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PEER-REVIEWED CONFERENCE REPORT

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Editor Prof. Marc Peter Bonaca, University of Colorado, USA

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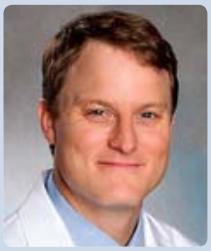
Letter from the Editor



Prof. Marc Bonaca

Dear colleagues,

Thank you for your interest in Medicom's summary of the ISTH 2020 congress. So far in 2020 we have transitioned to virtual congresses as we grapple with the COVID-19 pandemic. In spite of these challenges, this year's meeting was rich with novel science ranging from haemophilia to venous thromboembolism.

Focused sessions on anticoagulation provide novel insights for patients with cancer and atrial fibrillation as well as use during pregnancy. Finally.

Focused sessions on COVID-19 continue to elucidate the underlying biology of this condition including associated inflammation and coagulopathy. Early data evaluating risk of thrombosis during and after hospitalization as well as the role of anticoagulation underscores the complexity of optimal treatment in this growing pandemic.

We hope you find these summaries balanced, insightful and interesting. Most of all, we hope you are safe and healthy, and we wish you the best during these challenging times.

Sincerely,
Marc Bonaca

Biography

Marc P. Bonaca, MD, MPH, is a Cardiologist and Vascular Medicine Specialist who serves as the Executive Director of CPC Clinical Research and CPC Community Health at the University of Colorado Anschutz Medical Campus. He is the Director of Vascular Research and an Associate Professor of Medicine at the University of Colorado School of Medicine and the inaugural holder of the William R. Hiatt Endowed Chair in Cardiovascular Research.

Dr Bonaca earned his medical degree from the University of Connecticut School of Medicine and his Masters in Public Health at Harvard University. He served as a Medical House Officer at Brigham and Women's Hospital and Harvard Medical School. After completion of his training he joined the faculty of the Cardiovascular Division and Vascular Medicine section of Brigham and Women's Hospital and Harvard Medical School and became an Investigator at the TIMI Study Group.

Dr Bonaca's research focus is on ischemic risk in patients with atherosclerotic vascular disease, risk prediction, and risk modification through the use of pharmacologic and biologic therapies. His key areas of interest include patients with peripheral artery disease, polyvascular disease and diabetes with a focus on the breadth of risk including ischemic limb outcomes, microvascular complications and major adverse cardiovascular events.

Conflict of Interest Statement
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Haemophilia and Rare Bleeding Disorders

Novel gene therapy leads to normal FIX activity levels in severe haemophilia B

The B-AMAZE study showed that the novel gene therapy FLT180a achieved normal factor IX (FIX) activity levels in patients with severe haemophilia B. In addition, transaminitis could be prevented with a prophylactic, immunosuppressive regime [1].

The multicentre, open-label, phase 1/2 B-AMAZE study was presented by Dr Pratima Chowdary (Royal Free London NHS Foundation Trust, United Kingdom). Dr Chowdary explained, "The novel synthetic adeno-associated virus (AAV) capsid that we used in our study [AAVS3] has a 4 times higher liver transduction efficiency compared with a conventional one. The advantage is that with the same amount of dose or a lower dose you can potentially achieve factor IX in the normal range."

The study aimed to restore normal coagulation, thus eliminating the need for prophylaxis and additional treatment during surgery, trauma, and activity. The investigators assessed FLT180a dose levels in an escalating/descending adaptive design to determine a dose that would achieve FIX activity levels within the normal range (50% to 150%). Dr Chowdary presented data on 10 patients with moderate-to- severe or severe haemophilia B, who were negative for neutralising AAVS3 antibodies.

Participants were treated across 4 dose levels. Two patients received $4.5x10^{11}$ vg/kg and showed FIX activity levels just below the normal range, which remained stable through 24 months. In 2 patients receiving a $7.5x10^{11}$ vg/kg dose, a modest increase was observed in FIX expression compared with a $4x10^{11}$ vg/kg dose. As part of the adaptive design, 2 additional patients received a dose of $1.5x10^{12}$ vg/kg, 1 of whom demonstrated supraphysiological FIX activity levels and was commenced on prophylactic anticoagulation after an individualised risk assessment. The anticoagulation was stopped during long-term follow-up after a multidisciplinary discussion including the patient. He then developed a thrombosis of his arteriovenous fistulae. In the final cohort, 4 patients received $9.75x10^{11}$ vg/kg, which led to FIX activity levels within the normal range through week 26 (see Table).

The most common drug-related serious adverse event was transient transaminitis, which was observed in 4 patients and required supplemental immunosuppression. Immunosuppression in a refined regimen of $9.75x10^{11}$ vg/kg dose for the latest 3 patients in the highest dose group prevented transaminitis during the critical phase (4-16 weeks). There were no bleeding episodes.

Table: B-AMAZE FIX activity levels [1]

Dose level vg/kg	Mean FIX activity % (range)				
	Week 3	Week 26	Week 52	Week 78	Week 104
$1.5x10^{12}$ (n=2)	130.0 (92-168)	160.0* (67-253)	–	–	–
$4.5x10^{11}$ (n=2)	24.5 (24-25)	40.0 (35-45)	37.5 (36-39)	43.5 (40-47)	37.5 (37-38)
$7.5x10^{11}$ (n=2)	25.5 (25-26)	32.0* (9-55)	31.0* (2-60)	–	–
$9.75x10^{11}$ (n=4)	100.5 (73-142)	98.0** (57-139)	–	–	–

*Includes 1 patient with reduction in FIX expression following transaminitis.
**Data from 2 patients and includes 1 patient with reduction in FIX expression following transaminitis.

Successful strategy to prevent transaminitis

Transaminitis is the main vector-related complication of AAV gene transfer. As Dr Chowdary explained, "transaminitis is the single most frequent risk factor for loss of effect of gene therapy. Once you have it, you lose expression of the protein and once it is lost it is practically irreversible. Therefore, we believe strongly that prophylactic immunosuppression would be the right thing for individual patients." The B-AMAZE study was one of the first studies to develop a strategy for prevention and control of transaminitis during the high-risk period, consisting of prophylactic corticosteroid and tacrolimus therapy. No evidence of neutralising anti-FIX antibodies or infusion reactions was seen in any patients.

Dr Chowdary concluded that the FLT180a in a dose between 7.5 to $9.75x10^{11}$vg/kg achieved clinically meaningful, durable FIX activity levels in patients with haemophilia B, associated with independence from FIX replacement therapy and zero treated bleeds. However, careful dose titration seems to be necessary to identify the dose range required for sustained FIX activity in the normal range. In addition, continuous monitoring for transaminitis after the highest risk period is required for a good outcome.

1. Chowdary P, et al. LB/CO01.1, ISTH 2020 Virtual Congress, 12-14 July 2020.

Haemophilia gene therapy: progress and obstacles

The future of gene therapy for haemophilia patients looks bright. Prof. Amit Nathwani (University College London, United Kingdom) presented a review of promising gene therapy trial results in haemophilia B and A [1].

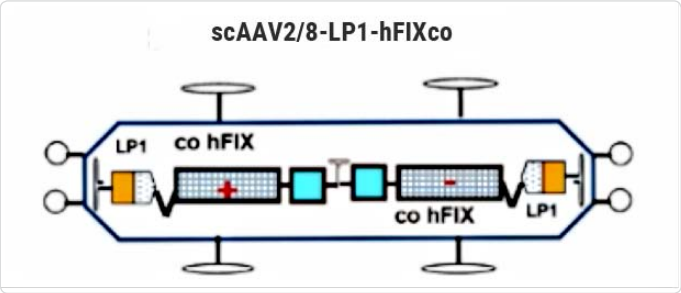
Among vectors of viral origin, and as far as is known to date, adeno-associated virus (AAV) vectors have the best safety profile. "AAV vectors can integrate into the host DNA but at frequencies that are quite low," Prof. Nathwani explained. However, this integration has only been shown in animal studies until today. A single administration of AAV vectors leads to stable long-term expression of transgenic protein.

Haemophilia B: fewer factor concentrates necessary

AAV comes in a variety of different serotypes (e.g. AAV2, AAV5, AAV8, AAV9) and selection of the most suitable capsid is required. For example, Prof. Nathwani and colleagues selected an AAV8-based capsid for their gene therapy programme in the B-AMAZE study, as an initial seroprevalence study showed that there was a lower immune response against AAV8 in comparison with AAV2.

In the B-AMAZE trial, the investigators developed a unique liver-specific factor IX (FIX) expression cassette, small enough to accommodate the self-complementary genome (see Figure). The vector makes its way to the liver by taking advantage of the strong tropism the capsid for this organ, thereby ensuring that transgenic FIX is synthesised at the natural site for FIX synthesis, leading to appropriate glycosylation of the transgenic protein.

