Residents Corner: Journal Club

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Discussion By

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Article: Association between Renin-Angiotensin system blockade discontinuation and all-cause mortality among persons with low estimated Glomerular filtration rate

Yoa Qiao et al
JAMA Intern Med 2020;180(5):718-726

With absence of consensus and conflicting evidence regarding benefitsts or otherwise of continued use of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARBs) versus discontinuation when glomerular filtration rate (GFR) is below 30 ml/min/1.73sq m, this retrospective cohort study based in Geisenger integrated health system, Pennsylvania, USA, sought answers for the following primary outcome and secondary outcome measures respectively: What is the risk of all-cause mortality, Major adverse cardiovascular events and end stage kidney disease (ESKD) in the subsequent 5 years, following a decision to continue or discontinue ACE-I/ARBs in patients with eGFR less than 30 ml/min/ 1.73 sq m ?

Methodology: Study design :Retrospective cohort study with propensity matching to balance for baseline covariates and a median of 2.9 year followup

Exclusion Criteria: included confounders and patient safety related factors

Statistical Analysis: Propensity matching, sensitivity analysis, Kaplan Meir survival analysis and Cox proportional regression were employed. Propensity matching is the cohort study's attempt to match the strategy of randomization in RCTs to minimize selection bias and thus ensure a fair comparison between exposed and unexposed groups. Sensitivity analysis serially excludes a factor at a time while retaining all other determinants of outcome to assess if effect remains the same. Kaplan Meir survival curves are generated based on cumulative probabilities of events or survival but cannot account for competing risks. Cox proportional regression are more robust measures of proportional contribution by each determinant similar to the straight line equations like $y = mx + c$.

Results: Of 3909 candidates, predominantly white, who met inclusion criteria 1235 discontinued ACE-I or ARB and 2674 did not. 1205 individuals in both limbs were carefully propensity matched. In all comparisons, but especially relevant being propensity matching, Hazard for death (HR 1.39 95 % CI, 1.20-1.60) and major cardiovascular events (HR 1.37 95% CI 1.20-1.56)was increased in the groups who discontinued ACE-I or ARB and there was no difference in ESKD (HR 1.19, 95 % CI 0.86-1.65). These trends were similar even in those whose GFR declined by 40% or more during 1 year while on ACE-I or ARBs, in those who continued versus those who discontinued ACE-I or ARB.

In terms of Absolute risk reduction and its reciprocal, the number needed to treat, 16 patients treated would save an additional life and for hyperkalemia and number needed to harm, about 16 patients treated would cause an additional hyperkalemia of greater than 5.5 meq/l.

Recommendations: This was a large study with a robust methodology. Being a retrospective cohort, although it could show positive associations between continuing usage of ACE-I or ARBs in a major mortality benefit without affecting onset of End stage kidney disease, strength of the association was not strong enough to imply causation. Residual confounding, missing data and selection bias could be a problem. We do not know about blinded interpretation of outcomes. Population was predominantly white so applicability to Pakistani or South Asian population is unknown. Safety concerns about Hyperkalemia and its careful preventive counselling and monitoring cannot be over emphasized.

A Randomized controlled trial such as Stop ACE-I should be able to confirm the hypothesis that these medications are lifesaving even at lower GFRs and should not be discontinued.

Article: Timing of Initiation of Renal-Replacement Therapy in Acute kidney injury.

The STAART Investigators.
NEJM 2020; 383:240-251

There is absence of consensus and discrepant findings regarding benefits or otherwise of early initiation versus delayed initiation of renal replacement therapy in patients with AKI in ICU, who do not have specific indications of dialysis. The hypothesis was that accelerated therapies may be beneficial. This multicenter Randomized controlled trial sought answers for the following primary outcome and

secondary outcome measures respectively: All-cause mortality at 90 days after randomization and dependence on RRT, a composite of death or dependence on RRT and
a major Adverse kidney event respectively besides several pre specified ancillary secondary outcomes

Methodology: Study design and setting: Open label RCT in 15 countries and 168 sites.

Inclusion criteria: Adults above 18 years of age with Stage 2 or 3 KDIGO AKI

Exclusion criteria: included confounders and patient safety related factors such as emergency indications, previous RRT, advanced CKD and uncommon causes of AKI. After a clinical equipoise determined for starting or delaying dialysis, 12-hour window allowed for study logistics

Randomization: 1:1 with variable block sizes and site stratification

Statistical analysis:

Sample size 3000 plus with 90 percent power with 15 percent relative between group difference and 6 percent absolute difference with 2 sided alpha 0.05 and estimated 3 percent attrition. Modified intention to treat analysis was performed.

Primary outcome of death used chi square test for categorical outcome and death at 90 days adjusted logistic regression analysis and Kaplan Meir time to event and log rank for comparisons. Additional pre specified subgroup analysis done. t-test was used for comparison of serum creatinine among survivors at 90 days. Linear regression was used for between group comparisons.

Results: Of 11,852 eligible candidates, 3019 were randomized with 1512 in accelerated group and 1507 in standard.

2927 were included in Modified intention to treat analysis. Groups were well balanced. RRT was initiated at a median of 6.1 hours in accelerated group and 31.1 hours in standard group.

Death at 90 days was no different (43.9 percent versus 43.7 percent in accelerated group and standard group. Relative risk 1.00 95% Confidence interval (0.93 - 1.09)

Dependence on renal replacement therapy was higher 10.4 percent in accelerated group versus 6 percent in standard with relative risk of 1.74 with 95 percent CI 1.24 to 2.43. Other key secondary outcomes were similar in both groups

In the sensitivity analysis using per protocol analysis, there were no difference in primary outcome in both groups.

Adverse events were higher in accelerated group (23 percent versus 16.5 percent) with risk ratio of 1.40 95% CI (1.21 - 1.62) with hypotension and hypophosphatemia most common.

Recommendations:

This was a multicenter international trial with a large sample size and good generalizability.

Although open label, because of a mortality as hard clinical primary endpoint, absence of blinding may not have made a difference. Results appear robust enough to suggest that there is no benefit to early renal replacement therapy in AKI in ICU settings in the absence of standard clinical and biochemical indications. In fact, the accelerated strategy may have more costs, adverse effects and dialysis dependence. Sponsors were not involved in data analytics or reporting and thus this was very important to publish a negative trial with major clinical implications.