Editorial

Sometimes neither water nor fire are more useful than friendship—a new risk score for prediction of contrast-induced nephropathy (CIN) and long-term adverse outcomes in patients undergoing coronary angiography

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Comment on: Ni Z, Liang Y, Xie N, *et al.* Simple pre-procedure risk stratification tool for contrast-induced nephropathy. J Thorac Dis 2019;11:1597-610.

Submitted Jun 11, 2019. Accepted for publication Jun 18, 2019.
doi: 10.21037/jtd.2019.06.51
View this article at: http://dx.doi.org/10.21037/jtd.2019.06.51

Non aqua non igni locis pluribus utimur quam amicitia.
Cicerone, Marco Tullio (106-43 a.C.) (De amicitia: VI, 32)

Coronary angiography (CA) and percutaneous coronary intervention (PCI) are an essential part of the standard management of patients with stable coronary artery disease (SCAD) and acute coronary syndrome (ACS). Improvements in PCI materials and techniques led over the years to the opportunity to treat coronary diseases of increasing anatomical complexity (1), at the cost of longer procedural times and larger doses of iodinated contrast media (ICM) to be used chasing optimal results (2). ICM carry a risk of contrast-induced acute kidney injury (CI-AKI) and such iatrogenic complication represents the third cause of acute renal failure in hospitalized patients, after renal hypoperfusion and medications (3). Although the pathophysiological mechanism of this association has not been completely clarified, both a direct ICM toxicity and indirect effects (i.e., viscosity-mediated renal vasoconstriction leading to medullary hypoxia) have been implicated (4,5). CI-AKI has been historically defined as the increase in the plasma creatinine level of at least 0.5 mg per deciliter or at least 25% increase from the baseline level within 2 to 5 days after exposure to contrast material (6). This led to large disputes about the correctness of such a definition in consideration of the low sensitivity of creatinine as an indicator of kidney function by itself. Despite in most cases such condition is reversible and the estimated glomerular filtration rate (eGFR) recovers in 5 to 10 days (7) many studies have shown that CI-AKI, even defined as small decrements in renal function, is associated with long term higher rates of cardiovascular events, heart failure, and requirement for dialysis (8,9). The acknowledgment that CI-AKI is associated with adverse outcomes substantially led to two consequences. First, the fear among physicians about ICM-mediated kidney damage resulted in an increasing withholding of contrast-based procedures from patients suffering from chronic kidney disease (the exaggerated consequence of such phenomenon being referred to as "renalism" by Chertow *et al.* (10). This also represents a source of a potential indication bias of all the studies investigating this subject, as patients perceived at "higher risk" are less likely to be exposed to contrast material than are patients perceived at "lower-risk". On the other hand, several risk scores were developed with the aim to predict such complication (11,12). In this issue of the *Journal of Thoracic Disease*, Ni *et al.* presented a new simple risk score with a good predictive ability on CI-AKI and severe short and long term outcomes as in-hospital mortality and three years death and major adverse cardiovascular events (MACE) in patients scheduled for CA (13). The authors retrospectively analyzed the data from 3,469 consecutive patients undergoing CA and that were randomly assigned to a development dataset (n=2,313) and a validation dataset (n=1,156). They first evaluated several variables associated with CI-AKI using univariable

