

Review Article

Acalabrutinib-Related Cardiac Toxicities in Patients with Chronic Lymphocytic Leukemia: A Meta-Analysis of Randomized Controlled Trials

Thura Win Htut¹, Myat Min Han², Kyaw Zin Thein³

¹Department of Haematology, Aberdeen Royal Infirmary, Foresterhill Health Campus, Aberdeen, UK

²Department of Internal Medicine, Interfaith Medical Center, NY, USA

³Division of Hematology and Medical Oncology, Oregon Health & Science University Knight Cancer Institute, Portland, OR, USA

Address correspondence to: Thura Win Htut, MBBS, MRCP (thura.winhtut@nhs.scot)

Source of Support: None. Conflict of Interest: None.

Received: Apr 26, 2021; Revision Received: Jul 28, 2021; Accepted: Sep 15, 2021

Htut TW, Han MM, Thein KZ. Acalabrutinib-related cardiac toxicities in patients with chronic lymphocytic leukemia: A meta-analysis of randomized controlled trials. *J Immunother Precis Oncol.* 2022; 5:43–47. DOI: 10.36401/JIPO-21-12.

This work is published under a CC-BY-NC-ND 4.0 International License.

ABSTRACT

Acalabrutinib, a second-generation and more selective Bruton's tyrosine kinase inhibitor, was developed to potentiate efficacy while minimizing ibrutinib-associated side effects. We undertook a systematic review and meta-analysis of randomized clinical trials to determine the risks of acalabrutinib-related cardiac toxicities in patients with chronic lymphocytic leukemia. Patients on acalabrutinib experienced higher risk of any-grade cardiac events (risk ratio, 1.75; $p = 0.01$) while there was a considerable trend toward statistical significance in the risk of any-grade atrial fibrillation (risk ratio, 2.56; $p = 0.05$). There was no significant increase in the risk of hypertension or high-grade cardiac events or atrial fibrillation in the acalabrutinib group.

Keywords: acalabrutinib, cardiac toxicities, atrial fibrillation, hypertension, chronic lymphocytic leukemia

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the commonest cause of adult leukemia due to the monoclonal proliferation of small, mature B cells.^[1,2] In the past, CD20 antibodies and chemoimmunotherapy were the mainstay of treatment for CLL. Recently, there have been therapeutic advances in CLL including targeted therapies against the pathway of the B-cell antigen receptor. Ibrutinib inhibits Bruton tyrosine kinase (BTK) and has yielded substantial benefit in survival in patients with CLL, including the high-risk disease group harboring TP53 mutation.^[2] However, ibrutinib is highly associated with cardiovascular toxicities especially in older patients.^[1–4] Acalabrutinib is a newer drug that selectively inhibits BTK, and was designed to potentiate efficacy with less ibrutinib-associated adverse effects.^[5,6]

A systematic review and combined meta-analysis of phase III randomized clinical trials (RCTs) was conducted to define the risk of cardiac events, atrial fibrillation (AF), and hypertension in patients with CLL treated with acalabrutinib.

METHODS

The systematic review was performed according to methods in the *Cochrane Handbook for Systematic Reviews* and reported per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.^[7] We used the keywords 'acalabrutinib OR ACP-196' AND 'chronic lymphocytic leukemia' in our literature search through MEDLINE, EMBASE databases, and meeting abstracts up to January 31, 2021. Our search was limited to 'humans' and 'randomized controlled trials.' We retrieved all studies written in English and non-English languages. Two investigators (KZT and TWH) independently reviewed all potential studies to assess eligibility for inclusion in our meta-analysis. We included the phase III RCTs studies comparing acalabrutinib-based regimens and a control group in oncogeriatric patients with CLL; and RCTs that mentioned cardiac adverse events, AF, and hypertension as adverse effects.

