

Cardiology

REVIEW®

VENOUS THROMBOEMBOLISM



Researchers Explore Venous Thromboembolism Rates in COVID-19 Patients

KENNY WALTER

SINCE THE BEGINNING OF THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC, venous thromboembolism (VTE) has been observed in infected patients. However, the reported rates of VTE in these patients has differed substantially.

A team, led by Stephan Nopp, MD, Clinical Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna, evaluated available data to estimate the prevalence of VTE in COVID-19 patients.

The investigators conducted a systematic literature search, finding 86 studies reporting VTE rates in 33,970 COVID-19 patients. Ultimately, the investigators excluded studies suspected to have a high risk of bias.

Overall, they included 66 studies with 28,173 patients in the final analysis. The mean age of the patient population was 62.6 years old, while 60% of the study was male and 20% of the patients were admitted to the intensive care unit (ICU).

The research team obtained pooled outcome rates within a random effects meta-analysis and performed subgroup analyses for different settings, including comparing intensive care unit (ICU) patients with non-ICU hospitalizations and screenings compared to no screenings. They also explored the association of D-dimer levels and VTE-risk. »

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COVID-19 Lockdown Linked to Decline in Acute Myocardial Infarction Hospitalizations

JONATHAN ALICEA

NEW DATA ANALYSIS OF THE ongoing French Cohort of Myocardial Infarction Evaluation (FRENCHIE) registry reveals a decline in hospital admission for acute myocardial infarction following the coronavirus disease 2019 (COVID-19) lockdown.

Although the reasons for such findings can only be speculative, the investigators noted that this marked decrease should encourage public health officials to provide appropriate messages that especially target those that are wary of utilizing health services during the pandemic.

Jules Mesnier, MD, of the University of Paris, and colleagues used registry data to quantify changes in myocardial infarction-related hospital admissions following the lockdown in France. Their assessment also compared admission changes between patients with ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI).

The FRENCHIE registry, which includes 21 participating centers, captures within 48 hours of symptom onset patients who present with either STEMI or NSTEMI. Therefore, Mesnier and colleagues used this timeframe to define recent acute myocardial infarction.

The investigators collected data over an 8-week period, which covered 4 weeks preceding lockdown and 4 weeks

following it.

Patients admitted to the hospital due to COVID-19 who had subsequently developed myocardial infarction were excluded in their analysis. On the contrary, patients admitted for myocardial infarction who were then diagnosed with COVID-19 were included.

The primary outcome sought by the investigators was change in number of hospital admissions for all types of myocardial infarction, NSTEMI, and STEMI between the weeks preceding and following lockdown.

Additional objectives included further subgroup analyses of admission change and overall change in mortality between both periods.

Thus, the team reported that between February 17 and April 12, 2020, a total of 1167 patients were consecutively admitted to the hospital for recent acute myocardial infarction. Of the total, 583 had STEMI and 584 had NSTEMI.

Overall admission decreased from 686 to 481 between the periods (-30% [incidence rate ratio, 0.69; 95% CI, 0.51-0.70]).

Furthermore, admissions for STEMI decreased from 331 to 252 (-24% [IRR, 0.72; 95% CI, 0.62-0.85]), and admissions for NSTEMI decreased from 355 to 229 (-35% [IRR, 0.64; 95% CI, 0.55-0.76]).

“Meanwhile, health authorities should be fully aware of the current situation in order to deliver appropriate public health messages...”

Patients who were ≥ 80 years ($n = 208$) had a more noticeable decline than those who were younger (IRR, 0.64; 95% CI, 0.48-0.86).

They also noted that this decrease in admission had no association with regional COVID-19 prevalence or subgroup characteristics, such as gender, history of diabetes, history of hypertension, and smoking habits.

In-hospital mortality was numerically higher after the lockdown than before it—25 (5%) of 481 patients vs 23 (3%) of 686, respectively. However, the team did not consider it statistically significant.

Such trends, therefore, may likely be attributed to patient fears of exposure to the virus in the hospital.

