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Talk of the Town

-A Midtown Journal Club Newsletter

A new COMPASS:

Rivaroxaban for Secondary CV Prophylaxis?

Article by Aleksan Kachatryan (PGY2)

Most patients with a history of coronary artery or peripehral artery disease are prescribed on aspirin for primary prophylaxis. Whether there is a role of long-term anticoagulation, on the other hand, is an evolving area of study.

The **COMPASS** trial (2017) investigated whether adding low-dose rivaroxaban in addition to ASA is beneficial. This was a double-blinded, multicenter, randomized clinical trial that enrolled 27,395 patients with a clinical history of CAD and PAD, with high-risk features such as polyvascular disease (≥2 vascular beds), eGFR ≤60 mL/min, heart failure, and/or diabetes mellitus.

Participants were divered into three groups: Group 1- ASA alone, Group 2- ASA + Rivaroxaban 2.5mg twice daily, or Group 3- Rivaroxaban 5mg twice daily. The primary efficacy outcome was a composite of cardiovascular death, stroke, or MI; the principal safety endpoint was major bleeding according to modified International Society on Thrombosis and Haemostasis (ISTH) criteria.

The ASA + Rivaroxaban group (Group 2) appeared to be the most successful--the primary outcome occurred in fewer patients in the ASA + Rivaroxaban group than in the aspirin-alone group (4.1% vs 5.4%; HR 0.76 [0.66, 0.86]). There was no significant difference in intracranial/fatal bleeding or death between these two groups, but overall major bleeding events occurred in more patients in the

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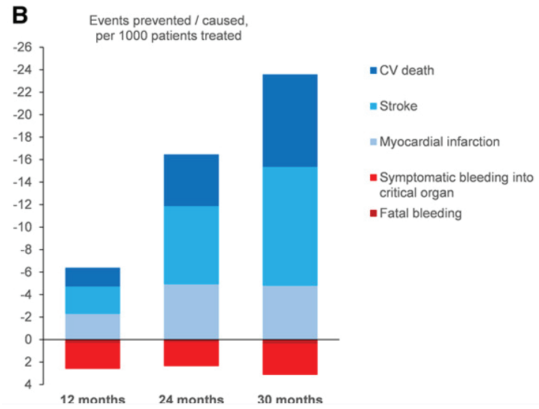
ASA + Rivaroxaban group (3.1% vs 1.9%; HR 1.70 [1.40, 2.05]). The Rivaroxaban group (Group 3) did not fare as well—there was no significant difference in primary safety outcomes but major bleeding events occurred in more patients compared to the ASA-only group.

A question still remains: **does the benefit clearly outweigh the risks?** A later repeat analysis of the data was published recently to look at the Net Clinical Benefit (NCB) of the addition of rivaroxaban to ASA. The NCB is a numerical representation of the benefits minus the risks, which is useful as it gives a single number to represent the usefulness of an intervention. (This is tested on STEP 3!) The authors found that cardiovascular events were more common than bleeding events, to begin with—and a reduction in cardiovascular events ("efficacy outcomes") was much greater than the increase in bleeding events ("risk outcomes"), resulting in an overall improved NCB. High-risk patients also saw the most NCB. In addition, the NCB continued to widen the longer the patients were treated.



Important limitations include exclusion of patients at sufficiently high risk of bleeding, and the benefit of treatment longer than 36 months is still unanswered. In addition, older populations of age≥75 were already shown to have higher rates of bleeding and lower benefit in the original 2017 paper, which the new analysis does not address. There will be some time until anticoagulation is accepted as a part of secondary prophylaxis for ASCVD events.

Second Booster for COVID-19

Article by Harim Kim (PGY3)

The Omicron variant of the SARS-CoV-2 virus caused a worldwide resurgence of COVID-19, especially causing high mortality in older adults. **A recent study in Israel** investigated whether a second booster Pfizer Vaccine can reduce COVID-19 cases and severe complications. The study inclu-ded data from 182,122 age/sex/risk-factor matched pairs subscribing to the Clalit Health Services, which covers more than half of the population of Israel.

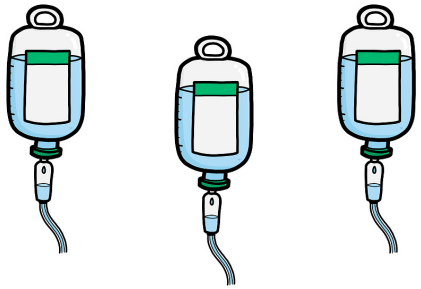
Inclusion criteria were 60 years of age or older and no previous positive SARS-CoV-2 PCR, while health care workers, persons in long-term care facilities, persons confined to the home, and persons who had interacted with the health care system during the previous 3 days were excluded. The median age of the matched pairs was 72 years (interquartile range 67 to 78), and 53% were women, and the two groups had a similar distribution of risk factors for Severe COVID-19.

The main outcomes were assessed over two follow-up periods of interest: days 7 to 30 after the fourth dose and days 14 to 30 after the fourth dose. Results showed that a fourth BNT162b2 dose provided early protection against PCR-confirmed SARS-CoV-2 infection (44-47% between days 7 to 30 and 49-54% between days 14-30), symptomatic Covid-19 (53-58% and 58-64% respectively), Covid-19–related hospitalization (59-74% and 63-79%), severe Covid-19 (50-74% and 48-77%), and Covid-19–related death (50-90% and 48-91%).