Two authors (TWH and MMH) independently extracted data. Of 150 records, after duplicates were removed, 15 potential studies were further explored (Fig. 1). Thirteen studies were not eligible because they did not

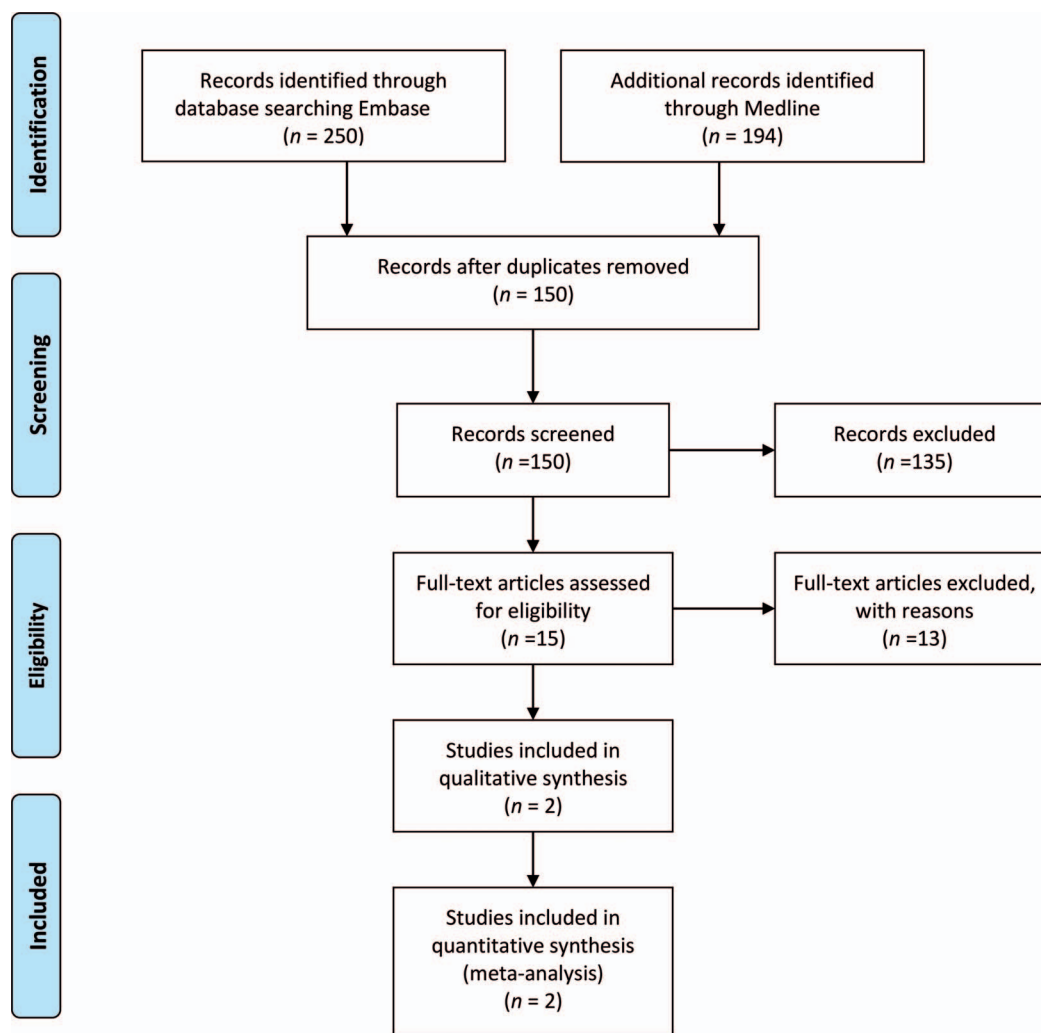


Figure 1. Study flow diagram in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

meet the eligibility criteria. The pooled risk ratio (RR) and risk difference (RD) with 95% CI were estimated for cardiac events, AF, and hypertension using the Mantel-Haenszel method. Cochrane RevMan software (version 5.3) was used to conduct all statistical analyses and risk of bias. I^2 and the Cochrane Q statistic were used to assess heterogeneity. A p -value < 0.05 was considered significant and $I^2 (> 50\%)$ was considered significantly heterogeneous. An $RR < 1.0$ was in favor of the study drug (acalabrutinib).

