Interventional Rounds

Acute Kidney Injury After Percutaneous Coronary Intervention: Rationale of the AKI-MATRIX (Acute Kidney Injury-Minimizing Adverse Hemorrhagic Events by TRansradial Access Site and Systemic Implementation of AngioX) Sub-Study

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Acute kidney injury (AKI) is an important complication of both diagnostic cardiac catheterization and percutaneous coronary intervention (PCI). A large body of evidence supports that AKI is related to volume of contrast used. Despite several measures are available to reduce the impact of contrast media on AKI, its incidence remains significant as other mechanisms of renal damage are involved. A new paradigm is established according to which bleeding prevention is at least as important as preventing recurrent ischemic events in the management of patients with acute coronary syndromes (ACS) undergoing an invasive approach. Periprocedural bleeding, which is consistently reduced by radial approach, is emerging as a risk factor for the development of AKI. Therefore, the role of vascular access as a measure to prevent AKI needs to be systematically assessed in randomized studies. To date, no prospective comparison on renal outcomes has been carried out in randomized trials between radial and femoral approach. The Minimizing Adverse hemorrhagic events by TRansradial access site and systemic Implementation of AngioX (MATRIX) trial (ClinicalTrials.gov identifier: NCT01433627) has been designed to test whether to minimize bleeding events by using radial access and bivalirudin, across the whole spectrum of patients with ACS undergoing PCI, will result in improved outcomes with respect to both ischemic and bleeding complications. The AKI-MATRIX sub-study will provide a unique opportunity to

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INTRODUCTION

Acute kidney injury (AKI) is an important complication of both diagnostic cardiac catheterization and percutaneous coronary intervention (PCI) and is associated with prolonged hospitalizations and worse outcomes [1]. Risk factors for AKI [2] include both patient-related and procedure-related features. Among these, vascular access may play a central role. To date, only registries with an imbalanced patients distribution across groups (Table I) have assessed a possible vascular access-related reduction in renal complications.

A recent report from the large retrospective Blue Cross Blue Shield of Michigan Cardiovascular Consortium (BMC2) database [4] and exploring the risks of AKI and nephropathy requiring dialysis (NRD) in patients treated with trans-radial intervention (TRI), as compared with trans-femoral intervention (TFI), demonstrates that TRI is associated with a significantly reduced risk of AKI (OR 0.76, 95% CI 0.62–0.92, Fig. 1). AKI has been defined in this study as an absolute increase in serum creatinine (sCr) >0.5 mg/dl. Noteworthy, the reduced incidence of AKI has been paralleled by a reduced incidence of bleeding (OR 0.47, 95% CI 0.36–0.63, Fig. 1). The authors have further explored whether the lower risk of AKI after TRI is actually mediated by the lower risk of bleeding by adjusting for bleeding as a potential intermediary mechanism. They have found that although bleeding is independently associated with AKI (OR 2.86, 95% CI 1.75–4.66), TRI-dependent bleeding reduction does not seem to be the mediator of the lower risk of AKI. Importantly, there has been no impact of hospital-level variability, reflecting no impact of centers’ volume and experience in TRI, although information about contrast volume has not been reported.

These results confirm and expand previous data from the British Columbia Cardiac and Renal Registries [3], which explored the association between diagnostic or interventional cardiac catheterization and later onset of a composite end point consisting of a new chronic kidney disease (CKD) status within 6 months, either new-onset CKD or stage 4–5 CKD or NRD. Overall, the incidence of CKD onset within 6 months of the procedure was 0.9%. Importantly, this percentage is higher than the estimated annual incidence of CKD in the general population. Although the study did not report on post-procedural AKI, it demonstrated that femoral access was associated with a more than four-fold increased risk for the composite renal end point (Fig. 2) across the entire cohort (OR 4.36, 95% CI 2.48–7.66, P < 0.0001). The results were confirmed after propensity matching analysis, but the possibility of having introduced bias through a “center effect” could not be ruled out in this study. Actually, patients in the radial group had received a significantly lower amount of contrast (104 vs. 116 ml for coronary angiography and 208 vs. 243 ml for PCI, both P < 0.0001).

