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Research paper

Bleeding and thrombotic events in bevacizumab-treated patients with colorectal cancer on novel oral anticoagulants and antiplatelet medications

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ABSTRACT

Background: Bevacizumab is a humanized monoclonal anti-VEGF antibody often given in combination with fluorouracil-based chemotherapy as therapy for metastatic colorectal cancer (mCRC). The bleeding and thrombotic event rates in the setting of concurrent novel oral anticoagulants with and without aspirin and bevacizumab treatment in patients with mCRC remain unclear.

Methods: 462 patients with mCRC at Barnes-Jewish Hospital were identified between December 1, 2016 and December 1, 2021 and screened for concurrent treatment with bevacizumab and anticoagulant or antiplatelet therapy. Demographic and clinical information was extracted by electronic chart review.

Results: 21 patients were identified who received bevacizumab and either apixaban or rivaroxaban for mCRC treatment. Aspirin was prescribed in some of these patients within three years of starting apixaban or rivaroxaban. Of the 13 patients without aspirin prescription, nine were given apixaban, and four were given rivaroxaban while on bevacizumab. Four out of nine of the patients who received apixaban had epistaxis, and only one case resulted in any treatment discontinuation. Three out of four of the patients who received rivaroxaban experienced bleeding, and one of these three patients discontinued bevacizumab. We also looked at eight patients who had received aspirin. Two out of seven patients who received apixaban/bevacizumab/aspirin experienced bleeding and discontinued a medication. The patient who received rivaroxaban/bevacizumab/aspirin experienced bleeding and discontinued bevacizumab. No patient experienced adverse thrombotic events.

Conclusions: Patients with mCRC treated with bevacizumab and apixaban with no history of aspirin use within three years have a relatively low risk of bleeding that warrants treatment discontinuation.

1. Introduction

Bevacizumab is a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), a molecule implicated in tumor angiogenesis [1,2]. Bevacizumab inhibits tumor-induced vessel growth and facilitates chemotherapy delivery to the tumor by normalizing the vasculature. Inhibition of VEGF by bevacizumab can cause both bleeding and thromboembolic events. Antagonizing VEGF may lead to impaired endothelial cell regeneration, rendering the vasculature more prone to bleeding [3]. VEGF inhibition may also increase the risk of thrombosis by lowering VEGF-mediated production of nitric oxide (NO) and prostacyclin (PGI_2) that suppress endothelial cell activation and other pro-coagulant changes [4]. Other side effects include proteinuria, hypertension, gastrointestinal perforation, and delayed wound healing [5–8].

The Food and Drug Administration (FDA) has approved bevacizumab for a number of indications, including metastatic colorectal cancer (mCRC), hepatocellular carcinoma (HCC), non-small-cell lung cancer (NSCLC), ovarian cancer, and glioblastoma [9–14]. While it is a commonly used treatment for mCRC as first- and second-line therapies, its use in other gastrointestinal malignancies, including pancreatic, neuroendocrine, and biliary tract cancers, has yet to receive FDA approval. Administering bevacizumab with chemotherapeutics has been associated with an increased bleeding risk, although most bleeding events are mild and self-limited [10,11,13].

Cancer patients are at an increased risk for thrombotic events,

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including deep vein thrombosis (DVT) and pulmonary embolism (PE) [15]. In addition, a significant portion of cancer patients are older than 65 and are more likely to have cardiovascular comorbidities, such as atrial fibrillation (AF) [16,17]. To mitigate the risk of thrombus formation and recurrence, anticoagulants are often prescribed to patients with DVT, PE, or AF [18–20]. Conventional anticoagulant agents for these patients include warfarin and low molecular weight heparin (LMWH) [21–23]. Previous studies have confirmed the relative safety of patients with mCRC receiving these conventional anticoagulation agents concurrently with bevacizumab [22,24,25]. The use of antiplatelet therapy is also common in this same population. The most commonly used antiplatelet is aspirin, which antagonizes platelet activation by inhibiting enzyme cyclooxygenase 1 (COX-1) [26,27].