Figure: FIX-expressing AAV vector used in the phase 1/2 haemophilia B gene therapy trial B-AMAZE. Adapted from [1]



Prof. Nathwani and his team introduced this FIX-expressing vector in 10 patients with haemophilia B. Patients revealed significant changes in bleeding phenotypes, shifting from severe to mild, and a dose-dependent increase in FIX levels, which is still stable after 10 years. "In all 10 patients, we observed an 87% drop in bleeding rates. Additionally, we noticed a 66% reduction in FIX concentrate usage," he said. No long-term toxicities or inhibitor formation were observed. The only AAV-related adverse event was an asymptomatic rise in ALT levels, which typically took place between 2 to 26 weeks after gene therapy. The investigators observed transaminitis in 4 of the 6 patients treated with high dosages but not in any patient treated at the low-dose levels. This complication has been reported with all AAV serotypes that have been administered systemically, regardless of the target disease.

Haemophilia A: a paradigm shift?

With the results of the B-AMAZE study in mind, Prof. Nathwani questioned if the same AAV approach can be used for the more complicated and more common haemophilia A. He explained that gene therapy programmes started in haemophilia B and not in haemophilia A because factor VIII (FVIII) cDNA is large, difficult to package, and expression of the FVIII gene leads to poor expression profiles when compared with other proteins of similar size (e.g. FVII). For successful gene therapy, researchers had to overcome these obstacles. They succeeded in creating small codon optimised FVIII expression cassettes in which the B domain –which is not required for FVIII/cofactor activity– is deleted. "By taking out the B-domain, we remained just within the packaging limits of AAV vectors," Prof. Nathwani explained.

In mice, codon optimisation of FVIII cDNA resulted in a 10-fold higher expression [2]. In patients with severe haemophilia A, FVIII levels rose to a peak of 64 IU/dL 1 year after administration of a single dose of a codon-optimised recombinant (r)AAV5 capsid pseudotyped vector made using baculovirus/SF9 cells in 2 doses (i.e. 6×10^{13} vg/kg and 4×10^{13} vg/kg) [3,4]. A 96% reduction in bleeding rates was observed in the 6×10^{13} vg/kg dose group, the other dose showed similar efficacy with 92% reduction. Many of the patients did not bleed at all, following a single administration of the rAAV5 vectors. None of the patients developed neutralising antibodies to FVIII and the only adverse event was asymptomatic grade 1 transaminitis. FVIII gene therapy might be licensed towards the end of this year for patients with severe haemophilia A.

Prof. Nathwani concluded that "gene therapy can be life-changing," and that AAV-mediated gene therapy has the potential to shift the paradigm in the treatment for haemophilia patients.

1. Nathwani A. SOA01.01, ISTH 2020 Virtual Congress, 12-14 July 2020.
2. Mcintosh J et al. Blood 2013;121:3335-3344.
3. Pasi KJ, et al. Abstract LB 01.2. ISTH 2019 Congress, 6-10 July 2019; Melbourne, Australia.
4. Pasi KJ, et al. New Engl J Med 2020;382:29-40.

Recombinant factor VIII safe and effective in PUPs A-LONG study

In the first prospective study of an extended half-life recombinant factor VIII (rFVIII) treatment for previously untreated patients with severe haemophilia A, rFVIII was well tolerated. Promisingly, the high-titre inhibitor rate was lower than that seen in the literature [1].

The development of alloantibody inhibitors that interfere with prophylaxis and treatment is the largest safety concern in infants with severe haemophilia A, as it occurs in up to 37% of the infant population. Recombinant FVIII products offer a technological solution by reducing the risk of formation of alloantibody inhibitors against FVIII, as well as prolonging the half-life of the protein.

The open-label, single-arm, multicentre, phase 3 PUPs A-LONG study investigated the safety and efficacy of rFVIII prophylaxis in previously untreated patients with severe haemophilia A, who were all male and under the age of 6. Of the 103 patients who received at least 1 dose, 80 were below 1 year old, 20 had a positive family history of inhibitors, and 82 had high-risk haemophilia genotype. The study was completed by 84.5% of the participants. Episodic treatment was started by 81 participants; of these, 69 switched to prophylaxis. Another 20 patients were on prophylaxis from the beginning. The primary endpoint of the study was inhibitor development, and a secondary endpoint was the annualised bleeding rate (ABR).

In total, 31.1% of the participants developed inhibitors, and 15.6% developed high-titre inhibitors (≥5 BU/mL). Median time to inhibitor development was 9 exposure days (range 1-53 days). A treatment-related serious adverse event was seen in 27.2% of participants. One patient died due to an intracranial haemorrhage, which happened during the screening period prior to the first dose of the medication and was therefore not treatment related.

The authors concluded that the inhibitor rate seen in this study was in the expected range, but high-titre incidence was lower than that reported in the literature.

1. Königs C, et al. OC 03.2, ISTH 2020 Virtual Congress, July 12-14.

What's New in Anticoagulation

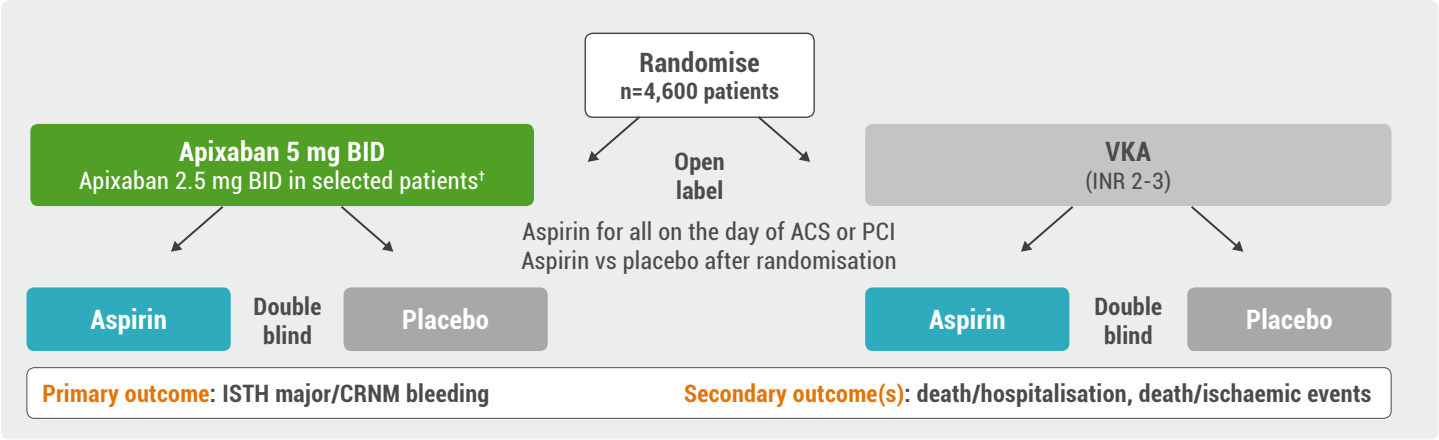
Finding the sweet spot of anticoagulation in AF patients with ACS

Patients with both atrial fibrillation (AF) and acute coronary syndrome (ACS) are constantly trapped between the Scylla of bleeding and Charybdis of ischaemic events. The large AUGUSTUS trial showed that dual therapy with a direct oral anticoagulant (DOAC) and a $P2Y_{12}$ inhibitor is safer than triple therapy with aspirin or VKA use in this challenging patient population [1].

Prof. Renato D. Lopes (Duke University School of Medicine, USA) reviewed this challenging patient population and raised 2 important questions: "whether we should use triple or double therapy for patients with AF and ACS/percutaneous coronary intervention (PCI), and what drug combination we should prescribe" [2]. Patients with AF and coronary artery disease have overlapping indications for antithrombotic therapy. Coronary stenting in patients with AF and a high stroke risk is a problem because to prevent both stent thrombosis and stroke, a combination of dual antiplatelet therapy (DAPT) and oral anticoagulant is necessary, which comes with high bleeding risk.

The AUGUSTUS trial compared the safety of standard-dose apixaban with a vitamin K antagonist (VKA) in addition to low-dose aspirin or placebo, on a background of concomitant $P2Y_{12}$ inhibitor therapy for 6 months in patients with AF and recent ACS or PCI (see Figure) [1]. The primary study endpoint was major or clinically relevant non-major bleeding. Secondary outcomes included death or hospitalisation and a composite of ischaemic events. The trial enrolled 4,614 patients with ACS or had undergone an elective PCI and were planning to take a $P2Y_{12}$ inhibitor. They were randomly assigned to open-label apixaban or a VKA. Additionally, patients in both groups were either treated with a placebo or aspirin. Among the patients who underwent randomisation, 37.3% had ACS and underwent PCI, 23.9% had medically managed ACS, and 38.8% underwent an elective PCI [1].