In a much smaller single-center registry [5] with a more stringent definition (increase in sCr >0.5 mg/dl or 50% within 72 hr), TFI was no longer associated with increased risk of AKI after propensity matching (OR 1.48, 95% CI 0.72–3.04, P = 0.286). Of note, patients in the TFI group had received a lower volume of contrast (165 vs. 180 ml, P < 0.001). Finally, in a retrospective database of primary PCI performed at high volume Italian urban centers [6], TFI was an independent predictor of AKI (OR 1.56, 95% CI 1.02–2.39, P = 0.042) after adjustment for possible confounders and despite being associated with lower contrast use (189 vs. 207 ml, P < 0.001). As expected in high-risk patients with acute coronary syndromes (ACS), overall AKI (defined as increase in sCr >0.5 mg/dl or 25% within 72 hr) incidence was much higher (12.7%) than other studies.

In summary [7], observational data suggest an advantage of TRI over TFI in terms of reduction of the risk of AKI, although they are only hypothesis-generating. Actually, it may be argued that the supposed benefits of TRI might be due to the selection bias, which is inherent in registries. Else, they might be mediated by lower bleeding complications, lower cholesterol embolization syndrome (CES), or a combination of both (Table II). Importantly, no prospective comparison on renal outcomes has been carried out in randomized trials of TRI versus TFI. In this article, we present the rationale of a sub-study from the Minimizing Adverse hemorrhagic events by TR ansradial access site and systemic Implementation of AngioX (MAT RIX) program, the AKI-MATRIX, and discuss the potential mechanisms by which radial access may lead to lower incidence of AKI.

MATERIALS AND METHODS

The ongoing MATRIX study (ClinicalTrials.gov identifier: NCT01433627) is a multicenter, prospective
trial incorporating several levels of randomization and planning to enroll at least 8,200 patients undergoing diagnostic catheterization and at least 6,800 patients undergoing PCI. The aim of the MATRIX is to assess whether a combined mechanical and pharmacological bleeding avoidance strategy consisting in (1) TRI (as compared to TFI) and (2) bivalirudin infusion (as compared to unfractionated heparin plus provisional glycoprotein IIb/IIIa inhibitors) decrease the 30-day incidence of death, myocardial infarction, and stroke or BARC-defined type 3 and 5 major bleeding complications.

Fig. 2. Comparison of radial and femoral access site on adverse renal events at 6 months after diagnostic catheterization and PCI. The aim of the MATRIX is to assess whether a combined mechanical and pharmacological bleeding avoidance strategy consisting in (1) TRI (as compared to TFI) and (2) bivalirudin infusion (as compared to unfractionated heparin plus provisional glycoprotein IIb/IIIa inhibitors) decrease the 30-day incidence of death, myocardial infarction, and stroke or BARC-defined type 3 and 5 major bleeding complications.

TABLE I. Overview of Published Studies Exploring the Association Between Vascular Access and Renal Complications After Cardiac Catheterization or PCI

<table>
<thead>
<tr>
<th>Time period</th>
<th>Procedure</th>
<th>Patients number</th>
<th>TFI</th>
<th>TRI</th>
<th>Primary endpoint definition</th>
<th>Primary endpoint incidence</th>
<th>Access site comparison</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999–2005</td>
<td>Cardiac catheterization or PCI</td>
<td>67,824 (25,960 propensity matched)</td>
<td>54,144 (79.8%)</td>
<td>13,680 (20.1%)</td>
<td>New CKD status within 6 months</td>
<td>0.9%</td>
<td>TFI Vs TRI OR 4.36 (95% CI 2.48–7.66)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2010–2012</td>
<td>PCI</td>
<td>82,225 (17,714 propensity matched)</td>
<td>73,310 (89.2%)</td>
<td>8,915 (10.8%)</td>
<td>AKI (sCr &gt;0.5 mg/dl)</td>
<td>2.6%</td>
<td>TRI Vs TFI OR 0.76 (95% CI 0.62–0.92)</td>
<td>0.004</td>
</tr>
<tr>
<td>4/2009–9/2012</td>
<td>Cardiac catheterization or PCI</td>
<td>1,637 (1,374 propensity matched)</td>
<td>641 (39.2%)</td>
<td>996 (60.8%)</td>
<td>AKI within 72 hr (sCr &gt;0.5 mg/dl or 50%)</td>
<td>3.7%</td>
<td>TRI Vs TFI OR 1.48 (95% CI 0.72–3.04)</td>
<td>0.286</td>
</tr>
<tr>
<td>2011–2013</td>
<td>Primary PCI</td>
<td>1,330 (450 propensity matched)</td>
<td>494 (37.1%)</td>
<td>836 (62.9%)</td>
<td>AKI within 72 hr (sCr &gt;0.5 mg/dl or 25%)</td>
<td>12.7%</td>
<td>TRI Vs TFI OR 1.56 (95% CI 1.02–2.39)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