“These concerns might have been amplified by the general message that people should stay at home.,” they wrote.

Another notable explanation may involve reduced exposure to air pollution, a known trigger of acute myocardial infarction. The investigators did not consider both explanations to be mutually exclusive.

Mesnier and team acknowledged a need to conduct the study with a longer survey period beyond the first month and after the end of lockdown.

“Meanwhile, health authorities should be fully aware of the current situation in order to deliver appropriate public health messages,” they concluded. “This is crucial in countries still fighting COVID-19, but also in the case of a second wave in countries that are past the first wave of the pandemic, or in case another pandemic occurs in the future.”

The study, “Hospital admissions for acute myocardial infarction before and after lockdown according to regional prevalence of COVID-19 and patient profile in France: a registry study,” was published online in *The Lancet Public Health*. ■

VENOUS THROMBOEMBOLISM

(Venous Thromboembolism Rates, continued from the cover)

The overall VTE-prevalence estimate was 14.1% (95% CI, 11.6-16.9), 40.3% (95% CI, 27.0-54.3) with ultrasound-screening, and 9.5% (95% CI, 7.5-11.7) without screening.

The investigators found in subgroup analysis high heterogeneity, with a VTE-prevalence of 7.9% (95% CI 5.1-11.2) in non-ICU and 22.7% (95% CI 18.1-27.6) in ICU patients. The prevalence of pulmonary embolism in non-ICU patients was 3.5% (95% CI, 2.2-5.1) and 13.7% (95% CI, 10.0-17.9) in ICU patients.

Patients developing VTE had higher D-dimer levels (weighted mean difference 3.26 $\mu\text{g/ml}$; 95% CI, 2.76-3.77) than non-VTE patients.

“VTE occurs in 22.7% of patients with COVID-19 in the ICU, but VTE risk is also increased in non-ICU hospitalized patients,” the authors wrote. “Patients developing VTE had higher D-dimer levels. Studies evaluating thromboprophylaxis strategies in patients with COVID-19 are needed to improve prevention of VTE.”

Recently, investigators noted a low rate of post-discharge VTE following a COVID-19 hospital stay.

The findings suggested empiric post-discharge thromboprophylaxis is not necessary, supporting the American College of Chest Physicians recommendation of not offering it.

Lara Roberts, MBBS, MD, MRCP, FRCPath, and colleagues reported the rates of post-discharge VTE and compared the rates with those following medical admission in the pre-COVID era. The team considered hospital-associated VTE as any VTE diagnosed during or following a medical admission of more than 48 hours or postoperatively and occurring up to 90 days of discharge.

There were 2863 COVID-19 admission and 84 hospital-associated VTE episodes. Of the episodes, 11% occurred post-discharge at a median of 8 days (range, 3-33 days). The proportion of patients who developed hospital-associated VTE was 4.8 per 1000 discharges (within 42 days of discharge).

Overall incidence in the COVID-19 and 2019 medical admissions cohorts was lower than the rate of symptomatic VTE reported in the placebo arm of previous studies investigating extending thromboprophylaxis post-medical admission (1.2% to 1.7%).

The study, “Risk of venous thromboembolism in patients with COVID-19: A systematic review and meta-analysis,” was published online in *Research and Practice in Thrombosis and Haemostasis*. ■



Study Finds Concerning Lack of Influenza Vaccination Among ASCVD Patients

JONATHAN ALICEA

WITH THE ONSET OF INFLUENZA SEASON, patients with morbidities, such as atherosclerotic cardiovascular disease (ASCVD), face an increased risk of mortality, severity of infection, and hospital readmissions. Influenza vaccinations, however, have been shown to reduce such risks in these types of patients.

New survey data collected from 2008-2016 reveals that nearly 1/3 of adults with ASCVD did not get vaccinated for influenza. Furthermore, this lack of vaccination is higher among vulnerable sociodemographic groups.