logistic regression analysis and then performed a stepwise multivariable logistic regression analysis to identify independent predictors of contrast-induced nephropathy (CIN). After multivariable adjustments, the authors identified 5 variables related to CIN, namely hypotension, congestive heart failure (CHF), age >5 years, acute myocardial infarction (AMI) and serum creatinine (sCR) ≥1.5 mg/dL. A weighted integer coefficient value based upon beta value was assigned to these variables. Therefore, a risk score model was constructed where the final risk score for each patient represented the sum of integer coefficients. The risk score was validated throughout the validation cohort showing good predictive ability on CIN (c statistic 0.829), in-hospital mortality (c statistic 0.909) and long-term adverse outcomes (c statistic for three years MACE 0.730). Of interest, the authors compared the predictive ability of their score with two pre-existing and validated scores, namely the Mehran (11) and the ACEF (12) risk scores showing similar accuracy in predicting short and long adverse outcomes. Despite the study has its major limitation in the retrospective and "single-center" design, the authors should be congratulated for the effort to confirm the relationship between several simple anamnestic variables and the incidence of CIN. The benefit of a risk model including only pre-procedural data is self-evident, and on the other hand, represents the most important limitation of the widely adopted Mehran risk score that instead accounts also for the impact of post-procedural variables as the volume of contrast administered and the use of intra-aortic balloon pump. The age, creatinine and ejection fraction (ACEF) (12) risk score mentioned by the authors shares the advantage of considering only three simple clinical variables to predict worse outcomes. However, it should be acknowledged that it was first designed as a mortality risk score for patients undergoing elective cardiac surgery (14) and was only later validated by Andò *et al.* (12) as a model to predict AKI among patients with ST-elevation myocardial infarction treated with primary PCI.

As stated above, the variables identified by Ni *et al.* as independently related to CIN are well-recognized patient-related risk factors for such complications. Several previous studies showed that pre-existing CKD represents the most significant risk feature and that the increase in risk is likely to continue with the decline in eGFR (15). In this context, the choice of the Authors to put a dichotomic value of sCR in their risk model could be considered as debatable. However, continuous variables as eGFR have a rather complex grading system with several categories and would require calculation using a computer. The choice of authors can be then justified as a pursuit of simplification. The role of AMI as a predictor of CIN could be easily perceived in a simplistic manner, as patients with ACS are more likely to undergo complex revascularization procedures requiring a larger amount of contrast media. However, Reinstadler *et al.* (16) found a significant association between microvascular injury and onset of AKI in a cohort of patients undergoing cardiac MR following STEMI, while there was no influence of contrast media. This data highlights the potential role of a cardio-renal "cross-talk" in the context of ACS and that hemodynamic instability represents a risk-factor *per-se*. For the same reason, the impact of CHF and hypotension can be easily understood in the light of the renal hypoperfusion frequently associated with such conditions. This would open a "marginal" discussion about the real impact of the currently adopted prevention strategy of volume expansion to prevent CI-AKI. Even if this consideration goes beyond the scope of this commentary paper, it would be an interesting matter of research to understand if isotonic fluid administration before CA just helps the kidney to "washout" the contrast media or could play a nobler role in correcting hypotension. A surprising finding of the paper by Ni and co-authors is instead the apparently uninfluential impact of diabetes on the risk of CIN. Although diabetes is commonly cited as a risk factor and included in other predictive models of CI-AKI (11), two aged studies suggested that it does not increase the risk of CIN among patients with normal kidney function (17,18). In particular, in accordance with the results of Ni *et al.* data from the Iohexol Cooperative Study showed that diabetes was not an independent risk factor but rather amplified susceptibility only in patients with underlying chronic kidney disease (18).

Further than confirming the impact of several baseline features on the risk of CIN, the work of Ni *et al.* allows us to speculate on several themes. CIN is one of the best examples of the modern era of Medicine where for a potentially severe complication or disease we have "more ways to predict, than ways to prevent". We daily face with a myriad of papers suggesting scores with a variable level of complexity referred to this or that subset of patients, none prevailing on each other because of the several contexts of development and validation. Quite the reverse, strategies to prevent the diseases "predicted" are often no more than a handful or sometimes, paradoxically even no one. In hence, among many pre-treatments suggested across the years to prevent kidney damage from ICM, only isotonic NaCl solution resisted to the benchmark of the evidence-based