For abbreviations see the text.
across the whole spectrum of ACS patients undergoing early invasive management [8,9].

The primary endpoint of the current AKI-MATRIX sub-study is the incidence of AKI, defined as an absolute (>0.5 mg/dl) or relative (>25%) increase in sCr within 48 hr from the highest pre-intervention value [10,11] in patients undergoing TRI versus TFI. We conservatively assume a 5% incidence of AKI in the TFI group, although the incidence of AKI in contemporary studies of PCI in ACS may be threefold higher [12]. Available data [4] suggest a possible 25% relative risk reduction (RRR) in CI-AKI incidence with TRI approach across unselected populations undergoing PCI. We hypothesize a 33% RRR of AKI with TRI in the MATRIX study, which enrolls medium-to-high risk ACS patients [8,9]. Thus, with 3,400 patients per group undergoing PCI, we would have >93% power of detecting a reduction in the incidence of AKI to 3.3% in the TRI group at the 5% alpha level (Fig. 3).

All data will be adjusted by several factors including clinical and procedural variables and antithrombotic regimens. The association between the occurrence of bleeding complications and AKI will be also explored, and corrected for, in the comparison between the two randomly allocated vascular access sites. A prespecified subgroup analysis will be performed in patients with established CKD (i.e., with an effective glomerular filtration rate (eGFR) <60 ml/min per 1.73 m²) [13]. To further explore the clinical implications of a standardized definition, we will assess the incidence of AKI also by using the new KDIGO [13] definition (increase in sCr by ≥0.3 mg/dl within 48 hr). Of note, KDIGO guidelines also define as AKI any increase in sCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days, and any urine volume <0.5 ml/kg/h for 6 hr. These two latter definitions will be employed according to clinical data availability. Finally, we will assess the association between post-procedural eosinophilia [14] and AKI and whether a difference exists between left and right radial access in terms of reduced incidence of AKI and, in turn, whether it is mediated by a reduced amount of administered contrast with left radial access, as well as it has been extensively reported for fluoroscopy and procedural times [15].

**DISCUSSION**

**The Established Role of Contrast and the Issue of a Standardized Definition**

A large body of evidence supports that AKI is related to the volume of iodinated contrast media [16], whenever adjusted to baseline renal function [17,18], which in turn remains the most important predictor of AKI, NRD, and in-hospital death [19]. Nonetheless, the evaluation of renal function with either sCr or sCr-derived formulas (Cockcroft-Gault, MDRD, CKD-EPI) is considered inaccurate. These formulas have been actually developed for steady-state conditions and are not conceptually applicable to patients undergoing PCI, especially during ACS. These patients may have fluctuating sCr either because of fluctuating effective GFR or because of fluctuations in creatinine production and, importantly, in fluid balance. Even though the incidence of sCr increases is generally lower among

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**TABLE II. Potential Advantages and Drawbacks of Radial Access in Preventing Renal Adverse Events After Cardiac Catheterization and/or PCI**

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Drawbacks</th>
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<tbody>
<tr>
<td>Lower incidence of access-site bleeding and related hemodynamic instability.</td>
<td>Several catheter exchanges and use of higher contrast volume because of tortuous anatomy of brachial and subclavian arteries and aorta.</td>
</tr>
<tr>
<td>Lack of catheter manipulation in the abdominal aorta and reduced incidence of cholesterol embolization in the renal arteries.</td>
<td>Use of higher contrast volume because of increased procedural complexity with smaller guiding catheters (insufficient catheter backup and poor anatomy visualization).</td>
</tr>
<tr>
<td>Use of lower contrast volume by experienced radial operators/centers.</td>
<td>Higher risk of crossover to femoral access in elderly, low-weight and female patients.</td>
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</table>
patients undergoing early and sustained periprocedural hydration, it is unclear whether it represents true differences in effective GFR (namely, an AKI), the effect of a hemodilution, or some combination of both [20]. Hence, small post-procedural sCr increases in patients with baseline preserved renal function are likely to have minimal, if any, prognostic impact [10].

