Real world data on treatment patterns and bleeding complications in cancer-associated thrombosis - an unselected population-based cohort from the TROLL registry

Kappe og artikkel

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Norsk sammendrag

Bakgrunn: Internasjonale retningslinjer anbefaler for tiden direktevirkende perorale antikoagulantia (DOAK) som førstelinjebehandling for kreft-assosiert trombose (KAT). Sett bort fra kliniske studier, finnes det imidlertid lite data angående bruk av DOAK hos pasienter med KAT.

Mål: Denne studien utforsket endringen i behandlingsmønstre på antikoagulasjon over 15 års periode og analyserte insidensrater, samt 6- og 12-måneders kumulativ insidens av blødningskomplikasjoner hos pasienter med KAT, basert på krefttyper under antikoagulasjonsbehandling.

Metode: Pasienter i alderen ≥18 år med aktiv kreft og førstegangs venøs tromboembolisme (VTE) i perioden 2005-2020 ble identifisert gjennom Venøs **T**rombose **R**egister på Østf**OL**d sykehus (TROLL register). Behandlingsmønstre ved antikoagulasjon og antikoagulasjons-relaterte blødningshendelser var utfallsmål.

Resultater: Medianalder hos 842 inkluderte pasienter ved diagnosetidspunktet var 69 år (IQR 61-77 år), og 443 (52,6 %) var menn. 526 pasienter (62,5 %) hadde lungeemboli, mens 255 (30,3 %) hadde dyp venetrombose. 713 (85,8 %) pasienter ble foreskrevet lavmolekylært heparin (LMWH), mens 64 (7,7 %) fikk DOAK og 54 (6,5 %) mottok vitamin K-antagonister som initial antikoagulasjonsbehandling. Bruken av DOAK, som førstegangsbehandling, økte gradvis fra 3% i 2013 til 18,0 % i 2020. Insidensraten av større blødninger var 6,9 (95 % KI 5,2 – 9,2) per 100 personår og 10,1 (95% KI 8.0 – 12.9) for klinisk relevant ikke-alvorlig blødning (CRNMB).

Konklusjon: De fleste av pasientene behandles fremdeles primært med LMWH. Imidlertid kan et gradvis økende bruk av DOAK observeres. Totalt sett er blødningskomplikasjoner i klinisk praksis sjeldne og kan sammenlignes med det som er rapportert i randomiserte studier.

Engelsk abstract

Background: Direct oral anticoagulants are increasingly recommended by several international guidelines as first-line treatment for cancer-associated thrombosis (CAT). However, data regarding treatment patterns and adherence to guidelines in patients with CAT is scarce.

Objectives: To explore anticoagulant treatment patterns in patients with CAT and to estimate the overall incidence rates and 6- and 12-month cumulative incidence of bleeding events.

Methods: Patients aged ≥18 years with active cancer and diagnosed with a first-time venous thromboembolism between 2005 and 2020 were identified through The Venous **T**hrombosis **R**egistry in Østf**OL**d Hospita**L** (TROLL registry). Outcome measures were patterns of anticoagulant treatment during the study period and bleeding events.

Results: Median age of 842 included patients at the time of diagnosis was 69 years (IQR 61-77 years), and 443 (52.6%) were men. 526 patients (62.5%) had pulmonary embolism and 255 (30.3%) deep vein thrombosis. Low-molecular-weight heparin (LMWH) was prescribed in 713 (85.8%) patients, whereas 64 (7.7%) received DOACs and 54 (6.5%) vitamin K antagonists as initial anticoagulant treatment. Prescription of DOACs, as initial treatment, increased gradually from 3.0% to 18.0% from 2013 to 2020. Incidence rate for major bleeding was 6.9 (95% CI 5.2 – 9.2) per 100 person-years and 10.1 (95% CI 8.0 – 12.9) for clinically relevant non-major bleeding (CRNMB).

Conclusion: Most patients were treated with LMWH. However, a gradual shift in treatment towards DOACs was observed. Overall, bleeding complications were rare in the real-life and comparable to that reported in randomized trials.

Innledning

Prosjektoppgaven er skrevet som en artikkel med tittel "Real world data on treatment patterns and bleeding complications in cancer-associated thrombosis - an unselected population-based cohort from the TROLL registry" og en tilhørende kappe på norsk. Det er tilsiktet at artikkelen skal publiseres i internasjonalt tidsskrift innen fagene i hematologi og onkologi. Per februar 2023 er artikkelens sammendrag/«abstract» sendt til den internasjonale kongressen for trombose og hemostase (ISTH 2023) for vurdering av studiens presentasjon i kongressen juni 2023.

Jeg, som førsteforfatter, hadde først og fremst ansvar for dataanalyse, resultattolkning og skriving av manuskriptutkast. Gjennomgangen av TROLL-registeret og planlegging av artikkelen pågikk i 2021. Registeret ble organisert og oppdatert av forskningssykepleiere Camilla Tøvik Jørgensen og Heidi Hassel Pettersen. I januar 2022 begynte arbeidet med prosjektet. Jeg arbeidet først med strukturering av data og gjennomførte så analyser på STATA under supervisjon av stipendiat Camilla Tøvik Jørgensen. Jeg fikk gjennom skriveperioden opplæring i statistiske metoder og laget komplekse og relevante dataanalyser. I januar og februar 2023 besto arbeidet mest av tolkning av resultater fra vår studie, samt andre studier med tilsvarende tema. Mine veiledere, professor Waleed Ghanima og Andreas Stensvold, og medforfatterne Mazdak Tavoly og Sigrid Brækkan fra senter av Tromboseforskning i Tromsø, har i løpet av artikkelskrivingen vurdert teksten. De har bidratt med å vinkle og tilpasse artikkelen for et bredere forskningsmessig nedslagsfelt, som i fagene akuttmedisin, hematologi og onkologi som kan berøre kreft-assosiert trombose.

Hovedformålet med prosjektet var å undersøke behandlingsmønstre for kreft-assosiert trombose og blødningskomplikasjoner under behandling med antikoagulasjon i perioden 2005-2020. Dette er for å danne et bilde om hvordan anbefalingene i internasjonale retningslinjer blitt fulgt opp ved Sykehuset Østfold.

Bakgrunn

Venøs tromboembolisme (VTE) er en hyppig forekommende komplikasjon hos kreftpasienter. I løpet av de siste tiårene har insidensen av VTE hos pasienter med aktiv kreft tredoblet seg, mens den for pasienter behandlet med kjemoterapi eller målrettet kreftbehandling har økt med 3-6 ganger (1). Pasienter med kreftassosiert trombose (KAT) har høyere risiko for mortalitet og sykelighet og har en tendens til å bruke mer ressurser innad i helsesektoren sammenlignet med kreftpasienter uten VTE (2-5). Pasienter med KAT har økt

risiko for VTE-residiv, samtidig som de har økt risiko for blødning sammenlignet med VTE-pasienter uten kreft (6). I denne sammenhengen er behandlingen og omsorgen for KAT-pasienter et spesielt utfordrende klinisk problem.

Tradisjonelt har KAT blitt behandlet med lavmolekylært heparin (LMWH) (7). Nylig har flere studier bekreftet effektiviteten og sikkerheten til direktevirkende orale antikoagulantia (DOAK) hos de fleste pasientene med KAT (8-11). Dette har medført at flere DOAK er blitt godkjent og anbefalt i internasjonale retningslinjer som et behandlingsalternativ for pasienter med KAT. Sammenlignet med LMWH kan noen DOAK-preparater øke risikoen for alvorlige blødninger selv om disse effektene anses å være små, kan dette være en av grunnene til motviljen til å bruke DOAK hos kreftpasienter (12-16). Et spørreskjema om KAT-behandling utført i 2021 avslørte at 21,2 % av legene aldri hadde foreskrevet en DOAK, hovedsakelig på grunn av mangel på erfaring og manglende kunnskap om dens bruks- og sikkerhetsprofil, uønskede bivirkninger, interaksjoner med andre legemidler, eller nasjonale forskrifter som begrenser anvendelsen av DOAK-er hos KAT-pasienter (17). Det finnes begrensede data omhandlende etterlevelse av klinisk praksis til retningslinjer hos KAT-pasienter.

Forskningsspørsmål

Denne prosjektoppgaven hadde forskningsspørsmål formulert som:

1- Hvilke antikoagulasjonsmidler har blitt gitt til en uselektert gruppe pasienter med kreft-assosiert trombose ved SØ?
2- Hvor hyppig forekommer blødninger hos pasienter med kreft-assosiert trombose under antikoagulasjon?
3- Hvilke typer kreft er mest assosiert med blødning hos pasienter med kreft-assosiert trombose?