Studies have shown that novel oral anticoagulants (NOACs) are noninferior to warfarin and heparin for treatment of venous thromboembolism [28–30]. However, the safety of NOAC use with bevacizumab in mCRC has not been widely reported. These NOACs, including apixaban and rivaroxaban, are rapidly replacing conventional anticoagulants for use in therapeutic anticoagulation due to their convenient oral administration without required laboratory monitoring and lower bleeding risks [31]. In our study, we assess whether the combination of bevacizumab and apixaban or rivaroxaban increases the bleeding or thrombotic risks of patients with mCRC.

2. Materials and methods

The Washington University Institutional Review Board approved this retrospective cohort study. Barnes-Jewish Hospital's Epic electronic health record system was queried to identify patients with mCRC who received a NOAC and bevacizumab at Barnes-Jewish Hospital from December 2016 to December 2021. The 2016–2021 timeframe was chosen, as NOACs like apixaban and rivaroxaban were approved in the early 2010s, and a 5-year review period likely provided an adequate span of time for their widespread adoption and use. A total of 462 patients with mCRC were identified (Fig. 1). Patients who did not receive treatment with both bevacizumab and either apixaban or rivaroxaban, as well as those with a prior history of taking both apixaban and rivaroxaban or using dabigatran, edoxaban, or betrixaban, and those whose administration of bevacizumab and either apixaban or rivaroxaban overlapped for less than one month were excluded from the study. As a result of this selection process, 21 patients with mCRC were identified as being on apixaban or rivaroxaban while receiving bevacizumab. Out of the 21 patients included in the study, eight of them had a history of using aspirin within three years prior to starting either bevacizumab or apixaban/rivaroxaban. The usage of medications by each patient was confirmed through a thorough review of their medical charts to ensure accuracy.

For each of the 21 patients, we compared the start date of bevacizumab and the start date of NOAC to identify the first bleeding or thrombotic event that took place after the patient began receiving both medications. In the event that a patient had a bleeding or a thrombotic event at an outside hospital, the occurrence was documented in their medical records and was accessible for the purposes of this study. Each bleeding event was categorized as epistaxis, hemoptysis, central nervous system bleeding, or gastrointestinal (GI) bleeding. Thrombotic event categories included arterial thrombosis, PE, DVT, and intra-abdominal venous thrombosis. We also reviewed whether anticoagulation or bevacizumab was discontinued after the first adverse event.

3. Results

Out of the 21 patients who received bevacizumab and a NOAC, 16 patients were on apixaban (9 patients without history of aspirin usage and 7 patients with prior aspirin usage), and 5 patients were on rivaroxaban (4 patients without history of aspirin usage and 1 patient with prior aspirin usage) (Table 1). This report defines patients with previous aspirin usage as those with a history of taking aspirin within three years prior to or during taking either bevacizumab or apixaban/rivaroxaban. The most common reason for taking NOAC was for treating either a DVT or PE. 10 out of 21 patients (47.6 %) were treated with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) and FOLFIRI (fluorouracil, leucovorin, and irinotecan). The rest received various combinations of

