Our panel of experts highlight the most important research articles across the spectrum of topics relevant to the field of clinical practice

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Parsa A, Kao WH, Xie D *et al.*; AASK Study Investigators; CRIC Study Investigators. *APOL1* risk variants, race and progression of chronic kidney disease. *N. Engl. J. Med.* 369(23), 2183–2196 (2013).

For decades, it has been observed that African–Americans experience a more rapid progression of chronic kidney disease (CKD) in virtually every etiology of kidney disease. This has been ascribed to more severe hypertension, poor risk factor control and noncompliance. Heretofore, a search for genetic determinants among African–Americans has been unrevealing. High-density lipoprotein cholesterol particles contain major apolipoproteins A-I and A-II, and minor apolipoproteins, including A-IV, A-V, C-I, C-II, C-III, D, E, F, H, J, L, M, O and P. Polymorphisms of these apolipoproteins have been associated with changes in reverse cholesterol transport function, oxidation and now, most recently, altered catabolism. High-density lipoprotein is filtered in the glomerulus and then catabolized by the proximal tubular cells. A mutant form of apo-L has been described in African–Americans that may have a protective effect against trypanosomes. *APOL1* polymorphisms have a prevalence of approximately 30 and 2% among African–Americans and Caucasians, respectively. In this paper, data from two clinical studies, one exclusively in nondiabetic African–Americans with hypertension (AASK) and the other in patients screened for CKD (CRIC), variants in the gene for *APOL1* were assessed according to whether they had two high-risk *APOL1* variants (*APOL1* high-risk group) or 0 or 1 copy (*APOL1* low-risk group) [1]. In both studies, among those with and without diabetes, there was a more rapid progression of CKD, including the need for dialysis, in African–Americans with two alleles containing mutant variants of the *APOL1* gene. This and other studies suggest that *APOL1* variants are associated with a 50–100% increased risk of rapid progression of CKD and may be related to a toxic or adverse process invoked by proximal tubular cell catabolism of this apoprotein. So, in summary, *APOL1* genetic abnormalities appear to be a major genetic basis for the difference between rates of progression of CKD between African–Americans and Caucasians.

– Written by Peter A McCullough

Chen HH, Anstrom KJ, Givertz MM *et al.*; NHLBI Heart Failure Clinical Research Network. Low-dose dopamine or low-dose nesiritide in acute heart failure with renal dysfunction: the ROSE Acute Heart Failure randomized trial. *JAMA* 310(23), 2533–2543 (2013).

The ROSE trial is the third clinical trial conducted by the NIH National Heart Lung and Blood Institute Heart Failure Clinical Research Network [2]. This network has taken on the challenge of testing conventional approaches in acutely decompensated heart failure (ADHF) and previously had reported neutral results in both the DOSE trial and CARRESS-HF [3,4]. In the double-blind ROSE trial, 360 subjects with ADHF and chronic kidney disease were randomized in a factorial with 2:1 active treatment:placebo, such that approximately one-third of the population received,

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in addition to standard diuretic-based decongestive therapy, low-dose dopamine (2 µg/kg/min infusion), while another third received low-dose nesiritide (human recombinant B-type natriuretic peptide; 0.005 µg/kg/min infusion for 72 h). The primary end points were total cumulative urine volume and change in serum cystatin C. While the dopamine and nesiritide strategies both resulted in larger increases in urine output as compared with the placebo group (228 and 278 ml, respectively), these changes were small and not statistically significant. Cystatin C levels were not elevated (~1.1 mg/dl) at baseline and there were no meaningful changes in this measure. There were no significant differences in symptoms, days alive and free from heart failure, hospitalization at 60 days or mortality. Of note, the rates of type 1 cardiorenal syndromes were approximately 24% in the ROSE trial and were unaffected by treatment allocation. For both dopamine and nesiritide, there have been a significant number of trials and analyses with larger sample sizes showing no benefit in critically ill patients. For low-dose dopamine (<5 g/kg/min), a meta-analysis of 3359 subjects in 61 trials showed that, while dopamine resulted in a 24% rise in urine output, there was no difference in death or the need for kidney replacement therapy [5]. ROSE can add to our knowledge of anticipated effects with dopamine in patients with chronic kidney disease in that it resulted in a smaller increase in urine output (~3%) than those with normal renal function. In addition, it had no impact on cystatin C or hospitalization or death. For nesiritide, ASCEND-HF randomized 7141 patients with ADHF to 24–168 h (median 42 h) of nesiritide (2 µg/kg bolus, then 0.01 µg/kg/min) or placebo [6]. While nesiritide was associated with minor improvements in symptoms at 6 and 24 h, there were no differences in prespecified primary end points, including rehospitalization and death. There were no differences in the rates of >25% reduction in estimated glomerular filtratration. Rates of acute kidney injury (AKI) or type 1 cardiorenal syndrome were again not reported. In terms of nesiritide, ROSE adds the understanding that longer durations of a lower dose infusion with no bolus confer no benefit over placebo. Future approaches in preventing or treating type 1 cardiorenal syndrome should de-emphasize older therapies and focus on newer agents and more sophisticated biomarkers of AKI to complement serum creatinine, which has false-positive elevations in cases of hemodynamic reductions in filtration and, in the setting of true AKI, rises much later after the damage has occurred.