Materiale, metode og etikk

Denne studien er en prospektiv studie basert på data fra Venøs **T**rombose **R**egister på Østf**ol**d sykehus (TROLL register). TROLL er et enkeltsenter VTE-register i Sykehuset Østfold som ble etablert i 2005. Registerdataene for studien omfattet pasienter som fortløpende ble diagnostisert og/eller behandlet eller fulgt opp for VTE ved trombosepoliklinikken ved Sykehuset Østfold. Detaljert informasjon om TROLL-registeret har blitt beskrevet i tidligere publikasjon (18)

Alle pasienter ≥ 18 år med diagnosen KAT registrert i TROLL mellom januar 2005 og mai 2020 var kvalifisert for studieinkludering. KAT er definert som en venøs tromboembolisme, inkludert lungeembolisme (LE), dyp venetrombose (DVT), splanchnic venetrombose og venetrombose i øvre ekstremitet (UEDVT), hos pasienter med aktiv kreft. Pasientene måtte ha en symptomatisk eller tilfeldig oppdaget førstegangs VTE-diagnose som ble verifisert radiologisk ved pulmonalangiografi (CTPA), V/Q scintigrafi, kompresjonsultralyd (CUS), abdominal CT, magnetisk resonansavbildning (MR) eller obduksjon. Aktiv kreft ble i studien definert som kreftdiagnose bekreftet de siste 6 månedene, kreft under pågående kreftbehandling, tilbakevendende kreft med lokal spredning eller metastaser, eller hematologisk kreft som ikke var i fullstendig remisjon (15). Eksklusjonskriterier omfattet pasienter med tidligere VTE-episode, enhver sinusvenetrombose eller overfladisk tromboflebitt, samt pasienter uten aktiv kreft eller med diagnostisert kreft etter VTE-diagnose. Registeret ble manuelt gjennomgått og oppdatert for komplettering av manglende data og utfall vedrørende pasienter med KAT innen mai 2020, og ytterligere data fra pasientjournaler ble samlet inn fra andre helseinstitusjoner.

Studiepopulasjonen ble karakterisert ved demografi, risikofaktorer for VTE, VTE-typer samt lokalisasjon og typer av kreft. Kreft ble kategorisert i henhold til den internasjonale statistiske klassifikasjonen av sykdommer og beslektede helseproblemer, 10. utgave (ICD-10).

Det primære utfallet var antikoagulasjonsbehandlingsmønstre i 2005-2020. Følgende antikoagulantia midler ble vurdert: LMWH (dalteparin og enoksaparin), vitamin K-antagonist (VKA) og DOAK (rivaroksaban, edoksaban, apiksaban og dabigatran). Antikoagulasjonsbehandling ble kategorisert som initial eller sekundær. Initialbehandling ble definert som den første antikoagulasjonsbehandlingen etter KAT-diagnose som varte i mer enn to uker. Sekundærbehandling ble definert som antikoagulasjonsmidlet som pasientene gikk over til fra den første behandlingen. Behandlingsperioder mindre enn to uker ble ikke registrert som hovedbehandling (initial eller sekundær) da mange pasienter ble behandlet med LMWH før den initiale behandlingsfasen eller av andre årsaker. Det var ingen øvre begrensning på total behandlingsvarighet. Bruken av DOAK, som initialbehandling, ble observert ved de vanligste kreftgruppene og ved de kreftformene som ifølge litteraturen er assosiert med høyere blødningsrisiko (øvre og nedre gastrointestinaltraktus, og urogenital kreft) (16).

De sekundære utfallene var alvorlige, og klinisk relevante ikke-alvorlige blødninger (CRNMB) under antikoagulasjonsbehandling. Blødning ble undersøkt med insidensrater og

kumulative insidenser i henhold til forskjellige kreftdiagnoser. Blødningshendelser ble identifisert ved oppfølging i trombosepoliklinikken eller ved gjennomgang av pasientenes journaler. Blødningshendelser ble klassifisert i henhold til «Control of Anticoagulation Subcommittee av International Society on Thrombosis and Haemostasis» (ISTH) som alvorlig blødning eller CRNMB (19, 20). Oppfølgingstid for alle pasientene som fikk blødning startet fra datoen for KAT-diagnose til datoen for blødningshendelsen, mens pasienter som ikke fikk blødning ble fulgt opp til siste dag av antikoagulasjonsbehandling, dødsdato eller slutten av studieperioden (7. mai 2020), avhengig av hva som inntraff først.

Kategoriske variabler ble beskrevet med frekvenser og prosenter, mens kontinuerlige variabler med medianer med tilsvarende interkvartile avstander. Insidensrater ble analysert for alvorlige blødninger og CRNMB blant de vanligste krefttypene og blant de, ifølge litteratur, er assosiert med høyere blødningsrisiko, som nevnt ovenfor. CRNMB-hendelser ble ikke sensurert før analyse av alvorlige blødninger hvis CRNMB oppstod før alvorlige blødninger. Alvorlige blødningshendelser ble sensurert før CRNMB hvis alvorlige blødninger oppstod før CRNMB, i tilfelle endring av behandling etter alvorlige blødninger. Insidensrater ble beregnet for blødningshendelser delt på persontid med risiko for total forekomst og 100 personår med 95 % konfidensintervall (KI). Kumulative insidenser med 95 % konfidensintervall av blødningshendelser ved 6 og 12 måneder ble beregnet ved bruk av 1-Kaplan-Meier (1-KM) analyser, med død som konkurrerende faktor ved analyse av alvorlige blødninger. For tidstrendanalyser ble insidensrater beregnet og stratifisert til 3-årsperioder mellom 2005 og 2020 som antall samlede blødningshendelser delt på risikotiden. Valget av 3-årsperioder var hensiktsmessig da man studerte en 15-årsperiode og reduserte den tilfeldige variasjonen fra år til år, og år 2020 frem til studieslutt i mai måned ble inkludert i perioden 2017-2020. Alle statistiske analyser ble utført i Stata for Windows (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Regional komité for medisinsk og helsefaglig forskningsetikk (REK) med referansenummer 267223 har godkjent studien for deltakere som har gitt skriftlig informert samtykke eller som var døde.

Diskusjon og konklusjon

Denne studien så på data om behandlingsmønstre og blødningskomplikasjoner hos pasienter diagnostisert med KAT sett opp mot gjeldende praksis og forskning. Gjennom hele studieperioden var LMWH det hyppigst foreskrevne legemiddel som initialbehandling.

Imidlertid var DOAK det mest anvendte legemiddelet som sekundærbehandling og ble i økende grad brukt som førstelinjebehandling.

Gjeldende internasjonale retningslinjer anbefaler LMWH eller DOAK for initialbehandling hos pasienter med KAT. Nylig har flere retningslinjer anbefalt DOAK fremfor LMWH som initialbehandling ved fravær av kontraindikasjoner for DOAK. (12, 16). I denne studien fikk de fleste pasientene LMWH (85,8 %) som initialbehandling og bare 7,7 % ble foreskrevet DOAK. Flere andre studier har rapportert om lignende funn (5, 21, 22). Noen studier har imidlertid rapportert en mye høyere andel (opptil 50 %) av DOAK-er som initialbehandling hos pasienter med KAT. Imidlertid, disse studiene inkluderte færre pasienter med gastrointestinal eller urogenital kreft eller inkluderte pasienter med aktiv kreft opp til 5 år før KAT-diagnose, i stedet for seks måneder før KAT-diagnose, noe som kan være mulige forklaringer på den høyere DOAK-anvendelsen (23-25).

Ved å undersøke behandlingsmønstre kunne vi observere en trend mot økende administrasjon av DOAK, både som initial- og sekundærbehandling hos pasienter med KAT. Prostatakreft var krefttypen der DOAK-bruk økte mest. DOAK-bruken gikk ned hos pasienter med nedre og øvre gastrointestinale og gynekologiske svulster, spesielt mot slutten av studieperioden. Da vi observerte generelt lav anvendelse av DOAK-er i vår studie, kan dette indikere at klinisk praksis følger nyere retningslinjer. En annen studie rapporterte lignende funn om økt DOAK-administrasjon, men det ble ikke presentert data for behandlingsmønstre i henhold til forskjellige krefttyper (5). Vi tror imidlertid at bruken av DOAK ved KAT vil øke blant ulike krefttyper, da den beviste sikkerheten, effekten og tilliten til DOAK virker øker med tiden. Vi antar bedre etterlevelse, livskvalitet og prognose for pasienter med KAT ved bruk av DOAK, da det er mindre inngripende å ta piller sammenlignet med å ta injeksjoner daglig.

Før implementering av DOAK i KAT-behandling, byttet pasienter med KAT sjelden antikoagulantia i løpet av kreftsykdommen. I vår studie fant vi at de fleste pasienter fortsatte med den initiale behandlingen, derimot ble det funnet en dramatisk økning av DOAK-bruk som sekundær behandling i 2013, og ved slutten av denne studien observerte man at nesten alle pasienter da mottok DOAK som sekundærbehandling. Så vidt man vet, har ingen studier rapportert om antikoagulasjonsbehandling både som initial- og sekundærbehandling.

I vår studie observerte vi at 12-måneders kumulativ insidens av alvorlige blødninger var 7,0 %, noe som støttes av andre studier (23, 24). Selv om høyere kumulativ insidens er rapportert i tidligere studier, inkluderte disse studiene flere pasienter med urogenitale, gastrointestinale

og intrakranielle svulster eller pasienter som hovedsakelig ble behandlet med VKA (6, 26, 27).

Analysen av blødningsinsidens over tid viste stabile trender. Den økte forekomsten av CRNMB observert i 2011-2013 er vanskelig å forklare, men DOAK-anvendelsen er en usannsynlig årsak da de fleste pasienter fikk LMWH før blødningshendelsene.

Blødningshendelser forekom hyppigere ved kreft i nedre gastrointestinaltraktus, urinveier, mannlige kjønnsorganer og respirasjonsorganer eller mediastinum, noe som er i samsvar med tidligere studier (23, 27). Sammenlignet med to nyere studier observerte vi høyere kumulativ insidens av blødninger i vår studie, spesielt hos pasienter med kreft i nedre gastrointestinaltraktus (6,9% vs 4,6%) og lungekreft (10,0% vs 4,2%). Disse studiene definerte aktiv kreft som ble bekreftet i løpet av de siste 5 årene før KAT-diagnose eller brukte VKA-antikoagulasjon med lavere INR-verdi, noe som kan forklare de observerte forskjellene mellom foreliggende og tidligere studier (23, 29).