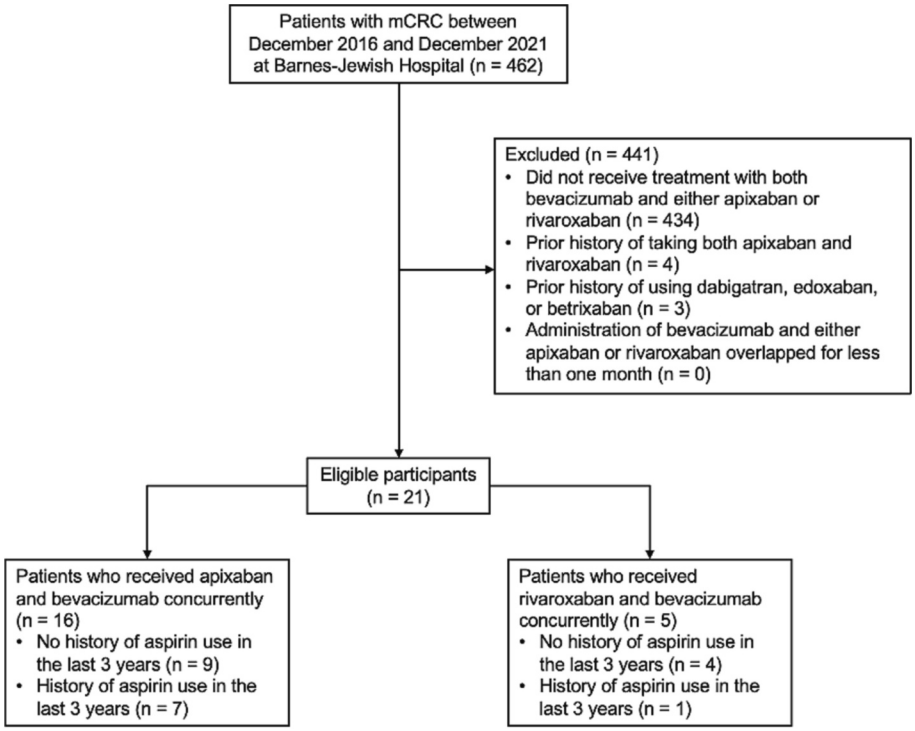

Fig. 1. Flowchart for patient selection and categorization.

Table 1
Patient characteristics, NOAC and aspirin use, and bleeding outcomes.

Patient number	Sex	Age	Race	Chemotherapy regimen	Indication for NOAC	Aspirin (Y/N)	Bleeding event (Y/N)	Time to bleeding (days)	Type of bleeding event	Discontinued anticoagulant or bevacizumab after event (Y/N)
Apixaban										
1	F	47	White	FOLFIRI, FOLFOX	DVT treatment	N	Y	687	Epistaxis	Y
2	F	71	Black	FOLFIRI, FOLFOX	PE treatment	N	Y	159	Epistaxis	N
3	M	60	White	FOLFIRI, FOLFOX, 5FU	PE treatment	N	Y	57	Epistaxis	N
4	F	47	White	FOLFIRI, FOLFOX, 5FU	DVT treatment	N	Y	295	Epistaxis	N
5	F	71	Black	FOLFIRI, FOLFOX	PE treatment	N	N			
6	M	72	White	FOLFIRI, FOLFOX	PE treatment	N	N			
7	F	51	White	FOLFOX, 5FU	DVT prophylaxis	N	N			
8	F	57	White	FOLFOX, Capecitabine	DVT treatment	N	N			
9	M	79	White	5FU	DVT prophylaxis	N	N			
10	M	63	White	FOLFIRI, FOLFOX	DVT treatment	Y	Y	234	GI bleed	Y
11	F	68	Black	FOLFOX	PE treatment	Y	Y	307	GI bleed	Y
12	M	61	White	FOLFIRI, FOLFOX, 5FU	PE treatment	Y	N			
13	F	54	White	FOLFOX	PE treatment	Y	N			
14	M	75	White	5FU	Atrial fibrillation	Y	N			
15	F	65	White	FOLFIRI, FOLFOX	PE treatment	Y	N			
16	M	51	White	FOLFIRI, FOLFOX	Splenic infarction	Y	N			
Rivaroxaban										
17	F	52	Black	FOLFIRI, FOLFOX	DVT treatment	N	Y	132	Hemoptysis	N
18	M	67	Black	FOLFIRI, FOLFOX, 5FU	PE treatment	N	Y	470	Epistaxis	N
19	F	58	White	FOLFIRI, FOLFOX	DVT treatment	N	Y	319	GI bleed	Y
20	M	60	White	FOLFIRI, FOLFOX	PE treatment	N	N			
21	F	60	Black	Capecitabine, 5FU	DVT treatment	Y	Y	287	GI bleed	Y

Abbreviations: DVT = deep vein thrombosis; PE = pulmonary embolism.

FOLFOX, FOLFIRI, 5-FU, and capecitabine.

