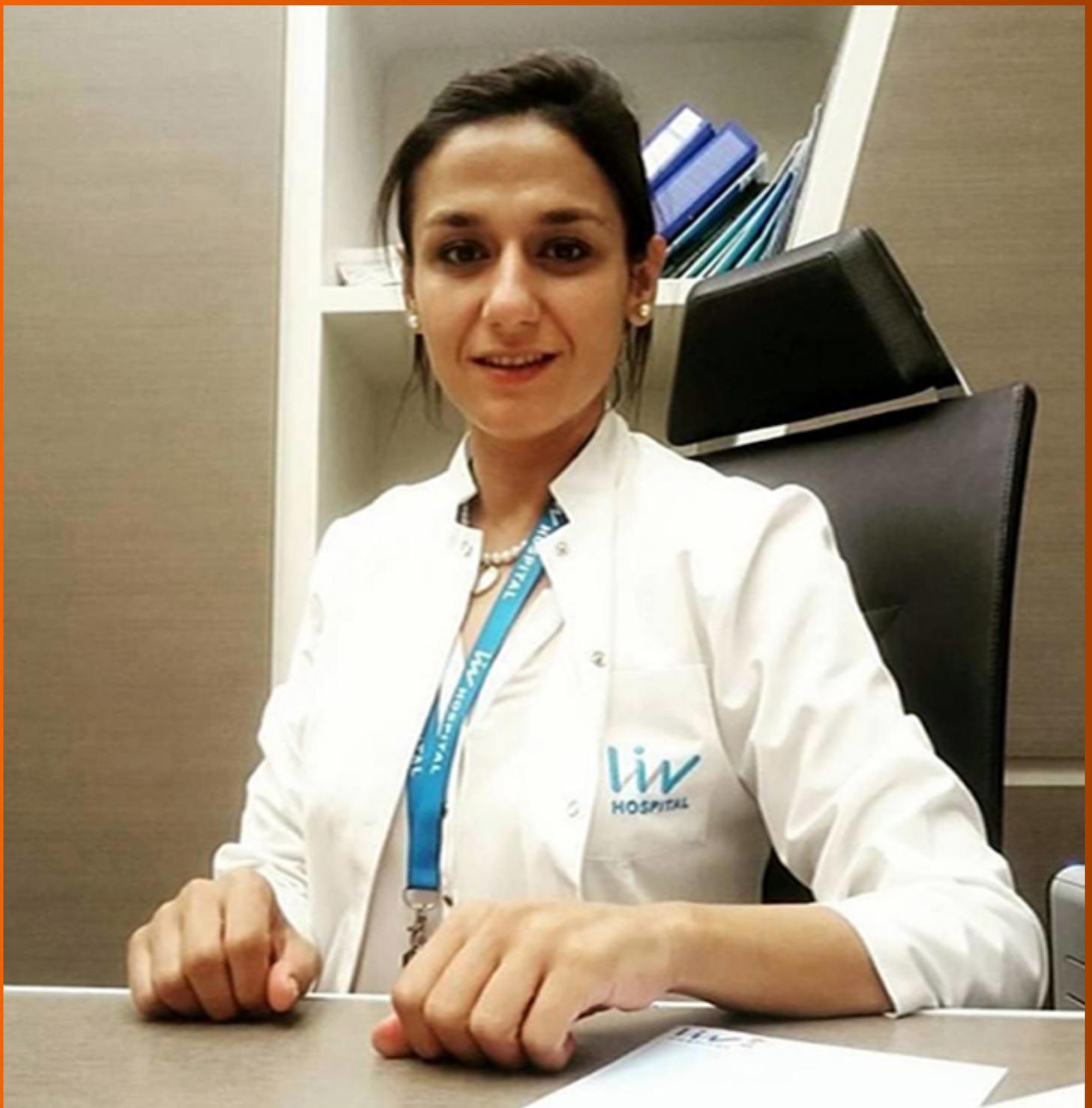


# World Journal of *Gastrointestinal Oncology*

*World J Gastrointest Oncol* 2019 October 15; 11(10): 768-932



## Contents

Monthly Volume 11 Number 10 October 15, 2019

**EDITORIAL**

- 768 Cancer-specific metabolism: Promising approaches for colorectal cancer treatment  
*Jeong KY*

**REVIEW**

- 773 Race, the microbiome and colorectal cancer  
*Royston KJ, Adedokun B, Olopade OI*
- 788 Targeted agents for second-line treatment of advanced hepatocellular carcinoma  
*Personeni N, Pressiani T, Bozzarelli S, Rimassa L*
- 804 Precision medicine in gastric cancer  
*Bonelli P, Borrelli A, Tuccillo FM, Silvestro L, Palaia R, Buonaguro FM*

**MINIREVIEWS**

- 830 Endoscopic management of esophageal cancer  
*Ahmed O, Ajani JA, Lee JH*

**ORIGINAL ARTICLE****Basic Study**

- 842 MicroRNA-320a suppresses tumor progression by targeting PBX3 in gastric cancer and is downregulated by DNA methylation  
*Li YS, Zou Y, Dai DQ*

**Retrospective Study**

- 866 Evaluation of the safety and effectiveness of direct oral anticoagulants and low molecular weight heparin in gastrointestinal cancer-associated venous thromboembolism  
*Recio-Boiles A, Veeravelli S, Vondrak J, Babiker HM, Scott AJ, Shroff RT, Patel H, Elquza E, McBride A*

**Retrospective Cohort Study**

- 877 Fat clearance and conventional fixation identified ypN0 rectal cancers following intermediate neoadjuvant radiotherapy have similar long-term outcomes  
*Chen N, Sun TT, Li ZW, Yao YF, Wang L, Wu AW*

**Observational Study**

- 887 Acylcarnitine: Useful biomarker for early diagnosis of hepatocellular carcinoma in non-steatohepatitis patients  
*Takaya H, Namisaki T, Kitade M, Shimozato N, Kaji K, Tsuji Y, Nakanishi K, Noguchi R, Fujinaga Y, Sawada Y, Saikawa S, Sato S, Kawaratani H, Moriya K, Akahane T, Yoshiji H*

**META-ANALYSIS**

- 898 Prognostic and pathological impact of tumor budding in gastric cancer: A systematic review and meta-analysis  
*Guo YX, Zhang ZZ, Zhao G, Zhao EH*
- 909 Abnormally expressed circular RNAs as novel non-invasive biomarkers for hepatocellular carcinoma: A meta-analysis  
*Jiang YL, Shang MM, Dong SZ, Chang YC*

**CASE REPORT**

- 925 Gastric submucosa-invasive carcinoma associated with Epstein-Barr virus and endoscopic submucosal dissection: A case report  
*Kobayashi Y, Kunogi T, Tanabe H, Murakami Y, Iwama T, Sasaki T, Takahashi K, Ando K, Nomura Y, Ueno N, Kashima S, Moriichi K, Takei H, Fujiya M, Okumura T*

**ABOUT COVER**

Editorial Board Member of *World Journal of Gastrointestinal Oncology*, Naciye Cigdem Arslan, MD, Assistant Professor, Surgeon, Surgical Oncologist, General Surgery, Istanbul Medipol University, Esenler 34320, Istanbul, Turkey

**AIMS AND SCOPE**

The primary aim of *World Journal of Gastrointestinal Oncology (WJGO, World J Gastrointest Oncol)* is to provide scholars and readers from various fields of gastrointestinal oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

*WJGO* mainly publishes articles reporting research results and findings obtained in the field of gastrointestinal oncology and covering a wide range of topics including islet cell adenoma, liver cell adenoma, adenomatous polyposis coli, appendiceal neoplasms, bile duct neoplasms, biliary tract neoplasms, hepatocellular carcinoma, islet cell carcinoma, pancreatic ductal carcinoma, cecal neoplasms, colonic neoplasms, colorectal neoplasms, hereditary nonpolyposis colorectal neoplasms, common bile duct neoplasms, duodenal neoplasms, esophageal neoplasms, gallbladder neoplasms, etc.