Figure: The 2x2 factorial design of the AUGUSTUS trial. Adapted from [1]



BID, twice daily; INR, international normalised ratio; VKA, vitamin K antgonist.

† 2.5 mg dose for patients with 2 or more of the follwing criteria: age ≥80 years, weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.

Adding aspirin increases bleeding

Results from the AUGUSTUS trial showed that 14.7% of patients treated with VKA had major or clinically relevant non-major bleeding compared with 10.5% of patients with apixaban, both a clinically relevant and statistically significant difference both for non-inferiority and superiority (HR 0.69; 95% CI 0.58-0.81; P<0.001). This effect was the same with and without aspirin. "This is the beauty of the 2 by 2 factorial design, the results are independent from each other, so you recognise the treatment effect that exists independent from aspirin," Prof. Lopes explained.

In addition, apixaban-treated patients had a lower incidence of death or hospitalisation in comparison with patients treated with VKA (23.5% vs 27.4%; HR 0.83; 95% CI 0.74-0.93; P=0.002). No significant differences were observed in ischaemic events between the apixaban and VKA groups; however, the trial was not powered for these outcomes. Death or hospitalisation and ischaemic events in the aspirin group were similar compared with the placebo group [1].

Regardless of the anticoagulation therapy, aspirin use was more deleterious than beneficial: a 11.4% absolute risk reduction in bleedings was found with the combination of apixaban and placebo compared with VKA and aspirin. "This means we have to treat only 9 patients with the dual therapy including apixaban to prevent a bad bleeding compared with the triple therapy," Prof. Lopes explained.

"The AUGUSTUS trial is the only trial that also included medically managed patients with ACS. Therefore, in the whole spectrum of coronary artery disease the data from apixaban being safer than vitamin K antagonists is very consistent," Prof. Lopes concluded.

1. Lopes R, et al. N Engl J Med 2019;380:1509-1524.
2. Lopes RD. SOA 05.03, ISTH 2020 Virtual Congress, 12-14 July.

Lower embryopathy risk with DOAC versus VKA during pregnancy

Many patients receiving oral anticoagulation for venous thromboembolism (VTE) are in their reproductive years, but the potential for reproductive toxicity of direct oral anticoagulants (DOACs) in humans is not yet well established. A literature review evaluating pregnancy outcomes after DOAC exposure suggests DOACs have a lower risk of reproductive toxicity compared with vitamin-K antagonists (VKA) [1].

Dr Jan Beyer-Westendorf (UNI-Klinikum Carl Gustav Carus Medizinische Klinik I, Germany) pointed out that planned pregnancies in women on DOACs require a careful risk-benefit assessment, and that individualised decisions need to include patient perspective, preferences, and fears [1]. DOACs are small molecules that can cross the placenta. Previously, an increased transfer of dabigatran, rivaroxaban, and apixaban to the foetal site of the placenta was shown in a human placental model. Thus, DOAC exposure during pregnancy should be minimised and switching to low molecular weight heparins (LMWH) is indicated when a pregnancy is diagnosed. Yet, DOACs are not strictly contraindicated in pregnancy: product information, for example of rivaroxaban, recommend using the agent with caution.

In 2016, Dr Beyer-Westendorf published a first case collection on DOAC exposure in pregnancy including 233 separate cases, of which 137 had reported outcomes. At that time, there was insufficient data to judge a possible embryotoxic risk of DOACs. The current data collection performed in 2020 included 593 separate cases. Most women had to take DOACs as prophylaxis or treatment for VTE. These cases yielded 316 known outcomes: 55.4% of the pregnancies ended with live birth and 21.8% with miscarriages. In 22.8% of cases, pregnancies were terminated electively. Only 3.8% of abnormalities were compatible with embryotoxicity. Reassuringly, no specific abnormality pattern emerged. "This is very different from warfarin, where abnormalities are more frequent and show a distinct embryotoxic pattern," Dr Beyer-Westendorf explained.

Since 2016, there is a guideline for DOACs exposure in pregnancy [2]. In case of a planned pregnancy, DOACS should be switched to an alternative anticoagulant pre-conceptually. In case of unintended pregnancy while on a DOAC, patients should discontinue DOACs immediately and switch to LMWH. However, inadvertent exposure to a DOAC is not sufficient ground for termination of pregnancy, and the guidelines recommend early obstetric review and foetal monitoring in the guideline. Dr Beyer-Westendorf recommended to re-assess the need for anticoagulation in all patients that plan a pregnancy. In some women, ASA may be an alternative. If a patient is concerned about the lack of DOAC safety data, she should switch to LMWH. If LMWH are not accepted, they should stay on DOAC until the pregnancy is confirmed and then switch to LMWH. "Do not counsel towards termination but advocate close monitoring of pregnancy instead," Dr Beyer-Westendorf recommended considering the low risk of DOACs in early pregnancy.

1. Beyer-Westendorf J. SOA 10.03, ISTH Virtual Congress 2020, 12-14 July.
2. Cohen N, et al. J Thromb Haemost 2016;14:1673-1676.

Higher thrombotic risk in NSCLC patient with *ALK* rearrangement

A retrospective observational study showed that anaplastic lymphoma kinase gene (ALK) rearrangement in lung cancer patients is associated with a 3 to 4 times elevated thrombotic risk compared with *ALK*-negative lung cancer patients [1].

Chromosomal translocations involving *ALK* are rare oncogenic events found in 3-5% of non-small-cell lung cancers (NSCLC). Prior studies have shown that *ALK* rearrangement in NSCLC patients might confer an elevated risk for cancer-associated venous thromboembolism (VTE). Dr Hanny Al-Samkari (Massachusetts General Hospital, USA) and colleagues compared the risk for VTE and arterial thrombosis of 400 NSCLC patients with *ALK* rearrangement with 800 NSCLC patients without *ALK* rearrangement who were treated between 2009 and 2019. They performed multivariable time-to-event analysis to assess the risk of first venous or arterial thrombosis in both groups and controlled for covariates that impact thrombotic risk, e.g. known thrombophilia, in the VTE model.

Dr Al-Samkari pointed out that the *ALK* group had more favourable characteristics compared with the non-*ALK* group. *ALK* patients were considerably younger (mean age 50 vs 66 years; P<0.001), significantly fitter with 87.2% of *ALK* patients having an ECOG performance status 1 or 2 vs 54.1% of the non-*ALK* group. In addition, patients in the *ALK* group smoked much less (29.9% vs 77.1%) and had significantly lower or similar rates of other VTE risk factors (e.g. brain metastases, obesity, prior VTE). The *ALK* group also had significantly lower rates of other arterial thrombosis risk factors such as hypertension, hyperlipidaemia, atherosclerosis, diabetes, or atrial fibrillation. Despite these differences, the initial overall VTE rate was significantly higher (42.7%) in the *ALK* group compared with the non-*ALK* group (28.6%). Likewise, the rate of recurrent VTE was significantly elevated in the *ALK*-group (13.5% vs 3.1%). Despite significantly lower rates of all major arterial thrombosis risk factors, arterial thrombosis rates were similar in the 2 groups (5.0% vs 4.4%). In addition, the VTE-free survival was lower than in the non-*ALK* group.

"Keep in mind that the *ALK* group was nearly 2 decades younger and had far less risk factors. Despite these differences they had a 4-fold increase in VTE risk and a 3-fold increase in arterial thrombosis risk in NSCLC," Dr Al-Samkari explained. Therefore, patients with NSCLC harbouring an *ALK* rearrangement may have a distinct benefit from the use of pharmacologic thromboprophylaxis.

1. Al-Samkari H, et al. OC 10.2.ISTH 2020 Virtual Congress, 12-14 July.

COVID-19 and Thrombosis

Crosstalk between inflammation and coagulation in severe COVID-19 infections

In a special session at this year's virtual meeting, member of the ISTH COVID-19 Task Force Prof. Roberta Gualtierotti (University of Milan, Italy) highlighted haemostatic changes in patients with severe COVID 19 [1].

Transmission of the novel coronavirus occurs via direct contact or respiratory droplets. The virus enters by binding to the ACE2 receptor expressed on bronchial and alveolar epithelial cells, endothelial cells, and monocytes in the lung. "Evidence speaks in favour of the role of endothelial cells in severe COVID-19, both as culprits and victims of the inflammatory state and consequent coagulopathy," Prof. Gualtierotti explained.