For patients without previous aspirin usage, the bleeding event rates for apixaban users and rivaroxaban users were 44.4 % (4 out of 9 patients) and 75 % (3 out of 4 patients), respectively (Table 1). The corresponding median times between starting bevacizumab and the first bleeding event for these patients were 7.3 months and 10.3 months, respectively. For patients with records of aspirin usage, the bleeding rates associated with apixaban and rivaroxaban were 28.6 % (2 out of 7 patients) and 100 % (1 out of 1 patient), respectively. For these patients, the respective median times between initiating bevacizumab and the first bleeding event were 8.7 months and 9.3 months. Overall, apixaban had a lower adverse event rate compared to rivaroxaban when controlled for previous aspirin usage. We identified no thrombotic events in any of the patients taking bevacizumab with a NOAC.

The types of bleeding events associated with each NOAC/aspirin combination were noted (Table 1). All four apixaban users without prior aspirin usage who experienced an adverse event had epistaxis. One of these patients (25 %) discontinued bevacizumab after the event. In comparison, all two apixaban users who have used aspirin in the past and have experienced an adverse event had GI bleeding that led to discontinuation of either medication. Among the three rivaroxaban users who had an adverse bleeding event with no history of aspirin use, one had hemoptysis, and another had epistaxis, while the remaining patient had GI bleeding. Patients with either hemoptysis or epistaxis continued both bevacizumab and their anticoagulant after the event. In contrast, the patient with GI bleeding discontinued bevacizumab after the event. The one rivaroxaban user who has used aspirin in the past experienced a GI bleed and discontinued bevacizumab. None of the adverse bleeding events reported in our study resulted in death or warranted transfusion.

In this study, the bleeding events (10 events) outnumbered the thrombotic events (0 events). The discontinuation of either bevacizumab or the anticoagulant was observed for 0 % (0 out of 1) of hemoptysis events, 20 % (1 out of 5) of epistaxis events, and 100 % (4 out of 4) of GI bleeding episodes (Table 1).

4. Discussion

In our study, the patients prescribed with apixaban experienced lower rates of bleeding events than those prescribed with rivaroxaban when controlled for previous aspirin usage. For apixaban users without prior aspirin use, all of the adverse events were epistaxis that usually did not result in discontinuation of any treatment. In comparison, rivaroxaban users without prior aspirin usage experienced a wider range of events, including hemoptysis, epistaxis, and GI bleeding that more often led to at least partial discontinuations of their treatment.

Administering bevacizumab in combination with conventional anticoagulation therapy has been shown not to increase the risk of severe bleeding in patients with mCRC [22]. A randomized phase III clinical trial by Hurwitz et al. followed 789 mCRC patients who received warfarin plus irinotecan, leucovorin, fluorouracil and either bevacizumab or placebo. The study showed no significant added risk of bleeding with warfarin [10]. Another phase III study conducted by Saltz et al. evaluated 1369 patients who received either FOLFOX or XELOX in combination with either bevacizumab or placebo. 35 % of the patients received warfarin, while the remainder received LMWH. The results again showed no additional risks for bleeding with conventional anticoagulation agents [11].

The more recent CARAVAGGIO and SELECT-D trials collectively suggest apixaban is associated with lower bleeding risks than rivaroxaban in cancer patients. The SELECT-D trial is a randomized multicenter clinical trial that followed patients with solid or hematologic malignancies presenting with venous thromboembolic events that were treated with either rivaroxaban or dalteparin, an LMWH. The study reported a higher bleeding rate associated with rivaroxaban than with dalteparin [32]. The CARAVAGGIO trial is a multinational randomized controlled trial that compared apixaban and dalteparin for treating cancer-associated thrombosis and reported a slightly lower bleeding rate associated with apixaban (3.8 %) than with dalteparin (4.0 %) [33]. The results of these two studies are consistent with our findings that suggest apixaban might be associated with a lower bleeding risk than rivaroxaban in patients with mCRC.