Denne studien har flere styrker. Alle pasienter ble identifisert gjennom TROLL-registeret, som er et løpende og kontinuerlig oppdatert register. I motsetning til andre regioner og land hvor pasienter med KAT følges opp av onkologer, henvises flertallet av pasienter med VTE, inkludert KAT, til trombosepoliklinikken ved Sykehuset Østfold og dermed blir inkludert i registeret. Vi tror at de fleste pasienter diagnostisert med KAT ved Sykehuset Østfold i løpet av studieperioden har blitt identifisert og inkludert i denne studien. Identifisering og kartlegging av blødningshendelser ved oppfølging tillater inkludering av de fleste blødningskomplikasjoner knyttet til antikoagulasjonsbehandling.

Vår studie har noen begrensninger. Selv om de fleste pasientene ble henvist til trombosepoliklinikken og dermed registrert i TROLL, kan vi ikke utelukke at noen pasienter har blitt fulgt opp utenfor Sykehuset Østfold. Å skille mellom initial- og sekundærbehandling var i noen tilfeller vanskelig å vurdere da det var overlappende behandlingsperioder. Ovennevnte kan ha ført til en over- eller underestimering av både hyppighet og andelen brukte antikoagulasjonsmidler ved initial- og sekundærbehandling. Det kan også ha manglet data om enkelte blødningshendelser hos pasienter som søkte medisinsk hjelp i andre helseinstitusjoner. Vi tror imidlertid at alle VTE-pasienter, inkludert de med KAT, som bodde i nedslagsfeltet trolig ble fulgt opp ved Sykehuset Østfold. Blødningshendelser fanget opp på andre sykehus ville derfor sannsynligvis blitt fanget opp i TROLL-registeret ved et oppfølgingsmøte.

De fleste pasienter diagnostisert med KAT ble fortsatt behandlet med LMWH, imidlertid ble det observert et gradvis skifte mot økende anvendelse av DOAK. DOAK-er ble oftest brukt hos pasienter med kreft i mannlige kjønnsorganer og respirasjonsorganer eller mediastinum. Insidensen av blødningshendelser ble observert å være stabil over tid.

Kilder

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Vedlegg

- Vedlegg 1: Redegjørelse fra hovedveileder
- Vedlegg 2: Real world data on treatment patterns and bleeding complications in cancer-associated thrombosis - an unselected population-based cohort from the TROLL registry
- Vedlegg 3: Tilleggsmateriale til artikkel

Redegjørelse fra hovedveileder

Zygimantas startet arbeidet med prosjektet i 2021. Han har jobbet jevnt og trutt med prosjektet både i de avsatte prosjektperioder, men også innimellom og ved siden av studietiden. Zygimantas har vist stor interesse og engasjement for forskningen fra starten av.

Arbeidet i prosjektet omfattet analyse av et register kalt TROLL. TROLL er et lokalt register for venøs tromboembolisme (VTE) ved Sykehuset Østfold. Per i dag er det registrert ca. 7000 pasienter i TROLL med diverse typer VTE. Prosjektet fokuserer på kreft-assosiert trombose der hovedformålet er å undersøke behandlingsmønstre for kreft-assosiert trombose og forekomsten av blødningskomplikasjoner under behandling med antikoagulasjon. Sekundære formål omfatter kartlegging av typer kreft assosiert med VTE og typer venøse tromboser.

Han fant at administrasjon av direktevirkende perorale antikoagulantia (DOAK), som førstegangsbehandling, økte fra 3,0 % til 18,0 % fra 2013 til 2020, mens de fleste pasientene ble behandlet primært med lavmolekylært heparin (LMWH). Zygimantas har også sett at det er høyere risiko for å få alvorlige blødninger hos pasienter med kreft i nedre gastrointestinaltraktus, urinveier og kvinnelige kjønnsorganer, noe som har blitt observert i andre lignende studier. Samt at han har observert at de vanligste krefttypene hos pasientene var kreft i nedre gastrointestinaltraktus, mannlige kjønnsorganer og i respirasjonsorganer.

Prosjektet til Zygimantas innebar avanserte statistiske metoder inkludert beregning av insidens og overlevelsesanalyser. Han organiserte datasettet først og deretter analyserte dataene og tolket resultatene. Zygimantas skrev førsteutkastet til manuskriptet i løpet av høsten 2022/vinteren 2023, som medforfattere kommenterte og reviderte i etterkant. Dette utkastet ble revidert i flere omganger inntil det var klart til innsending i starten av februar. Med andre ord bidro han i alle deler av utarbeidelsen av denne artikkelen som danner grunnlaget for oppgaven. Selv om han fikk veiledning av undertegnede og av flere medlemmer av vår forskningsgruppe (Forskningsgruppe for trombose og hemostase ved Sykehuset Østfold), arbeidet han selvstendig, lærte selv bruken av STATA og diverse statistiske metoder. Arbeidet resulterte i et manuskript som skal sendes inn til Acta Oncologica.

Zygimantas har arbeidet selvstendig, og har utført arbeidet på en meget tilfredsstillende måte. Det han gjorde var imponerende og var langt over gjennomsnittet av det som forventes av en

medisinstudent. Han viste gjennom dette prosjektet stor interesse for forskning, forståelse av forskning og faget, analytisk tenkning, struktur og organisering, og gjennomføringsevne.

Dessuten er han veldig behagelig å jobbe med og ble godt likt av hele min forskningsgruppe. Han bør absolutt satse på et PhD-prosjekt og er hjertelig velkommen til å slutte seg til min forskningsgruppe.

Waleed Ghanima,

Forskningssjef, overlege og professor.

Artikkel

Real world data on treatment patterns and bleeding complications in cancer-associated thrombosis - an unselected population-based cohort from the TROLL registry

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Abstract

Background: Direct oral anticoagulants are increasingly recommended by several international guidelines as first-line treatment for cancer-associated thrombosis (CAT). However, data regarding treatment patterns and adherence to guidelines in patients with CAT is scarce.

Objectives: To explore anticoagulant treatment patterns in patients with CAT. To calculate overall incidence rates and 6- and 12-month cumulative incidence of bleeding events.

Methods: Patients aged ≥18 years with active cancer and diagnosed with a first-time venous thromboembolism between 2005 and 2020 were identified through The Venous **T**hrombosis **R**egistry in Østf**OL**d Hospita**L** (TROLL registry). Outcome measures were patterns of anticoagulant treatment during the study period and bleeding events.

Results: Median age of 842 included patients at the time of diagnosis was 69 years (IQR 61-77 years), and 443 (52.6%) were men. 526 patients (62.5%) had pulmonary embolism and 255 (30.3%) deep vein thrombosis. Low-molecular-weight heparin (LMWH) was prescribed in 713 (85.8%) patients, whereas 64 (7.7%) received DOACs and 54 (6.5%) vitamin K antagonists as initial anticoagulant treatment. Prescription of DOACs, as initial treatment, increased from 3.0% to 18.0% from 2013 to 2020. Incidence rate for major bleeding was 6.9 (95% CI 5.2 – 9.2) per 100 person-years and 10.1 (95% CI 8.0 – 12.9) for clinically relevant non-major bleeding (CRNMB).

Conclusion: Most patients were treated with LMWH. However, a gradual shift in treatment towards DOACs was observed. Overall, bleeding complications were rare and comparable to that reported in randomized trials.

Introduction

Venous thromboembolism (VTE) is a frequently occurring complication in patients with cancer. In the past decades the incidence of VTE in patients with active cancer has increased threefold while for patients treated with chemotherapy or targeted cancer treatment it has increased up to six-fold (1). Patients with cancer-associated thrombosis (CAT) are at higher risk of mortality and morbidity and tend to consume more health care compared to cancer patients without VTE (2-5). Moreover, patients with CAT have an increased risk of recurrent VTE simultaneously as they have an increased risk of bleeding compared to VTE patients without cancer (6). In this context, the care for CAT patients is a particularly vexing clinical problem.

Traditionally, CAT has been treated with low-molecular-weight heparin (LMWH) (7). More recently, several studies have confirmed the efficacy and safety of direct-acting oral anticoagulants (DOAC) in patients with CAT (8-11). Consequently, several DOACs have been approved and recommended by international guidelines as an alternative or first-line treatment option for patients with CAT. However, several uncertainties are still present regarding the usage of DOACs in CAT, including possible drug-drug interactions and the higher risk of bleeding in gastrointestinal and genitourinary malignancies. (12-16). Consequentially, physicians may be reluctant to prescribe DOAC in patients with CAT. Furthermore, limited data exist regarding the adherence of clinical practice to guidelines in CAT patients. Accordingly, the primary aim of this study was to assess anticoagulant treatment patterns in patients with CAT during the period 2005-2020. The secondary aim was to access bleeding events.

Methods

Study design and population

This was a prospective study based on data retrieved from The Venous **T**hrombosis **R**egistry in Østf**OL**d Hospita**L** (TROLL registry). TROLL is a single-center VTE registry in Østfold county, Norway. The registry, which was established in 2005, includes consecutive patients diagnosed and/or treated or followed up for VTE at the thrombosis outpatient clinic at Østfold Hospital. Detailed information about the TROLL registry has been described previously (17).