However, the study is subject to several limitations--first, the follow-up time available was only one month, and therefore they were not yet able to assess longer-term effects, including possible waning of the effect. Second, as with any observational study, the potential for confounding exists; however, they tried to avoid this confounding factor bv rigorous matching. Overall, a fourth dose of the BNT162b2 vaccine appears to be effective in reducing the short-term risk of Covid-19–related outcomes among persons who had received a third dose at least 4 months earlier.

BATTLE OF FLUIDS:

Plasmalyte vs Normal Saline For DKA



Article by Eliva Yunasan (PGY2)

Diabetic ketoacidosis (DKA) is one of the most commonly encountered emergencies in medical practice. While fluid therapy is a cornerstone of the management of DKA, the choice of fluid therapy is still debated. Many guidelines recommend Normal Saline (NS) 0.9% as the fluid of choice for DKA. It is inexpensive and widely available. Unfortunately, giving a large amount of NaCl can result in hyperchloremia that may lead to non-anion gap metabolic acidosis. Plasma-Lyte (PL) on the other hand, contains lower chloride (98 in PL vs 154mEq/L in NS), but higher acetate (27mEq/L).

The **SCOPE-DKA** trial (2021) investigated whether PL will result in faster resolution of severe DKA and whether PL increases ketone generation compared to NS. A cluster, cross-over, open-label randomized control phase 2 trial, SCOPE -DKA trial was conducted at seven rural and metropolitan Australian ICUs. The study was divided into two 6-month interventions where all each center administered either NS or PL, with one month of washout period in the middle which patients were not recruited into the study. Inclusion criteria were all patients ≥ 16 years old with severe DKA defined as pH ≤ 7.25, blood glucose > 250 mg/dL, and admission to ICU based on physician judgment. Exclusion criteria were age <16 years old, contraindication to fluid administration, suspicion of HHS.

Of 93 patients enrolled, 3 patients were excluded due to missing data, leaving 48 patients in the PL group and 42 patients in the NS group. DKA resolution by the 24 hr mark since ICU admission was significantly different between the two groups: 69% with PL vs 36% with NS. (OR 4.24 [1.68-10.72], p=0.002). By 48 hours, however, most patients in both groups had resolution of DKA without significant difference in rate: 96% vs 86% (OR 3.93 [0.73-21.16], p=0.11). There were no differences in median blood ketones (in mmol/L) in both groups (median 0.3 [interquartile range 0.1-0.5] vs 0.3 [0.1-0.5]). Adverse events such as hypoglycemia, hypophosphatemia, and hypokalemia were also similar between groups.

This study comes with some limitations. As a phase 2 trial, it was not powered enough nor designed for the intentional of finding differences in clinical outcomes and the results should be considered exploratory.. There was also more non-adherence in the PL group, where substantial NS was used, likely secondary to the use of NS for drug dilution. Nonetheless, it does appear that plasmalyte may have advantages over NS regarding earlier resolution of DKA without increasing ketone levels.

Provoked or Unprovoked? ESTROGEN-Associated VTE Recurrence

Article by Siham Hussien (PGY2)

It is well known that estrogen-containing contraceptives are associated with a two- to six-fold increase risk of VTE; however, studies regarding recurrent DVTs from estrogen have shown conflicting results.

A recent **systematic review** estimated the incidence rate of recurrent VTE after discontinuation of anticoagulation treatment in women whose first episode of VTE was related to estrogen-containing contraceptives. Several databases were searched from 2009 – 2021 for prospective and retrospective studies, among which fourteen studies met the inclusion criteria.

The overall pooled recurrence rate was **1.57** (95% -CI: 1.10-2.23 I2= 82%) per 100 patient-years, which was lower than the 3% threshold typically used in hematology. When studies were grouped based on different durations of patient follow-up, recurrence rates were 2.73 (95%-CI: 0.00–3643; I2= 80%) for studies with ≤1-year follow-up, 1.35 (95%-CI: 0.68–2.68; I2= 44%) for studies with 1-5 years, and 1.42 (95%-CI: 0.84–2.42; I2= 78%) for studies with >5 years.

Limitations of the study included large heterogeneity across studies as well as the lack of sub-group analysis for different estrogen formulations—which hurts the generalizability of findings. Also notably, there were no randomized controls trials found regarding the subject. Nonetheless, it does appear that short-term anticoagulation therapy rather than life-long therapy may be appropriate for women with a history of estrogen-associated VTEs.

Novel Therapeutics

Dual Agonists and TRI-Agonists: an Evolving Story of Incretins

Named by Belgian physiologist La Barre in 1932, incretins refer to a group of hormones such as GLP-1 and GIP-1 that conveys signals between the gut and the endocrine pancreas. Classically incretins have been thought to all stimulate insulin release and decrease glucagon secretions, thereby overall increasing insulin release after meals (the "incretin effect"). More recnet develoments have shown that the cross-talk is more complicated than it seems, and a modest increase in glucagon via GIP actually leads to increased insulin release. The recent **SURPASS-1** trial showed that Tirzepatide, a dual GLP-1/GIP agonist, leads to robust weight loss and diabetic control, that exceed what is typically seen with single GLP-1 agonists. This June, a tri-agonist of GLP-1, GIP, and Glucagon as successfully finished Phase 1 Trials. Further development in this fascinating field is to be expected.

<ToTT newsletter>
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