**INDEXING/ABSTRACTING**

The *WJGO* is now indexed in Science Citation Index Expanded (also known as SciSearch®), PubMed, and PubMed Central. The 2019 edition of Journal Citation Reports® cites the 2018 impact factor for *WJGO* as 2.758 (5-year impact factor: 3.220), ranking *WJGO* as 52 among 84 journals in gastroenterology and hepatology (quartile in category Q3), and 131 among 229 journals in oncology (quartile in category Q3).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Lu-Lu Qi*  
 Proofing Production Department Director: *Yun-Xiaojuan Wu*

<b>NAME OF JOURNAL</b> <i>World Journal of Gastrointestinal Oncology</i>
<b>ISSN</b> ISSN 1948-5204 (online)
<b>LAUNCH DATE</b> February 15, 2009
<b>FREQUENCY</b> Monthly
<b>EDITORS-IN-CHIEF</b> Monjur Ahmed, Rosa M Jimenez Rodriguez, Pashtoon Murtaza Kasi
<b>EDITORIAL BOARD MEMBERS</b> <a href="https://www.wjgnet.com/1948-5204/editorialboard.htm">https://www.wjgnet.com/1948-5204/editorialboard.htm</a>
<b>EDITORIAL OFFICE</b> Jin-Lei Wang, Director
<b>PUBLICATION DATE</b> October 15, 2019

<b>COPYRIGHT</b> © 2019 Baishideng Publishing Group Inc
<b>INSTRUCTIONS TO AUTHORS</b> <a href="https://www.wjgnet.com/bpg/gerinfo/204">https://www.wjgnet.com/bpg/gerinfo/204</a>
<b>GUIDELINES FOR ETHICS DOCUMENTS</b> <a href="https://www.wjgnet.com/bpg/GerInfo/287">https://www.wjgnet.com/bpg/GerInfo/287</a>
<b>GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH</b> <a href="https://www.wjgnet.com/bpg/gerinfo/240">https://www.wjgnet.com/bpg/gerinfo/240</a>
<b>PUBLICATION MISCONDUCT</b> <a href="https://www.wjgnet.com/bpg/gerinfo/208">https://www.wjgnet.com/bpg/gerinfo/208</a>
<b>ARTICLE PROCESSING CHARGE</b> <a href="https://www.wjgnet.com/bpg/gerinfo/242">https://www.wjgnet.com/bpg/gerinfo/242</a>
<b>STEPS FOR SUBMITTING MANUSCRIPTS</b> <a href="https://www.wjgnet.com/bpg/GerInfo/239">https://www.wjgnet.com/bpg/GerInfo/239</a>
<b>ONLINE SUBMISSION</b> <a href="https://www.f6publishing.com">https://www.f6publishing.com</a>

## Retrospective Study

**Evaluation of the safety and effectiveness of direct oral anticoagulants and low molecular weight heparin in gastrointestinal cancer-associated venous thromboembolism**

Alejandro Recio-Boiles, Sumana Veeravelli, Jessica Vondrak, Hani M Babiker, Aaron J Scott, Rachna T Shroff, Hitendra Patel, Emad Elquza, Ali McBride

**ORCID number:** Alejandro Recio-Boiles (0000-0002-5423-3112); Sumana Veeravelli (0000-0002-7179-6996); Jessica Vondrak (0000-0001-7570-8538); Hani M Babiker (0000-0002-9368-6296); Aaron J Scott (0000-0002-0301-3072); Rachna T Shroff (0000-0003-0066-2672); Hitendra Patel (0000-0001-8746-2600); Emad Elquza (0000-0003-3383-7950); Ali McBride (0000-0002-9430-4675).

**Author contributions:** Recio-Boiles A, Patel H, Elquza E, and McBride A designed and drafted the study concept. Recio-Boiles A, Vondrak J, and Veeravelli S collected the data. Recio-Boiles A, Elquza E, and McBride A performed data analysis and interpretation. Recio-Boiles A, Babiker HM, Scott AJ, Shroff RT, Elquza E, and McBride A contributed to writing, revising and editing the manuscript. All authors helped to perform the research, revision of the manuscript and have approved the final version.

**Institutional review board**

**statement:** This study has a statement on ethics approval by the Institutional Review Board of University of Arizona Cancer Center, which is a part of the University of Arizona The Human Subjects Protection Program.

**Informed consent statement:**

Patients were not required to give

**Alejandro Recio-Boiles, Hani M Babiker, Aaron J Scott, Rachna T Shroff, Emad Elquza,** Department of Medicine, Hematology and Medical Oncology, University of Arizona Cancer Center, Tucson, AZ 85724, United States

**Sumana Veeravelli, Jessica Vondrak,** Department of Medicine, Internal Medicine Residency Program, University of Arizona, Tucson, AZ 85725, United States

**Hitendra Patel,** UC San Diego Health Moores Cancer Center, La Jolla, CA 92093, United States

**Ali McBride,** University of Arizona College of Pharmacy, Tucson, AZ 85725, United States

**Corresponding author:** Alejandro Recio-Boiles, MD, Assistant Professor of Medicine, Department of Medicine, Hematology and Medical Oncology, University of Arizona Cancer Center, 1515 N Campbell Ave, Tucson, AZ 85724, United States.

[areciomd@email.arizona.edu](mailto:areciomd@email.arizona.edu)

**Telephone:** +1-520-6264703

**Fax:** +1-520-6268095

**Abstract****BACKGROUND**

Gastrointestinal cancer (GICA) is associated with a higher incidence of venous thromboembolism (VTE) compared to other solid tumors, moreover, recurrent VTE and major bleeding (MB) complications during anticoagulation treatment have an associated increase rate. GICA-VTE remains a challenging clinical scenario with MB concerns for utilization of direct oral anticoagulants (DOAC), especially with active cancer therapies.

**AIM**

To evaluate patient risk factors, effectiveness (VTE) and safety (MB) of DOACs and low molecular weight heparin (LMWH) in patients with active GICA-VTE.

**METHODS**

A retrospective chart review of patients receiving DOACs and LMWH with GICA and symptomatic or incidental VTE treated at comprehensive cancer center from November 2013 to February 2017 was performed. Inclusion criteria included active GI cancer diagnosed at any stage or treatment +/- 6 mo of VTE diagnosis,

informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** All authors declare no conflicts-of-interest related to this article.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited manuscript

**Received:** February 26, 2019

**Peer-review started:** February 27, 2019

**First decision:** July 31, 2019

**Revised:** September 3, 2019

**Accepted:** September 12, 2019

**Article in press:** September 12, 2019

**Published online:** October 15, 2019

**P-Reviewer:** Cao ZF, Lin Q, Markopoulos AK

**S-Editor:** Dou Y

**L-Editor:** A

**E-Editor:** Qi LL



whom were prescribed 6 mo or more of DOACs or LMWH. The Chi-squared test was used for overall and the Fisher exact test for pairwise comparisons of the proportions of patients experiencing recurrent VTE and MB events. Odds ratios were used to compare the relative odds of the occurrence of the outcome given exposure to the risk factor.

## RESULTS

A total of 144 patients were prescribed anticoagulation, in which 106 fulfilled inclusion criteria apixaban (27.3%), rivaroxaban (34.9%) and enoxaparin (37.7%), and 38 were excluded. Patients median age was 66.5 years at GICA diagnosis and 67 years at CAVTE event, with 62% males, 80% Caucasian, 70% stage IV, pancreatic cancer (40.5%), 30% Khorana Score ( $\geq 3$  points), and 43.5% on active chemotherapy. Sixty-four percent of patients completed anticoagulation therapy (range 1 to 43 mo). Recurrent VTE at 6 mo was noted in 7.5% ( $n = 3$ ), 6.8% ( $n = 2$ ) and 2.7% ( $n = 1$ ) of patients on enoxaparin, apixaban and rivaroxaban, respectively (all  $P = \text{NS}$ ). MB at 6 mo were 5% ( $n = 2$ ) for enoxaparin, 6.8% ( $n = 2$ ) for apixaban and 21.6% ( $n = 8$ ) for rivaroxaban (overall  $P = 0.048$ ; *vs* LMWH  $P = 0.0423$ ; all other  $P = \text{NS}$ ). Significant predictors of a primary or secondary outcome for all anticoagulation therapies included: Active systemic treatment (OR = 5.1, 95%CI: 1.3-19.3), high Khorana Score [ $\geq 3$  points] (OR = 5.5, 95%CI: 1.7-17.1), active smoker (OR = 6.7, 95%CI: 2.1-21.0), pancreatic cancer (OR = 6.8, 95%CI: 1.9-23.2), and stage IV disease (OR = 9.9, 95%CI: 1.2-79.1).

## CONCLUSION

Rivaroxaban compared to apixaban and enoxaparin had a significantly higher risk of MB on GICA-VTE patients with equivocal efficacy.