While most infections lead to mild-to-moderate respiratory symptoms, about 5% of the patients progress to a more severe and systemic disease with acute lung injury, eventually leading to acute respiratory distress syndrome, shock, and multiple organ dysfunction associated with a peculiar coagulopathy and an increased mortality risk [2]. Among hospitalised patients with severe COVID-19-associated pneumonia, respiratory failure with hypoxia is frequent. Moreover, evidence suggest that patients with 1 or more pre-existing risk factors such as obesity, diabetes, and dyslipidaemia may be more at risk of developing severe COVID-19.

In severe COVID-19, inflammation is caused by immune dysregulation. Prof. Gualtierotti emphasised that "severe COVID-19 is characterised by hyperinflammation, triggering a series of pathogenic mechanisms that further amplify the inflammatory state and activate coagulation and other systems, and by a [COVID-19-associated] peculiar coagulopathy. Hypercoagulability leads to a prothrombotic state." She pointed out "that a bidirectional crosstalk does exist between inflammation and coagulation." Severe COVID-19 is a paradigm of this crosstalk. Coagulation activation induces microvascular thrombosis – a phylogenetically preserved mechanism that, in the end, is an attempt by the body to prevent the spreading of pathogens. "However, when uncontrolled, this may lead to multiple organ dysfunction," she warned.

Previous studies have reported a cumulative incidence of venous thromboembolism in severe COVID-19 of about 30% at 21 days of follow-up in patients hospitalised in different intensive care units with COVID-19, despite routine thrombosis prophylaxis [1]. Prof. Gualtierotti presented data from Milan, demonstrating a slightly higher incidence of venous thromboembolism (31.6% at 21 days) but this analysis included not only ICU but also intermediate care patients [3].

While many patients with severe COVID-19 experience coagulopathies that may resemble other systemic coagulopathies associated with severe infections and systemic inflammation, e.g. disseminated intravascular coagulation (DIC) and consumption coagulopathy, none of these fully fit the description of COVID-19-associated coagulopathy. DIC is rarely seen in severe COVID 19 infection other than pre-terminal multiple organ failure. In case of COVID-19, fibrinogen is not reduced but increased. Thrombotic microangiopathy is an expression of microvascular involvement and the development of fibrin and microthrombi. In COVID-19, haemolysis and thrombocytopenia are not typical features. In secondary hemophagocytic lymphohistiocytosis, fibrin formation is caused by survival of histiocytes and failure of normal cytotoxic cells to abandon the triggering antigen. Sepsis is associated with DIC and cytokine storm is an umbrella term, including a variety of inflammatory aetiologies with overwhelming systemic inflammation, leading to hemodynamic instability, multiple organ dysfunction, and death. "However, none of these terms fully describes COVID-19-associated coagulopathy," Prof. Gualtierotti concluded.

1 Gualtierotti R. COVID19.02. ISTH 2020 Virtual Congress, 12-14 July.
2 Wu Z, McGoogan JM. JAMA 2020;323:1239-1242.
3 Martinelli I, et al. 2020. Submitted for publication.

COVID-19 associated with higher VTE rates relative to influenza

COVID-19 patients showed much higher rates of thrombotic complications compared with influenza patients. Dutch study results suggest this may be due to possible specific effects of SARS-CoV-2 on the coagulation system.

"An activation of blood coagulation was already announced in the first studies on COVID-19 patients at the beginning of this year," stated Dr Milou Stals (Leiden University Medical Centre, the Netherlands) [1]. Up to about 50% COVID-19 patients in ICU sustain thrombotic complications, with 87% of them experiencing pulmonary embolism and 7% ischaemic stroke [2,3]. In general-ward patients, the incidence is suggested to be 5-10 % [3,4].

The presented retrospective cohort study aimed to compare the cumulative incidence of thrombotic events of hospitalised COVID-19 patients and hospitalised influenza patients [1]. These results intended to clarify whether thrombotic complications are prompted through the presence of conventional risk factors or a specific, SARS-CoV-2-associated pro-coagulative effect. Besides incidence of venous thromboembolism (VTE) and arterial thromboembolism in COVID-19 versus influenza patients, the study also looked at a potential link between pre-existing anticoagulation treatment at admission and later thrombosis during hospitalisation.

The study included data on COVID-19 patients (n=579) hospitalised at 3 Dutch hospitals between 24 February and 25 April 2020. All patients were treated with thrombosis prophylaxis but investigations for VTE were only performed in case of clinical suspicion. Data on the included influenza patients (n=27,980) were obtained from the Statistics Netherlands database. As this data did not allow for discrimination between general-ward and ICU patients, comparisons were only possible for VTE incidence rates of all hospitalised influenza patients. Cumulative incidences of VTE were calculated with Kaplan-Meier analysis for the COVID-19 patients only. Baseline characteristics within the COVID-19 group showed a mean age of 67, 66% males, and 13% of long-term anticoagulated patients at admission.

After adjustment for the competing risk of death, the cumulative 30-day incidence of VTE and arterial thromboembolism together in the COVID-19 group was 19.6% for general-ward plus ICU patients, with 5.3% incidence on the general ward and 34.1% on ICU. Looking at VTE alone, the respective incidences were: 17.8%, 3.8%, and 32.5%. There was a large difference with the influenza group, which showed a VTE incidence of only 1.04% in hospitalised patients. As for long-term anticoagulant treatment at hospital admission, this led to a lower risk of thrombotic complications in general (HR 0.09) and especially in VTE (HR 0.04).

Dr Stals concluded that the much higher incidence of thrombotic complications in COVID-19 patients implies a specific effect of SARS-CoV-2 on coagulation, which is currently under further investigation in the Netherlands.

1. Stals MAM, et al. LB/CO01.4, ISTH Virtual Congress 2020, 12-14 July.
2. Klok FA, et al. Thromb Res. 2020;191:148-150.
3. Middeldorp S, et al. J Thromb Haemost. 2020;18(8):1995-2002.
4. Lodigiani C, et al. Thromb Res. 2020;191:9-14.

Therapeutic anticoagulation not associated with lower mortality rates in COVID-19 ICU patients

A cohort study of nearly 3,000 COVID-19 patients in intensive care did not reveal any advantages in preventing death by medicating with anticoagulation at therapeutic dosage. Obesity and high D-dimer levels were among the recognised independent factors associated with VTE.

A strong association has been found between coagulation-related complications like venous thromboembolism (VTE) and COVID-19 [1-4]. "As a result, it has been hypothesised that the hypercoagulability in patients with COVID-19 may be a key mechanistic pathway leading to multiple organ failure and death and it has gained considerable attention as a potential therapeutic target," said Dr Hanny Al-Samkari (Massachusetts General Hospital, USA) [4]. Up to now, no randomised controlled trial data is available to give guidance on the optimal prophylactic dose of anticoagulation for critical patients in ICU. Dr Al-Samkari and his team set up a large 67-centre cohort study conducted in US centres to provide robust estimates on the effect of therapeutic anticoagulation.

The analysis included data on patients' first 14 days of ICU, which was collected by manually reviewing charts at the different sites (n=3,239). After the database was locked on 8 May 2020, all enrolled patients had a follow-up of ≥28 days. Coagulation complications were defined as X-ray confirmed VTE, ischaemic stroke, major bleeding, severe coagulopathy, heparin-induced thrombocytopenia, and disseminated

intravascular coagulation. To identify predictors of VTE, a multivariable logistic regression was fitted. To evaluate the effect of anticoagulation on survival, a target trial emulation distinguished between receivers and non-receivers of therapeutic anticoagulation in the 2 days following ICU admission, using a Cox model that adjusted for confounders with inverse probability weighting. In addition, subgroups were pre-specified for analysis: age, sex, BMI, mechanical ventilation on ICU day 1, and D-dimer levels on ICU days 1 or 2. The included patients from all over the USA had a median age of 61 years, 64% were males, 66% were intubated, and 42% had vasopressor treatment on ICU day 1.

The results showed that 39.3% of participants died, 43.4% discharged alive within 4 weeks, and 17.4% were still hospitalised at 28 days. VTE was sustained by 6.3% (n=204), while 2.8% (n=90) suffered from major bleeding during their first 14 days in ICU. Of note, 60 of the 90 major bleedings occurred under therapeutic anticoagulation. "Patients with a confirmed VTE had a mortality rate similar to the cohort as a whole; however, patients with major bleeding had a much higher mortality rate, exceeding 60%," reported Dr Al-Samkari. The target trial emulation identified several variables that were independently associated with VTE: male sex (OR 1.7), BMI≥40 (OR 2.08), and high D-dimers (OR 2.5 for levels between 2,501-10,000 ng/mL and OR 4.2 for levels >10,000 ng/mL). Of the 2,809 patients included in the target trial emulation, 384 received therapeutic anticoagulation and 2,425 did not. The overall characteristics of these 2 groups were comparable, and the risk of death within the first 28 days after ICU admission was similar with a hazard ratio of 1.12. Hazard ratios of the subgroup analysis were not significant (see Figure). "Our findings do not support empiric use of therapeutic anticoagulation in critically ill patients with COVID-19," Dr Al-Samkari concluded.

