

A systematic review and meta-analysis of randomized controlled trials on primary ambulatory thromboprophylaxis (PATP) in patients with ovarian cancer receiving chemotherapy

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INTRODUCTION

- Venous thromboembolism (VTE) is one of the most common complications in cancer patients and is associated with poor prognosis.
- Ovarian cancer (OC) is a highly thrombogenic cancer according to the Khorana score (KS) (score 1) in outpatient setting. OC cells promote thrombin generation and induce fibrin degradation which play a major role in thrombogenesis and cancer metastasis.
- Chemotherapy damages vascular endothelium and augments the procoagulant effect of cancer cells by multiple mechanisms, and therefore, imposes an additional risk factor for VTE. Cancer-associated thrombosis is the second leading cause of death in cancer patients.
- Thus, in recent years, PATP becomes an area of interest and has been considered as a potential therapy in ambulatory cancer patients undergoing chemotherapy with an ultimate aim of attempting to reduce the incidence of VTE and potentially improve survival.

AIM

- We undertook a systematic review and meta-analysis of randomized controlled trials (RCTs) to determine the benefit of PATP in patients with OC who are on chemotherapy.

METHOD

- We systematically conducted a comprehensive literature search using MEDLINE and EMBASE databases through November 30, 2019 using the following keywords; 'low-molecular weight heparin' OR 'direct oral anticoagulant' AND 'ovarian cancer'.
- The references of all potential studies were also reviewed for any additional relevant studies. The RCTs with reduction in VTE as a primary or secondary end-point were incorporated in the analysis.
- The primary meta-analytic approach was a random effects model using the Mantel-Haenszel (MH) method.
- It was used to calculate the estimated pooled risk ratio (RR), and risk difference (RD) with 95% confidence interval (CI).
- Heterogeneity was assessed with I² and Cochran's Q-statistic. A 'P value' of <0.05 was considered significant and I² > 50% was considered substantially heterogeneous.

REFERENCES

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2. Khorana AA, Soff GA, Kakkar AK, Vadhan-Raj S, Riess H, Wun T et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med.* 2019;380(8):720-8. doi:10.1056/NEJMoa1814630.

RESULTS

- A total of 433 patients with OC from subsets of two RCTs (SAVE-ONCO and CASSINI) were included in our meta-analysis.
- SAVE-ONCO trial enrolled unselected cancer patients while CASINI trial enrolled cancer patients with Khorana Score ≥ 2 .
- The prophylactic doses of anticoagulants were used; semuloparin in SAVE-ONCO and rivaroxaban in CASSINI trials.
- The PATP duration ranged from 3-5 to 6 months.
- The randomization ratio was 1 to 1 in both studies.
- The I² statistic showed moderate heterogeneity among RCTs, and random effects model was applied.
- The incidence of VTE was 2 (0.9%) in PATP group and 4 (1.8%) in control group.
- The pooled RR was not statistically significant at 0.69 (95% CI: 0.08–5.67, P = 0.73). The absolute RD was -0.03 (95% CI: -0.17 to 0.11, P = 0.66).

| Study | Study type | Number of patients | | Types of cancer | Anticoagulant (dose & duration) | Primary efficacy outcome measure | Type of Chemotherapy | Number of VTE events | |
|---|---|--------------------|---------------|-----------------|---------------------------------------|----------------------------------|----------------------|----------------------|---------------|
| | | Control | Anticoagulant | | | | | Control | Anticoagulant |
| SAVE-ONCO Agnelli et al., subgroup (2012) | Randomized, double-blind, multicenter trial | 191 | 188 | Ovary | Semuloparin 20 mg/D median 3.5 months | Reduction in VTE | Data not available | 1 | 0 |
| CASSINI Khorana et al., subgroup (2019) | Double-blind, randomized trial | 24 | 30 | Ovary | Rivaroxaban 10mg/D 180 days | Reduction in VTE | Data not available | 1 | 4 |

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

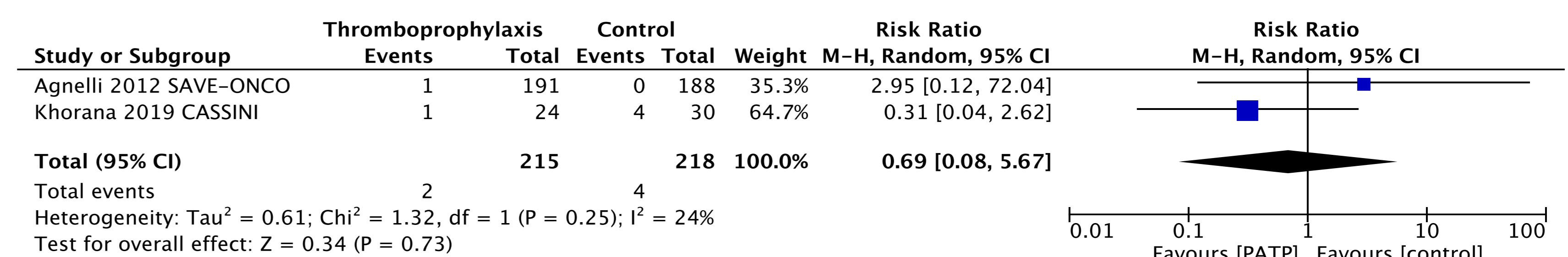


Figure 1a. Pooled risk ratio for venous thromboembolism in patients with ovarian cancer receiving primary ambulatory thromboprophylaxis vs control

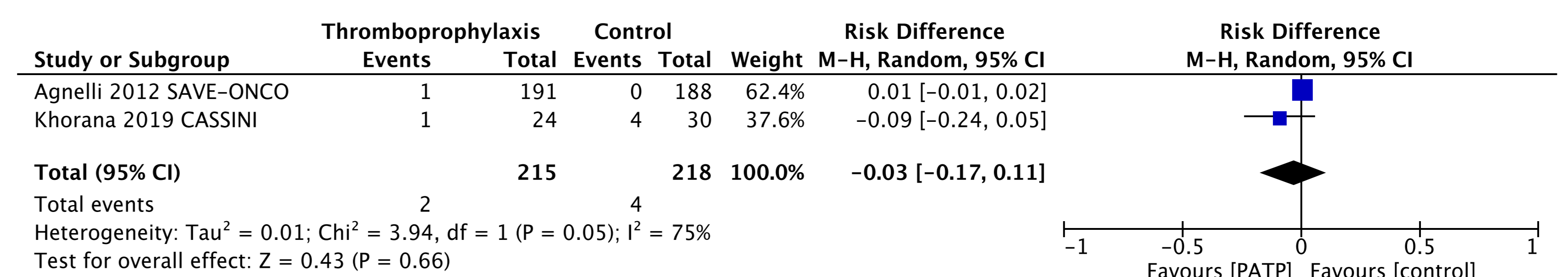


Figure 1b. Pooled risk difference for venous thromboembolism in patients with ovarian cancer receiving primary ambulatory thromboprophylaxis vs control

CONCLUSIONS

- Our meta-analysis demonstrated that the VTE incidence in OC patients is low in both PATP and control groups.
- There was no statistically significant reduction in VTE by providing PATP to ambulatory patients with OC who are on chemotherapy.
- Hence, routine PATP should not be recommended in ambulatory patients with OC.
- Further randomized trials are needed in the future to determine the high-risk subset of OC who may benefit from PATP.

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