**Key words:** Direct oral anticoagulants; Low molecular weight heparin; Gastrointestinal cancer; Venous thromboembolism; Cancer associated thrombosis; Clinical risk

©The Author(s) 2019. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Our study shows similar efficacy of low molecular weight heparin as compared to apixaban and rivaroxaban. However, side effect profiles of these new direct oral anticoagulants (DOAC)'s may lead to a preferred use of apixaban, which had lower bleeding events in the highly sensitive gastrointestinal cancer (GICA) patient population. GICA-venous thromboembolism (VTE) is a high-risk patient subpopulation and warrants additional dedicated prospective clinical analysis of the efficacy and safety of DOACs. In addition, evaluation of clinical predictors that may influence the risk of VTE recurrence and major bleeding should include GICA as a high-risk group.

**Citation:** Recio-Boiles A, Veeravelli S, Vondrak J, Babiker HM, Scott AJ, Shroff RT, Patel H, Elquza E, McBride A. 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* 2019; 11(10): 866-876

**URL:** <https://www.wjgnet.com/1948-5204/full/v11/i10/866.htm>

**DOI:** <https://dx.doi.org/10.4251/wjgo.v11.i10.866>

## INTRODUCTION

Venous thromboembolism (VTE) is a common occurrence in cancer patients, specifically in those patients with advanced disease. Cancer-associated VTE (CAVTE) has a three-fold higher risk of recurrent VTE, poorer prognosis and carries with it a significant morbidity and mortality burden as compared to those patients without malignancy<sup>[1,2]</sup>. The goal of anticoagulation therapy is to prevent VTE recurrence while balancing the risk of bleeding events. Two major randomized controlled clinical trials (RCTs) (CLOT<sup>[3]</sup> and LITE<sup>[4]</sup>) demonstrated improved outcomes without secondary safety signals for low molecular weight heparin (LMWH), although 3 other RCTs (CANTHANOX<sup>[5]</sup>, ONCENOX<sup>[6]</sup> and CATCH<sup>[7]</sup>) showed equivocal outcomes compared to vitamin K antagonists (VKA) (Table 1)<sup>[3-7]</sup>. The CLOT trial is the only RCT with mortality benefit at 12 mo in the non-metastatic subgroup (HR = 0.50, 95%CI:

0.27-0.95). Several guidelines including the American Society of Oncology (ASCO)<sup>[8]</sup>, the European Society of Medical Oncology<sup>[9]</sup>, the American College of Chest Physicians<sup>[10]</sup>, and the National Cancer Comprehensive Network<sup>[11]</sup>, recommend LMWH-based therapy over warfarin as the preferred VTE treatment in cancer patients.

Gastrointestinal cancer (GICA) is associated with a higher incidence of VTE compared to other solid tumors<sup>[12]</sup>. The VTE incidence (per 100 person-years/percent of patients) based on GI site is gastroesophageal 50/7-14, pancreatic 20/5-60, colorectal and anal 13.7/3-10, and hepatobiliary cancer 4.6/2-15<sup>[13]</sup>. Moreover, recurrent VTE and major bleeding (MB) complications during anticoagulation treatment of GICA patients are increased as compared to other cancer types. (HR = 5.1, 95% CI: 2.3-11.3 and 1.3, 95% CI: 0.3-5.6, VTE and MB respectively)<sup>[14]</sup>. Several therapies contribute to increased bleeding while on chemotherapy as noted with angiogenesis inhibitors (*e.g.*, bevacizumab<sup>[15]</sup>) and chemotherapy-induced thrombocytopenia (*e.g.*, gemcitabine)<sup>[16]</sup>. Recurrent VTE and MB complications due to secondary VTE prophylaxis remain a salient issue in treating patients with CAVTE with VKA and LMWH.

Direct oral anticoagulants (DOACs) have been shown to be non-inferior to warfarin for VTE treatment (Table 2)<sup>[17-26]</sup>. Four major phase III trials with pooled-analysis of patients with active cancer and VTE suggest that apixaban, rivaroxaban, dabigatran, and edoxaban have independently shown similar efficacy to LMWH plus VKA while having less associated MB<sup>[27-30]</sup>. LMWH remained the preferred treatment regimen for CA-VTE until 2018 when it was challenged by edoxaban in a positive non-inferior open-label RCT for primary-VTE recurrence outcome albeit at the expense of higher MB rate and increased bleeding events in patients with upper GICA<sup>[31]</sup>. A recent study evaluated rivaroxaban to dalteparin to cancer patients with VTE that yielded a 6-mo non-significant VTE recurrence rate and the safety profile for major bleeds in both arms were not significant. However, noticeable MB was seen with upper GI malignancies and these patients were subsequently excluded from trial enrollment<sup>[32]</sup>. Cancer-associated VTE in GI malignancy remains a challenging clinical scenario with a lack of data for utilization of DOACs in the setting of primary treatment and secondary prophylaxis, thus the need for a safer DOAC in patients with active GI-CAVTE remains an open question.

Our objective was to retrospectively evaluate cancer patient risk factors, effectiveness, and safety of DOACs and LMWH in patients with active GICA-VTE at The University of Arizona Cancer Center (UACC).

## MATERIALS AND METHODS

A retrospective chart review of patients receiving DOACs and LMWH with GICA and symptomatic or incidental VTE treated at UACC between November 2013-February 2017 was performed. We obtained prior to initiating research an Institutional Review Board approval Protocol Number: 1508054987 and further obtained a waiver of personal health information authorization [45 CFR 164.512(i)(2)(ii)]: As the use or disclosure of protected health information involves no more than minimal risk to the individuals and the research could not practicably be conducted without the waiver. GI malignancy included any Gastro-esophageal or junction cancer (squamous and adenocarcinoma), pancreatic cancer (adenocarcinoma), neuroendocrine tumors, colorectal cancer (including appendix and cecum), anal cancer, and hepatobiliary cancer (pathology-confirmed). Any treatment for cancer, prior to, current with, or posterior to CAVTE diagnosis and any stage including recurrent or metastatic cancer were included. Acute symptomatic or incidental deep vein thrombosis (DVT) or pulmonary embolism (PE) diagnosed by venous duplex ultrasound, computed tomography (CT) with intravenous (IV) contrast, ventilation/perfusion (V/Q) scan and/or PE pulmonary angiography protocol by CT or magnetic resonance imaging with IV contrast was required. Primary endpoints included recurrent DVT, nonfatal PE, or fatal PE. Adverse events such as MB included a Hg drop of  $\geq 2$  g/dL, transfusion of  $\geq 2$  units of pack of red blood cells (PRBC), bleeding in a critical site, or bleeding contributing to death<sup>[33]</sup>.

Patients who were prescribed 6 mo or more of DOACs [rivaroxaban and apixaban] or LMWH (enoxaparin) at UACC by retrospective review of medical records were included. Only patients receiving Federal Drug Administration (FDA)-approved VTE dosage were included: Rivaroxaban (Xarelto FDA-approved November 2, 2012) at 15 mg BID for 3 wk, then 20 mg daily and Apixaban (Eliquis FDA-approved August 21, 2014) at 10 mg BID for 7 d, then 5 mg twice daily, and Enoxaparin (Lovenox) at 1 mg/kg/dose every 12 h or 1.5 mg/kg once daily). Crossover of up to a month of

**Table 1 Clinical trials for low molecular weight heparin primary efficacy and secondary safety compared to vitamin K antagonist**

Study (yr)	InterventionLM WH	Reported efficacy (rVTE) (%)	Reported safety (MB) (%)	Control VKA	Reported efficacy (rVTE) (%)	Reported safety (MB) (%)	Mortality Benefit at 12 mo
CLOT (2003) <sup>[3]</sup>	Dalteparin	9.0	6.0	Warfarin	17.0	4.0	HR 0.50, 95%CI: 0.27-0.95
LITE (2006) <sup>[4]</sup>	Tinzaparin	7.0	0.0	Warfarin	16.0	2.1	NS
CANTHANOX (2002) <sup>[5]</sup>	Enoxaparin	10.5	5.0	Warfarin	21.1	12.0	NS
ONCENOX (2006) <sup>[6]</sup>	Enoxaparin	6.3	6.5	Warfarin	10.0	2.1	NS
CATCH (2015) <sup>[7]</sup>	Tinzaparin	7.2	2.6	Tinzaparin + Warfarin	10.5	2.4	NS

LMWH: Low molecular weight heparin; VKA: Vitamin K antagonist; rVTE: Recurrent venous thromboembolism; MB: Major bleeding.