1. Helms J, et al. Intensive Care Med. 2020;46:1502-1503.
5. Middeldorp S, et al. J Thromb Haemost. 2020;18(8):1995-2002.
2. Al-Samkari HT, et al. Blood. 2020;136(4):489-500.
3. Cui S, et al. J Thromb Haemost. 2020;18:1421-1424.
4. Al-Samkari HT. LB/CO01.2, ISTH Virtual Congress 2020, 12-14 July.

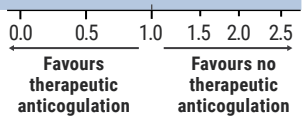
COVID-19 not associated with heightened VTE risk after discharge

A study performed in Belgium revealed a rather low incidence of venous thromboembolism (VTE) in discharged COVID-19 patients, and so data do not warrant a recommendation for prescription of extended thromboprophylaxis on a regular basis [1].

As the use of low-molecular-weight heparin (LMWH) appears to be linked to a better prognosis for hospitalised COVID-19 patients, every COVID-19 patient at University Hospital Leuven receives LWMH at prophylactic dosage, with ICU patients receiving an intermediate dose [2]. Yet, limited

Figure: Subgroup analysis of the target trial emulation comparing anticoagulated versus not anticoagulated patients. Adapted from [1]

	Anticoagulated	Not Anticoagulated	Adjusted Hazard Ratio (95%)	Forest Plot
	No. Deaths/ No. Patients (%)			
Overall	179 / 384 (46.6)	887 / 2425 (36.6)	1.12 (0.92-1.35)	
Age (years)				
≤60	70 / 183 (38.3)	275 /1147 (24.0)	1.17 (0.86-1.58)	
>60	109 / 201 (54.2)	612 / 1278 (47.9)	1.09 (0.88-1.35)	
Sex				
Male	130 / 264 (49.2)	592 /1549 (38.2)	1.12 (0.91-1.37)	
Female	49 / 120 (40.8)	295 /876 (33.7)	1.28 (0.94-1.75)	
Body mass index (kg/m²)				
<40	157 / 332 (47.3)	768 / 2084 (36.9)	1.13 (0.94-1.35)	
≥40	22 / 52 (42.3)	119 / 341 (34.9)	1.27 (0.73-2.23)	
Mechanically ventilated on ICU days 1				
Yes	155 / 304 (51.0)	664 / 1527 (43.5)	1.13 (0.94-1.35)	
No	24 / 80 (30.0)	233 /898 (24.8)	0.98 (0.59-1.62)	
D-dimer (ng/mL) on ICU days 1 or 2				
≤1,000	13 / 49 (26.5)	122 / 537 (22.7)	0.96 (0.51-1.82)	
1,001-2,500	30 / 73 (41.1)	14 / 483 (34.0)	1.13 (0.76-1.69)	
>2,500	105 / 190 (55.3)	215 / 457 (47.1)	1.05 (0.82-1.34)	



evidence is available on the incidence of VTE in discharged patients after COVID-19 hospitalisation, and whether extended prophylactic therapy is necessary.

To this end, Dr Matthias Engelen (University Hospital Leuven, Belgium) and colleagues evaluated data from 133 adult COVID-19 patients. Participants were screened with venous ultrasound (VUS), and their C-reactive protein (CRP) and D-dimer levels were measured at 6 weeks after discharge. In high-risk patients, CT-pulmonary angiogram and ventilation/perfusion scans were also carried out. Mean age of the study subjects was 58 years, 63% were male, and the median length of hospitalisation lasted 10 days. Of the participants, 38% had been admitted to ICU, 60% needed mechanical ventilation, and 4% required extracorporeal membrane oxygenation (ECMO). Unsurprisingly, the median number of days spent in hospital was significantly longer for ICU patients (25 days) than non-ICU patients (7 days).

D-dimer levels generally increased during hospitalisation to maximum value, then significantly dropped before discharge, and were found significantly lower 6 weeks later. Distinguishing values for D-dimers between ICU and non-ICU patients showed higher levels for the ICU patients only while in hospital but not after discharge. Levels of CRP generally followed the same pattern as D-dimers, but lower levels of CRP in ICU patients at discharge were noticed, maybe attributable to their lengthier mean hospital stay.

Extended thromboprophylaxis was given to 38% of ICU and 13% of non-ICU patients only, leaving the greater part of COVID-19 patients without LMWH after discharge. Yet, no symptomatic VTE occurred in the study population after discharge and there was only 1 asymptomatic popliteal vein thrombosis. This equals a very low VTE rate of 0.8%, while the non-fatal bleeding rate during hospitalisation was 1.5%. "So, despite widely reported higher incidence of in-hospital VTE, we report very low incidence of VTE in patients discharged after COVID-19 hospitalisation in a centre with a high-dose prophylactic strategy and asymptomatic screening for all patients at follow-up in a well-defined ill population with rather low rates of extended thromboprophylaxis," Dr Engelen summarised the findings. This suggest that extended thromboprophylaxis of COVID-19 patients after hospitalisation is not routinely needed.

1. Engelen MM, et al. LB/CO01.3, ISTH Virtual Congress 2020, 12-14 July.
2. Tang N, et al. J Thromb Haemost. 2020;18:1094-1099.

What's New in Venous Thromboembolism

Residual pulmonary obstruction may predict risk of VTE recurrence

A pooled analysis identified initial pulmonary vascular obstruction index (PVOI) >35% and residual PVOI >5% as cut-off values for prognosis of venous thromboembolism (VTE) recurrence after a first pulmonary embolism (PE).

Experiencing a first episode of PE entails a substantial risk of VTE recurrence and case fatality [1]. "Guidelines do not really take into account all the variability between patients, e.g. for a patient with an unprovoked PE, a life-long anticoagulant therapy is recommended, but only one third of these patients will have benefits from this treatment, leaving the others exposed to hard to justify haemorrhagic risks," Dr Robin Chaux (University Hospital St. Etienne, France) explained, pointing to a need of improved scores to predict recurrence [2]. A promising candidate for risk stratification is the PVOI level.

"In literature, significant associations were found between PVOI and VTE recurrence, but the results are still quite discordant between studies," said Dr Chaux. Furthermore, cut-off values that are used also vary between studies [3-5]. So, apart from evaluating PVOI as potential independent risk factor for VTE recurrence, this analysis by Dr Chaux and colleagues set out to find discriminating threshold values of PVOI to estimate VTE recurrence [1].

To create a substantial sample size, the investigators pooled data of 922 patients from 2 observational studies and 1 randomised controlled trial [3,4,6]. An initial PVOI

was determined at the index PE and residual PVOI after 3-6 months of initial anticoagulation therapy. VTE recurrence was defined as objectively confirmed PE or deep vein thrombosis. Study subjects had a history of unprovoked PE in 64.9%.

VTE recurred in 16.2% of patients, and 47.1% received extended anticoagulation over >12 months. Initial PVOI >35% (HR 1.61; 95% transition HR 1.07-2.43) and residual PVOI >5% (HR 1.63; 95% CI 1.06-2.50) were both significantly associated with the risk of VTE recurrence. "So, we have found that initial PVOI and residual PVOI seem to be independent predictors of VTE recurrence after first PE," said Dr Chaux. He concluded, "For the future, we hope that these results, maybe not alone, will help to more accurately detect patients with high risk of VTE recurrence and provide help in clinical decision-making for adapting anticoagulation therapy."

1. Prandoni P, et al. Haematologica. 2007;92:199-205.
2. Chaux R. OC10.1, ISTH Virtual Congress 2020, 12-14 July.
3. Tromeur C, et al. Eur Respir J. 2018;51:1701202.
4. Chopard R, et al. Am J Cardiol. 2017;119:1883-1889.
5. Raj L, et al. Thromb Haemost. 2019;119:1489-1497.
6. Planquette B, et al. Thromb Res. 2016;148:70-75.

Risk of checkpoint inhibitor-associated thromboembolic events important for cancer prognosis

A single-centre cohort study found a venous thromboembolism (VTE) incidence of over 10% in cancer patients treated with immune checkpoint inhibitors (ICI). VTE was further associated with an elevated mortality risk [1].