– Written by Peter A McCullough

Kansagara D, Dyer E, Englander H, Fu R, Freeman M, Kagen D. Treatment of anemia in patients with heart disease: a systematic review. *Ann. Intern. Med.* 159(11), 746–757 (2013).

All patients with heart disease are intentionally or inadvertently screened for anemia with routine complete blood counts and measurement of serum hemoglobin (Hb). Prior observational studies have shown a consistent association between anemia and incident myocardial infarction, heart failure hospitalization, stroke and cardiovascular death [7]. Hence, among patients with heart disease, Hb has been a treatment target in a series of randomized trials. This meta-analysis considered trials of blood transfusions, iron or erythropoiesis-stimulating agents (ESA) in adults with anemia and congestive heart failure or coronary heart disease. Data from six trials and 26 observational studies indicated that liberal transfusion protocols do not improve short-term mortality rates compared with less aggressive protocols, possibly with the exception of patients with acute coronary syndromes. Evidence from three trials of intravenous iron found improved short-term exercise tolerance and quality of life in patients with heart failure. Results from 17 trials of ESA therapy found that they offered no consistent benefits, but their use may be associated with harm, such as venous thromboembolism, worsening heart failure and stroke. Thus, an increasing Hb level in itself appears to confer benefit with respect to an improvement in symptoms; however, there may be off-target effects of the methods that raise Hb, which probably negate any benefit. For example, transfusion is known to be an oxidative stress on the body, particularly with older units of transfused blood, and is associated with increased mortality. The cumulative dose of ESA has been shown to be associated with progressive cardiovascular toxicity and, thus, erases any benefit of raising Hb [8]. Finally, in patients with heart failure who are iron deficient, iron, which is needed in large quantities for myoglobin and other cardiomyocyte intracellular structures, may directly improve cardiac function and, thus, additional study in this area is warranted.

– Written by Peter A McCullough

Marra AR, Edmond MB. New technologies to monitor healthcare worker hand hygiene. *Clin. Microbiol. Infect.* 20, 29–33 (2014).

Nosocomial infections impact significantly on hospitalized patients, healthcare workers and facilities, and the cost of healthcare delivery. Hand hygiene has been and remains an important component of infection prevention programs and is cost effective; however,

despite enormous efforts on behalf of infection programs, hand washing compliance remains problematic. Policing hand hygiene is practically difficult, especially if you believe that individual practices may be different if one feels they are being observed versus not being observed. Marra and Edmond report on an electronic surveillance approach to monitoring hand hygiene. The technology uses a series of sensors that can detect alcohol vapors (from alcohol sanitizers). Healthcare workers wear monitors that alert when hand hygiene was completed (green light and ping noise on credit card size badge) or red and a different alert noise when hand hygiene was not completed. Prior to testing of this system, hand hygiene was measured to be at 66% and after the intervention was a mean of 92%. Data on each healthcare worker is collected by a central monitoring system and can be used for educational purposes. Linking such data to smartphone devices may further expand the utility of such electronic approaches. This paper is an interesting read as it identifies the potential use of electronic technology to impact on hand hygiene compliance, which we know is an important component of infection prevention programs. Changing behaviors are always a challenge and innovative technology to provide reminders – even for practices that should be routine – is not a bad idea. Clearly more needs to be done to fully appreciate the potential impact that such technology may offer.

– Written by Joseph M Blondeau

Hill K, Reilly JL, Keefe RS *et al.* Neuropsychological impairments in schizophrenia and psychotic bipolar disorder: findings from the Bipolar–Schizophrenia Network on Intermediate Phenotypes (B-SNIP) study. *Am. J. Psychiatry* 170, 1275–1284 (2013).

There is evidence that cognitive impairment is present in schizophrenia as well as those with bipolar disorder, both in euthymic and symptomatic states. In this study, the authors attempted to test:

- The continuum model of cognitive dysfunction in psychosis by comparing the magnitude of cognitive impairment in schizophrenia and bipolar disorder with psychosis;
- Familiality of cognitive impairments across psychotic disorders;
- The influence of cluster A personality traits in nonpsychotic relatives.

Patients with a history of psychotic symptoms were recruited with at least one first-degree relative. Subjects were assessed using Structured Clinical Interview for Diagnostic and Statistical Manual Diagnosis (SCID), Positive and Negative Syndrome Scale, Montgomery Asberg Depression Rating Scale, Young Mania Rating Scale, Social Function Scale and Schizo–Bipolar Scale. First-degree relatives were assessed using SCID and Structured Interview for DSM-IV Personality. Healthy controls recruited through media and research registries were assessed using SCID. All participants were administered the Brief Assessment of Cognition in Schizophrenia (BACS) Scale.