LMWH to DOACs was allowed.

Patients were excluded if DOACs or LMWH were prescribed for any other reason not related to GI-CAVTE (*e.g.*, atrial fibrillation, VTE prophylaxis), when anticoagulation was contraindicated (*e.g.*, active bleed, high bleeding risk, thrombocytopenia, palliative, and hospice care) and in patients with other malignancy not related to a gastrointestinal site. Dabigatran was excluded due to an N of one patient. Edoxaban, tinzaparin, and dalteparin were not prescribed at UACC. Betrixaban was not included due to FDA approval on June 23, 2017, after the conclusion of the review.

GICA subgroup extracted from clinical trial delineations followed: Active cancer, defined as cancer diagnosed at any stage +/- 6 mo of VTE diagnosis. The Chi-squared test was used for overall and the Fisher exact test for pairwise comparisons of the proportions of patients experiencing VTE and MB events. Odds ratios (OR) were used to compare the relative of the occurrence of the outcome given exposure to the risk factor. The 95%CI was used to estimate the precision of the OR. Results were determined to be “statistically significant” when this value was less than or equal to 0.05.

## RESULTS

A total of 144 patients were prescribed anticoagulation, in which 106 fulfilled inclusion criteria and 38 were excluded non-malignant indication (atrial fibrillation  $n = 13$ ), palliative and hospice treatment interruption ( $n = 8$ ), VTE prophylaxis ( $n = 2$ ), other anticoagulation (VKA  $n = 7$  and IVC filter  $n = 1$ ), other concurrent malignancy ( $n = 5$ ), and outside records ( $n = 2$ ). Our analysis included patients on Apixaban ( $n = 29$ ), Rivaroxaban ( $n = 37$ ) and Enoxaparin ( $n = 40$ ).

Patients median age was 66.5 years old (range 37-83) at GICA diagnosis and 67 years old (range 37-83) at CAVTE event, and compromised of 62% males and 80% Caucasian (Table 3). The population was typical for those presenting with GI-CAVTE, with 70% having recurrent or metastatic disease, predominately composed of pancreatic cancer (40.5%), with a 30% predictive High Khorana Score ( $\geq 3$  points), and with 43.5% on active chemotherapy. The VTE distribution was 65%, 15%, and 20% for DVT, PE and DVT/PE, respectively. Identifiable risk factors for VTE were seen in 6 patients with recent surgery/hospitalization and 8 patients with diagnosed catheter-related VTE. Approximately, patients were 20% current smokers ( $n = 10$ ), 40% on active antiplatelet therapy ( $n = 53$ ) and 7.5% had previous VTE ( $n = 9$ ). Sixty-four percent of patients completed anticoagulation therapy (range 1 to 40 mo). Patients had similar baseline characteristics compared to Hokusai (Dalteparin  $n = 140$ ) (Raskob *et al*<sup>[31]</sup>, 2018), AMPLIFY (Apixaban  $n = 81$ ) (Agnelli *et al*<sup>[27]</sup>, 2015), and pooled-EINSTEIN (Rivaroxaban  $n = 71$ ) (Prins *et al*<sup>[28]</sup>, 2014) (Supplemental Table 1).

Recurrent VTE at 6 mo was noted in 7.5% ( $n = 3$ ), 6.8% ( $n = 2$ ) and 2.7% ( $n = 1$ ) of patients on enoxaparin, apixaban and rivaroxaban, respectively (all  $P = NS$ ,  $P = 0.0623$  for rivaroxaban *vs* LMWH, for rivaroxaban *vs* apixaban  $P = 0.1659$ , for apixaban *vs* LMWH  $P = 1.000$ ). VTE historical cancer subgroups comparison to Hokusai (11.3%), AMPLIFY (3.7%), and EINSTEIN (2.8%) showed no significant difference (all  $P = NS$ ). MB at 6 mo were 5% ( $n = 2$ ) for enoxaparin, 6.8% ( $n = 2$ ) for apixaban and a significantly higher 21.6% ( $n = 8$ ) for rivaroxaban (overall  $P = 0.048$ ; *vs* LMWH

**Table 2 Clinical trials for direct oral anticoagulants reported recurrent venous thromboembolism and reported mayor bleed outcomes compared to cancer subgroup**

Study	Intervention DOAC	Control	Reported efficacy (rVTE) (%)	Cancer subgroup efficacy (%)	Reported safety (MB) (%)	Cancer subgroup safety (%)	Yr
AMPLIFY <sup>[17]</sup>	Apixaban	Enoxaparin + Warfarin	2.30	3.70	0.6	2.3	2013
AMPLIFY-EXT <sup>[18]</sup>	Apixaban	Placebo	4.00	NA	0.2	NA	2013
RE-COVER <sup>[19]</sup>	Dabigatran	Heparin + Warfarin	3.10	3.10	1.60	4.20	2009
RE-COVER II <sup>[20]</sup>	Dabigatran	Heparin + Warfarin	2.30	2.40	1.20	< 1	2013
RE-MEDY <sup>[21]</sup>	Dabigatran	Warfarin	1.80	3.30	0.90	NA	2013
RE-SONATE <sup>[21]</sup>	Dabigatran	Placebo	0.40	NA	0.30	NA	2013
HOKUSAI-VTE <sup>[22]</sup>	Edoxaban	Warfarin	3.20	3.70	1.40	4.50	2013
EINSTEIN-Choice <sup>[25]</sup>	Rivaroxaban	Aspirin	1.50	NA	0.5	NA	2017
EINSTEIN-DVT <sup>[23]</sup>	Rivaroxaban	Enoxaparin+ Warfarin	2.10	3.40	0.8	14.4	2010
EINSTEIN-EXT <sup>[26]</sup>	Rivaroxaban	Placebo	1.30	2.10	0.7	12.3	2016
EINSTEIN-PE <sup>[24]</sup>	Rivaroxaban	Enoxaparin+ Warfarin	2.10	2	1.1	12.3	2012

DOAC: Direct oral anticoagulant; LMWH: Low molecular weight heparin; VKA: Vitamin K antagonist; rVTE: Recurrent venous thromboembolism; MB: Major bleeding.

pairwise  $P = 0.0423$ ; all other  $P = NS$ ). Historical CAVTE major bleed rate comparison was significantly different for rivaroxaban reported as 2.8% in the EINSTEIN trial ( $P = 0.0027$ ), and not different as reported in the Hokusai (4%), and AMPLIFY (2.3%), respectively.

Rivaroxaban had one recurrent non-fatal PE event and a significantly worse safety profile with 3 major bleed requiring PRBC, 2 critical bleeding sites (subarachnoid hemorrhage and retroperitoneal), and 3 fatal bleeds [hemopericardium ( $n = 2$ ) and upper GI bleed] ( $P = 0.0423$ ), whereas Apixaban had 2 recurrent DVT and 2 major bleeds. LMWH had 1 recurrent non-fatal bleed, 2 DVT, 1 major bleed and 1 fatal bleed [altered mental status presumed intracranial bleed, the family declined further investigation]. Including those events beyond 6 mo, 21.1% of DOACs patients had recorded bleeding events [2 additional major bleeds for apixaban and 2 for rivaroxaban (including another intra-operative fatal bleed following an urgent small bowel resection)] compared to 10% events of LMWH patients (2 more major bleeds) with non-significant difference ( $P$ -value 0.5610).

Significant predictors of a primary or secondary outcome for all anticoagulation therapies included: active systemic treatment (OR = 5.1, 95%CI: 1.3-19.3,  $P = 0.016$ ), high Khorana Score ( $\geq 3$  points) (OR = 5.5, 95%CI: 1.7-17.1,  $P = 0.003$ ), active smoker (OR = 6.7, 95%CI: 2.1-21.0,  $P = 0.012$ ), pancreatic cancer (OR = 6.8, 95%CI: 1.9-23.2,  $P = 0.002$ ), and stage IV disease (OR = 9.9, 95%CI: 1.2-79.1,  $P = 0.03$ ) (Table 4). Those who suffered a primary or secondary outcome were 17.4 times more likely to die within a month period, compared to those who didn't experience an event (CI: 4.7-63.4,  $P = 0.0001$ ). Antiplatelet therapy may have affected on four major bleeds (2 rivaroxaban and 2 enoxaparin), although was not a significant risk factor as 11 patients completed therapy without any outcome event ( $P = 0.479$ ).

