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## **Cardiovascular complications of ibrutinib: a systematic review and meta-analysis**

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### Objectives/Introduction

Ibrutinib is an irreversible inhibitor of Bruton's tyrosine kinase, a component of the B-cell receptor signalling pathway. Ibrutinib is highly effective in the treatment of chronic lymphocytic leukemia / small lymphocytic lymphoma and other B-cell lymphoproliferative diseases and is likely to become a paradigm-shifting therapy. Early clinical trials reported increased incidence of atrial fibrillation (AF) and bleeding in patients on ibrutinib when compared with alternative therapies. The objectives of this systematic review are to characterize the incidence rate and relative risk of AF and bleeding in patients receiving ibrutinib, compared with alternative therapies.

### Methods/Results

We conducted a systematic search of MEDLINE and EMBASE for articles and conference abstracts of studies of patients on ibrutinib that report either AF or bleeding events. The search yielded 1871 abstracts, from which we identified 22 studies, including 2152 patients on ibrutinib. Four were randomized controlled trials, 13 were prospective cohorts and 5 were retrospective. Pooled relative risks (95% confidence interval [CI]) of AF, any bleeding and major bleeding for ibrutinib recipients compared with alternative therapies were 3.9 (2.0-7.5,  $p < 0.0001$ ), 2.7 (1.6-4.5,  $p < 0.0001$ ), and 1.7 (1.0, 2.9,  $p = 0.07$ ), respectively. Pooled incidence of AF, any bleeding and major bleeding for patients receiving ibrutinib were 3.3 (2.5-4.1), 20.2 (18.33-22.05) and 2.8 (2.0-3.5) per 100 patient-years, respectively. The pooled incidence (95% CI) of AF, any bleeding and major bleeding among patients receiving an alternative therapy in the four randomized trials was 0.8 (0.3-1.6), 11.6 (9.1-14.4) and 1.9 (1.1-2.8) per 100 patient-years, respectively.

### Conclusion

Ibrutinib increases the risk of incident AF and bleeding compared with alternative therapies. The incidence of AF in ibrutinib recipients exceeds the incidence rate reported in the general population while the major bleeding rate in ibrutinib recipients is similar to the major bleeding rate seen in clinical trials of direct oral anticoagulants. Further research is needed to determine the incidence of AF and bleeding in "real-world" ibrutinib recipients, the mechanism and implications for therapy of these complications.