The study, which was led by Gowtham Grandhi, MD, MPH, of MedStar Union Memorial Hospital in Maryland, assessed the prevalence of adults with ASCVD who lacked the influenza vaccination during the past year. The investigators were also interested in analyzing the characteristics of this subpopulation, such as race/ethnicity, family income, insurance status, education level, and usual source of care.

To do this, they used data from the Pooled Medical Expenditure Panel Survey (MEPS) from which they included ASCVD adults ≥ 40 years.

The population's ASCVD status was acquired through self-reporting and/or *International Classification of Diseases, Ninth Revision* diagnosis of coronary heart

While previous studies have shown significant disparities in influenza vaccination access and uptake, this is the first study to our knowledge that has assessed the prevalence of and socio-demographic disparities in vaccination among a nationally representative sample of adults with ASCVD,

disease, peripheral heart disease, and/or cerebrovascular disease.

Furthermore, vaccination status was ascertained through self-reporting. An individual was considered having received vaccination if they had done so within 12 months

prior to completing the survey.

All data was analyzed starting on April 2020.

Of all 131,881 adults assessed from the pooled data, 19,793 (15.7%) had ASCVD. The investigators noted this proportion corresponds to 22.8 million US adults annually.

As many as 7028 (32.7%) of the ASCVD population reported not having received their influenza vaccination within the past year, which represents 7.4 million adults.

This lack was significantly higher among adults aged 40-64 years (46.4% [OR, 2.32; 95% CI, 2.06-2.62]) as well as non-Hispanic Black (40.8% [OR, 1.24; 95% CI, 1.10-1.41]), and Hispanic (39.9% [OR, 1.03; 95% CI, 0.88-1.22]) individuals.

Proportions were also higher among those without a usual source of care (56.6% [OR, 2.00; 95% CI, 1.71-2.33]), uninsured individuals (64.9% [OR, 2.05; 95% CI, 1.63-2.58]), those of lower family income levels (35.1% [OR, 1.14; 95% CI, 1.01-1.27]), and those with a lower level of completed education (34.4% [OR, 1.25; 95% CI, 1.12-1.40]).

The investigators considered these subpopulations to be

high-risk characteristics.

Further, among adults with ≥ 4 high-risk characteristics, 1171 (59.7% [OR, 6.06; 95% CI, 4.88-7.53]) were not vaccinated—compared with only 503 (18.9%) in those with 0 characteristics.

“While previous studies have shown significant disparities in influenza vaccination access and uptake, this is the first study to our knowledge that has assessed the prevalence of and socio- demographic disparities in vaccination among a nationally representative sample of adults with ASCVD,” the investigators noted.

Furthermore, they expressed concern over how these findings interplay with the recent emergence of coronavirus disease 2019 (COVID-19). Thus, Grandhi and colleagues stressed the importance of enhancing and making more accessible influenza vaccinations in at-risk patients with ASCVD.

The study, “Sociodemographic Disparities in Influenza Vaccination Among Adults With Atherosclerotic Cardiovascular Disease in the United States,” was published online in *JAMA Cardiology*. ■

CARDIOVASCULAR

Ustekinumab Associated with Increased Risk of Serious Cardiovascular Events

SAMARA ROSENFELD

THE INITIATION OF USTEKINUMAB TREATMENT IS ASSOCIATED WITH an increased risk of acute coronary syndrome or stroke in patients with a high baseline cardiovascular risk, according to the findings of a recent study.

The results suggested ustekinumab should be prescribed with caution to patients at high cardiovascular risk.

Florence Poizeau, MD, and colleagues assessed whether the initiation of ustekinumab treatment was associated with an increased risk of severe cardiovascular events. They conducted the study using the French national health insurance database which covered 98% of the population living in France and included sociodemographic data and exhaustive data on all reimbursements for health-related expenditures, dispensed drugs with date of issue, any investigation, and hospitalization discharge codes. The team extracted data on all the individuals who had at least 1 reimbursement for ustekinumab between April 1, 2010 and December 31, 2016.