medicine. In the recent large prospective PRESERVE trial, 5,177 patients at risk for renal complications (median eGFR, 50 mL/min/1.73m²) were randomly assigned to receive intravenous NaCl or sodium bicarbonate solution, and oral N-acetylcysteine or placebo, in a 2×2 factorial design (19). In this well-conducted and sufficiently powered clinical trial using a relevant primary outcome of major adverse kidney events (MAKE), i.e., a composite end-point including death, dialysis or a persistent decline in GFR at 90 days, there was no benefit of sodium bicarbonate over NaCl or of N-acetylcysteine over placebo. Trials investigating a potential preventive role of other medications, i.e., statins, led to controversial results and were mostly limited by methodological biases (heterogeneous populations, small sample size, rate and dosages of administrations). Additional non-pharmacological technique as ischemic pre-conditioning showed renal benefit before ICM-exposition for CA (20), but further studies are warranted to confirm the value of such method. The striking results of the PRESERVE trial could lead to a provocative question: why don't we just give intravenous water to every patient committed for ICM administration? The answer to such a "simplistic" solution comes from another landmark trial facing this topic. The AMACING trial (21), which randomly assigned 660 patients undergoing contrast-enhanced procedures to receive either peri-procedural intravenous isotonic saline or no intravenous fluids, there was no significant difference in the incidence of acute kidney injury between the hydration group and the no-hydration group. On the opposite, a higher rate of symptomatic heart failure was recorded in patients receiving prophylactic hydration, thus highlighting that in subjects with well-preserved renal function and normal hydration status, the benefit of preventive hydration should be weighed against any potential risk in a perfectly patient-tailored approach.

Another concern raising from the paper by Ni *et al.* is that recently the role of CI-AKI as a causal factor of worse long-term poor outcomes was questioned. Lassnigg *et al.*, showed that both small postsurgical elevations and small decrements in plasma creatinine levels (≤0.5 mg per deciliter) were associated with increased 30-day mortality (22). A meta-analysis by Coca *et al.* (23), revealed that preventive interventions that reduced the incidence of AKI, failed to reduce the risk of long-term downstream adverse events as death or development of CKD. These findings pointed out some doubts about a direct cause-effect correlation between CI-AKI and adverse outcomes. The adverse prognosis may be probably related to risk factors increasing risk of CI-AKI which are negatively related also to long term outcomes.

In light of all these considerations, we should ask ourselves if we really needed another score to predict ICM-mediated kidney injury. However, the present score should be of help to remember us single and easy to assess variables which are related to CI-AKI. Currently, data keep on showing a relationship between CI-AKI and poor outcomes. The recent POSEIDON trial (24) reported an overall incidence of CI-AKI of 11.4% and notably these patients had a higher rate of all-cause mortality and myocardial infarction at six months. Actually, it is difficult to establish if this relation is merely associational and if CI-AKI is a real mediator of adverse prognosis or no more than a marker of increased risk. However, it is undeniable that CI-AKI appears to be more than just a "creatinopathy". Liu *et al.* highlighted that all existing scores (including Mheran and ACEF), while performing well for CIN prediction, they all had low predictive accuracy for three years MACE (25). The work of Ni *et al.* deserves the merit to suggest a risk model with a remarkable predictable power not only on CIN but also on long-term major adverse outcomes. In our opinion, the future challenge will be to identify predictors able to discriminate between patients experiencing "real" ICM-mediated kidney damage, likely to be associated with a bad prognosis, and patients in whom we just observe fluctuation in plasma creatinine of uncertain significance. This would be of pivotal clinical relevance to avoid an exaggerated and unjustified "renalist" approach and, on the other hand, to properly select patients deserving specific preventive strategies and a stricter follow-up. The work of Ni and co-authors goes in this direction as the score suggested can be considered as a good-friend for physician who cares for patients at risk of CIN, and as in the famous citation of Cicerone, a friend sometimes is more useful than water.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved.

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Cite this article as: De Filippo O, D'Ascenzo F, Piroli F, Budano C, De Ferrari GM. Sometimes neither water nor fire are more useful than friendship—a new risk score for prediction of contrast-induced nephropathy (CIN) and long-term adverse outcomes in patients undergoing coronary angiography. J Thorac Dis 2019;11(7):2675-2679. doi: 10.21037/jtd.2019.06.51