All patients ≥ 18 years old with a diagnosis of CAT registered in TROLL between January 2005 and May 2020 were eligible for study inclusion. Patients were required to have a first-time VTE diagnosis, symptomatic or incidental, that was radiologically verified by computed tomography pulmonary angiography (CTPA), V/Q scintigraphy, compression ultrasound (CUS), abdominal CT, magnetic resonance imaging (MRI) or autopsy. CAT was defined as a venous thrombotic event including PE (with or without DVT), DVT, splanchnic vein thrombosis and upper extremity deep vein thrombosis (UEDVT), in patients with active cancer. Active cancer was defined as diagnosis confirmed in the past 6 months, within the previous 6 months or ongoing anti-cancer treatment, recurring with local or distant spreading, or hematological malignancy that was not in complete remission (15). Exclusion criteria were previous VTE diagnosis, any cerebral venous sinus thrombosis or superficial thrombosis, and patients without active cancer or diagnosed with cancer after the VTE diagnosis. The registry is continuously reviewed and was for the present study updated for completion of missing data and outcomes concerning patients with CAT.

Study variables

Demographic, clinical and cancer-related data gathered included age, BMI, smoking status, risk factors for VTE, localization of VTE and site of malignancy. Cancers were evaluated according to the International Statistical Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM) and grouped into the following 15 categories: Ear, nose and throat; upper gastrointestinal tract (esophagus, stomach and small intestine); lower gastrointestinal tract (colon, rectum and anus); hepatobiliary (liver and bile) and pancreatic; skin, bone and other connective tissue; breast; male genital organs (prostate, testicles and penis); gynecological (cervical, uterine, ovarian, vaginal and vulvar) ; urinary tract (kidneys, bladder and urethra); central nervous system (eye, brain and spinal cord); endocrine organs

(thyroid, adrenal and others); hematological (lymphoid, hematopoietic or related tissue); as well as separate categories for secondary or unspecified primary cancer and multiple primary cancer from different sites.

Study outcomes

The primary outcome was anticoagulant treatment patterns during 2005-2020. Following anticoagulant agents were assessed: LMWH (dalteparin and enoxaparin), vitamin K antagonist (VKA), and DOAC (rivaroxaban, edoxaban, apixaban and dabigatran). Anticoagulant treatment was categorized as initial or secondary. Initial treatment was defined as the first anticoagulant treatment after CAT diagnosis lasting more than two weeks. Secondary treatment was defined as the anticoagulant agent that the patients switched to from the initial treatment. Treatment periods less than two weeks were not registered as main treatments (initial or secondary) since many patients received LMWH as bridging therapy for the initial treatment phase or for other reasons. There was no restriction on total treatment duration. Prescription of DOAC, as initial treatment, was assessed in the most common cancer groups and in the cancers which according to the literature are associated with higher risk of bleeding (upper and lower gastrointestinal tract, and genitourinary malignancies) (16).
The secondary outcomes were major and clinically relevant non-major bleeding (CRNMB) events during anticoagulant treatment. Bleeding was accessed by incidence rates and cumulative incidences according to different malignancies. Bleeding events were identified at follow-up visits in the thrombosis outpatient clinic or by reviewing patients' medical records. Bleeding events were classified according to Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) classification as major bleeding or CRNMB (18, 19). Follow-up time for all bleeding events started from the date of CAT diagnosis to the date of bleeding event, while patients without bleeding events were followed up to the last day of anticoagulant treatment, date of death or the end of study period (May 7. 2020), whichever occurred first.

Statistical analysis

Categorical variables were expressed as frequencies with percentages and continuous variables as medians with corresponding interquartile ranges (IQRs). Incidence rates were analyzed separately for major bleeding and CRNMB and stratified according to most common cancer groups and those according to literature associated with higher risk of bleeding (as

described above). CRNMB events were uncensored in the analysis of major bleeding if CRNMB occurred prior to major bleeding. When analyzing CRNMB, major bleeding was censored if it occurred prior to the CRNMB event and changed the anticoagulant treatment. Incidence rates were computed for bleeding events divided by person-time at risk with overall incidence and 100 person-years with 95% confidence intervals (CI). Cumulative incidences, with 95% confidence intervals (CIs) of bleeding events at 6 and 12 months were calculated using 1-Kaplan-Meier (1-KM) analyses with death as competing risk when analyzing major bleeding. For time trend analyses incidence rates were calculated for 3-year periods between 2005 and 2020 as the number of overall incident bleeding events divided by the time at risk. The choice of 3-year periods was convenient since we studied a 15-year period and reduced the year-to-year random variation, and bleeding events in the year 2020 until 7 May was included in the period of 2017-2020. All statistical analyses were conducted in Stata for Windows (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC).

Ethics and approvals

The Regional Ethics Committee (reference number 267223) approved the study for participants who had provided written informed consent and waived consent for deceased subjects.

Results

In total, 4673 patients with a first-time VTE were registered in TROLL between January 2005 and May 2020. Of these, 842 patients (18.0%) were diagnosed with CAT and included in the present study. Median age was 69 years (IQR 61–77 years) and 443 (52.6%) were males. Patient characteristics and risk factors associated with VTE are displayed in Table 1. The most common VTE diagnosis was PE in 526 patients (62.5%) followed by DVT in 255 (30.3%) patients (Table 1).

Cancer groups

The five most common cancers were lower gastrointestinal tract 151 (17.9%), male genital organs 109 (13.0%), respiratory or mediastinal 100 (11.9%), hematological 70 (8.3%), and breast 70 (8.3%) (Figure 1). 357 patients (42.4%) had metastatic disease. Further characteristics according to cancer site are summarized in Supplemental Table S1.

Treatment patterns

Initial treatment prescription for CAT consisted of LMWH administered to 713 (85.8%), DOAC to 64 (7.7%) and VKA to 54 (6.5%) patients. Median duration of the initial treatment phase was 144.5 days (IQR 61-221). As expected, treatment patterns shifted during the study period. VKA prescriptions declined from 28.2% to 0% from 2005/2006 to 2019/2020, whereas prescription of DOACs increased from 3.0% in 2013/2014 to 18.0% in 2019/2020 (Figure 2A).

Most patients (598/713, 83.9%) continued LMWH treatment without switching anticoagulant agent. Secondary anticoagulant treatment was prescribed in 139 (16.7%) patients. Of these, 110 (79.1%) patients switched from LMWH or VKA to DOAC, 21 (15.1%) patients switched from DOAC or VKA to LMWH. Median treatment duration of secondary anticoagulant treatment was 128.5 days (IQR 48-219). Secondary anticoagulant treatment with DOACs increased from 66.7% (6/9) to 94.7% (54/57) from 2013 to 2020 (Figure 2B).

The largest increase of DOAC prescription as initial treatment between 2013 and 2020 was observed in patients with male genital organs and respiratory or mediastinal cancers, from 4.8% to 57.1% and 7.1% to 40.0% respectively. Patients with lower gastrointestinal tract, gynecological and upper gastrointestinal tract cancers were prescribed DOACs in 23.3%, 15.4% and 14.3% of cases respectively in 2017/2018. However, no patients with gynecological and upper gastrointestinal tract cancers were prescribed DOACs in 2019/2020, while only 11.5% of patients with lower gastrointestinal tract cancer received DOACs (Figure 3).

Bleeding

A total of 107 (12.7%) patients suffered from one or more bleeding events, of which 48 (44.9%) consisted of major bleeding and 59 (55.1%) of CRNMB events. The overall incidence rate per 100 person years was 6.9 (95% CI 5.2-9.2) for major bleedings and 10.1 (95% CI 8.0-12.9) for CRNMB (Table 2).

The time trend analysis of bleeding incidence rates of the 3-year periods declined during the study period. Major bleeding incidence rates decreased from 7.9 per 100 person-years in 2005-2007 to 5.8 per 100 person-years in 2017-2020. Incidence rates of CRNMB events revealed an increasing trend from 5.4 per 100 person-years in 2005-2007 to 13.2 in 2011-

2013 and thereafter attenuating to 9.6 per 100 person-years in 2017-2020 (Figure 4); The 6- and 12-month cumulative incidences were 5.6% (95% CI 4.1 – 7.7%) and 7.0% (95% CI 5.1 – 9.5%) for major bleedings and 7.2% (95% CI 5.5 – 9.4%) and 10.5% (95% CI 7.9 – 13.9%) for CRNMB, respectively (Table 2 and Figure 5). Competing risk by death analysis revealed a nonsignificant reduction for 6- and 12-month cumulative incidences of major bleeding events (data not shown).

Most bleeding events were observed in patients with cancer in lower gastrointestinal tract (22.4%), urinary tract (11.2%), male genital organs (10.3%) and in respiratory or mediastinal organs (10.3%). Incidence rate of any bleeding per 100 person years was 37.1 (95% CI 21.1-65.4) in urinary tract cancers, 24.8 (95% CI 13.3-46.0) in gynecological cancers, 18.2 (95% CI 10.1-32.9) in respiratory or mediastinal organs, 17.7 (95% CI 11.8-26.3) in lower gastrointestinal tract and 8.5 (95% CI 4.7-15.4) in male genital organs. Further results displaying MB and CRNMB events with incidence rates and cumulative incidences according to cancers are summarized in Supplementary Tables S2 and S3.

Discussion

The present study provides real-world data on treatment patterns and bleeding complications in patients diagnosed with CAT. Throughout the study period, LMWH was the most frequently prescribed agent as initial anticoagulant treatment. However, DOACs were the most prescribed agent as secondary treatment and are gaining ground as the first-line initial treatment.

