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International abstracts

- Apixaban and dalteparin in active malignancy-associated venous thromboembolism: the ADAM VTE trial

  McBane RD 2nd., Wysokinski WE, Le-Rademacher JG, Zemla T, Ashrani A, Tafur A, et al. J Thromb Haemost 2020;18:411–21

Venous thromboembolism (VTE) is associated with substantial morbidity and mortality in patients with cancer. Anticoagulant management is challenging for these patients because of an increased propensity for thrombosis recurrence and anticoagulant-associated major bleeding. Two contemporary trials (HOKUSAI and SELECT-D) have compared direct oral anticoagulants, edoxaban, and rivaroxaban, with LMWH. A systematic review and meta-analysis [1] of literature data comparing DOACs versus low molecular weight heparin in this high-risk population, highlighted that DOAC treatment was associated with lower risk of 6-month recurrence of VTE but with a higher risk of major bleeding.

The current trial (ADAM VTE) is a multicenter, randomized, open-label superiority trial, designed to test the hypothesis that apixaban is associated with a significantly lower rate of major bleeding, compared to dalteparin, for acute VTE treatment in patients with active cancer. Patients were randomized at a 1:1 ratio to receive either apixaban or dalteparin. Patients randomized to apixaban received 10 mg twice daily for seven days followed by 5 mg twice daily. Those assigned to dalteparin received weight-based subcutaneous therapy at 200 IU/kg once daily for the first month followed by 150 IU/kg for months 2 through 6. Each month, patients were evaluated for body weight, platelet count, and creatinine clearance given the impact of these variables on anticoagulant management.

The primary safety endpoint included any episode of major bleeding. Major bleeding was defined as overt bleeding plus a hemoglobin decrease of ≥ 2 g/dL; or transfusion of ≥ 2 units of packed red blood cells; or intracranial, intraspinal/epidural, intracardial, retroperitoneal, periarticular, intramuscular with compartment syndrome, or fatal bleeding. Clinically relevant non-major bleeding (CRNMB) was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, an unscheduled contact with the health care team, or temporary anticoagulant cessation. The secondary safety endpoint included a composite of major bleeding and CRNMB. The secondary efficacy endpoint was any thromboembolic recurrence including DVT, pulmonary embolism (PE), fatal PE, or arterial thromboembolism.

The study was designed as a superiority trial with 80% power at a one-sided type I error rate of 0.05 to detect a difference in major bleed rate, assuming a six-month cumulative incidence of 6% in the dalteparin arm and 1.4% in the apixaban arm. On the basis of these assumptions, a sample size of 300 patients (150 per arm) was required.

The primary outcome of major bleeding up to six months occurred in 0 of 145 patients (0%) assigned to apixaban and 2 of 142 patients (1.4%) assigned to dalteparin (P = 0.138; HR and 95% CI not estimable because of no bleeding event in the apixaban arm). Recurrent VTE occurred in one patient (0.7%) in the apixaban group and nine (6.3%) in the dalteparin group (HR: 0.099, 95% CI: 0.013–0.780, P = 0.0281). For the secondary composite bleeding endpoint (major or CRNMB), nine (6%) patients in each arm had an event (HR: 0.931, 95% CI: 0.43–2.02, P = 0.88). More patients randomized to dalteparin stopped therapy compared to the apixaban arm (22 vs. 6; P = 0.0012). Negative impact on overall quality of life was significantly higher for dalteparin patient group. As such, providing an oral alternative to parenteral therapy has the potential to improve compliance and outcomes.

The principal limitations of ADAM VTE study were that the trial was not powered to determine survival differences, the sample was relatively small with 6% patient loss (16/300) to

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follow-up, and the predefined primary outcome could not be analyzed because of the lower-than-anticipated major bleeding rates for both treatment arms. Results from the randomized open-label CARAVAGGIO trial, which has a similar design yet larger patient sample (1155 patients), have been recently published [2]. Among cancer patients with proximal deep vein thrombosis or pulmonary embolism, this trial highlighted that apixaban was noninferior compared with subcutaneous dalteparin on prevention of recurrent venous thromboembolism. There was no increase in major bleeding (gastrointestinal or nongastrointestinal).

These trial results add support to the hypothesis that direct oral anticoagulants provide a safe and effective alternative to LMWH for cancer patients with acute VTE [3].

Clinical characteristics (metastatic disease at presentation, concurrent chemotherapy, pulmonary embolism at presentation) and tumor type (in particular gastrointestinal and genitourinary malignancies which are associated with a high-risk of bleeding) need be taken into account during multidisciplinary discussion for the appropriate treatment option.

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■ Preeclampsia and cardiovascular disease in a large UK pregnancy cohort of linked electronic health records: a caliber study
Leon LJ, McCarthy FP, Direk K, Gonzalez-Izquierdo A, Prieto-Merino D, Casas JP, et al. Circulation 2019;140:1050—60

Preeclampsia is a common disease responsible for around 14% of maternal deaths and a major cause of perinatal morbidity and mortality. It affects 2—8% of pregnancies worldwide and is defined as hypertension onset and proteinuria in the second half of pregnancy. Yet, the associations between hypertensive disorders during pregnancy and common cardiovascular disorders have not been investigated in a large-scale population.

The present study was designed as a population-based cohort study investigating the association between preeclampsia, hypertensive disorders of pregnancy (HDP) and subsequent diagnosis of 12 different cardiovascular disorders in addition to chronic hypertension.

