinib."
- We considered eligible all randomized controlled trials (RCTs) comparing ibrutinib with any control group (placebo, no-treatment or standard care, non-pharmacological interventions or any active drug).
- All RCTs were considered for inclusion irrespective of patients' baseline conditions, background therapy, ibrutinib dose, study follow-up or language of publication.
- The primary outcomes were the incidence of ventricular arrhythmias and mortality from these ventricular arrhythmias.
- For both outcomes we used a broad definition of the conditions.
- Ventricular arrhythmias were defined as:

→**sustained wide-complex monomorphic or polymorphic tachycardia**

→ **with heart rate greater than 120 beats/min for at least 30 seconds or reported by investigators as an adverse event.**

- This systematic review and meta-analysis conducted by the principles set in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement.
- Q statistic of Chi-square value test and I2 index (inconsistency index) were used to evaluate the heterogeneity of individual studies contributing to the pooled estimate.

## FIGURES




| Study | Intervention | Controls | Relative risk | 95% CI | z | P | Weight (%) Fixed | Weight (%) Random |
|---|---|---|---|---|---|---|---|---|
| O'Brien | 15/756 | 4/749 | 3.715 | 1.239 to 11.143 | | | 48.91 | 48.91 |
| Byrd RESONATE OSU | 1/308 | 0/307 | 2.990 | 0.122 to 73.123 | | | 5.77 | 5.77 |
| Burger RESONATE 2 | 2/135 | 0/134 | 4.963 | 0.241 to 102.424 | | | 6.44 | 6.44 |
| Brown RESONATE MDACC | 2/127 | 0/127 | 5.000 | 0.242 to 103.127 | | | 6.44 | 6.44 |
| O'Brien II Phase 2 NHLBI | 1/51 | 0/51 | 3.000 | 0.125 to 71.960 | | | 5.84 | 5.84 |
| Winqvist Swedish Compassionate | 1/95 | 0/95 | 3.000 | 0.124 to 72.730 | | | 5.80 | 5.80 |
| Wang | 2/50 | 0/50 | 5.000 | 0.246 to 101.590 | | | 6.51 | 6.51 |
| Tsang | 17/100 | 0/100 | 35.000 | 2.133 to 574.191 | | | 7.54 | 7.54 |
| Chanan-Khan HELIOS | 3/287 | 0/287 | 7.000 | 0.363 to 134.915 | | | 6.74 | 6.74 |
| Total (fixed effects) | 44/1909 | 4/1900 | 5.974 | 2.836 to 12.583 | 4.703 | <0.001 | 100.00 | 100.00 |
| Total (random effects) | 44/1909 | 4/1900 | 4.683 | 2.172 to 10.095 | 3.939 | <0.001 | 100.00 | 100.00 |

**Test for heterogeneity**

| | |
|---|---|
| Q | 2.8445 |
| DF | 8 |
| Significance level | P = 0.9437 |
| $I^2$ (inconsistency) | 0.00% |
| 95% CI for $I^2$ | 0.00 to 1.71 |

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- **Figure 1: Meta-Analysis of Binary Outcome Measures- Forest Plot**
- **Figure 2: Data compiled for Forest Plot**

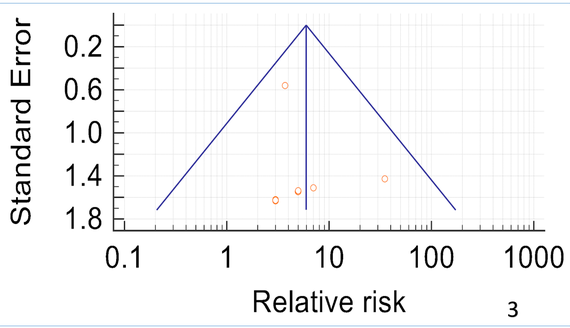


**Figure 3: Funnel plot analysis did not reveal asymmetry around the axis for the treatment effect in the following outcomes (p < 0.05 by Begg and Mazumdar's test or Egger's test).**

## RESULTS

- In 3,809 patients being treated with Ibrutinib, the incidence of ventricular arrhythmias was almost 5-fold higher in patients being treated with Ibrutinib compared to patients on other treatment regimens

→ RR 4.82, 95% CI 2.22-10.45, p <0.0001

- On meta-regression, when plotting log odds ratio of incidence of ventricular arrhythmias (y-axis) against duration of therapy (x-axis), incidence increased further with longer duration of treatment (coefficient = 0.344, p=0.0001).

## CONCLUSION

- For patients treated with Ibrutinib**, there was a markedly higher rate of ventricular arrhythmias compared to patients on all other treatment regimens.**
- Currently, there are no evidence-based guidelines regarding the utility and method of surveillance, choice between pharmacological treatment or interventional therapy, and the safety and efficacy of regarding ibrutinib cessation for ventricular tachycardias.
- Meta-regression showed a trend towards increased incidence of ventricular arrhythmias with longer duration of treatment reached statistical significance.
- There needs to be more surveillance for ventricular arrhythmias, and it should be considered a potential major side effect, which can increase morbidity and mortality, for patients initiating Ibrutinib.

## REFERENCES

- Available Upon Request

## DISCLOSURES: NONE