Current international guidelines recommend LMWH or DOACs for initial anticoagulant treatment in patients with CAT. Recently, some guidelines have favored DOACs over LMWH as initial treatment, although depending on cancer site. (12, 16). In the present study, most patients received LMWH (85.8%) as initial treatment and only 7.7% were prescribed DOACs. Several other studies have reported similar findings (5, 20, 21). However, some studies have reported a much higher prescription frequency (up to 50%) of DOACs as initial treatment in patients with CAT. Including fewer patients with gastrointestinal or genitourinary malignancies and extending the time frame of active cancer to five years rather than six months may be possible explanations for the higher DOAC prescription rate (22-24).

Studying treatment patterns allowed us to observe a trend towards increasing prescription of DOACs, both as initial and secondary anticoagulant treatment in patients with CAT. Male genital malignancies, mainly prostate cancer, were among malignancies in which DOAC prescription increased the most. However, DOAC prescription decreased in patients with lower and upper gastrointestinal tract and gynecological malignancies, particularly towards the end of the study period. Although we observed an overall low prescription frequency of DOACs, this may indicate clinical practice adhering to recent guidelines. Trends in treatment patterns have not been reported extensively. One study reported similar findings regarding increasing DOAC prescription during their study (5). However, no data was presented for treatment patterns according to malignancies.

Prior to DOACs patients with CAT rarely changed anticoagulant treatment during the course of their cancer disease. In this study we found that most patients continue with the initial treatment. However, a dramatic increase of DOAC prescription as secondary treatment was found in 2013 with almost all patients receiving DOAC as secondary treatment the end of this study. To our knowledge, no studies have reported anticoagulant treatment both as initial and secondary anticoagulant.

In the present study we observed the 12-month cumulative incidence of major bleeding being 7.0 %, which is supported by others (22, 24). Although, higher cumulative incidences have been reported previously, these studies included more patients with genitourinary, gastrointestinal and intracranial malignancies or prescribed mainly VKA anticoagulation (6, 25, 26).

The analysis of bleeding incidence rates over time was revealed stable. The increased incidence rate of CRNMB observed in 2011-2013 is difficult to explain (Figure 4). However, DOAC prescription is an improbable reason as most patients received LMWH prior to the bleeding event.

Bleeding events occurred more frequently in lower gastrointestinal tract, urinary tract, male genital and respiratory or mediastinal malignancies, which is in accordance with previous studies (24, 27). However, compared to two recent studies we observed higher cumulative incidences of bleeding particularly in patients with lower gastrointestinal tract (6.9% vs 4.6%) and lung malignancies (10.0% vs 4.2 %) Defining active cancer as confirmed within the previous 5 years and prescribing VKA anticoagulation with low targeted therapeutic range may be explanation for the observed differences (22, 28).

The present study has several strengths. All patients were identified through the TROLL registry, which is an ongoing and continuously updated registry. Opposed to other regions and countries in which patients with CAT may be followed up by oncologists, the majority of patients diagnosed with VTE, including CAT, are referred to the thrombosis outpatient clinical at Østfold hospital and thus included in the registry. Accordingly, we believe that most patients diagnosed with CAT in Østfold region, Norway, during the study period have been identified and included in the present study. In addition, identifying bleeding events at in person follow-up visits enables registration of most bleeding complications related to anticoagulant treatment.

Our study has also some limitations. Although most patients were referred to the thrombosis outpatient clinic and thus registered in TROLL, we cannot exclude that some patients have been followed up in other settings. Distinguishing between initial and secondary treatment was difficult to assess in some cases as there were overlapping treatment periods. This may have led to an over- or underestimation of both frequency and anticoagulant agents of initial and secondary treatment. Additionally, there could have been missing data on some bleeding events in patients that did seek medical help in other health care institutions. However, VTE patients, including those with CAT, living in the catchment area would likely be followed up at Østfold hospital. Events diagnosed in other hospitals would therefore likely be captured in the TROLL registry at a later visit.

Conclusion

Most patients diagnosed with CAT were still treated with LMWH. However, a gradual shift towards increasing prescription of DOACs was observed. DOACs were most often used in patients with male genital and respiratory or mediastinal malignancies. Incidence rates of bleeding events were observed being stable over time.

Author contributions

ZZ and WG planned the study. ZZ drafted the first version of the manuscript. ZZ performed and interpreted all statistical analyzes with the assistance of CTJ and SB. WG, MT, CTJ and SB did critical revision of the content. All authors were responsible for carefully reading and approving the final manuscript for publication.

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Tables and figures

Table 1 Patient characteristics and risk factors

	Total VTE (n=842)	PE (n=526)	DVT (n=255)	Splanchnic (n=37)	UEDVT (n=24)
Age (median, IQR)	69 (61-77)	69 (61-76)	69 (61-78)	64 (59-71)	60,5 (54-70)
Male (n, %)	443 (52.6)	273 (51.9)	140 (54.9)	17 (46.0)	13 (54.2)
Symptomatic VTE (n, %)	649 (77.1)	339 (64.4)	242 (94.9)	Missing[1]	17 (70.8)
Smoking	136 (16.2)	81 (15.4)	39 (15.3)	11 (29.7)	5 (20.8)
Risk factors (n, %)					
BMI over 30	294 (34.9)	171 (32.5)	100 (39.2)	14 (37.8)	9 (37.5)
Immobilization	48 (5.7)	32 (6.1)	14 (5.5)	0 (0)	2 (8.3)
Trauma	13 (1.5)	5 (1.0)	6 (2.4)	0 (0)	2 (8.3)
Surgeries (orthopedic and other types)	174 (20.7)	109 (20.7)	51 (20.0)	8 (21.6)	6 (25.0)
Contraception and hormone replacement therapy[2]	9 (2.3)	5 (2.0)	3 (2.6)	1 (5.0)	0 (0)
Flights over 4 hours	14 (1.7)	9 (1.7)	4 (1.6)	0 (0)	1 (4.2)
Family history of VTE	24 (2.9)	13 (2.5)	8 (3.1)	2 (5.4)	1 (4.2)
Known thrombophilia	5 (0.6)	4 (0.8)	1 (0.4)	0 (0)	0 (0)

PE: pulmonary embolism; DVT: deep vein thrombosis; UEDVT: upper extremity deep vein thrombosis; IQR: interquartile range
1: Symptoms on splanchnic VTE were not registered in the registry.
2: Percentage of females