## DISCUSSION

### Review of anticoagulation in cancer treatment

The treatment of VTE in cancer patients aims at reducing mortality and morbidity and improving quality of life, but there are potentially life-threatening challenges - namely hemorrhagic risk and the high rate of recurrence. Until the mid-2000s, the standard treatment for acute CAVTE consisted of initial therapy with LMWH or unfractionated

**Table 3** Baseline characteristics of the study population

Baseline characteristics	LMWH (%)	DOACs (%)	Apixaban (%)	Rivaroxaban (%)
N (%)	40	66	29 (44)	37 (56)
Age at cancer diagnosis (median years)	66	67	68	65
(range)	37-80	37-83	43-83	37-79
Age at VTE event (median years)	66	68	68	65
(range)	40-80	37-83	43-83	37-79
Weight (median kg)	71.0	73.0	69.5	77.0
(range)	42-130	42-168	42-168	56-130
Gender (Male)	18 (45)	41 (62)	17 (59)	24 (65)
Race (white)	32 (80)	52 (79)	21 (72)	31 (84)
Current smoker	10 (25)	12 (18)	6 (21)	6 (15)
Antiplatelet therapy	5 (12.5)	8 (12)	5 (17)	3 (8)
Prior treated VTE	2 (5)	7 (11)	2 (7)	5 (13)
Cancer diagnosis				
Pancreas	15 (37.5)	28 (42)	14 (50)	14 (38)
Colon	8 (20)	18 (27)	8 (25)	10 (27)
Rectal	2 (5)	5 (8)	1 (3.5)	4 (11)
NET	3 (7.5)	4 (6)	1 (3.5)	3 (8)
Gastric	4 (10)	3 (5)	1 (3.5)	2 (5)
Esophageal	0	3 (5)	1 (3.5)	2 (5)
Appendix	1 (2.5)	3 (5)	2 (7)	1 (3)
Biliary	3 (7.5)	1 (1)	1 (3.5)	0
GEJ	1 (2.5)	1 (1)	0	1 (3)
HCC	3 (7.5)	0	0	0
Stage at VTE diagnosis				
I	1 (2.5)	1 (1)	1 (3.5)	0
II	7 (17.5)	7 (11)	3 (10.75)	4 (10)
III	3 (7.5)	12 (19)	3 (10.75)	9 (25)
IV	29 (72.5)	46 (69)	22 (75)	24 (65)
Prior chemotherapy	24 (40)	24 (36)	11 (38)	13 (35)
Current chemotherapy	24 (40)	29 (47)	18 (62)	13 (35)
VTE diagnosis				
PE/DVT	11 (27.5)	8 (12)	5 (17)	3 (8)
PE	7 (17.5)	8 (12)	2 (7)	6 (16)
DVT	22 (55)	50 (75)	22 (75)	28 (76)
Identifiable risk factor		10 (16)	5 (17)	5 (14)
Recent surgery/Hospitalization	2 (5)	4 (6)	3 (10)	1 (3)
Central venous catheter	2 (5)	6 (9)	2 (7)	4 (11)
Khorana score				
Low	11 (27.5)	19 (28)	7 (24)	12 (32)
Intermediate	18 (45)	25 (38)	11 (38)	14 (38)
High	11 (27.5)	22 (34)	11 (38)	11 (30)
Therapy completion	25 (62.5)	43 (65)	20 (69)	23 (62)
Anticoagulation length (median mo)	4	6.5	8	6
(range)	1-33	0.3-40	2-29	0.3-40

VTE: Venous thromboembolism; PE: Pulmonary embolism; DVT: Deep vein thrombosis; NET: Neuroendocrine tumor; GEJ: Gastro-esophageal junction; HCC: Hepatocellular carcinoma; DOAC: Direct oral anticoagulant; LMWH: Low molecular weight heparin.

heparin followed by a transition on long-term therapy with an oral anticoagulant with a VKA as the standard of care. The first study (CLOT trial) to challenge this paradigm showed that a specific LMWH, namely dalteparin, was more effective than oral anticoagulation in reducing the risk of recurrent thromboembolism in cancer patients, with a HR 0.48 (95% CI: 0.30-0.77;  $P = 0.002$ ) over the 6-mo study period. There were

**Table 4 Clinical risk factors of a primary or secondary outcome for all anticoagulation therapies**

Clinical risk factor	Odds ratio	95%CI	Significance level
Active treatment	5.1	1.3-19.3	$P = 0.0167$
Khorana score high	5.5	1.7-17.1	$P = 0.0033$
Active smoker	6.7	2.1-21.0	$P = 0.0012$
Pancreatic cancer	6.8	1.9-23.2	$P = 0.0023$
Stage IV	9.9	1.2-79.1	$P = 0.0306$
Death after an event	17.4	4.7-63.4	$P < 0.0001$

no differences between groups regarding bleeding rates (14% *vs* 19%;  $P = 0.09$ ) or mortality rates at 6 mo (39% *vs* 41%;  $P = 0.53$ )<sup>[34]</sup>. After a plethora of supportive research, LMWH became the new standard of care with significantly lower primary recurrent VTE events balanced by an improved secondary MB profile, although not cancer-site specific.

### **Effectiveness and safety of DOAC vs LMWH**

The utilization of DOACs in cancer patients provides another form of primary and secondary VTE prophylaxis, which must be weighed, based on safety profiles in our study population. In 2019 a systemic review and network meta-analysis, extracted data for “active cancer patient subpopulation” from major DOACs RCT have reported similar rates of VTE recurrence (HR = 0.74, 95%CI 0.54-1.01) and MB (HR = 1.78, 95%CI 1.11-2.87) in DOACs as compared to LMWH, although lower to VKA<sup>[35]</sup>. To our knowledge, we present the first and largest retrospective analysis with long-term outcome data of DOACs in patients with GICA and VTE, which showed a non-significant risk of recurrent VTE and worse safety profile compared to rivaroxaban, *vs* apixaban or enoxaparin, by indirect comparison<sup>[27-29]</sup>. Our reported safety profile is consistent with the clinical practice experience literature among non-valvular atrial fibrillation patients on DOACs indirect comparison, whereas apixaban appears to have a lower risk of bleeding than rivaroxaban and any other DOACs<sup>[35]</sup>. Furthermore, rivaroxaban matched to other DOACs patients had a significantly higher risk of MB (HR = 1.82, 95%CI: 1.36-2.43) compared to apixaban patients<sup>[36]</sup>. The most recently published systemic review and meta-analysis which included the only 2 published RCTs on this topic to date<sup>[31,32]</sup> showed that DOACs have a higher incidence of 6-mo major bleeds compared to LMWH for CAVTE (RR: 1.74 (95%CI: 1.05-2.88))<sup>[37]</sup>.

There are significant safety concerns for MB with edoxaban<sup>[31]</sup>, and rivaroxaban<sup>[32]</sup> in the treatment of GICA-VTE, despite demonstrated non-inferiority in recurrent VTE efficacy to LMWH. Edoxaban was non-inferior for clinically relevant nonmajor bleeds (HR = 1.38; 95%CI: 0.98), however it had a significant risk for major bleeds (HR = 1.77, 95%CI: 10.3-3.04,  $P = 0.04$ ), where upper GI bleeds were associated with half of all major bleeds events and were mainly in patients with GICA with (17 of a total 33 events,  $P = 0.02$  for interaction in the safety population)<sup>[31]</sup>. In our cohort, 4 out of 10 upper GI major bleed events occurred while on DOACs through the 6-mo interval. Although, safety profile for major bleeds on the rivaroxaban study was not significant, a noticeable difference in MB events was identified in patients with upper GI malignancies and consequently a midterm safety analysis elected to exclude their enrollment<sup>[32]</sup>. It is worth noting that in the Select-D trial, major bleeds occurred more frequently in GICA than in all other included malignancies (13 *vs* 4,  $P = 0.0102$ ) in both arms 5/6 (83%) events on dalteparin and 8/11 (73%) events in rivaroxaban. Surprisingly, pancreatic cancer had no major bleeds contrary to our experience (8/10 rivaroxaban bleeds). Moreover, Mcbane *et al*<sup>[38]</sup> have presented at 2018 American Society of Hematology preliminary data with regards of oral apixaban therapy associated with significant low MB and VTE recurrence compared to dalteparin in treatment of CAVTE although unknown patient characteristics at present (ADAM-VTE trial pending publication). Cancer-associated VTE in GI malignancy remains a challenging clinical scenario with a lack of data for utilization of DOACs in the setting of primary treatment and secondary prophylaxis, thus the need for a safer DOAC in patients with active GI-CAVTE remains an unmet need.