RESULTS

The characteristic features of included studies are summarized in Table 1.^[5,6] A total of 833 patients with CLL from two phase III RCTs were eligible: $n = 526$ in ELEVATE-TN, and $n = 307$ in ASCEND. Studies compared acalabrutinib and obinutuzumab versus acalabrutinib monotherapy versus obinutuzumab and chlorambucil in the ELEVATE-TN trial and acalabrutinib versus investigator's choice chemotherapy (idelalisib and rituximab or bendamustine and rituximab) in the ASCEND trial.

Three hundred fifty-seven patients with treatment-naïve CLL in ELEVATE-TN study and 154 patients with relapsed or refractory CLL in the ASCEND study, received acalabrutinib. We applied the fixed effects model as the I^2 statistic for heterogeneity, which was low, suggesting homogeneity among RCTs. Any-grade cardiac events were reported in 13.7% of participants in the acalabrutinib group compared with 7.8% in the control group, with an RR of 1.75 (95% CI, 1.13–2.73; $p = 0.01$) (Fig. 2A) and RD of 0.06 (95% CI, 0.02–0.10; $p = 0.007$). High-grade cardiac events were reported in 4.3% of patients in the acalabrutinib arm and 3.1% of patients in the non-acalabrutinib arm. The pooled RR was not statistically significant at 1.43 (95% CI, 0.65–3.16; $p = 0.37$) (Fig. 2B). The incidence of any-grade AF was 4.1% of patients receiving acalabrutinib compared with 1.9% of patients in the control group. There was a trend toward statistical significance in the pooled RR (RR, 2.56; 95% CI, 0.99–6.64; $p = 0.05$) (Fig. 2C). High-grade AF was observed in 0.58% in the study arm versus 0.6% in the control arm and the RR was 1.10 (95% CI, 0.21–5.79; $p = 0.91$) (Fig. 2D). Any-grade hypertension was reported in

Table 1. Characteristics of the studies included in the meta-analysis

| | ELEVATE-TN trial | | | ASCEND trial | |
|--|--|---------------------------|-----------------------------|---|---|
| Total no. of patients | 526 | | | 307 | |
| First author (Year) | Sharman (2020) ^[5] | | | Ghia (2020) ^[6] | |
| Study type | Randomized, multicenter, open-label study | | | Randomized, multicenter, open-label study | |
| Study phase | III | | | III | |
| Type of cancer | Treatment-naïve chronic lymphocytic leukemia | | | Relapsed or refractory chronic lymphocytic leukemia | |
| Line of treatment | First line | | | Second line onward | |
| Median follow-up | 28.3 months | | | 16.1 months | |
| No. of patients in each arm of study | 178 | 179 | 169 | 154 | 153 |
| Age, y | | | | | |
| Median (range) | 70 (65–75) | 70 (66–75) | 71 (67–76) | 68 (32–89) | 67 (34–90) |
| ≥ 75 y (%) | 29.6 | 27.9 | 29.5 | 22 | 20 |
| No. of prior therapies, median (range) | Not applicable | Not applicable | Not applicable | 1 (1–8) (Majority 79%, 1–2 prior therapies) | 2 (1–10) (Majority 73%, 1–2 prior therapies) |
| Treatment rendered | Acalabrutinib + obinutuzumab | Acalabrutinib monotherapy | Obinutuzumab + chlorambucil | Acalabrutinib monotherapy | Idealalisib + rituximab (or) bendamustine + rituximab |
| Median duration of exposure | 27.7 mos. | 27.7 mos. | 5.6 mos. | 15.7 mos. | 5.6–11.5 mos. |
| No. of cardiac events | | | | | |
| Any grade | 50 | 13 | | 20 | 12 |
| High grade | 17 | 3 | | 5 | 7 |
| Atrial fibrillation | | | | | |
| Any grade | 13 | 1 | | 8 | 5 |
| High grade | 1 | 0 | | 2 | 2 |
| Hypertension | | | | | |
| Any grade | 21 | 6 | | 5 | 5 |
| High grade | 9 | 5 | | 3 | 1 |