In addition, our study also suggests that having a history of previous aspirin usage increases the risk of developing a more serious adverse event in apixaban users. All bleeding events related to apixaban usage without previous aspirin prescription was epistaxis. In contrast, all adverse events experienced by apixaban users with history of aspirin usage were GI bleeds that led to discontinuation of a medication.

All adverse events in this study were bleeding events. The NOAC's inhibition of various factors in the coagulation pathway may contribute to the occurrence of bleeding events [3,4]. On the other hand, the lack of thromboembolic events speaks to the effectiveness of the NOACs in preventing these events, including venous thromboembolisms like DVT and PE, the most common types of cancer-associated thrombosis [34].

Our study has several limitations. First, the number of patients in our study is small, rendering our findings more vulnerable to bias. In particular, our study only included one patient with a history of aspirin usage that was on rivaroxaban. The small sample size in our study posed limitations in conducting meaningful statistical analysis. Despite this, our study provides valuable insights and can serve as a foundation for future studies with larger sample sizes and more advanced statistical analysis. Due to the constraints of the limited sample size, our findings should be considered as hypothesis-generating. Second, our study did not normalize our findings based on the durations for which the patient was on bevacizumab, the durations they received their anticoagulant, and the overlap between these two. It is possible that a prolonged duration of either treatment and/or prolonged overlap between the two could have resulted in a higher incidence and greater severity of adverse events. Future studies can be conducted with a larger patient sample and appropriate statistical analysis.

5. Conclusions

Our findings are consistent with the hypothesis that apixaban may be safely given to patients with mCRC while they are on treatment with bevacizumab, especially when they have not taken aspirin in the past three years. In our study, all patients taking apixaban who did not have a history of aspirin usage and experienced an adverse event had mild epistaxis. Meanwhile, the use of rivaroxaban in combination with bevacizumab, whether with or without a history of aspirin use, appeared to carry some risk of bleeding. We also find that co-therapy with NOACs and bevacizumab does not appear to increase the risk of adverse thrombotic events. These findings provide additional data for clinicians evaluating the use of concurrent bevacizumab and anticoagulation in patients with mCRC.

CRediT authorship contribution statement

SR: Writing-original draft, investigation, data curation, analysis. CW: Data curation. SHD: Writing-reviewing and editing. JJS: Writing-reviewing and editing. ZIH: Conceptualization, supervision, writing-reviewing and editing.