The authors recreated a UK population-based cohort using the electronic health records from 1997 to 2016. A preeclampsia file was retained if a related ICD10 code was found. Data from the pregnancy register were retained if they were considered complete (> 20 weeks’ gestation), occurred between January 1, 1997 and December 31, 2016, and were between 11 to 49 years old at each estimated pregnancy end date. Cardiovascular disorders selected as outcomes were stroke, intracerebral hemorrhage, subarachnoid hemorrhage, myocardial infarction, stable angina, unstable angina, coronary heart disease, peripheral arterial disease, abdominal aortic aneurysm, atrial fibrillation, and heart failure.

The study cohort included 1,899,150 unique pregnancies from 1,303,365 women. A total of 434,955 (33.37%) women had more than 1 pregnancy during the follow-up period. A total of 31,478 (2.42%) women had 33,344 preeclamptic pregnancies, of which 25,554 (76.64%) occurred in the first pregnancy, 5,811 (17.43%) in the second, and 1,797 (5.93%) in the third or later pregnancy. Compared to women without a history of preeclampsia, women having at least one preeclamptic event had a higher hazard ratio (HR) for all 12 cardiovascular events (HR: 1.69; 95% CI: 1.57—1.81), cardiovascular mortality (HR: 2.12; 95% CI: 1.49—2.99) and chronic hypertension (HR: 4.47; 95% CI: 4.32—4.62), except for intracerebral hemorrhage and abdominal aortic aneurysm. The magnitude of the associations of preeclampsia with specific cardiovascular disorders was homogenous, with a similar pattern observed for HDP and a slightly further raised risk for preterm preeclampsia (delivery before 37 weeks gestation). Differences in cumulative incidence curves were apparent within one year of the first index pregnancy. Preeclampsia and HDP almost double the risk of a subsequent cardiovascular event and preterm preeclampsia leads to an even higher risk after a median follow-up of 9.25 years.

The present study adds evidence to the available recommendations from the American Heart Association and the European Society of Cardiology, which focused mainly on preeclampsia as a screening tool for cardiovascular risk. This study is the largest contemporaneous population-based cohort study reporting for the first time the association between preeclampsia, HDP, and preterm preeclampsia with sub-types of stroke, peripheral vascular disease, and atrial fibrillation, and also confirming the association with heart failure and coronary heart disease. A potential explanation of this association is that HDP and cardiovascular disorders share risk factors such as hypertension and obesity.

The present results strongly suggest that HDP should be considered as a natural screening tool for premature cardiovascular events. Therefore, the age for cardiovascular screening, and particularly for hypertension, needs to be reduced for women with a history of hypertensive disorders during pregnancy.

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■ Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy
Lodigiani C, Iapichino G, Carenzo L, Cecconi M, Ferrazzi P, Sebastian T, et al. Thromb Res 2020;191:9—14

Very early in the COVID-19 epidemic, the elevation of coagulation markers accompanying the cytokine storm was one of the concerns of medical teams confronted with non-exceptional venous and arterial thromboembolic (TE) complications and sometimes lethal. The authors of this Italian retrospective study aimed to describe and characterize venous and arterial thrombotic events in a population of patients with confirmed COVID-19, hospitalized in a university hospital in Milan.

The main objective, composite, included pulmonary embolism (PE) and deep venous thrombosis (DVT) confirmed in imaging, and
cardiovascular events [acute coronary syndrome (ACS)/myocardial infarction (MI), ischemic stroke], as reported in medical records. During the period considered for this analysis, no screening strategy for venous thromboembolic disease (VTE) in COVID-19 patients was in place. The diagnosis was sought after symptoms of DVT, an unexplained clinical worsening of respiratory function, or a rapid increase in D-dimer levels. The secondary endpoint was disseminated intravascular coagulation (DIC).

The data extracted concerned 388 files of consecutive patients of average age 66 years, hospitalized between February 13, 2020 and April 13, 2020, of which 68% were men. Screening tests were performed before or within 24 hours of admission in 97% of the cases. At the time of the study, 26 patients were still hospitalized. Slightly more than a quarter (26%) of patients died in hospital and 16% had to go through an intensive care unit (ICU). These patients received prophylaxis for VTE as well as 75% of patients admitted to medical services.

TE events occurred in 7.7% of discharged or dead patients, which corresponds to a cumulative rate of 21%, calculated by including patients still hospitalized at the time of the analysis. This cumulative rate was 27.6% for patients in the ICU and 6.6% for patients who remained in non-intensive care. Regarding VTE, only 44 patients had an imaging test, 16 of them were positive; PE was diagnosed in almost 2/3 of them (63%). Half of them were diagnosed within 24 hours of admission. The respective AIC and SCA/IDM rates were 2.5% and 1.1%. Eight patients (2.1%) had biological criteria for DIVC.

This study reinforces the observation that TE complications are an integral part of the COVID-19 picture and that they can be present at an early stage. The rate of VTE events is close to 8%, which is high despite the wide use of prophylaxis. However, it is probably still underestimated in particular due to the selection of patients benefiting from "active" research for TE complications. In view of the higher entry rates and the rapid increase in D-dimer rates during the 1st week of hospitalization in patients who died, this research should be widened to the greatest number. In addition, the diagnosis was made within 24 hours of admission in half of the cases, a large number of events could not be prevented by prophylaxis in hospital. This raises the question of prophylaxis in ambulatory patients from the early phase of COVID-19, an idea reinforced by the anti-inflammatory benefit of LMWHs suggested in other studies.

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