March 2022 Issue

Talk of the Town

-A Midtown Journal Club Newsletter

CONTRAST-INDUCED Nephropathy: A MYTH?

Iodinated contrast media for computed tomography (CT) has been long thought to be associated with development of acute kiney injury (AKI). However, recent studies suggest that the risk may have been overstated. Based on observational studies, a concensus statement in 2020 by the American College of Radiology and the National Kidney Foundation suggested that contrast-**associated** AKI and contrast-**induced** AKI should be distinguished. Furthermore, the true risk of contrast-induced AKI independent of other coexisting factors (nephrotoxic medications, fluctuating volume status) may be minuscule for patients with a eGFR >30ml/min/1.73m2 on modern contrast agents (Davenport et al., *Radiology* 2020).

More recently, **Goulden et al.** reviewed kidney function in 156,000 total adult patients (mean age 53, mean eGFR 86) in the region of Alberta, Canada whose D-dimer levels were measured for evaluation of suspected pulmonary embolism. All patients were included regardless of the number of times creatinine were measured, or whether the patient did or did not receive a CT angiogram (CTA). This was to avoid selection bias and confounding-- if studies were to include only patients who had multiple creatine measurements, the recruitment would be skewed towards those who had a higher suspicion of AKI development. Alternatively, if studies were to include only those received the CT angiogram, the patient population may be skewed towards those who had a lower suspicion of AKI development, as providers would avoid CTAs in patients with a higher risk factors. Patient without a baseline eGFR within 2 hours of the D-dimer result, or patients who went through renal replacement therapy were nonetheless excluded.

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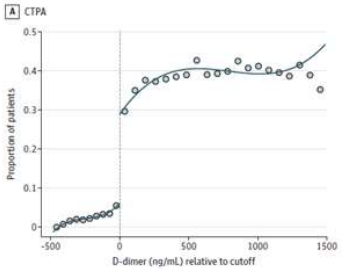

The study used a fuzzy **regression discontinuity design**. In simple terms, when we are trying to establish the relation between CTA and long-term renal function, there can be numerous confounders such as age, baseline eGFR, diabetes, etc. However, the CTA exposure is different from all other factors as there typically is a sharp cutoff where the CTA is ordered or not, which is the D-dimer level. Let's say that the threshold is 500 ng/ml. There should NOT be a large difference in age, baseline eGFR, etc between patients with a D-dimer value of 499 ng/ml and 501 ng/ml-- only the rate of CTA exposure will differ. Therefore, by comparing those who received a CTA versus those who did not amongst patinets **at the D-dimer threshold**, one can estimate what CTA's effect is without having to worry about any other possible confounders. The researchers can then scale the association between D-dimer and long-term eGFR (6 mo) by the difference in CTA exposure at the threshold, to find the estimated causal effect of CTA exposure on the long term eGFR. Results showed **no** evidence for an association of CTA exposure with 6-mo eGFR (mean change -0.4% [-4.9, 4.0]), need for renal replacement (RD 0.07% [-0.47, 0.61]), mortality (RD 0.3% [-2.9, 3.2]). Difference in the rate of AKI was also non-significant but analysis was limited by missing data. Findings were mostly similar in subgroup analysis for CIN risk factors. Overall, the authors concluded that there is **no** evidence for a harmful effect on long-term kidney function from intravenous contrast administered for CTA in a emergency setting.

Article by Harim Kim (PGY2), Jeayoung Park (PGY2)

Why Do We Do That? – A Classic Trials Review

Early Clopidogrel with Fibrinolysis for STEMI

The **CLARITY** trial was a randomized, double-blind, placebo controlled, in 23 countries and 319 sites. The study enrolled 3491 patients who were 18–75 years who presented after onset of ischemic discomfort <12 hours, who met ST elevation or LBBB criteria who were treated with fibrinolytic anticoagulant and aspirin. Exclusion criteria included treatment with clopidogrel within 7 days prior to enrollment, contraindication to tPA, and those who received a higher dose of anticoagulants than criteria.

Article by Siham Hussien (PGY1)

Patients were randomized 1:1 to receive either clopidogrel, 300 mg loading dose and then 75 mg once daily or placebo on top of standard fibrinolytic therapy + aspirin. The primary endpoint was a composite of death or recurrent MI by start of angiography or an occluded artery (TIMI flow grade 0/1)-- there was an absolute reduction of 6.7% (15.0% vs. 21.7%, odds ratio [OR] 0.64 [0.53, 0.76], p<0.001). There was no difference in mortality at time of angiography, but the rate of CV death, recurrent MI or ischemia leading to the need for revascularization in 30 days were lowered by 20% (11.6% vs 14.1%, p=0.03). The rate of major bleeding were similar between groups.

Overall, in patients who have MI with ST elevation and receive aspirin + fibrinolytic therapy, adding clopidogrel improved the patency rate of the infarct-related artery and reduced ischemic complications.

Can You Mix-and-Match COVID Vaccines?

