Dear Colleagues,

The Committee on Patient Protection is pleased to share with you our Society's Position Statement on the Safety of Fluorescein Angiography on Patients with Kidney Disease.

This recommendation aims to highlight the safety of fluorescein angiography, a common diagnostic procedure done in patients with retinopathy, in relation to Contrast-Associated AKI (CA-AKI). The creation of this position statement has been a long time coming, with new guidelines on CA-AKI released in recent years. Local studies and data have also been emerging, strengthening our available evidence.

Together with our Ophthalmology colleagues, we hope this guide will improve the care of our CKD patients needing fluorescein angiography, with the goal of lessening procedural delays and costs.

The Committee on Patient Protection

PHILIPPINE SOCIETY OF NEPHROLOGY

Position Statement on the Safety of Fluorescein Angiography on Patients with Kidney Disease

RATIONALE

Contrast Associated AKI (CA-AKI), is any Acute Kidney Injury (AKI) as defined by the KDIGO Guidelines, occurring within 48 hours after administration of contrast agents (MacDonald 2022). CA-AKI remains to be a dreaded complication following procedures usually requiring iodinated contrast. Controversy still exists in its diagnosis and management with monitoring and prophylactic protocols differing both internationally and locally.

Fluorescein Angiography (FA) is a common diagnostic tool that uses sodium fluorescein, a non-iodinated contrast, to visualize the retina. The widespread use of this modality in patients with both diabetes (DM) and chronic kidney disease (CKD) has led to a debate as to whether this type of contrast procedure may affect kidney function significantly or whether keen monitoring of kidney function and nephrology consultation is warranted prior to its conduct.

To date, there are no established standards or local protocols with practices varying depending on institutional requirements. Most centers necessitate repeat laboratory tests and nephrology subspecialty clearance in patients with elevated SCr, cut-off values of which still differ per center. Medical clearance along with routine testing of laboratories has led to some delays in imaging and management as well as unwarranted costs for patients. Hence, there is a need to review recent data and establish a consensus regarding the association of FA and CA-AKI, specifically in patients who are more prone to AKI such as those with CKD.

Footnote:
*Criteria for CKD [Chronic Kidney Disease] KDIGO 2012 - GFR <60 ml/min/1.73 m2 or markers of kidney damage [albuminuria, urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imaging, history of kidney transplantation] present for > 3 months.
*CKD is classified by 1. GFR [***G1*** Normal or high ≥90, ***G2*** Mildly decreased 60-89, ***G3a*** Mildly to moderately decreased 45-59, ***G3b*** Moderately to severely decreased 30-44, ***G4*** Severely decreased 15-29, ***G5*** Kidney failure <15] and 2. Albuminuria/UACR [***A1*** Normal to mildly increased <30 mg/g, ***A2*** Moderately increased 30-300 mg/g, ***A3*** Severely increased >300 mg/g].
* Criteria for AKI

RECOMMENDATION

Fluorescein angiography poses no to minimal risk of clinically significant CA-AKI in all stages of CKD, including those on dialysis. Hence, subspecialty nephrology referral for clearance and acute monitoring of laboratory parameters may not be necessary.
(Strong recommendation, Low-Moderate quality of evidence)

REVIEW OF EVIDENCE

Contrast-Induced AKI (CI-AKI) is differentiated from CA-AKI, as an AKI that can be definitively linked to contrast administration, implying direct causation. CI-AKI is the term previously used in literature and trials. Post-contrast AKI (PC-AKI) is synonymous with CA-AKI and implies correlation but not causation (Thomsen, 2018). The latest guidelines advocate the use of CA-AKI as more appropriate in clinical practice, delegating the use of CI-AKI only in studies with well-matched control groups, where direct causation of contrast media administration and AKI can be established. (Davenport, 2020) [Refer to Table 2] (Macdonald, 2022).

In this position statement, the term CA-AKI will be used. Though, we acknowledge the change in terminology was only adapted recently and previous literature and studies still refer to CA-AKI as CI-AKI.

As of this writing, there are no randomized controlled trials investigating the association of FA and CA-AKI. Most studies are in the form of retrospective reviews and prospective cohorts, enrolling patients with stable CKD with or without diabetes.