5.1% of participants in the acalabrutinib arm compared with 3.4% in the control arm. The pooled RR was observed at 1.40 (95% CI, 0.69–2.87; $p = 0.35$) (Fig. 2E). Similarly, 2.3% of patients treated with acalabrutinib and 1.9% of patients treated with non-acalabrutinib-based regimens experienced high-grade hypertension and the RR was not statistically significant at 1.13 (95% CI, 0.44–2.89; $p = 0.80$) (Fig. 2F).

DISCUSSION

BTK is nonreceptor protein kinase expressed on B lymphocytes. BTK is the key element of the B-cell antigen receptor signaling pathway, which is essential for survival of B cells.^[8] Acalabrutinib, is an oral small-molecule BTK inhibitor. Unlike ibrutinib, acalabrutinib was designed for selective inhibition of BTK with the aim of maximizing efficacy in patients with CLL without the off-target effects on other kinases, such as Tec protein tyrosine kinase (TEC), EGFR, and ITK. Recently two phase III trials, ELEVATE-TN^[5] and ASCEND^[6], have demonstrated the benefits of acalabrutinib on progression-free survival in the patients with both treatment-naïve and relapsed or refractory CLL.

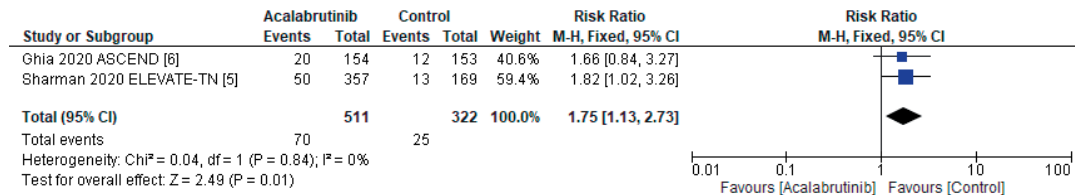
Our meta-analysis showed that patients on acalabrutinib experienced a higher incidence of any-grade cardiac events in the group of patients treated with acalabrutinib than non-acalabrutinib-based chemoimmunotherapy

with the RR of 1.75 ($p = 0.01$). Furthermore, there was a trend toward statistical significance in the risk of any-grade atrial fibrillation in the acalabrutinib group than patients in a group treated with other chemoimmunotherapy (RR, 2.56; $p = 0.05$). Nevertheless, our meta-analysis found no statistically significant increase in the risk of any grades of hypertension and high-grade cardiac events or atrial fibrillation in the acalabrutinib arm compared with the control group.

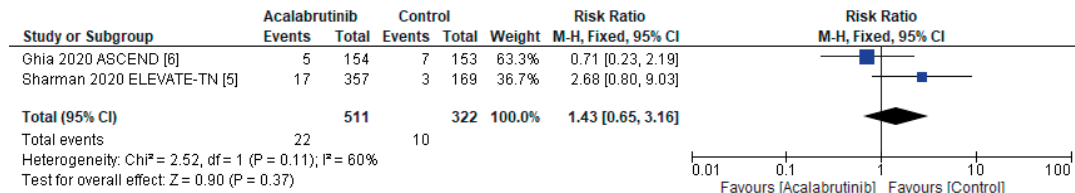
In the National Center for Biotechnology Information's Gene Expression Omnibus, McMullen and colleagues observed the potential functional roles of BTK and TEC under conditions of cardiac stress; both transcripts were expressed in human cardiac tissues and conditions of AF contributed to higher BTK and TEC expressions than sinus rhythm.^[9] The initial registration studies of ibrutinib showed the incidence of AF ranged from 3% to 6%, whereas the recent phase II trial (NCT01500733)^[10], which studied an older population (age > 65) who had 17p deletion, showed that 16% of patients developed AF at 28-month follow-up.^[1,2] Archibald et al^[4] also described their Mayo Clinic experience in which 16% of 298 patients with CLL (median age, 68) developed treatment-emergent AF at 2-year follow-up. History of AF and heart failure were shown to be the two preeminent risk factors.