Ethical statement

The presented work constitutes an original contribution by the authors and has not been previously published elsewhere. The paper is not currently under consideration for publication elsewhere. The authors have conducted their research and analysis in a thorough and comprehensive manner, accurately representing their findings.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] N. Ferrara, VEGF and the quest for tumour angiogenesis factors, Nat. Rev. Cancer 2 (2002) 795–803.
[2] N. Ferrara, K.J. Hillan, H.-P. Gerber, W. Novotny, Discovery and development of bevacizumab, an anti-VEGF antibody for treating cancer, Nat. Rev. Drug Discov. 3 (2004) 391–400.
[3] S. Kilickap, H. Abali, I. Celik, Bevacizumab, bleeding, thrombosis, and warfarin, J. Clin. Oncol. 21 (2003) 3542, author reply 3543.
[4] T. Kamba, D.M. McDonald, Mechanisms of adverse effects of anti-VEGF therapy for cancer, Br. J. Cancer 96 (2007) 1788–1795.
[5] S. Wu, C. Kim, L. Baer, X. Zhu, Bevacizumab increases risk for severe proteinuria in cancer patients, J. Am. Soc. Nephrol. 21 (2010) 1381–1389.
[6] M. Li, D.L. Kroetz, Bevacizumab-induced hypertension: clinical presentation and molecular understanding, Pharmacol. Ther. 182 (2018) 152–160.
[7] W.-X. Qi, Z. Shen, L.-N. Tang, Y. Yao, Bevacizumab increases the risk of gastrointestinal perforation in cancer patients: a meta-analysis with a focus on different subgroups, Eur. J. Clin. Pharmacol. 70 (2014) 893–906.
[8] F.A. Scappaticci, et al., Surgical wound healing complications in metastatic colorectal cancer patients treated with bevacizumab, J. Surg. Oncol. 91 (2005) 173–180.
[9] R.S. Finn, et al., Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma, N. Engl. J. Med. 382 (2020) 1894–1905.
[10] H. Hurwitz, et al., Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer, N. Engl. J. Med. 350 (2004) 2335–2342.
[11] L.B. Saltz, et al., Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study, J. Clin. Oncol. 26 (2008) 2013–2019.
[12] H.S. Friedman, et al., Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma, J. Clin. Oncol. 27 (2009) 4733–4740.
[13] A. Sandler, et al., Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer, N. Engl. J. Med. 355 (2006) 2542–2550.
[14] R.A. Burger, et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer, N. Engl. J. Med. 365 (2011) 2473–2483.
[15] J.A. Heit, et al., Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study, Arch. Intern. Med. 160 (2000) 809–815.
[16] D. Cinar, D. Tas, Cancer in the elderly, North. Clin. Istanbul 2 (2015) 73–80.
[17] S.M. Dunlay, A.M. Chamberlain, Multimorbidity in older patients with cardiovascular disease, Curr. Cardiovasc. Risk Rep. 10 (2016) 3.
[18] C. Kearon, S.R. Kahn, Long-term treatment of venous thromboembolism, Blood 135 (2020) 317–325.
[19] L. Duffett, L.A. Castellucci, M.A. Forgie, Pulmonary embolism: update on management and controversies, BMJ 370 (2020), m2177.
[20] W. Akhtar, W.C. Reeves, A. Movahed, Indications for anticoagulation in atrial fibrillation, Am. Fam. Physician 58 (1998) 130–136.
[21] S.R. Deitcher, et al., Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period, Clin. Appl. Thromb. Hemost. 12 (2006) 389–396.
[22] N.B. Leighl, et al., Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study, Br. J. Cancer 104 (2011) 413–418.
[23] G.H. Lyman, et al., Venous thromboembolism prophylaxis and treatment in patients with cancer: American Society of Clinical Oncology clinical practice guideline update 2014, J. Clin. Oncol. 33 (2015) 654–656.
[24] J. Hambleton, et al., Bevacizumab does not increase bleeding in patients with metastatic colorectal cancer receiving concurrent anticoagulation, J. Clin. Oncol. 22 (2004), 3528-3528.
[25] A. Recio-Boiles, et al., Evaluation of the safety and effectiveness of direct oral anticoagulants and low molecular weight heparin in gastrointestinal cancer-

associated venous thromboembolism, World J. Gastrointest. Oncol. 11 (2019) 866–876.
[26] E.H. Awtry, J. Loscalzo, Aspirin, Circulation 101 (2000) 1206–1218.
[27] A.M. Iqbal, R.A. Lopez, O. Hai, Antiplatelet medications, in: StatPearls, StatPearls Publishing, 2022.
[28] G. Agnelli, et al., Apixaban for the treatment of venous thromboembolism associated with cancer, N. Engl. J. Med. 382 (2020) 1599–1607.
[29] M.H. Prins, et al., Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies, Thromb. J. 11 (2013) 21.
[30] S. Schulman, et al., Extended use of dabigatran, warfarin, or placebo in venous thromboembolism, N. Engl. J. Med. 368 (2013) 709–718.
[31] C.H. Yeh, K. Hogg, J.I. Weitz, Overview of the new oral anticoagulants: opportunities and challenges, Arterioscler. Thromb. Vasc. Biol. 35 (2015) 1056–1065.
[32] A.M. Young, et al., Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D), J. Clin. Oncol. 36 (2018) 2017–2023.
[33] W. Ageno, et al., Bleeding with apixaban and dalteparin in patients with cancer-associated venous thromboembolism: results from the Caravaggio study, Thromb. Haemost. 121 (2021) 616–624.
[34] N.B. Abdol Razak, G. Jones, M. Bhandari, M.C. Berndt, P. Metharom, Cancer-associated thrombosis: an overview of mechanisms, risk factors, and treatment, Cancers 10 (2018) 380.