The incidence of contrast-induced AKI (CI-AKI) varies depending on patient population, risk factors and, especially, definition used [10]. A standardized definition is therefore needed in order to correctly evaluate any strategy for CI-AKI prevention [11]. To this purpose the 2013 KDIGO guidelines [13], which now encompass both more stringent criteria of sCr increase and the issue of urine output decline (which is not always routinely measured after PCI), will likely become a consensus for defining both occurrence and severity of CI-AKI.

In addition, an accurate prediction of the risk of CI-AKI in the pre-procedural phase is of utmost importance in patients with ACS, in whom there is only limited possibility to implement preventive measures. Left ventricular dysfunction and hemodynamic instability resulting in impaired systemic perfusion before exposure to contrast are key contributing factors in this setting. The use of algorithms [21–23] may serve as a guide in planning both the procedure and the strategies to prevent CI-AKI. Indeed, the identification of patients at risk has a direct impact in targeting prophylactic interventions, such as controlled volume expansion [24] and minimization of contrast [18]. Despite these measures, the incidence of AKI after PCI remains significant, as other mechanisms of renal damage are involved.

The Relationship Between Contrast Volume and Vascular Access: Is the Operator the True Mediator?

TRI has a steeper learning curve than TFI and failed access and radial artery complications are high early on, and decrease as operators become more skilled. Interestingly, in the RIVAL study [25] there was a significant interaction for the primary outcome with benefit for TRI in the highest tertile volume radial centers (HR 0.49, \(P = 0.015\)). Operators’ experience in TRI is crucial to reduce contrast especially in more challenging cases [26]. In elderly patients with advanced atherosclerosis, tortuosity of aorta and subclavian arteries may result in greater technical difficulty during TRI, exposing patients to higher contrast use and catheter exchanges (Table II), which overwhelm the advantages of TRI. In a study on octogenarians undergoing elective PCI from the radial approach, concerns have arisen about possible detrimental renal effects related to higher contrast load due to procedural complexity [27].

To this purpose, a strategy of systematic pre-procedural risk assessment and the use of TRI only in selected elderly patients is likely to maximize the benefits offered [27].

Is Bleeding the Elusive Link Between Vascular Access and AKI After PCI?

TRI has been gaining operators’ and patients’ preference at both sides of the Atlantic [28,29]. The main advantage of TRI is the very low incidence of relevant vascular access site-related bleeding; it allows early patient mobilization and thus early discharge with a drop in hospital costs [30]. In addition, significant cost savings derive by reduced complications [31].

A meta-analysis has shown that TRI reduces the odds of major bleeding up to 73% as compared to TFI [32]. Interestingly, this dramatic reduction in bleeding complications was associated with a trend toward lower death, myocardial infarction, or stroke (OR 0.71, 95% CI 0.49–1.01, \(P = 0.058\)). It is currently believed that the lower risk of hemodynamic instability due to bleeding plays a central role in preventing low-output states that are detrimental for renal function and lead to poorer in-hospital outcomes [33]. In the RIVAL study [34], indeed, a reduction in bleeding-related complications with TRI, leading to a reduced 30-day mortality risk, was observed in the STEMI group. In the RIFLE-STEACS study [35], which included STEMI patients admitted at four Italian centers experienced in TRI, the 30-day rate of net adverse clinical events, including a composite of ischemic and bleeding complications, was significantly reduced (13.6% vs. 21%, \(P = 0.003\)). In particular TRI was associated with significantly lower rates of cardiac mortality (5.2% vs. 9.2%, \(P = 0.020\)) and bleeding (7.8% vs. 12.2%, \(P = 0.026\)).