The retrospective study tried to fill the knowledge gap concerning potential increased thromboembolic risk for cancer patients who are treated with ICI. Dr Florian Moik (Medical university of Vienna, Austria) and colleagues explored the likelihood of arterial thromboembolism (ATE) and VTE in a cohort of 580 patients who were treated with ICI at the Medical University of Vienna between 2015 and 2018. They also carried out an assessment of risk factors as well as a possible clinical impact. The most common cancer diagnosis identified in the chart review was melanoma in 35.6% and non-small-cell lung cancer in 27.2% of the cases. Of the ICI-treated subjects, 89.1% were at stage 4 of their disease. Median age was 64 years, BMI 24.5, and 40.5% of patients were female.

Over a median follow-up of 13.1 months, the cumulative incidence of VTE was 10.8% (95% CI 7.1-15.4), with deep vein thrombosis and pulmonary embolism most frequently diagnosed. Predictors for VTE were previous history of VTE and disease stage. Of note, VTE only happened in patients at disease stage 4. The cumulative incidence rate of ATE was 3.5% (95% CI 2.1-5.4). In this group, acute vascular occlusion, ST-elevation myocardial infarction, and ischaemic stroke occurred equally often.

In addition, VTE occurrence was linked to an increased mortality risk (transition HR 3.05; 95% CI 2.00-4.66). Likewise, VTE was associated with disease progression. There was no distinction in VTE rates for different types of cancer or for different ICI agents. Also, ECOG (Eastern Cooperative Oncology Group) performance status, Charlson-Comorbidity-Index, and Khorana Score were not associated to VTE. ATE occurrence was not associated with increased mortality (HR 1.38; 95% CI 0.68-2.81).

The researchers concluded that cancer patients treated with ICI bear a substantial risk of VTE and ATE. They also pointed to the negative impact of VTE on survival in affected patients.

1 Moik F, et al. PB2162, ISTH Virtual Congress 2020, 12-14 July.

Less diagnostic delay in CTEPH diagnosis with novel algorithm

In the prospective, international InSHAPE II study, a non-invasive strategy for early identification of chronic thromboembolic pulmonary hypertension (CTEPH) after acute pulmonary embolism (PE) proved both accurate and cost-saving [1].

The diagnostic delay of CTEPH after acute PE is over 1 year and associated with increased mortality. Dr Gudula Boon (Leiden University Medical Center, the Netherlands) and her colleagues developed a non-invasive screening strategy comprising a 'CTEPH prediction score' and 'CTEPH rule-out criteria' aimed at diagnosing CTEPH earlier and limiting the number of required echocardiograms. "Six predictors [e.g. unprovoked PE, hypothyroidism, and diagnostic delay >2 weeks] have been identified that are highly probable for CTEPH and we included them in our score," Dr Boon explained. The CTEPH rule-out criteria were only applied on low-risk patients with a presence of CTEPH-specific symptoms. According to these criteria, patients with at least 1 ECG criteria and/or abnormal NT-proBNP values were referred to echocardiography. Included were 424 patients from 6 hospitals in the Netherlands, Poland, and Belgium. Of these participants, 69% were judged low-risk and 31% high-

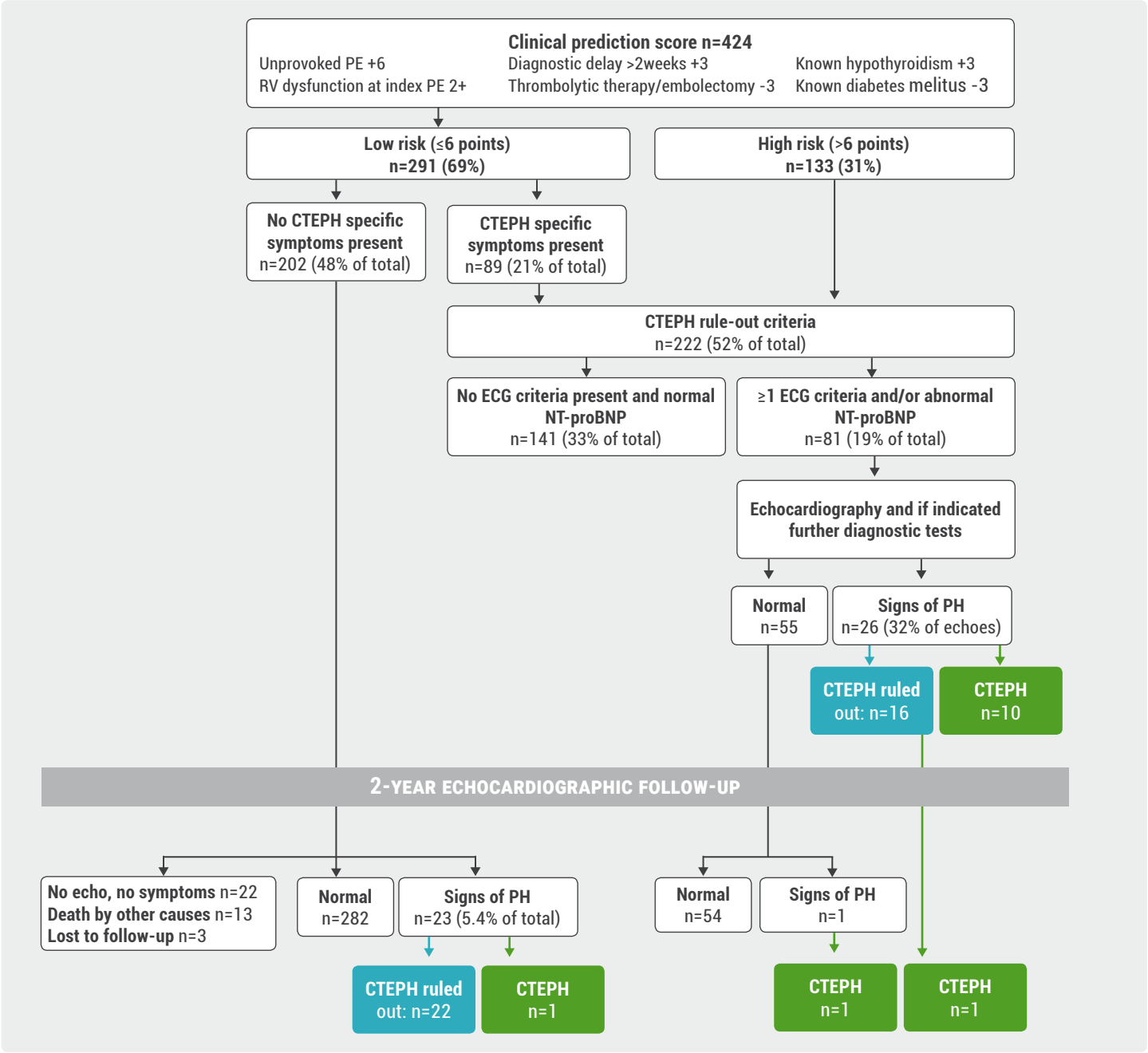
risk. Of all participants, 48% were low-risk patients without CTEPH-specific symptoms, and 21% were low-risk patients with symptoms.

Successful identification of almost all CTEPH patients

The algorithm successfully ruled out 342 of 343 patients (see Figure). One missed case by the algorithm translates into a failure rate of 0.29%. "There was only 1 missed case who had persistent symptoms. However, this patient would also have been missed if echocardiography had been performed initially," Dr Boon explained. With the algorithm, CTEPH was diagnosed within 4 months after the index PE diagnosis, which is less diagnostic delay than the average. In addition, echocardiography was avoided in 81% of patients.

1. Boon G, et al. OC.10.3, ISTH Virtual Congress 2020, 12-14 July.

Figure: CTEPH screening algorithm applied at 3 months after diagnosis and 2-year follow-up results [1]



CTEPH, chronic thromboembolic pulmonary hypertension; ECG, electrocardiography; NT-proBNP, N-terminal pro-brain natriuretic peptide; PE, pulmonary embolism; PH, pulmonary hypertension; RHC, right heart catheterisation; RV, right ventricular.

Pearls of the Posters

Surgical bleeding risk most important determinant of bleeding outcomes

Results from the PAUSE study showed that neither type nor dose of direct oral anticoagulant (DOAC) influenced bleeding outcomes in AF patients undergoing elective surgery. The procedure itself carries the most evident bleeding risk for the patients [1].

The Perioperative Anticoagulant Use for Surgery Evaluation (PAUSE) study prospectively assessed a standardised perioperative management strategy in 3 cohorts of patients treated with a DOAC (i.e. apixaban, dabigatran, or rivaroxaban) who needed an elective surgery. The aim of the study, presented by Dr Kira MacDougall (Staten Island University Hospital, USA), was to compare rates of major bleeding, arterial thromboembolism, any bleeding (composite of major bleeding and clinically-relevant non-major bleeding), and any thromboembolism (composite of arterial and venous thromboembolism) according to DOAC type and dose, surgery-related bleeding risk, patient´s renal function, and age.