### **Risk of VTE/Bleed treatment failure**

Our study had similarly high numbers of patients with GI-CAVTE, particularly with cancers of the pancreas (40.5%), consistent with the predictive Khorana risk score for VTE based model by cancer site (Khorana Score stomach and pancreatic cancer site OR = 4.3, 95%CI: 1.2-15.6)<sup>[39]</sup>. We hypothesize that a high Khorana score may also

predict anticoagulation treatment failure and worse outcomes. Interestingly, during the development of, a clinical predictor of recurrent VTE Ottawa score, the derivation population sample recognized GICA and Stage IV cancer to be at an increased risk for efficacy failure, like our report, although only Lung Cancer and Stage I were included in the validation tool due to a potential statistical limitation<sup>[40]</sup>. Similar to our cancer center exploratory DOAC cohort, another population-based study has documented Stage IV pancreatic cancer as the strongest predictor of VTE recurrence and bleeding among active cancer patients on LMWH followed by VKA (HR = 6.38, 95%CI: 2.69-15.13)<sup>[41]</sup>.

There is a gap in knowledge of predictive variables for MB in active cancer patients that was addressed by the RIETE group's bleed risk stratification of the general population which included all cancer (OR = 1.7, 95%CI: 1.4-2.2) among others clinical risk items, receiving LMWH plus VKA<sup>[42]</sup>. Kamphuisen *et al*<sup>[43]</sup> on behalf of the CATCH trial presented the first pre-specified second analysis were a metastatic stage, older age (> 75 years old) and intracranial lesions described on clinical risk considerations in CAVTE with LMWH (tinzaparin) for major bleed. We found that active systemic treatment and active smoker significantly contributed to treatment failure, regardless of the therapy modality or packs per year smoked, respectively (Table 4). Antiplatelet therapy in "real world" appeared not to contribute to an excess bleed, although we do not recommended combination use unless there is a premising cardiovascular indication. Due to LMWH treatment failure (recurrent VTE or MB) and other patient referred inconveniences (*e.g.*, subcutaneous administration), an unmet need remains to be filled by emerging, effective, safe and more convenient therapies like DOAC.

### Limitations

A major limitation of this study is the small sample size of the GICA tumor types, which resulted in wide confidence intervals. Another limitation is the retrospective nature of our analysis, which is unable to capture clinically relevant non-major bleeds due to a lack of detailed documentation to further delineate unscheduled contacts physician recommendations, interruptions in treatment, motives for discontinuation or transition, and patients' preference or discomfort with their treatment. Current clinical trials from multi-center participation will maximize sample size and appropriately power comparison of DOACs with LMWH in which the primary safety outcome should be the rate of major bleed (*e.g.*, apixaban *vs* dalteparin, ADAM-VTE; NCT02585713, pending publication)<sup>[38]</sup>. Furthermore, GI-CAVTE is a high-risk subpopulation deserves additional prospective clinical analysis of the efficacy and safety of DOACs. In addition, evaluation of clinical predictors that may influence the risk of VTE recurrence and MB could include GICA as a high-risk group. At the present time, ASCO clinical practice guidelines update prefers LMWH on patients with an increase risk for bleeding (*e.g.*, GI malignancy) due to the increased of the reported major bleeds events with DOACs when treating existing CAVTE, until data from ongoing trials and real-world practice provides more safety information<sup>[44]</sup>.

## ARTICLE HIGHLIGHTS

### Research background

Venous thromboembolism (VTE) is a common occurrence in cancer patients, specifically in those patients with advanced disease. The goal of anticoagulation therapy is to prevent VTE recurrence while mitigating the safety side effects of therapy, mainly major bleed (MB). Gastrointestinal (GI) cancers are associated with a high incidence of thromboembolic events and an even higher risk of bleeding events while on active chemotherapy. Recurrent VTE efficacy and MB safety complications due to secondary VTE prophylaxis remain a noticeable limitation in treating patients with cancer-associated VTE (CAVTE) with vitamin K antagonist and low molecular weight heparin (LMWH). Direct oral anticoagulants (DOACs), a newer set of agents with easier access and administration for CAVTE, have promising effectiveness outcomes although there is a safeness hesitance to utilize these agents in select subsets of high-risk cancer patients.

### Research motivation

The current role of DOACs in cancer patients is still unfolding and current treatment guidelines recommend them as a preferred option. Since the advent of DOACs, our clinical practice has noticed an unusual safety profile often having to be addressed by changes in administration, holding of therapy, cessation of therapy or switching to another treatment regimen. We wanted to analyze the efficacy and safety outcome of our own institutional real-world experience with DOAC's in the GI cancer setting.

### Research objectives

The goal of our study was to evaluate our institutional outcomes of DOACs and LMWH in patients with active GICA-VTE at The University of Arizona Cancer Center based on safety and

efficacy reported events.

### Research methods

Subjects were extracted from a retrospective chart review of GI cancer patients treated at our comprehensive cancer center for incidental or symptomatic VTE with either DOACs or LMWH. Outcomes events, recurrent VTE and MB, were recorded from patients with an active GI malignancy and concurrent anticoagulation therapy at and beyond 6 mo.

### Research results

Patients on apixaban ( $n = 29$ ), rivaroxaban ( $n = 37$ ) and LMWH ( $n = 40$ ) met inclusion criteria. Recurrent VTE at 6 mo was noted in 7.5% ( $n = 3$ ), 6.8% ( $n = 2$ ) and 2.7% ( $n = 1$ ) of patients on LMWH, apixaban and rivaroxaban, respectively (all  $P = NS$ ). MB at 6 mo was 5% ( $n = 2$ ) for LMWH, 6.8% ( $n = 2$ ) for apixaban and 21.6% ( $n = 8$ ) for rivaroxaban (overall  $P = 0.048$ ; *vs* LMWH  $P = 0.0423$ ; all other  $P = NS$ ). Beyond six-months, MB rates were 21% and 10% for DOACs and LMWH ( $P = NS$ ), respectively, while maintaining efficacy. Significant predictors of any outcome for all anticoagulation therapies included: active systemic treatment (OR = 5.1, 95%CI: 1.3-19.3), high Khorana Score ( $\geq 3$  points) (OR = 5.5, 95%CI: 1.7-17.1), active smoker (OR = 6.7, 95%CI: 2.1-21.0), pancreatic cancer (OR = 6.8, 95%CI: 1.9-23.2), and stage IV disease (OR = 9.9, 95%CI: 1.2-79.1).

### Research conclusions

Rivaroxaban compared to apixaban and LMWH had a significantly higher risk of major bleeding on GICA-VTE patients with equivocal efficacy.

### Research perspectives

Our study shows similar efficacy of LMWH as compared to apixaban and rivaroxaban. Nonetheless, the safety profiles of these new DOACs have to lead to the preferred use of apixaban, which had lower bleeding events in the high-risk GI cancer patient population.

---

## ACKNOWLEDGEMENTS

---

The University of Arizona Hematology and Medical Oncology Fellowship program for supporting their trainees' research interests and goals.