In the ASCEND trial, the median age was 67 and 21% were age 75 and older. Eight of 154 patients (5%) treated with acalabrutinib reported atrial fibrillation, seven of

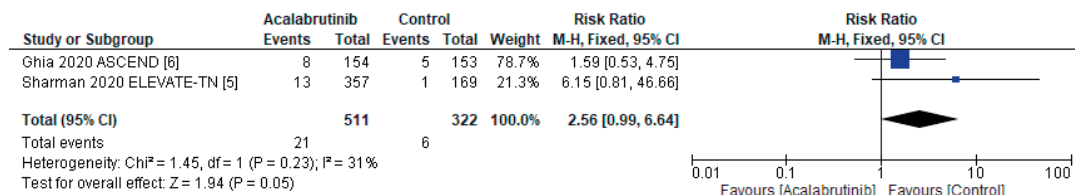
A.



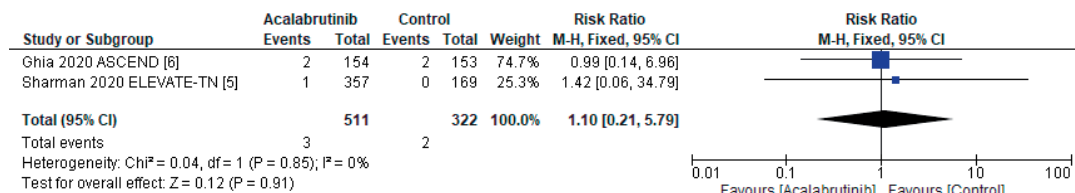
B.



C.



D.



E.



F.

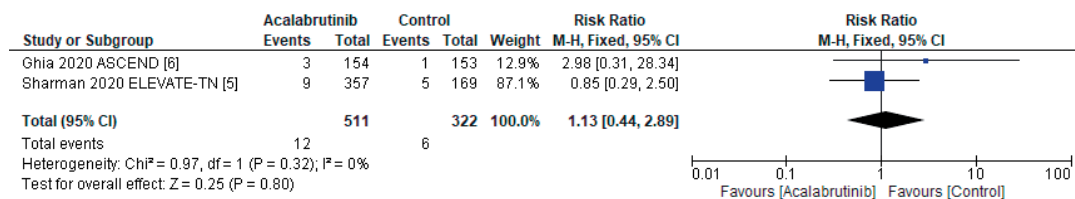


Figure 2. Pooled risk ratios for (A) any-grade and (B) high-grade cardiac events, (C) any-grade and (D) high-grade atrial fibrillation, and any-grade (E) and high-grade (F) hypertension in patients with chronic lymphocytic leukemia receiving acalabrutinib versus control.

whom had underlying hypertension, including one patient who had existing ischemic heart disease. However, atrial fibrillation was reported in only 3% of non-acalabrutinib-based regimens. The median age was 70 and approximately 30% were age 75 and older in the ELEVATE-TN trial. The incidence of AF was 3% in the acalabrutinib and obinutuzumab group, 4% in the acalabrutinib monotherapy group, and 1% in the obinutuzumab and chlorambucil group. The differences in the risk of AF may be explained by the differences in patient selection criteria or background patient characteristics. Recently, results of the phase III ELEVATE-RR (NCT-2477696) trial^[11], which randomized ibrutinib versus acalabrutinib in previously treated patients with CLL, was presented at the 2021 American Society of Clinical Oncology annual meeting: acalabrutinib showed noninferior progression-free survival while conferring lower incidence of AF in the acalabrutinib arm.