The study included 3,007 patients in 3 cohorts: 41.8% in the apixaban cohort, 22.2% in the dabigatran cohort, and 36% in the rivaroxaban cohort. One-third of all patients underwent a high-bleed-risk surgery. The results suggest that DOAC type does not affect either bleeding or thromboembolism outcomes. Of note, the DOAC dose regimen (apixaban 5 mg vs 2.5 mg, dabigatran 150 mg vs 110 mg, and rivaroxaban 20 mg vs 15 mg) did also not influence the endpoints.

In general, the incidence of major bleeding was low (<2%), but it was higher in patients that underwent a high-bleed-risk surgery. In patients treated with apixaban, the bleeding risk was significantly higher in the high-bleed-risk group compared with the low-bleed-risk group (2.96% vs 0.59%; P=0.001; see Table). This was not the case in dabigatran-treated patients. In the rivaroxaban-treated patients, there was only a numerical difference between the high- and the low-risk group. Further, the rate of arterial thromboembolic events was generally low in all patients, regardless of the risk-group, and neither renal function nor age showed significant differences in bleeding or thromboembolism outcomes.

1 MacDougall K, et al. PB2054, ISTH 2020 Virtual Congress, 12-14 July.

Similar bleeding rates in patients with VTE and AF treated with DOACs

A retrospective study from a French emergency department including 525 patients with venous thromboembolic disease (VTE) and atrial fibrillation (AF) found no difference in bleeding risk during therapy with direct oral anticoagulants (DOACs) for these medical conditions [1].

The use of DOACs is an integral part in the management of different indications such as AF and VTE; and, as with any anticoagulation treatment, their use may be associated with the occurrence of haemorrhagic complications. Using information from a database in an emergency department, a retrospective study assessed the incidence of haemorrhage in patients with VTE or AF.

Table: Bleeding and thromboembolism outcomes for surgical bleeding risk. Adapted from [1].

	Apixaban		Dabigatran		Rivaroxaban	
Outcome	**High risk (n=406)**	**Low risk (n=851)**	**High risk (n=228)**	**Low risk (n=440)**	**High risk (n=373)**	**Low risk (n=709)**
Major bleeding n(%) 95% CI	12(2.96) 1.7-5.09	5(0.59) 0.25-1.37	2(0.88) 0.24-3.14	4(0.91) 0.35-2.31	11(2.95) 1.65-5.2	9(1.27) 0.67-2.39
P-value	P=0.001		P=1.000		P=0.059	
Any bleeding (MB+CRNB) n(%) 95% CI	23(5.67) 3.8-8.36	15(1.76) 1.07-2.89	7(3.07) 1.4-6.2	12(2.73) 1.57-4.71	25(6.70) 4.58-9.71	20(2.82) 1.83-4.32
P-value	P<0.001		P=0.809		P=0.004	
Arterial thromboembolism n(%) 95% CI	1(0.25) 0.04-1.38	1(0.12) 0.02-0.66	1(0.44) 0.08-2.44	3(0.68) 0.23-1.99	2(0.54) 0.15-1.93	2(0.28) 0.08-1.02
P-value	P=0.542		P=1.000		P=0.612	
Any thromboembolism n(%) 95% CI	7(1.72) 0.84-3.52	2(0.24) 0.06-0.85	3(1.32) 0.45-3.8	4(0.91) 0.35- 2.31	3(0.80) 0.27-2.34	2(0.28) 0.08-1.02

CI, confidence interval; CRNB, clinically-relevant non-major bleeding; MB, major bleeding.

The majority of the 525 included patients were treated with a DOAC (i.e. dabigatran, rivaroxaban, or apixaban) for AF (71.6%), another 149 (28.4%) were treated for VTE. Patients with both VTE and AF were excluded. In total, 95 patients were admitted due to haemorrhage: 27 VTE patients (28.4%) and 68 AF patients (71.6%).

The percentage of haemorrhage was comparable in both indications: 18.4% in the VTE group compared with 18.3% in patients with AF. The AF subgroup was significantly older, had more hypertension, and more strokes (all differences P<0.001) compared with the VTE patients. In addition, they had a higher incidence of myocardial infarction, more associated treatments, and a higher haemorrhagic risk score. Despite these striking differences, a subgroup analysis that compared only those patients with AF with bleedings with VTE patients with bleedings showed that only the age difference persisted (78.6 ± 10.2 years in the group with AF compared with 60.6 ± 21.1 in the VTE group; P<0.001).

The authors concluded that despite the distinct differences between AF and VTE patients with DOACs, those who experience bleedings do not differ except for age. Thus, age should be the main concern with regard to bleeding risk when DOACs are prescribed.

1 Moustafa F, et al. PB1128, ISTH 2020 Virtual Congress, 12-14 July.

Physical rehabilitation improves health outcomes after pulmonary embolism

Outpatient rehabilitation over 6 weeks improved functional constraints in patients who suffered from exertion dyspnoea after sustaining a pulmonary embolism [1,2].

Pulmonary embolism (PE) may have long-term effects on patient's health status. Long-term consequences include decreased functional capacity with chronic exercise limitations that are observed in many patients. Dr Stephan Nopp (Medical University Vienna, Austria) and colleagues aimed to evaluate the possible benefits of outpatient physical rehabilitation for PE patients with persisting symptoms.

The analysis included 22 patients with physical rehabilitation between 2012 and 2019 with a median age of 47.5 years, among them 32.8% women, and 57.1% had been diagnosed with deep vein thrombosis when the PE happened. All of them suffered from dyspnoea upon exertion with a New York Heart Association (NYHA) ≥ class II, and 45.5% had arterial hypertension.

The study subjects completed a physical rehabilitation programme with 3-4 hours of exercise, patient education, and physiotherapy with multi-professional supervision thrice weekly over 6 weeks. A change in 6-minute-walk-test (6MWT) was defined as primary outcome, while other parameters like performance on the cycle ergometer, inspiratory muscle strength, and extremity strength served as secondary outcomes. As also long-term advantages were of interest, follow-up took place until 39 months (median value) after completion of physical rehabilitation. The beginning of physical rehabilitation was set around 19 weeks after the acute PE. The mean value for 6MWT at baseline was 556.1 m.

Directly after completion of the physical rehabilitation programme, clinically meaningful ameliorations in 6MWT were observed with a mean change of 49.4 m (P<0.001). Furthermore, test for constant work rate, maximal inspiratory pressure, and strength in upper and lower extremities showed significant progress (all P-values <0.001). A rate of 78% of the patients reported amelioration of their health condition at long-term follow-up. Altogether, the investigators see a potential benefit of physical rehabilitation for patients with chronic functional limitations and advocate further research.

1. Nopp S, et al. PB2457, ISTH Virtual Congress 2020, 12-14 July.
2. Nopp S, et al. J Clin Med. 2020;9(6):1811.

Guidelines adherence reduces bleeding risk after surgery and childbirth for VWD patients

A retrospective, single-centre cohort study following 30 patients with Von Willebrand Disease (VWD) who underwent major surgery or childbirth revealed that adherence to current guidelines can reduce the risk of major bleeding events to an acceptable range [1].

Patients with VWD, the most common heritable bleeding disorder, are at increased bleeding risk from invasive procedures. To prevent complications, prophylactic treatment is often administered and recommended in current guidelines. For patients undergoing major surgery, several factor replacement options exist. The current study assessed how closely real-world practice in large centres is aligned with national guidelines and how the recommendations influence post-operative bleeding and/or thrombosis.

The analysis included 30 VWD patients who underwent major surgery or childbirth (both vaginal delivery or caesarean section) and received factor replacement. Patients were eligible to receive any available factor replacement concentrate. The timing of dosing of the factor concentrates relative to the previous dose was collected, as well as the duration of factor replacement. Surgical complications (i.e. bleeding or thrombotic complications) were recorded.

Over a 13-year period, 30 participants underwent 41 major operations or childbirths. The majority of the patients undergoing major surgery achieved 100 IU/dL at the time of surgery, the level recommended by the UK guideline [2]; all patients maintained levels over 50 IU/dL for the first 7 days following the surgery, but not all patients achieved target Von Willebrand factor ristocetin cofactor (VWF:RCo) level consistently for 7 days following the surgery.

The patients undergoing childbirth received the first dose of factor replacement at the beginning of labour. Of the patients who gave birth, 98% were at or above target levels for factor VIII and VWF:RCo. No patient with type 3 VWD underwent childbirth during the study period.

Only 2 patients developed bleeding complications, 1 of them major with a bleeding rate of 2.4%. Over the study period, no episode of thrombosis was observed, which was unexpected because many patients achieved supra-physiologically factor VIII levels particularly in the first 5 days post-procedure.