In patients with and without CKD, two retrospective studies found no association between FA and AKI, regardless of baseline kidney function or presence of co-morbidities (Chung 2014, Lee 2017). Meanwhile, a large retrospective study involving 979 subjects which used a different definition for CIN and CI-AKI (Table 1), noted the incidence to be 7.3% and 6.4% respectively. Their data showed a U-shaped distribution with higher incidence rate in Stage 1 (10.3%) and Stage 5 (29%). In their survival analysis, only CKD stage 3-5 was associated with ESRD progression. It is important to note, however, that these patients may be following a natural course of CKD and the statistical significance may not indicate a causal relationship (Yun 2019). Conversely, in the only local study available, a prospective cohort by Naidas et al identified 2.8% of subjects to have developed CI-AKI post-FA. Despite this, there was no prolonged worsening of renal function as evidenced by an increase in SCr in the study population which included both high and low risk groups. Moreover, when broken down according to risk stratification, those classified as intermediate [eGFR 30 - 59 mL/min] and high risk [eGFR ≤29 mL/min] even had a documented improvement in eGFR post-procedure (Naidas 2020).

In patients with both Type 2 Diabetes Mellitus (T2DM) and CKD, two retrospective cohorts revealed no significant increase in SCr and eGFR post-FA (Kameda 2009, Kim 2016). In contrast, only one small prospective study in patients with T2DM with and without CKD concluded otherwise. In this study, nine out of 44 patients had CI-AKI (Increase in SCr 25% or an absolute increase of ≥0.5 mg/dl) after FA exposure (Alamzadeh 2011). Almalki et al further elaborated the possibility of subclinical AKI as measured by other biomarkers. In this prospective study in patients with T2DM (N=100) , only one subject developed AKI as defined by SCr. However, 11 subjects were noted to have an increase in serum Cystatin C and 40 subjects had an increase in NGAL (Almalki 2017). Though the increase in these biomarkers was significant, the routine use of these parameters as standard in the diagnosis of AKI along with the relevance of subclinical AKI remains to be validated.

The review of Gumabon et al summarized the findings of some of the aforementioned studies. This meta-analysis included six studies with a total of 1555 subjects. In this analysis, diagnosis of CI-AKI was noted in 6.8% (106) patients. Furthermore, sex, DM, and CKD were not associated with an increased risk for AKI. Low hemoglobin and albumin levels were found to be associated with CI-AKI but not as independent risk factors as analyzed in the regression analysis. Though a statistically significant difference in serum creatinine values pre- and post-exposure [mean difference 0.05 (0.02, 0.07), p = 0.14] was found, the absolute value increase seems insignificant (0.02 to 0.07 mg/dL) (Gumabon et al 2020).

In view of the current evidence, most of the studies reported no association of FA and AKI, even in patients with pre-existing CKD or T2DM (Kameda et al 2009 , Chung et al 2014, Kim et al 2016, Lee et al 2017). Some studies noted a small percentage of CI-AKI in their study population, however, these were not clinically significant (Almalki et al 2017, Naidas et al 2020, Gumabon et al 2020). Moreover, elevated SCr levels in these reports went to baseline levels in a few days without the need for intervention, apart from oral hydration. Summary of incidences from all studies range from 0-20% (note that only one study had an incidence of 20% and the rest ranged from 0-7.3%). Only one study reported an adverse long term outcome of ESRD progression in those with CKD 3-5 who had CIN/CI-AKI post FA (Yun et al 2019). However, this data must be interpreted with caution as the decline in renal function may reflect the natural course of CKD progression and may not imply causation. More trials are needed to conclude the possibility of subclinical AKI through biomarker monitoring.

There were no studies that included patients on peritoneal or hemodialysis. However, it is sensible to infer that the possible kidney injury from the procedure will be clinically insignificant in those already on dialysis.

Based on these, FA poses no to minimal risk of clinically significant AKI. In standard doses, the procedure may be done without the need for subspecialty nephrology consultation and acute kidney function monitoring.