Poizeau and the investigators defined severe

cardiovascular events as either acute coronary syndrome with hospitalization in the intensive care unit or ischemic stroke with hospitalization in any department, identified using the hospitalization discharge codes. Drug exposure was defined as the initiation of treatment with ustekinumab.

Overall, 98 patients who experienced severe cardiovascular events and were included in the main analysis. A majority of the patients were men (63%) with a median age of 57 years old and 78% were at high cardiovascular risk. Most patients (91%) had psoriasis, while 4% had Crohn disease and 2% had both.

Across the study population, the OR for the case-time control analysis was 2.41 (95% CI, .83-7.01). Among those at high cardiovascular risk, there was a significantly increased risk of a serious cardiovascular event in the first 6 months after ustekinumab initiation (OR, 4.17; 95% CI, 1.19-14.59). The risk was not observed among patients at low cardiovascular risk (OR, .3; 95% CI, .03-3.13). »

INFLUENZA VACCINATION

(continued)

The investigators conducted 2 sensitivity analyses. In the first, the team widened the definition of triggering circumstances by adding reinitiation and dose increase. The OR for a serious cardiovascular event was 3.41 (95% CI, 1.15-10.15). For those at high cardiovascular risk, the OR was 4.62 (95% CI, 1.36-15.61), while among low cardiovascular risk patients, the OR was 1 (95% CI, .08-12.56).

The second sensitivity analysis expanded the definition of serious cardiovascular events. The team added patients with unstable angina and those hospitalized in non-ICU wards with acute coronary syndrome. The OR for a serious cardiovascular event was 1.75 (95% CI, .86-3.56). Among patients with high cardiovascular risk, the OR was 3.2 (95% CI, 1.29-7.92). For low cardiovascular risk patients, the OR was .21 (95% CI, .02-1.69).

Based on the findings, the investigators noted a close collaboration between cardiologists and biologic prescribers could be beneficial to evaluate the risk of serious cardiovascular events for patients who receive ustekinumab.

The study, "Association Between Early Severe Cardiovascular Events and the Initiation of Treatment With the Anti-Interleukin 12/23p40 Antibody Ustekinumab," was published online on *JAMA Dermatology*. ■

CHRONIC KIDNEY DISEASE

No Cardiovascular Benefit from Phosphate Binders in Chronic Kidney Disease Patients

KENNY WALTER

THERE MIGHT NOT BE A CARDIOVASCULAR BENEFIT FOR CHRONIC KIDNEY DISEASE (CKD) patients prescribed phosphate binders, according to new research.

An international team, led by Nigel D. Toussaint, MBBS, FRACP, PhD, Department of Nephrology, The Royal Melbourne Hospital, assessed the effects of non-calcium-based phosphate binders on intermediate cardiovascular markers in patients suffering from chronic kidney disease.

For patients with chronic kidney disease, higher serum phosphate levels is linked to increased fibroblast growth factor 23 (FGF23) levels, arterial calcification, and cardiovascular mortality. However, there has only been limited trial assessing phosphate-lowering therapies, with only modest efficacy in lowering serum phosphate and FGF23 found during short-term follow-up with patients.

While phosphate binders like lanthanum have been prescribed to help reduce the risk of bone and cardiovascular disease, the effect of these agents on cardiovascular markers is uncertain.

In the multicenter, double-blind, randomized trial, the investigators examined 278 patients with stage 3b or 4 chronic kidney disease and serum phosphate greater than 1.00 mmol/L (3.10 mg/dl). Each patient received either 500 mg of lanthanum carbonate (n = 138) or a matched placebo (n = 140) 3 times daily for 96 weeks.

The mean age of the study was 63.1 years old and the patient population was 69% male. The mean estimated glomerular filtration rate (eGFR) of 26.6 ml/min per 1.73 m² and 45% and 32% of participants had diabetes and cardiovascular disease, respectively.

The mean serum phosphate was 1.25 mmol/L (3.87 mg/dl), the mean pulse wave velocity was 10.8 m/s, and 81.3% of the study population had abdominal aortic calcification at baseline.