Of note, the median duration of treatment and follow-up was longer in acalabrutinib monotherapy or based therapy than non-acalabrutinib-based therapies in both ELEVATE-TN and ASCEND trial, which may ultimately lead to the emergence of therapy-related cardiac toxicities. The median duration of treatment (ELEVATE-TN trial) was 27.7 months in the acalabrutinib containing regimens, and 5.6 months in the control group. Likewise, median duration of exposure in the ASCEND trial, was 15.7 months for acalabrutinib monotherapy compared with 5.6–11.5 months in the non-acalabrutinib therapies.

One of the limitations of our meta-analysis is that only limited number of RCTs are currently available. Nonetheless, we observed that acalabrutinib containing regimens were attributable to higher incidence of any-grade cardiac events. Moreover, there was a considerable trend toward statistical significance in the risk of any-grade AF, yet there was no significant increase in the risk of any grades of hypertension and high-grade cardiac events or AF in the acalabrutinib arm compared with the control group. Second, longer duration in the median treatment and follow-up in the acalabrutinib containing regimens in both trials may ultimately confound the number of therapy-related adverse events. The third limitation is that acalabrutinib was given to patients with relapsed and refractory CLL in ASCEND trial where previous heavy exposure of chemoimmunotherapy may affect the risk of developing therapy-related adverse events in those groups of patients. Detailed patient data meta-analysis from those studies, which could explore the actual relationship and the potential risk factors to develop acalabrutinib-related cardiac toxicities, are recommended.

CONCLUSION

Our meta-analysis depicted that patients in acalabrutinib-based regimens experienced higher risk of any-grade cardiac events with the RR of 1.75 and there was a trend toward statistical significance in the risk of any-grade AF. There was no significant increase in the risk of any grades of hypertension and high-grade cardiac events or atrial fibrillation in the acalabrutinib group. Longer follow-up of these population and future further prospective studies are necessary to determine the actual relationship and the potential risk factors to develop cardiac toxicities in oncogeriatric patients with CLL who received acalabrutinib.

References

1. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med.* 2014;371:213–223.
2. Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med.* 2015;373:2425–2437.
3. Farooqui M, Valdez J, Soto S, Bray A, Tian X, Wiestner A. Atrial fibrillation in CLL/SLL patients on ibrutinib. *Blood.* 2015;126:2933.
4. Archibald WJ, Rabe KG, Kabat BF, et al. Atrial fibrillation in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib: risk prediction, management, and clinical outcomes. *Ann Hematol.* 2021;100:143–155.
5. Sharman JP, Egyed M, Jurczak W, et al. Acabrutinib with or without obinutuzumab versus chlorambucil and obinutuzumab for treatment-naïve chronic lymphocytic leukaemia (ELEVATE-TN): a randomised, controlled, phase 3 trial. *Lancet.* 2020;395:1278–1291.
6. Ghia P, Pluta A, Wach M, et al. ASCEND: Phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol.* 2020;38:2849–2861.
7. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
8. Hendriks RW, Yuvaraj S, Kil LP. Targeting Bruton's tyrosine kinase in B cell malignancies. *Nat Rev Cancer.* 2014;14:219–232.
9. McMullen JR, Boey EJ, Ooi JY, Seymour JF, Keating MJ, Tam CS. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. *Blood.* 2014;124:3829–3830.
10. Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with TP53 aberrations: a phase 2, single-arm trial. *Lancet Oncol.* 2015;16:169–176.
11. Byrd JC, Hillmen P, Ghia P, et al. First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. *J Clin Oncol.* 2021;39(15 suppl):7500.