The authors concluded that by close adherence to national guidelines for factor VIII and VWF:RCo replacement in VWD patients undergoing major surgery or delivery, the risk of major bleeding can be reduced to an acceptable level of 2.4%. However, even within a tertiary referral centre, adherence to guidelines showed to be suboptimal. In the future, levels between certain values should be maintained (not just above a certain level) to try to minimise the risk of thrombosis. Continuous dosing, greater knowledge of the pharmacokinetics of the factor replacements between different VWD patients, and the advent of new therapeutic options, e.g. recombinant VWF, would be suitable to reach this goal.

1 Craven B et al. PB1591, ISTH 2020 Virtual Congress, 12-14 July.
2 Laffan MA et al. Br J Haematol 2014;167:453-465.

Factor V Leiden mutation linked to atrial fibrillation

A novel cohort analysis from the Tromsø Study found that specifically men with factor V Leiden (FVL) mutation have an elevated risk for atrial fibrillation. However, FVL mutation was not identified as a general risk factor for ischaemic stroke [1].

Atrial fibrillation is an established prothrombotic disease that may lead to ischaemic stroke. The FVL mutation is known to be a risk for venous thromboembolism and is also connected with arterial disease and unfavourable outcomes of pregnancies in carriers. The aim of this sub-analysis, presented by PhD student Erin Mathiesen Hald (UiT The Arctic University of Norway, Norway), was to evaluate a possible association of FVL with atrial fibrillation and successive ischaemic stroke.

This analysis included data form a randomly selected sub-cohort of 3,663 subjects from the fourth survey of general population within the Tromsø Study (1994/1995). Blood samples from all participants were analysed for FVL genotype, and cases of atrial fibrillation and ischaemic stroke were determined until 31 December 2012. The risks for atrial fibrillation and ischaemic stroke in patients with FVL mutation were evaluated by calculation of hazard ratios (HR) using Cox proportional hazard regression models.

Among the study subjects, 545 had a diagnosis of atrial fibrillation and 314 suffered an ischaemic stroke. Of the participants, 235 (6.4%) were carriers of ≥ 1 risk allele in FVL. The regression identified an overall 1.4-fold higher risk of atrial fibrillation for study participants who carried an FVL mutation. Interestingly, only men but not women with FVL mutation had a 50% elevated relative risk for atrial fibrillation. Yet, their risk for ischaemic stroke was not significantly raised. Although the hazard of sustaining a stroke was enhanced in people who developed atrial fibrillation (HR 3.22), FVL mutation did not contribute to this risk.

1 Hald EM, et al. PB2052, ISTH Virtual Congress 2020, 12-14 July.

Increased rates of arterial thromboembolism in cancer patients

An observational investigation of Danish registry data showed an increased risk of arterial thromboembolism (ATE) for cancer patients when compared with the general population, especially for older cancer patients.

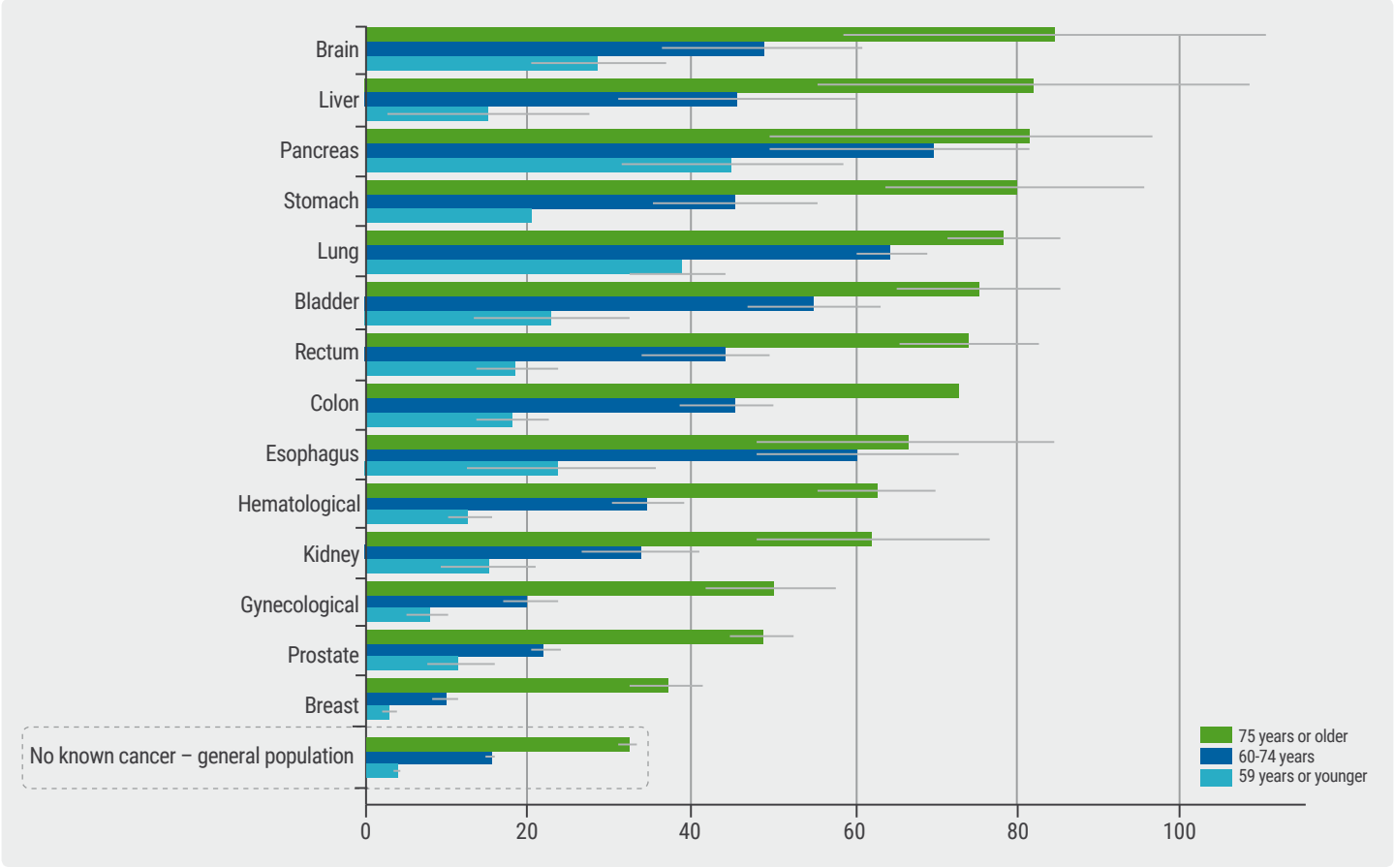
Although the association of cancer and venous thromboembolism is well known, little data is available on the occurrence of ATE in patients with malignant tumours [1]. Thus, Dr Frits Mulder (Amsterdam UMC, University of Amsterdam, the Netherlands) and colleagues set out to evaluate the risk of ATE in cancer patients versus the general population.

The analysis included registry data from a cohort of 458,462 adult patients with a first-time cancer diagnosis between 1997 and 2017 and 1,375,386 participants from the general population matched by sex and age Median age was 69 years for both groups. Primary outcome was the assessment of ATE consisting of a composite of myocardial infarction, stroke (i.e. ischaemic or unspecified), and peripheral artery occlusion. At 6 and 12 months of the study, cumulative incidences were calculated per 1,000 person-years and cause-specific hazard ratios for ATE were assessed between groups by using a Cox regression model.

At 6 and 12 months, the cumulative incidences of ATE were 1.50% and 2.11% in the cancer patient group, while ATE was found in 0.76% and 1.48% of the general population cohort, respectively. Hazard ratios were 2.36 (6 months) and 1.87 (12 months). There were substantial risk differences depending on age and type of cancer, with higher incidences of ATE in patients over 75 years with e.g. brain, pancreas, stomach, lung, and bladder cancers and lower incidences in patients under 65 with breast, prostate, and gynaecological cancers (see Figure).

1. Mulder F, et al. PB2127, ISTH Virtual Congress 2020, 12-14 July.

Figure: ATE incidence rate for each cancer type during the first 6 months after cancer diagnosis [1]



Per 1,000 person-years with 95% confidence interval.

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- Thrombotic Complications: SARS-COV-2 versus Influenza
- Safety and Efficacy of rFVIIIFc in Untreated Patients with Haemophilia
- Outpatient Pulmonary Rehabilitation post-Pulmonary Embolism
- ALK Rearrangement is a Major Risk Factor for Venous and Arterial Thrombosis in Non-Small Cell Lung Cancer
- DOAC bleeding events: atrial fibrillation vs venous thromboembolism
- Pregnancy and DOACs

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