The investigators sought a primary outcome of carotid-femoral pulse wave velocity,



which was analyzed using a linear mixed effects model for repeated measures. They also sought secondary outcomes of abdominal aortic calcification and serum and urine markers of mineral metabolism.

After 96 weeks, the investigators found pulse wave velocity did not significantly differ between the treatment and placebo group. Abdominal aortic calcification, serum phosphate, parathyroid hormone, FGF23, and 24-hour urinary phosphate also did not differ between the treatment group and placebo group at 96 weeks.

Serious adverse events also occurred in 63 (46%) of patients in the lanthanum group and 66 (47%) individuals in the placebo group.

While the recruitment to target was not achieved,

additional analysis suggested this was unlikely to have significantly affected the principle findings.

“In patients with stage 3b/4 CKD, treatment with lanthanum over 96 weeks did not affect arterial stiffness or aortic calcification compared with placebo,” the authors wrote. “These findings do not support the role of intestinal phosphate binders to reduce cardiovascular risk in patients with CKD who have normophosphatemia.”

The study represents the largest trial to look at the impact of lanthanum carbonate in patients with chronic kidney disease.

The study, “A Randomized Trial on the Effect of Phosphate Reduction on Vascular End Points in CKD (IMPROVE-CKD),” was published online in the *Journal of the American Society of Nephrology*. ■

SLEEP APNEA

Empagliflozin Improves CV Outcomes in Patients with Obstructive Sleep Apnea

JONATHAN ALICEA

PATIENTS WITH OBSTRUCTIVE SLEEP APNEA (OSA) who were treated with empagliflozin demonstrated similar improvements in cardiovascular (CV), hospitalization from heart failure, and mortality outcomes in comparison with non-OSA patients with CV disease and type 2 diabetes, according to data presented at the European Society of Cardiology (ESC 2020) Congress.

A post-hoc exploratory analysis of the EMPA-REG OUTCOME trial led by Henry Yaggi, MD, MPH, Associate Professor of Medicine at Yale School of Medicine, compared the incidence rates of various CV events in patients with and without OSA. Furthermore, they assessed the treatment effect of empagliflozin.

The EMPA-REG OUTCOME trial was a randomized placebo-controlled trial that included 7020 patients from 42 countries with type 2 diabetes, cardiovascular disease, and an estimated glomerular filtration rate of >30 mL/min/1.73 m².

The investigators then randomized patients 1:1:1 to receive 10 mg of empagliflozin, 25 mg of empagliflozin, or placebo once daily—in addition to their standard of care.

The findings from the study showed that the SGLT-2 inhibitor reduced HbA1C, systolic blood pressure (SBP), and waist circumference and weight in patients. Furthermore, it had reduced the risk of 3-point major adverse CV events by 14%, CV death by 38%, and hospitalization due to failure by 35%.

For their analysis, Yaggi and team assessed OSA »

based on investigator reports using MedDRA 18.0. They used adjusted event-rates per 100 patient-years to report incidence rates for outcomes.

Cox regression models were then performed to analyze the effects.

They then found that OSA occurred in 391 patients (5.6% [placebo, 5.4% and empagliflozin, 5.7%]).

The OSA population had a higher frequency of males than the non-OSA population (82.9% vs 70.8%), had a greater prevalence of obesity (BMI ≥ 35 kg/m²: 55.2% vs 18.2%), and more coronary artery disease (88.0 vs 74.9%).

They also discovered that over a median of 3.1 years, OSA patients at baseline experienced 1.3-2.0 fold higher event rates for 3-point major adverse CV events—when compared with non-OSA patients in the placebo group.

Additionally, those with OSA at baseline had almost double the event rates of CV death and all-cause mortality versus the placebo group.

The team, however, reported these outcomes were reduced by empagliflozin regardless of the presence of OSA at baseline.

“In this post-hoc exploratory analysis, patients with OSA had higher frequency of events for 3P-MACE, HHF and mortality,” they concluded. “The cardio-protective effects of empagliflozin was consistent in those with and without OSA at baseline.”