Although the results indicated that both schizophrenia and bipolar groups were significantly impaired in neuropsychological functioning compared with the healthy group, the magnitude of impairment was greater in the schizophrenia group ($F = 32.12$; $df = 1518$; $p < 0.001$). The impairment in the schizoaffective group was intermediate between those with schizophrenia and bipolar disorder. Furthermore, consistent with earlier studies, the cognitive deficits correlated significantly with social functioning.

Overall composite scores on BACS declined as affective features became less and persistence of psychosis more prominent ($r = -0.25$; $p = 0.001$). BACS composite scores were not significantly different between first-degree relatives of schizophrenia or psychotic bipolar clients but was significantly different in comparison with healthy controls ($F = 7.02$; $df = 2800$; $p = 0.001$). However, in the absence of cluster A or B traits, the composite BACS scores of relatives of the schizophrenia but not bipolar group were significantly different compared with the healthy volunteer group. This probably indicates selectivity or variable penetrance of familial risk affecting cognition across psychotic disorders. The study indicates that cognitive deficits occur in a continuum from bipolar disorder with psychotic symptoms to schizophrenia, with schizoaffective disorder somewhere inbetween.

While the findings are interesting and have significant implications for the understanding of cognitive impairments, the study has some limitations, which raise questions about the generalizability of the findings. For instance, patients that participated had to be stable enough to complete the protocol and scales, and needed to have a first-degree relative available and willing to participate. Furthermore, the medication effects on cognition were not controlled, although the authors argue that medications did not influence the results, as many medication trials failed to enhance cognition. The small sample size of relatives with axis II traits, which was used to establish a relationship between personality traits and cognitive deficits, is another limitation. Despite these, this study highlights the spectrum of cognitive deficits, which increase from bipolar disorder

with psychotic symptoms to schizophrenia, supporting a dimensional model, and replicates the significance of cognitive deficits in first-degree relatives in this group.

– Written by Ashok Krishnamoorthy & Lakshmi N Yatham

Jarrett RB, Minhajuddin A, Gershenfeld H, Friedman ES, Thase ME. Preventing depressive relapse and recurrence in higher-risk cognitive therapy responders: a randomized trial of continuation phase cognitive therapy, fluoxetine, or matched pill placebo. *JAMA Psychiatry* 70(11), 1152–1160 (2013).

Major depression, characterized by recurrences, relapses and residual symptoms, is one of the leading causes of the global burden of diseases. Although pharmacotherapy has remained an important aspect of the long-term treatment of depression, medications are often discontinued for a variety of reasons.

The objective of this study was to assess the efficacy of continuation of cognitive therapy in comparison with fluoxetine and placebo in cognitive therapy (CT) responders who were identified as being at high risk of relapse. The authors hypothesized that both CT and fluoxetine would reduce relapse and at 20 months, fewer patients in the CT group would relapse compared with the fluoxetine group.

The study subjects were recruited between March 2000 and July 2008 with a diagnosis of recurrent major depressive disorder, as per Structured Clinical Interview for Diagnostic and Statistical Manual Diagnosis-IV, with a Hamilton Rating Scale for Depression score of 14 or more. A total of 523 patients received 16–20 individual sessions of computed tomography (CT) over a 12-week period. Of the 292 responders, 241 were considered as being at high risk of relapse and were further randomized to receive either continuation of CT (C-CT; n = 86) or fluoxetine (n = 86), or placebo (n = 69), for 8 months. Of these, 181 who remained well were followed for 24 months post-treatment to assess relapse rates.

Relapse rates in the fluoxetine and C-CT group were nearly identical (18.0 and 18.3%, respectively), while the rates in the placebo group were significantly higher (i.e., 32.7%) during the 8-month treatment phase. This pattern persisted during the follow-up periods: relapse rates at 12-month (placebo: 42.7%; fluoxetine: 35%; C-CT: 35%) and 24-month (placebo: 56.3%; fluoxetine: 41.1%; C-CT: 45.2%) follow-up periods were similar in the fluoxetine and C-CT group but were significantly lower relative to the placebo group.

The generalizability of the findings of this study are limited for the following reasons:

- The study group had predominantly white females in their early 40s;
- Patients who dropped out of the study during the experimental phase were more likely to be younger males and with a short duration of illness;
- The study group had mainly unmedicated adults with recurrent major depressive disorder that responded to CT;
- Attrition rates were between 19 and 29%, and proportionately more in one site (32%).

The findings of this study have significant clinical implications. They suggest that depressed patients who have responded to CT but are at high risk of relapse can be effectively treated with either continuation of CT or a switch to fluoxetine. The positive aspects of this study are the stringent mode of C-CT delivery, identical medication appearance and preservation of randomization.

– Written by Ashok Krishnamoorthy & Lakshmi N Yatham

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