Bleeding is related with ischemic complications after PCI, especially during ACS [36]. Any measure aimed at reducing bleeding is expected to have a positive impact [37] on death, myocardial infarction, stent thrombosis, stroke, and on long-term outcomes [38,39] as well. The exact mechanisms underlying this relationship may include the cessation of evidence-based therapies in patients who suffer bleeding [40], the direct effects of blood transfusion used to treat bleeding [38], or greater prevalence of comorbidities in patients who bleed [41]. The most compelling evidence about the relationship between bleeding and negative outcomes is provided by interventional studies demonstrating that strategies aimed at reducing bleeding are associated with improved survival in patients with...
ACS [36] and in those undergoing PCI [23]. Importantly, a comprehensive analysis of populations enrolled in bivalirudin trials demonstrate that though any bleeding is deleterious, those which are non-access site related may impact even more on cardiovascular outcomes [42].

Periprocedural bleeding is emerging as a risk factor for the development of AKI: patients who experience bleeding have a higher likelihood of AKI, the incidence of which, in turn, correlates closely with bleeding severity, especially when hemoglobin decrease is higher than 3 g/dl [33] or hematocrit drop is higher than 6% [43]. These studies, although not adjusted for the vascular access, emphasize the close relationship between bleeding and AKI (Table II) and confirm the overall importance of volume of blood loss as a risk indicator.

**CES: An Under-Recognized Mechanism of AKI?**

CES has been hypothesized as one of the additional mechanisms contributing to AKI [44]. Autopsy studies demonstrate that the overall prevalence of CES is up to 30% after cardiac catheterization [45], although the real incidence in current practice remains unknown. Patients with CES may present with a spectrum of renal failure ranging from a subclinical to a lifethreatening disease, which is typically accompanied by evidence of extra-renal emboli [44]. However, the time course of CES is typically different from that of post-procedural AKI, with renal function declining over 2–8 weeks beyond the index event [44,46] and leading up to 30% patients to NRD and end stage renal disease within 6 months [47].

Catheter manipulations in the arterial bed disrupt aortic plaques, exposing the soft, cholesterol-laden plaque core to the arterial circulation. Scraping atherosclerotic debris into large lumen-guiding catheters is common with TFI [48]. The growing role of increasing invasive procedures on complex and elderly patients with generalized atherosclerosis as triggering factors for CES has been recently emphasized [47]. In addition, anticoagulants are hypothesized to initiate the disruption of complex plaques by causing internal hemorrhage or lysis of intra-intimal or cap thrombi [47]. Eosinophilia and elevation of C-reactive protein, both considered as markers of systemic inflammation and unstable plaques prone to disruption, have been described in patients with CES [14].

An advantage of TRI is to avoid passage through potentially atheromatous thoracic and abdominal aorta and closely to renal vessels (Table II), thus reducing the occurrence of embolization to the renal circulation [4,47]. Yet, during TRI the possibility of distal embolization of more proximal aortic plaques not only to epiaortic and retinal vessels [49] but also toward abdominal aorta cannot be actually ruled out. Although observational data [4] let hypothesize a possible protective role conferred by TRI on long-term renal outcomes by reducing clinically unapparent CES, the advantage of TRI in preventing CES remains to be proven.

**CONCLUSIONS**

A new paradigm is established according to which bleeding prevention is at least as important as preventing recurrent ischemic events in the management of patients with ACS, especially those undergoing an invasive approach. Periprocedural bleeding, which is consistently reduced by TRI, is emerging as a risk factor for the development of CI-AKI, whereas procedural complexity may overwhelm the established advantages of TRI. Hence, the role of vascular access as a measure to prevent AKI needs to be systematically assessed in randomized studies. The MATRIX trial has been designed to test whether to minimize bleeding events by means of an integrated pharmaco-mechanical strategy will result in improved outcomes with respect to ischemic events (primary endpoint) or to the combination of ischemic and bleeding complications (co-primary endpoint). The AKI-MATRIX sub-study will provide a unique opportunity to assess whether the advantages of TRI may reduce the risk of AKI after PCI across the whole spectrum of ACS patients.

**REFERENCES**


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