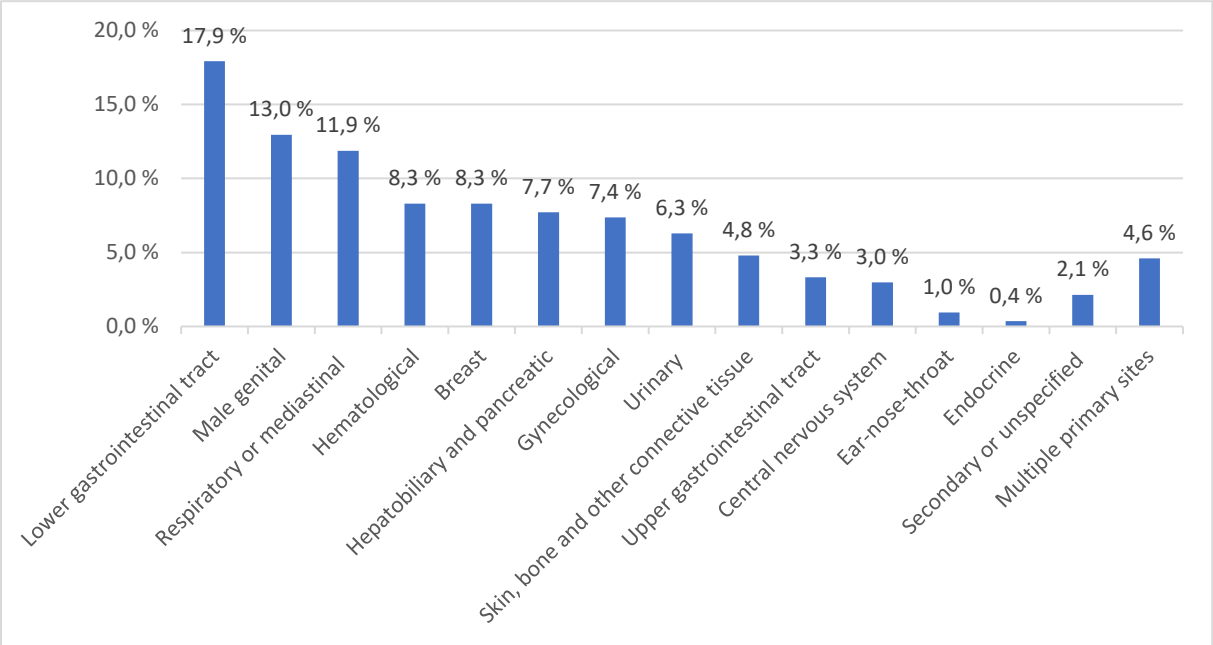


Figure 1 Distribution of cancers

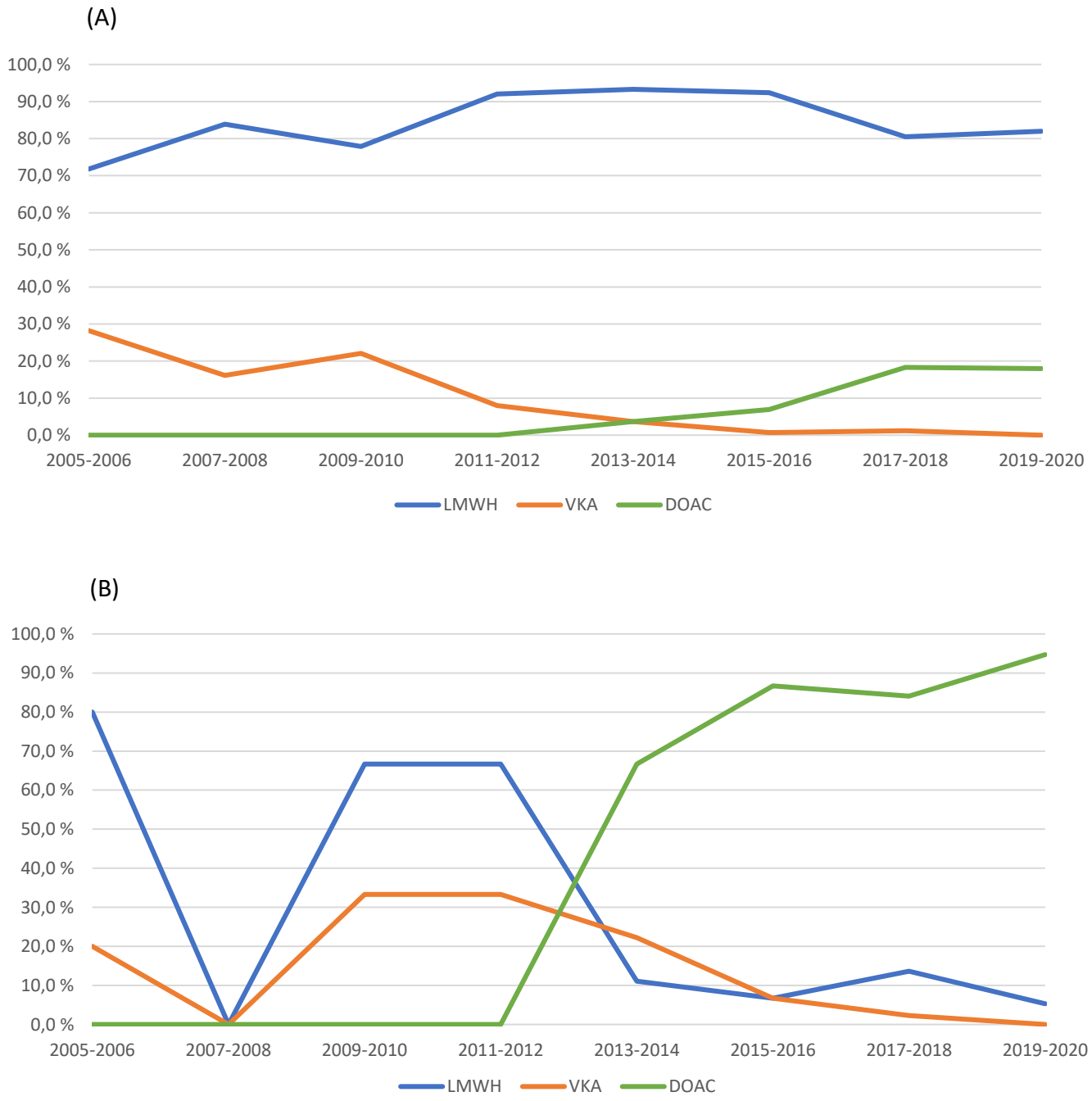


Figure 2 Time trends of initial (2A) and secondary anticoagulant treatment (2B) during 2005-2020. LMWH: Low-molecular-weight heparins; DOAC (Direct-Acting Oral anticoagulants); VKA (vitamin K antagonists); None of the patients was prescribed secondary anticoagulant treatment in 2007-2008.

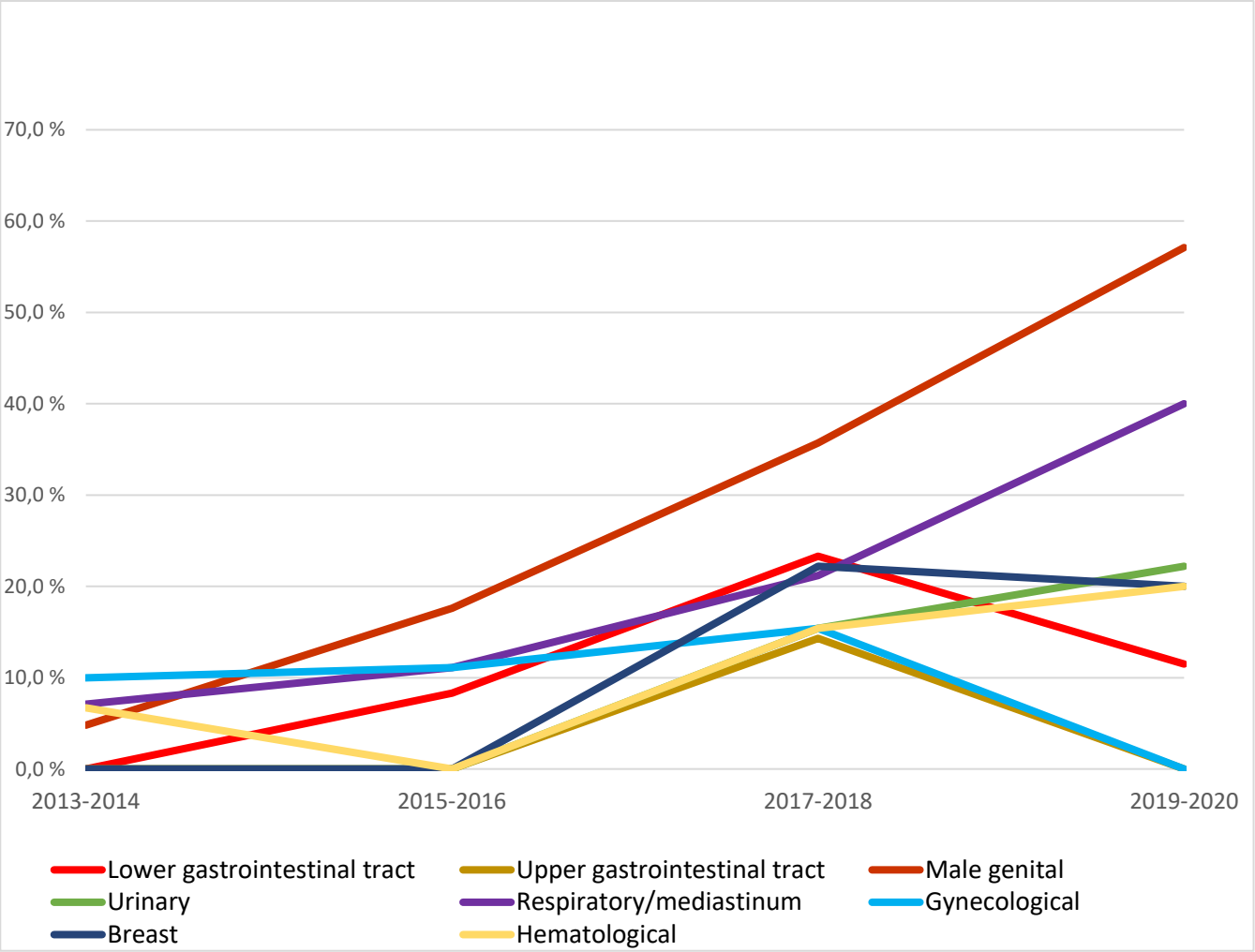


Figure 3 Proportion of patients receiving direct oral anticoagulants as initial treatment according to cancer site between 2013 and 2020.

Table 2 Incidence rates per 100 person years and cumulative incidences of bleeding in patients with cancer associated thrombosis

	Incidence rates per 100 person years (95% CI)	6-month cumulative incidence, % (95% CI)	12-month cumulative incidence, % (95% CI)
Any bleeding	16.1 (13.3-19.5)	11.6 (9.4-14.3)	16.0 (12.9-19.7)
Major bleeding	6.9 (5.2 – 9.2)	5.6 (4.1 – 7.7)	7.0 (5.1 – 9.5)
CRNMB	10.1 (8.0 – 12.9)	7.2 (5.5 – 9.4)	10.5 (7.9 – 13.9)

Any bleeding: Major bleeding + CRNMB; CRNMB: Clinically relevant non-major bleeding, CI: Confidence interval