Article by Elvina Yunasan (PGY1)

Three COVID-19 vaccines, Moderna, Johnson & Johnson, and Pfizer are authorized by FDA for boosters in the US. However, it is often difficult for patients to get the booster shot from the same brand they initially received. A study by **Atmar RL** et al. that was published at NEJM sheds light on this issue. This phase 1-2, open label clinical trial was conducted at 10 sites in the United States. Study participants completed a vaccination regimen at least 12 weeks prior. Those with a history of COVID-19 infection or monoclonal antibody infusion were excluded. Of the 458 participants, patients received either Moderna, J&J, and Pfizer as their primary vaccine, and then either a booster from the same company **(homologous)** or a different one **(heterologous)**.

Both homologous and heterologous booster shots stimulated neutralizing antibodies- for homologous boosters by factor of 4 to 20, and for heterologous ones by a factor of 6 to 73. The greatest increase in immune response was noted among participants who had a J&J primary series, followed by recipients of primary Pfizer and Moderna. T cell response was also evaluated. Cellular CD4 Th1 responses directed against the spike protein increased in all subgroups except for participants who received homologous J&J. CD8 T cell responses were more durable in J&J recipients. Side effect profiles were also similar, with injection site pain being the most common. The study was limited by a lack of non-boosted control group. Study was also underpowered to find if any of the combinations resulted in superior. Long term adverse effect and efficacy was yet unknown, because the participants were only followed for 1 month. Overall, any type of booster appears to offer better protection against COVID-19. Stay Boosted!

Editor's Choice

Are Statins' Side Effects Over-rated?

A recent **large-scale meta-analysis** assessed the prevalence of statin intolerance. The analysis included 176 studies (112 RCT, 64 cohort) and involved a total of 4,143,517 patients (mean age 60.5 years, 40.9% female, 81.1% Caucasian). In all studies patients were being treated with statins for either primary or secondary prevention. The pooled prevalence of statin intolerance was **9.1%**. The authors used the National Lipid Association's definition of statin intolerance which is any adverse effects related to the quality of life leading to the decision to reduce the dose or stop the use of a beneficial drug. The authors identified several patient related factors that were associated with an increased prevalence of statin intolerance including black and Asian race, obesity, increasing age, higher statin doses, chronic kidney disease, female sex, diabetes mellitus, alcohol consumption, and concomitant treatment with calcium-channel blockers or antiarrhythmic medications.

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Additionally, the authors found *no* significant difference in the prevalence of intolerance between **lipophilic** statins (atorvastatin, simvastatin, lovastatin, fluvastatin and pitavastatin) and **hydrophilic** statins (pravastatin and rosuvastatin). This study provided important support for the safety and tolerability of statin therapy, finding that the pooled prevalence of intolerance is fairly low (9.1%) in a large meta-anal ysis of RCTs and cohort studies. However, the generalizability of this analysis is limited to our patient population as many of the identified factors associated with an increased prevalence are present in the patients we see. It is also important to note that various societies and associations may use different definitions of statin intolerance and more generalized definitions go beyond muscle symptoms.

Review by Alex Gyftopoulos (PGY3)

WAR OF HEARTS:

Direct Oral Anticoagulants VS WARFARIN IN PATIENTS WITH AFIB

Article by Aleksan Khachatryan (PGY1)

The January 2022 edition of *Circulation* showcased a large **patient-level network meta-analysis** using the aptly named **COMBINE-AF** database, which pools data from four landmark clinical trials: ROCKET-AF, ARISTOTLE, ENGAGE AF-TIMI 48, and RE-LY.

Of note, meta-analyses using individual patient data allow analyses of the inidividual patient's time-to-event censored ("missing") survival data and application of consistent follow-up time across trials. A more thorough assessment of treatment effect heterogeneity is also possible. The particular study a total of 71,683 patients from the COMBI NE-AF database (29,362 to standard-dose DOAC, 13,049 to lower-dose DOAC, and 29,272 to warfarin). Intention-to-treat principle was followed (all patients were analysed regardless of dropout) and data up to 32 months were analyzed. No meaningful clinical differences (BMI, PMH, etc) were seen between the groups.

Compared to warfarin, patients randomized to **standard-dose DOACs** had a lower hazard of stroke or systemic embolism (3.01% vs 3.69%; HR 0.81 [0.74, 0.89]), as well as a lower hazard of all-cause deatrh, CV death, hemorrhagic or any stroke. The benefit was consistent over nearly all subgroups (age, sex, etc). Standard-dose DOACs had a lower hazard of fatal and intracranial bleeding, but a higher chance of GI bleed ing than warfarin. For **low-dose** DOACs no sign ificant difference in the risk of stroke or systemic embolism was seen, and in fact there was a **higher** risk of ischemic stroke (3.48 vs 2.34%; HR 1.35 [1.19, 1.54]). Overall, standard-dose DOACs appear to have favorable efficacy and safety compared to warfarin in patients with atrial fibrillation.

<ToTT newsletter>
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