The study, “Obstructive sleep apnoe and cardiovascular, heart failure and mortality outcomes with empagliflozin versus placebo in the EMPA-REG OUTCOME trial,” was presented at ESC 2020.

Investigators Discover Link Between Influenza Epidemics and Acute Cardiovascular Events

KENNY WALTER

WHILE IT IS WELL KNOWN THAT INFLUENZA could contribute to acute cardiovascular events during annual influenza epidemics, the actual burden of this association is not entirely known.

A team, led by Eric J. Chow, MD, US Centers for Disease Control and Prevention, examined acute cardiovascular events and determined the different risk factors for acute heart failure (aHF) and acute ischemic heart disease (aIHD) in adults with a hospitalization linked with laboratory-confirmed influenza.

In the cross-sectional study, the investigators examined data from the US Influenza Hospitalization Surveillance Network during the 2010-2011 through the 2017-2018 influenza seasons. The study population included 89,999 adults hospitalized with laboratory-confirmed influenza, which were identified through influenza testing ordered by a practitioner.

The researchers ascertained acute cardiovascular events using discharge codes from the International Classification of Diseases (ICD), Ninth Revision, Clinical Modification, and ICD, 10th Revision.

The investigators included age, sex, race/ethnicity, tobacco use, chronic conditions, influenza vaccination, influenza antiviral medication, and influenza type or subtype as exposures in logistic regression models.

The team also estimated marginal adjusted risk ratios and 95% confidence intervals to describe the factors associated with aHF or aIHD.

Among the nearly 90,000 adult patients, 80,261 had complete medical record abstractions and available ICD codes. The median age of this group was 69 years old and 11.7% of the study had suffered from an acute cardiovascular event.

The most common of these events were aHF (6.2%) and aIHD (5.7%). The investigators also found older age, tobacco use, underlying cardiovascular disease, diabetes, and renal disease were significantly associated with higher risk for the 2 heart disorders in adults hospitalized with laboratory-confirmed influenza.

The investigators did admit to some study limitations, mainly the under detection of cases was likely due to

influenza testing based only on practitioner orders. In addition, because acute cardiovascular events were identified by ICD discharge codes, they may be subject to misclassification bias.

Earlier this year, investigators found the influenza virus infections could be linked to respiratory and non-respiratory diagnoses, highlighting the broad scope of infection burden.

Chow also led this study, with the same patient population. However, in this study, the investigators abstracted demographic data; chronic medical conditions; clinical course and outcomes; and discharge summary data from each patient's medical record.

Of the patients with an acute diagnosis, 94.9% had ≥ 1 acute respiratory diagnosis and 46.5% had ≥ 1 acute non-respiratory diagnosis—5.1% had only acute non-respiratory diagnoses.

For the nearly 95% of patients with ≥ 1 acute respiratory diagnosis, 43.3% had underlying respiratory comorbidities and 51.3% were current or former tobacco users.

Those with only acute non-respiratory diagnoses had a significantly higher frequency of underlying comorbidities than those with respiratory diagnoses. Comorbidities included neurologic (29.9% vs 24.6%; $P < .001$); cardiovascular (51.2% vs 40%; $P < .001$); metabolic (51.5% vs 42%; $P < .001$); renal (33.3% vs 19.4%; $P < .001$); hepatic (6.5% vs 3.9%; $P < .001$); immunosuppressive (19.4% vs 16.8%; $P < .001$); and hematologic (5.8% vs 4.2%; $P < .001$) diagnoses.

A key takeaway from both studies in contracting influenza increases the risk of negative outcomes.

"In this population-based study of adults hospitalized with influenza, almost 12% of patients had an acute cardiovascular event," the authors wrote. "Clinicians should ensure high rates of influenza vaccination, especially in those with underlying chronic conditions, to protect against acute cardiovascular events associated with influenza."

The study, "Acute Cardiovascular Events Associated With Influenza in Hospitalized Adults," was published online in the *Annals of Internal Medicine*. ■