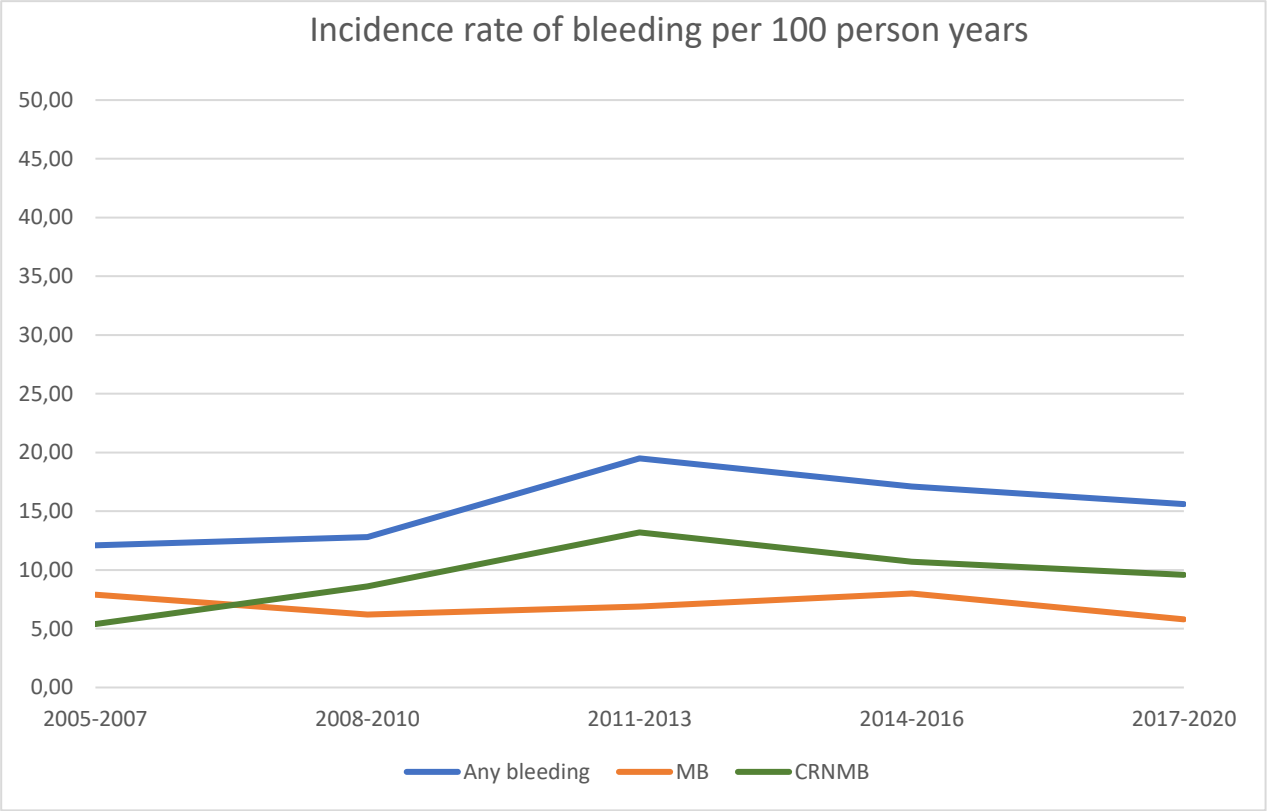
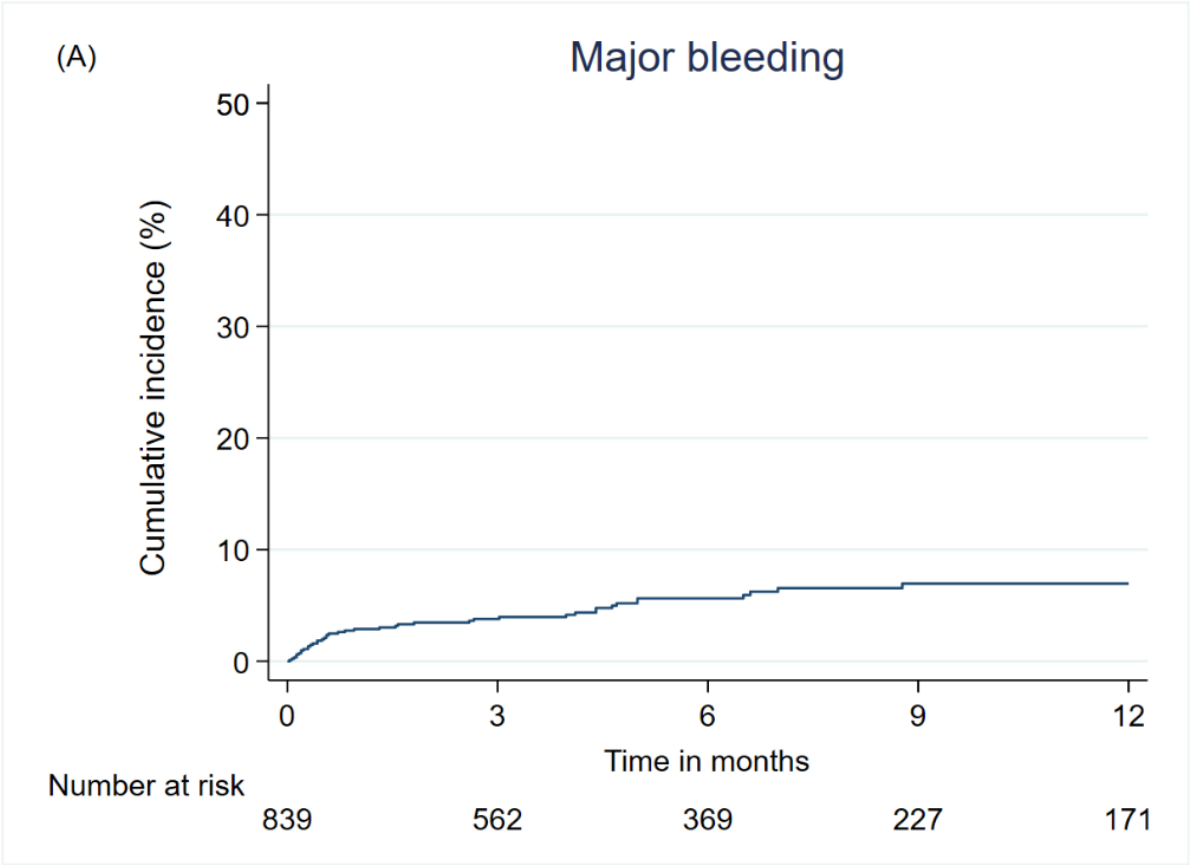


Figure 4 Time trends of bleeding incidence rate. Any bleeding: Major bleeding + CRNMB; MB: Major bleeding, CRNMB: Clinically relevant non-major bleeding



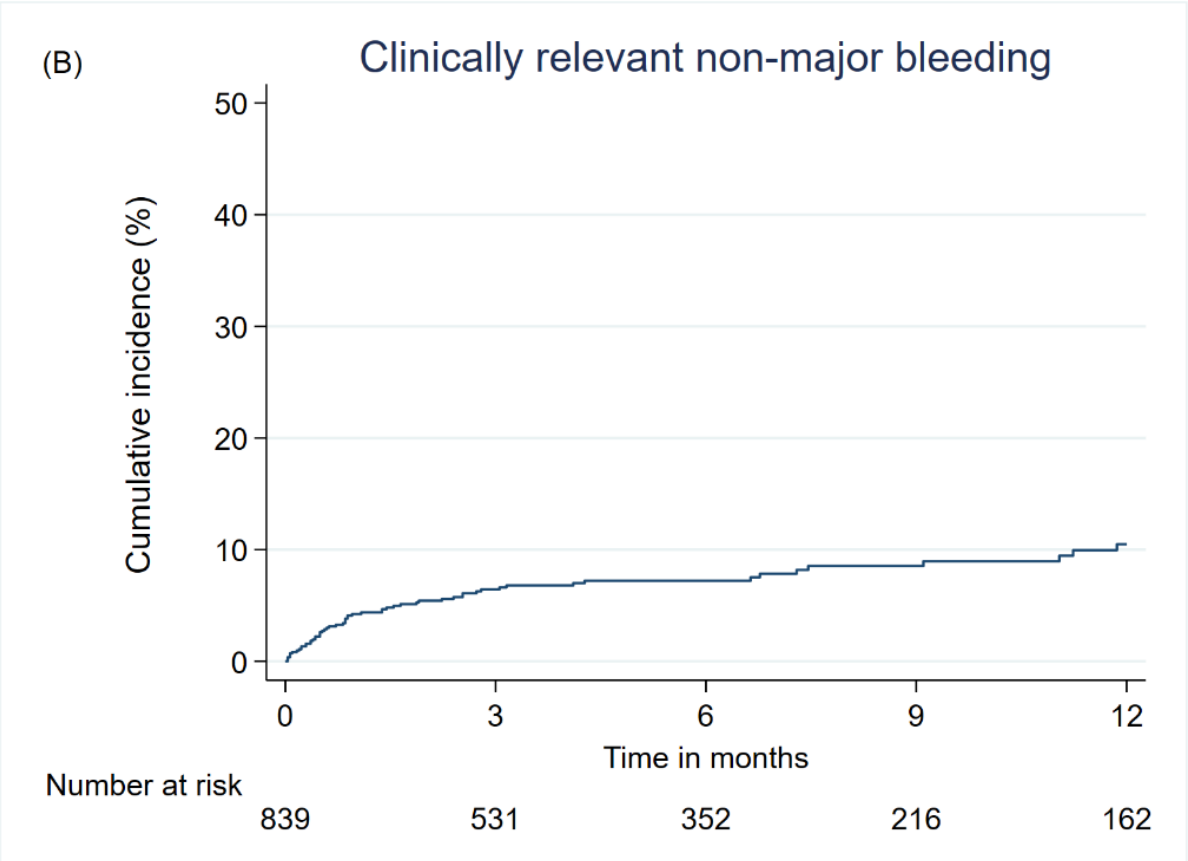


Figure 5 Cumulative incidence of major bleeding (A) and CRNMB (B)

Tilleggsmateriale

Supplemental Table 1 Distribution of cancers with and without metastases based on ICD-codes among patients with pulmonary embolism (PE), deep vein thrombosis (DVT), splanchnic thrombosis and upper extremity deep vein thrombosis (UEDVT)