---

## REFERENCES

---

- 1 **Sørensen HT**, Mellekjaer L, Olsen JH, Baron JA. Prognosis of cancers associated with venous thromboembolism. *N Engl J Med* 2000; **343**: 1846-1850 [PMID: [11117976](#) DOI: [10.1056/NEJM200012213432504](#)]
- 2 **Khorana AA**, Francis CW, Culakova E, Kuderer NM, Lyman GH. Thromboembolism is a leading cause of death in cancer patients receiving outpatient chemotherapy. *J Thromb Haemost* 2007; **5**: 632-634 [PMID: [17319909](#) DOI: [10.1111/j.1538-7836.2007.02374.x](#)]
- 3 **Lee AY**, Levine MN, Baker RI, Bowden C, Kakkar AK, Prins M, Rickles FR, Julian JA, Haley S, Kovacs MJ, Gent M; Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) Investigators. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med* 2003; **349**: 146-153 [PMID: [12853587](#) DOI: [10.1056/NEJMoa025313](#)]
- 4 **Hull RD**, Pineo GF, Brant RF, Mah AF, Burke N, Dear R, Wong T, Cook R, Solymoss S, Poon MC, Raskob G; LITE Trial Investigators. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med* 2006; **119**: 1062-1072 [PMID: [17145251](#) DOI: [10.1016/j.amjmed.2006.02.022](#)]
- 5 **Meyer G**, Marjanovic Z, Valcke J, Lorcerie B, Gruel Y, Solal-Celigny P, Le Maignan C, Extra JM, Cottu P, Farge D. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med* 2002; **162**: 1729-1735 [PMID: [12153376](#)]
- 6 **Deitcher SR**, Kessler CM, Merli G, Rigas JR, Lyons RM, Fareed J; ONCENOX Investigators. 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* 2006; **12**: 389-396 [PMID: [17000884](#) DOI: [10.1177/1076029606293692](#)]
- 7 **Lee AYY**, Kamphuisen PW, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; CATCH Investigators. Tinzaparin vs Warfarin for Treatment of Acute Venous Thromboembolism in Patients With Active Cancer: A Randomized Clinical Trial. *JAMA* 2015; **314**: 677-686 [PMID: [26284719](#) DOI: [10.1001/jama.2015.9243](#)]
- 8 **Lyman GH**, Khorana AA, Falanga A, Clarke-Pearson D, Flowers C, Jahanzeb M, Kakkar A, Kuderer NM, Levine MN, Liebman H, Mendelson D, Raskob G, Somerfield MR, Thodiyil P, Trent D, Francis CW; American Society of Clinical Oncology. American Society of Clinical Oncology guideline: recommendations for venous thromboembolism prophylaxis and treatment in patients with cancer. *J Clin Oncol* 2007; **25**: 5490-5505 [PMID: [17968019](#) DOI: [10.1200/JCO.2007.14.1283](#)]
- 9 **Mandalà M**, Falanga A, Roila F; ESMO Guidelines Working Group. Management of venous thromboembolism (VTE) in cancer patients: ESMO Clinical Practice Guidelines. *Ann Oncol* 2011; **22** Suppl 6: vi85-vi92 [PMID: [21908511](#) DOI: [10.1093/annonc/mdr392](#)]
- 10 **Kearon C**, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JRE, Wells P, Woller SC, Moores L. Antithrombotic Therapy for VTE

- Disease: CHEST Guideline and Expert Panel Report. *Chest* 2016; **149**: 315-352 [PMID: 26867832 DOI: 10.1016/j.chest.2015.11.026]
- 11 **Streiff MB**, Holmstrom B, Ashrani A, Bockenstedt PL, Chesney C, Eby C, Fanikos J, Fenninger RB, Fogerty AE, Gao S, Goldhaber SZ, Hendrie P, Kuderer N, Lee A, Lee JT, Lovrincevic M, Millenson MM, Neff AT, Ortel TL, Paschal R, Shattil S, Siddiqi T, Smock KJ, Soff G, Wang TF, Yee GC, Zakarija A, McMillian N, Engh AM. Cancer-Associated Venous Thromboembolic Disease, Version 1.2015. *J Natl Compr Canc Netw* 2015; **13**: 1079-1095 [PMID: 26358792]
  - 12 **Shah MA**, Capanu M, Soff G, Asmis T, Kelsen DP. Risk factors for developing a new venous thromboembolism in ambulatory patients with non-hematologic malignancies and impact on survival for gastroesophageal malignancies. *J Thromb Haemost* 2010; **8**: 1702-1709 [PMID: 20553384 DOI: 10.1111/j.1538-7836.2010.03948.x]
  - 13 **Martin LK**, Bekaii-Saab T. Management of venous thromboembolism in patients with advanced gastrointestinal cancers: what is the role of novel oral anticoagulants? *Thrombosis* 2012; **2012**: 758385 [PMID: 23024860 DOI: 10.1155/2012/758385]
  - 14 **Prandoni P**, Lensing AW, Piccioli A, Bernardi E, Simioni P, Girolami B, Marchiori A, Sabbion P, Prins MH, Noventa F, Girolami A. Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. *Blood* 2002; **100**: 3484-3488 [PMID: 12393647 DOI: 10.1182/blood-2002-01-0108]
  - 15 **Leigh NB**, Bennouna J, Yi J, Moore N, Hambleton J, Hurwitz H. Bleeding events in bevacizumab-treated cancer patients who received full-dose anticoagulation and remained on study. *Br J Cancer* 2011; **104**: 413-418 [PMID: 21245868 DOI: 10.1038/sj.bjc.6606074]
  - 16 **Hitron A**, Steinke D, Sutphin S, Lawson A, Talbert J, Adams V. Incidence and risk factors of clinically significant chemotherapy-induced thrombocytopenia in patients with solid tumors. *J Oncol Pharm Pract* 2011; **17**: 312-319 [PMID: 20823048 DOI: 10.1177/1078155210380293]
  - 17 **Agnelli G**, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Masiukiewicz U, Pak R, Thompson J, Raskob GE, Weitz JI; AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med* 2013; **369**: 799-808 [PMID: 23808982 DOI: 10.1056/NEJMoa1302507]
  - 18 **Agnelli G**, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI; AMPLIFY-EXT Investigators. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med* 2013; **368**: 699-708 [PMID: 23216615 DOI: 10.1056/NEJMoa1207541]
  - 19 **Schulman S**, Kearon C, Kakkar AK, Mismetti P, Schellong S, Eriksson H, Baanstra D, Schnee J, Goldhaber SZ; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009; **361**: 2342-2352 [PMID: 19966341 DOI: 10.1056/NEJMoa0906598]
  - 20 **Schulman S**, Kakkar AK, Goldhaber SZ, Schellong S, Eriksson H, Mismetti P, Christiansen AV, Friedman J, Le Maulf F, Peter N, Kearon C; RE-COVER II Trial Investigators. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation* 2014; **129**: 764-772 [PMID: 24344086 DOI: 10.1161/CIRCULATIONAHA.113.004450]
  - 21 **Schulman S**, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D, Kvamme AM, Friedman J, Mismetti P, Goldhaber SZ; RE-MEDY Trial Investigators; RE-SONATE Trial Investigators. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013; **368**: 709-718 [PMID: 23425163 DOI: 10.1056/NEJMoa1113697]
  - 22 **Hokusai-VTE Investigators**. Buller HR, Décousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH, Raskob GE, Schellong SM, Schwacho L, Segers A, Shi M, Verhamme P, Wells P. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013; **369**: 1406-1415 [PMID: 23991658 DOI: 10.1056/NEJMoa1306638]
  - 23 **EINSTEIN Investigators**. Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, Lensing AW, Misselwitz F, Prins MH, Raskob GE, Segers A, Verhamme P, Wells P, Agnelli G, Bounameaux H, Cohen A, Davidson BL, Piovella F, Schellong S. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**: 2499-2510 [PMID: 21128814 DOI: 10.1056/NEJMoa1007903]
  - 24 **EINSTEIN-PE Investigators**. Buller HR, Prins MH, Lensin AW, Decousus H, Jacobson BF, Minar E, Chlumsky J, Verhamme P, Wells P, Agnelli G, Cohen A, Berkowitz SD, Bounameaux H, Davidson BL, Misselwitz F, Gallus AS, Raskob GE, Schellong S, Segers A. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**: 1287-1297 [PMID: 22449293 DOI: 10.1056/NEJMoa1113572]
  - 25 **Weitz JI**, Lensing AWA, Prins MH, Bauersachs R, Beyer-Westendorf J, Bounameaux H, Brighton TA, Cohen AT, Davidson BL, Decousus H, Freitas MCS, Holberg G, Kakkar AK, Haskell L, van Bellen B, Pap AF, Berkowitz SD, Verhamme P, Wells PS, Prandoni P; EINSTEIN CHOICE Investigators. Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism. *N Engl J Med* 2017; **376**: 1211-1222 [PMID: 28316279 DOI: 10.1056/NEJMoa1700518]
  - 26 **Wells PS**, Prins MH, Levitan B, Beyer-Westendorf J, Brighton TA, Bounameaux H, Cohen AT, Davidson BL, Prandoni P, Raskob GE, Yuan Z, Katz EG, Gebel M, Lensing AWA. Long-term Anticoagulation With Rivaroxaban for Preventing Recurrent VTE: A Benefit-Risk Analysis of EINSTEIN-Extension. *Chest* 2016; **150**: 1059-1068 [PMID: 27262225 DOI: 10.1016/j.chest.2016.05.023]
  - 27 **Agnelli G**, Buller HR, Cohen A, Gallus AS, Lee TC, Pak R, Raskob GE, Weitz JI, Yamabe T. Oral apixaban for the treatment of venous thromboembolism in cancer patients: results from the AMPLIFY trial. *J Thromb Haemost* 2015; **13**: 2187-2191 [PMID: 26407753 DOI: 10.1111/jth.13153]
  - 28 **Prins MH**, Lensing AW, Brighton TA, Lyons RM, Rehm J, Trajanovic M, Davidson BL, Beyer-Westendorf J, Pap AF, Berkowitz SD, Cohen AT, Kovacs MJ, Wells PS, Prandoni P. Oral rivaroxaban versus enoxaparin with vitamin K antagonist for the treatment of symptomatic venous thromboembolism in patients with cancer (EINSTEIN-DVT and EINSTEIN-PE): a pooled subgroup analysis of two randomised controlled trials. *Lancet Haematol* 2014; **1**: e37-e46 [PMID: 27030066 DOI: 10.1016/S2352-3026(14)70018-3]
  - 29 **Schulman S**, Goldhaber SZ, Kearon C, Kakkar AK, Schellong S, Eriksson H, Hantel S, Feuring M, Kreuzer J. Treatment with dabigatran or warfarin in patients with venous thromboembolism and cancer. *Thromb Haemost* 2015; **114**: 150-157 [PMID: 25739680]
  - 30 **Raskob GE**, van Es N, Segers A, Angchaisuksiri P, Oh D, Boda Z, Lyons RM, Meijer K, Gudiz I, Weitz JI, Zhang G, Lanz H, Mercuri MF, Buller HR; Hokusai-VTE investigators. Edoxaban for venous thromboembolism in patients with cancer: results from a non-inferiority subgroup analysis of the Hokusai-VTE randomised, double-blind, double-dummy trial. *Lancet Haematol* 2016; **3**: e379-e387 [PMID:

- 27476789 DOI: [10.1016/S2352-3026\(16\)30057-6](https://doi.org/10.1016/S2352-3026(16)30057-6)]
- 31 **Raskob GE**, van Es N, Verhamme P, Carrier M, Di Nisio M, Garcia D, Grosso MA, Kakkar AK, Kovacs MJ, Mercuri MF, Meyer G, Segers A, Shi M, Wang TF, Yeo E, Zhang G, Zwicker JI, Weitz JI, Büller HR; Hokusai VTE Cancer Investigators. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. *N Engl J Med* 2018; **378**: 615-624 [PMID: [29231094](https://pubmed.ncbi.nlm.nih.gov/29231094/) DOI: [10.1056/NEJMoa1711948](https://doi.org/10.1056/NEJMoa1711948)]
  - 32 **Young AM**, Marshall A, Thirlwall J, Chapman O, Lokare A, Hill C, Hale D, Dunn JA, Lyman GH, Hutchinson C, MacCallum P, Kakkar A, Hobbs FDR, Petrou S, Dale J, Poole CJ, Maraveyas A, Levine M. 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* 2018; **36**: 2017-2023 [PMID: [29746227](https://pubmed.ncbi.nlm.nih.gov/29746227/) DOI: [10.1200/JCO.2018.78.8034](https://doi.org/10.1200/JCO.2018.78.8034)]
  - 33 **Schulman S**, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antithrombotic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692-694 [PMID: [15842354](https://pubmed.ncbi.nlm.nih.gov/15842354/) DOI: [10.1111/j.1538-7836.2005.01204.x](https://doi.org/10.1111/j.1538-7836.2005.01204.x)]
  - 34 **Vedovati MC**, Germini F, Agnelli G, Becattini C. Direct oral anticoagulants in patients with VTE and cancer: a systematic review and meta-analysis. *Chest* 2015; **147**: 475-483 [PMID: [25211264](https://pubmed.ncbi.nlm.nih.gov/25211264/) DOI: [10.1378/chest.14-0402](https://doi.org/10.1378/chest.14-0402)]
  - 35 **Rossel A**, Robert-Ebadi H, Combescurie C, Groscurin O, Stirnemann J, Addeo A, Garin N, Agoritsas T, Reny JL, Marti C. Anticoagulant therapy for acute venous thrombo-embolism in cancer patients: A systematic review and network meta-analysis. *PLoS One* 2019; **14**: e0213940 [PMID: [30897142](https://pubmed.ncbi.nlm.nih.gov/30897142/) DOI: [10.1371/journal.pone.0213940](https://doi.org/10.1371/journal.pone.0213940)]
  - 36 **Lip GY**, Keshishian A, Kamble S, Pan X, Mardekian J, Horblyuk R, Hamilton M. Real-world comparison of major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban, or warfarin. A propensity score matched analysis. *Thromb Haemost* 2016; **116**: 975-986 [PMID: [27538358](https://pubmed.ncbi.nlm.nih.gov/27538358/) DOI: [10.1160/TH16-05-0403](https://doi.org/10.1160/TH16-05-0403)]
  - 37 **Li A**, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. *Thromb Res* 2019; **173**: 158-163 [PMID: [29506866](https://pubmed.ncbi.nlm.nih.gov/29506866/) DOI: [10.1016/j.thromres.2018.02.144](https://doi.org/10.1016/j.thromres.2018.02.144)]
  - 38 **McBane II R**, Loprinzi CL, Ashrani A, Perez-Botero J, Leon Ferre RA, Henkin S, Lenz CJ, Le-Rademacher JG, Wysokinski WE. Apixaban and dalteparin in active malignancy associated venous thromboembolism. The ADAM VTE Trial. *Thromb Haemost* 2017; **117**: 1952-1961 [PMID: [28837207](https://pubmed.ncbi.nlm.nih.gov/28837207/) DOI: [10.1160/TH17-03-0193](https://doi.org/10.1160/TH17-03-0193)]
  - 39 **Khorana AA**, Kuderer NM, Culakova E, Lyman GH, Francis CW. Development and validation of a predictive model for chemotherapy-associated thrombosis. *Blood* 2008; **111**: 4902-4907 [PMID: [18216292](https://pubmed.ncbi.nlm.nih.gov/18216292/) DOI: [10.1182/blood-2007-10-116327](https://doi.org/10.1182/blood-2007-10-116327)]
  - 40 **Louzada ML**, Carrier M, Lazo-Langner A, Dao V, Kovacs MJ, Ramsay TO, Rodger MA, Zhang J, Lee AY, Meyer G, Wells PS. Development of a clinical prediction rule for risk stratification of recurrent venous thromboembolism in patients with cancer-associated venous thromboembolism. *Circulation* 2012; **126**: 448-454 [PMID: [22679142](https://pubmed.ncbi.nlm.nih.gov/22679142/) DOI: [10.1161/CIRCULATIONAHA.111.051920](https://doi.org/10.1161/CIRCULATIONAHA.111.051920)]
  - 41 **Chee CE**, Ashrani AA, Marks RS, Petterson TM, Bailey KR, Melton LJ, Heit JA. Predictors of venous thromboembolism recurrence and bleeding among active cancer patients: a population-based cohort study. *Blood* 2014; **123**: 3972-3978 [PMID: [24782507](https://pubmed.ncbi.nlm.nih.gov/24782507/) DOI: [10.1182/blood-2014-01-549733](https://doi.org/10.1182/blood-2014-01-549733)]
  - 42 **Ruiz-Giménez N**, Suárez C, González R, Nieto JA, Todolí JA, Samperiz AL, Monreal M; RIETE Investigators. Predictive variables for major bleeding events in patients presenting with documented acute venous thromboembolism. Findings from the RIETE Registry. *Thromb Haemost* 2008; **100**: 26-31 [PMID: [18612534](https://pubmed.ncbi.nlm.nih.gov/18612534/) DOI: [10.1160/TH08-03-0193](https://doi.org/10.1160/TH08-03-0193)]
  - 43 **Kamphuisen PW**, Lee AYY, Meyer G, Bauersachs R, Janas MS, Jarner MF, Khorana AA; CATCH Investigators. Clinically relevant bleeding in cancer patients treated for venous thromboembolism from the CATCH study. *J Thromb Haemost* 2018; **16**: 1069-1077 [PMID: [29573330](https://pubmed.ncbi.nlm.nih.gov/29573330/) DOI: [10.1111/jth.14007](https://doi.org/10.1111/jth.14007)]
  - 44 **Key NS**, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A. Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol* 2019; **JCO1901461** [PMID: [31381464](https://pubmed.ncbi.nlm.nih.gov/31381464/) DOI: [10.1200/JCO.19.01461](https://doi.org/10.1200/JCO.19.01461)]



Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-2238242  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