Table 1. Summary of Evidence

References	Study Design	Patient Population	No. of Patients	Volume of contrast	Cases with CA-AKI	Conclusion
Kameda et al, 2009	Retrospective cohort, single-center	Diabetic patients CKD stage 3-5	128 (99M, 29F)	2.5 ml of 10% solution	No cases of AKI CI-AKI not defined	In diabetic patients with CKD, eGFR did not change significantly following FA at CKD stage (3–5)
Chung et al, 2014	Retrospective, single-center	Not exactly defined	186	Not defined	4 out of 186 developed AKI due to other causes CI-AKI not defined	No AKI following FA
Lee et al, 2017	Retrospective, single-center	Non-dialytic CKD and non-CKD patients	160 (91M, 69F)	500 mg	2 developed AKI due to other causes AKI defined as 0.5mg/ml rise in SCr after FA	Acute renal function deterioration was not evident in patients undergoing FA regardless of baseline renal function and Comorbidities. FA safe in terms of AKI
Almalki et al, 2017	Prospective, single-center	T2DM with stable kidney function, with or without CKD	100 (71M, 29F)	5ml of 5% solution	1 developed AKI CI-AKI define 25% rise from baseline SCr, or absolute 0.5mg/dL increase in SCr 48-72h after contrast, 11 developed AKI by 25% increase in serum Cystatin-C, 40 developed AKI by 25% increase in urine NGAL	Possible subclinical AKI using newer biomarkers (serum cystatin-C and uNGAL), not detected by using SCr
Alamzadeh et al, 2011	Prospective cohort, single-center	T2DM with or without CKD	44 (22M, 22F)	500 mg	Nine patients Defined as an increase in SCr of ≥25% or an absolute increase of ≥0.5 mg/dl	Fluorescein could cause to renal injury in diabetic patients following FA
Rajput et al, 2017	Prospective cohort, single-center	T2DM CKD 3-5	11	5ml of 10% solution	No cases of AKI CI-AKI not defined	Normal dose of FA is safe in CKD 3A and 3B

Naidas et al, 2020	Prospective cohort, single-center	CKD and Non CKD	144 (38M, 106F)	5ml of 500mg solution	4 (2.8%) patients developed AKI CI-AKI defined as elevation of serum creatinine (≥25% or 0.5 mg/dL) within 72 hours of intravascular administration of contrast media in the absence of an alternative etiology	There was no prolonged or serious worsening of renal function based on SCr and eGFR before and after FFA
Kim et al, 2016	Retrospective, single-center	Diabetic, nondialysis CKD	80 (44M, 36F)	5ml of 10% solution	No AKI mentioned, CI-AKI not defined no significant differences BUN, SCr before and after fluorescein angiography eGFR was significantly increased after fluorescein angiography at CKD stage 3	FA is a relatively safe diagnostic examination in patients with diabetic retinopathy who did not receive dialysis due to the low-risk of renal function deterioration.
Yun 2019	Retrospective, multicenter	Adults with and without comorbids RRT, previous CT scan and CA excluded 43% CKD 3-5 63% DM	979 (38F)	250-500mg for 10 seconds	CIN 7.3% CIAKI 6.4% CIN criteria as >0.5 mg/dL or >25% in-crease in SCr level within 3 days after FA, and CI-AKI criteria as >= 0.3mg/dL increase within 2days or >= 50% increase within 7 days after FAG	FA may cause CIN and appeared to be a possible risk factor for ESRD progression. However, CIN or CI-AKI criteria themselves may overestimate AKI and require meticulous attention to the interpretation of results

Gumabon et al 2020	Meta-analysis	Adults with and without any co-morbids CKD-D excluded	6 studies, 1555	Variable per study 250-500mg	6.8% had CIN Hemoglobin ($p = 0.002$) and albumin ($p < 0.001$) levels may be associated with CIN but not independent risk factors for CIN (multivariable logistic regression, $p = 0.648$ and $p = 0.069$, respectively) Sex, DM, CKD not associated.	FA does not pose an increased risk for CIN.

Table 2. Definitions/Terminology

Term	Definition	Comment
Acute kidney injury (AKI)	Increase in creatinine >26 umol/L or 0.3 mg/dl in 48 hours, OR increase by >50%, which is known or presumed to have occurred within the 7 prior days OR urine output <5 mL/kg/hour for 6 - 12 hours	Defined on basis of KDIGO criteria, with staging by severity
Contrast associated acute kidney injury (CA-AKI)	AKI (as defined above) after a contrast procedure, includes CI-AKI and other causes of AKI such as acute tubular necrosis, acute interstitial nephritis and atheroembolic disease	"Associated" makes the distinction that AKI cannot be directly attributed to contrast
Post contrast acute kidney injury (PC-AKI)	AKI (as defined above) following a contrast procedure same as CA-AKI in definition	Here, "post contrast" is a descriptive term of chronology, not causation
Contrast induced nephropathy (CIN)	*Increase in creatinine of 44 umol/L or 0.5mg/dl or 25% from baseline after contrast administration*	*Seen in older literature, implies causality which remains unproven; time point not well established, from 24 to 72 hours*
Contrast induced acute kidney injury (CI-AKI)	*AKI (as defined above) after a contrast procedure, which can be attributed to contrast-induced kidney damage*	*Definition assumes that contrast caused AKI, which is now felt to be very rare and/or unproven causality*

Taken from 2022 Canadian Association of Radiologists Guidance on Contrast Associated Acute Kidney Injury
**Italicized terms are historical and not recommended for use.*

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