		Total VTE (n=842)	PE (n=526)	DVT (n=255)	Splanchnic (n=37)	UEDVT (n=24)
Cancer (n, %):						
Lower gastrointestinal tract:	Total	151 (17.9)	98 (18.6)	37 (14.5)	13 (35.1)	3 (12.5)
	Metastatic	85 (56.3)[1]	57 (58.2)	22 (59.5)	6 (46.2)	0 (0%)
Male genital:[2]	Total	109 (13.0)	60 (11.4)	47 (18.4)	0 (0)	2 (8.3)
	Metastatic	38 (34.9)	23 (38.3)	14 (29.8)	0 (0)	1 (50.0)
Respiratory or mediastinal:	Total	100 (11.9)	72 (13.7)	21 (8.2)	1 (2.7)	6 (25.0)
	Metastatic	34 (34.0)	24 (33.3)	8 (38.1)	0 (0)	2 (33.3)
Hematological:	Total	70 (8.3)	45 (8.6)	23 (9.0)	0 (0)	2 (8.3)
	Metastatic	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Breast:	Total	70 (8.3)	41 (7.8)	24 (9.4)	1 (2.7)	4 (16.7)
	Metastatic	42 (60.0)	26 (63.4)	14 (58.3)	0 (0)	2 (50.0)
Hepatobiliary and pancreatic:	Total	65 (7.7)	37 (7.0)	20 (7.8)	7 (18.9%)	1 (4.2)
	Metastatic	39 (60.0)	23 (62.2%)	10 (50.0)	5 (71.4)	1 (100.0)
Gynecological:	Total	62 (7.4)	35 (6.7)	24 (9.4)	2 (5.4)	1 (4.2)
	Metastatic	26 (41.9)	18 (51.4)	8 (33.3)	0 (0)	0 (0)
Urinary:[3]	Total	53 (6.3)	35 (6.7)	13 (5.1)	5 (13.5)	0 (0)
	Metastatic	21 (39.6)	16 (45.7)	5 (38.5)	0 (0)	0 (0)
Skin, bone and other connective tissue:	Total	40 (4.8)	24 (4.6)	13 (5.1)	0 (0)	3 (12.5)
	Metastatic	17 (42.5)	15 (62.5)	2 (15.4)	0 (0)	0 (0)
Upper gastrointestinal tract:	Total	28 (3.3)	21 (4.0)	4 (1.6)	2 (5.4)	1 (4.2)
	Metastatic	16 (57.1)	14 (66.7)	0 (0)	1 (50.0)	1 (100.0)
Central nervous system:[4]	Total	25 (3.0)	15 (2.9)	10 (3.9)	0 (0)	0 (0)
	Metastatic	2 (8.0)	1 (6.7)	1 (10.0)	0 (0)	0 (0)
Ear-nose-throat:	Total	8 (1.0)	6 (1.1)	2 (0.8)	0 (0)	0 (0)
	Metastatic	4 (50.0)	3 (50.0)	1 (50.0)	0 (0)	0 (0)

Endocrine:	Total	3 (0.4)	2 (0.4)	0 (0)	0 (0)	1 (4.2)
	Metastatic	2 (66.7)	1 (50.0)	0 (0)	0 (0)	1 (100.0)
Secondary or unspecified:	Total [5]	18 (2.1)	9 (1,7)	8 (3.1)	1 (2.7)	0 (0)
	Metastatic	16 (88.9)	9 (100.0)	6 (75.0)	1 (100.0)	0 (0)
Multiple primary sites:	Total	39 (4,6)	25 (4,8)	9 (3.5)	5 (13.5)	0 (0)
	Metastatic	15 (40.5)	11 (44.0)	2 (22.2)	2 (40.0)	0(0)

1: Including unspecified types of cancer without metastases
2: Cancer in penis, prostate and testicles
3: Cancer in kidneys, bladder and urethra
4: Cancer in eye, brain and spinal cord
5: Percentage of total cases per cancer type

Supplemental Table 2 Incidence rates for bleeding types per 100 years based on cancer types and treatment in CAT patients

	Total (n=107)	Major bleeding (n=48)	Clinically relevant non-major bleeding (n=59)
Type of cancer with incidence rate for bleeding per 100 person years (95% CI)			
Lower gastrointestinal tract	17.7 (11.8-26.3)	9.1 (5.3-15.7)	9.6 (5.6-16.5)
Male genital[1]	8.5 (4.7-15.4)	2.3 (0.7-7.1)	7.8 (4.2-14.4)
Respiratory or mediastinal	18.2 (10.1-32.9)	4.9 (1.6-15.1)	13.3 (6.6-26.5)
Hematological	7.4 (2.8-19.6)	3.7 (0.9-14.6)	5.5 (1.8-17.1)
Breast	12.1 (6.5-22.5)	4.7 (1.8-12.4)	7.3 (3.3-16.2)
Biliary and pancreatic	43.8 (22.8-84.2)	18.5 (7.7-44.4)	19.5 (7.3-51.9)
Gynecological	24.8 (13.3-46.0)	9.4 (3.5-25.0)	17.3 (8.3-36.4)
Urinary tract[2]	37.1 (21.1-65,4)	11.3 (4.2-30.1)	27.9 (14.5-53.6)
Skin, bone and other connective tissue	32.9 (16.4-65.7)	22.5 (10.1-50.1)	8.2 (2.1-32.8)
Upper gastrointestinal tract	42.9 (16.1-114.3)	10.2 (1.4-72.7)	32.2 (10.4-99.8)
Multiple primary sites	7.3 (2.4-22.7)	4.6 (1.2-18.5)	4.9 (1.2-19.5)
Secondary or unspecified	21.3 (3.0-151.1)	21.3 (3.0-151.1)	0
Endocrine	0	0	0
Central nervous system[3]	0	0	0
Ear-nose-throat	0	0	0

1: Cancer in penis, prostate and testicles
2: Cancer in kidneys, bladder and urethra
3: Cancer in eye, brain and spinal cord

Supplemental Table 3 Cumulative incidence rates of bleeding at 6 and 12 months based on cancer types and treatment in CAT patients

	Any bleeding (n=107)		Major bleeding (n=48)		CRNMB (n=59)	
	6-month cumulative incidence, % (95% CI; %)	12-month cumulative incidence, % (95% CI; %)	6-month cumulative incidence, % (95% CI; %)	12-month cumulative incidence, % (95% CI; %)	6-month cumulative incidence, % (95% CI; %)	12-month cumulative incidence, % (95% CI; %)
Type of cancer with incidence rate for bleeding per 100 years (n; incidence rate, 95% CI):						
Lower gastrointestinal tract	10.5 (6.3-17.2)	14.9 (9.2-23.4)	6.9 (3.6-12.7)	6.9 (3.6-12.7)	5.3 (2.5-10.8)	9.9 (5.2-18.3)
Male genital[1]	5.8 (2.4-13.5)	13.2 (6.4-26.3)	2.7 (0.7-10.5)	5.2 (1.6-16.2)	5.3 (2.2-12.3)	10.5 (4.7-22.6)
Urinary tract[2]	24.1 (14.0)	24.1 (14.0)	6.7 (2.2-19.3)	6.7 (2.2-19.3)	20.2 (11.0-35.6)	20.2 (11.0-35.6)
Hepatobiliary and pancreatic	13.8 (7.1-25.7)	23.3 (9.8-49.8)	6.7 (2.6-17.0)	14.5 (4.7-39.7)	7.3 (2.8-18.4)	7.3 (2.8-18.4)
Female genital	16.5 (8.9-29.4)	23.5 (11.6-44.1)	7.7 (2.9-19.4)	7.7 (2.9-19.4)	10.7 (5.0-22.4)	18.2 (7.4-40.9)
Respiratory or mediastinal	10.0 (5.0-19.6)	17.3 (8.7-32.8)	3.1 (0.7-13.1)	6.4 (1.9-20.3)	7.0 (3.2-15.0)	11.5 (4.7-26-4)
Skin, bone and other connective tissue	23.7 (11.8-44.3)	30.1 (15.5-53.2)	17.6 (7.5-38.1)	23.9 (10.9-47.7)	6.6 (1.6-24.8)	6.6 (1.6-24.8)
Breast	15.4 (8.2-27.8)	15.4 (8.2-27.8)	5.0 (1.6-15.0)	5.0 (1.6-15.0)	10.8 (4.9-22.6)	10.8 (4.9-22.6)
Hematological	4.6 (1.5-13.5)	4.6 (1.5-13.5)	3.0 (0.8-11.7)	3.0 (0.8-11.7)	3.0 (0.8-11.5)	3.0 (0.8-11.5)
Upper gastrointestinal tract	15.3 (5.0 - 41.2)	36.4 (11.4-81.6)	6.2 (0.9-36.8)	6.2 (0.9-36.8)	8.7 (2.3-30.7)	31.6 (7.9-82.6)
Multiple primary sites	8.3 (2.8-23.7)	8.3 (2.8-23.7)	5.6 (1.4-20.4)	5.6 (1.4-20.4)	5.4 (1.4-19.8)	5.4 (1.4-19.8)
Secondary or unspecified	6.3 (0.9-36.8)	6.3 (0.9-36.8)	6.3 (0.9-36.8)	6.3 (0.9-36.8)	0	0
Endocrine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Central nervous system[3]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Ear-nose-throat	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

1: Cancer in penis, prostate and testicles
2: Cancer in kidneys, bladder and urethra
3: Cancer in eye, brain and spinal cord