

# Implications of Renal Complications In Out Patient Referral for Coronary Angiography: Prospective Observational Study of 98 Cases

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## Abstract

The incidence of acute kidney failure remains high, due to the multiplication of interventional procedures on subjects at risk. It increases both morbi-mortality in hospitals and in the long term. The identification of patients at risk is primordial in order to implement the preventive measures, whose expansion remains the 'gold standard'. The realization of a coronary angiography in ambulatory care in this type of patient at risk is possible without increasing renal morbidity, under the cover of a good hydration.

**Introduction:** Acute renal failure is a complication that remains common after injection of contrast agent. It increases both morbidity and hospital mortality in the long term. We wanted to carry out a prospective observational study to evaluate the incidence of renal complications (acute renal failure, dialysis) of patients referred as an outpatient in our center for coronary angiography and who have benefited from measures of prevention of renal toxicity as recommended by learned societies.

**Methodology:** We conducted a prospective study at the Yves Le Foll hospital in Saint Brieuc over a period of 4 months from November 2015 to February 2016, in patients admitted on an outpatient basis for coronary angiography who had previously suspended all drugs with nephrotoxic potential and with hydration surrounding the examination. A survey card was developed to collect, after informed consent, sociodemographic data, risk factors, comorbidities, clinical and paraclinical data. All data was entered and analyzed using SPSS software version 18.0.

**Results:** Ninety-eight patients had an ambulatory coronary angiogram during this period. The sex ratio was 3.66 in favor of the male gender with an average age of 65 years. Three-quarters of the population (71%) had at least one risk factor for contrast-induced nephropathy. The mean clearance values before and after coronary angiography were almost similar (80  $\mu\text{mol/l}$ ) without significant variation. No impairment of renal function was observed in patients at risk regardless of the amount of contrast injected (range: between 30 and 277 ml). When patients accumulate risk factors for induced nephropathy in the contrast medium, there is an increase in the blood creatinine level with the number of factors but no significant change ( $p: 0.24$ ) of renal function after iodine injection.

**Conclusion:** The incidence of acute kidney injury remains high, due to the increase of intervention procedures in subjects at risk. The identification of these patients at risk is paramount in order to implement the preventive measures of which volume expansion remains the gold standard. The realization of an outpatient coronary angiography in this type of patient at risk is feasible without increasing renal morbidity with a good hydration.

**Keywords:** Kidney failure; Coronary angiography; Ambulatory; Hydration

## Introduction

Patients who require a scheduled intra-arterial catheterization procedure must have an estimate of the glomerular filtration rate according to the recommendations [1].

Several factors have been identified as acute renal failure risk markers post contrast injection [2]. The effect of risk factors is additive and the likelihood of developing AKI after percutaneous coronary intervention (PCI) increases rapidly with the number of risk factors.

We decided to carry out a prospective observational study to evaluate the incidence of renal complications (acute renal failure, dialysis) of patients referred as an outpatient in our center for coronary angiography, who have benefited from recommended renal toxicity measures [3,4].

## Patients and Methods

A prospective study was performed at the Yves Le Foll Hospital in Saint Brieuc over a period of 4 months (November 2015 to February 2016) in patients admitted on an outpatient basis for a coronary artery test. Included were hemodynamically stable coronary patients with

sufficient level of comprehension to call and return to hospital if necessary, residing within one hour of the examination center. They must not be home alone on the night of the exam, they must be reachable and must have the opportunity to take a shower home before the exam. Not included: dialysis patients, patients with contrast media within 48 h of coronary angiography, those with femoral coronary angiography and Ad hoc angioplasty.

At the request of their cardiologist, patients scheduled on an outpatient basis are admitted on the day of the examination at 7:30 am in the hospital, are fasting but take their usual treatment with a minimum

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of water beside ACE inhibitors, ARBs II, diuretics, allopurinol and metformin. Oral anticoagulants are suspended 48 h before the examination except in patients with mechanical valve prostheses.

A program of 4 exams per day is made by a coordinating nurse. Biological tests are carried out 48 h to 72 h before the procedure (hemogram, blood ionogram, creatinine, fasting blood glucose, known glycosylated hemoglobin if diabetic, lipid balance, blood grouping, blood crass, C-reactive protein).

Nephrotoxic drugs (Angiotensin-converting enzyme inhibitors or ACE inhibitors, angiotensin II receptors antagonists, diuretics, allopurinol, metformin) are suspended on the day of the examination; Metformin is resumed 48 h after ensuring the stability of renal function.

Intravenous hydration with isotonic saline solution is systematic upon admission; full-dose (1 ml/kg/h) for patients with preserved ventricular function and half dose for those who did not have echocardiography or had an altered ejection fraction. The release was carried out the same day in the afternoon at 16 h after at least 3 h of compression of the radial artery with a tourniquet and after having secured a good hemostasis. The results of 48 h renal function after the examinations were collected by fax on our server, or by direct contact with the laboratory that performed the blood test.

The parameters studied were:

- Clinical parameters: age, gender, constants and physical examination
- Cardiovascular risk factors, a history of kidney disease, coronary artery disease, and comorbidities.
- The indication of coronary artery disease
- Paraclinical parameters; Biology: hemogram, creatinine, lipid balance, C-reactive protein, creatinine 48 h after coronary angiography (in  $\mu\text{mol/L}$  and clearance according to the MDRD formula), electrocardiogram, cardiac ultrasound and coronary angiography (Pathway, quantity of contrast media, results, therapeutic strategy).

Acute renal insufficiency associated with the contrast agent is defined as a 25% increase in baseline serum creatinine or an increase of  $44 \mu\text{mol/L}$  (0.5 mg/dl) in serum creatinine 48 h following the injection of the product [1].

The elderly are defined by an age greater than 75 years.

Chronic renal failure is defined as creatinine clearance (MDRD)  $<60 \text{ ml/min /1.73 m}^2$  [1].

A questionnaire was developed to collect data after an informed consent. Averages and standard deviations were calculated using SPSS software version 18.0.

## Results

In total, we included 98 consecutive patients who underwent ambulatory coronary angiography. Patients range in age from 42 to 86 years. The average age of the study population is 65 years with a clear male predominance of 78.5% (77) whereas women make up only 21.5% (21) of the study population. Dyslipidemia is the major cardiovascular risk factor for 69 patients (70.4%). Fifty patients were hypertensive (51%), 25 diabetics of which 6 under insulin; 16 active smokers and 39 weaned. The other comorbidities were represented by lower limb arteriopathy in 11 patients (11.2%); chronic obstructive pulmonary disease (COPD) in 8 patients (8.2%), seven patients (7.1%) with a history of stroke and only five patients with a history of gout (5.1%). Given the upstream selection, only two patients had a known moderate chronic IR (clearance according to MDRD: 35 and 50 ml/min /1.73  $\text{m}^2$ ).

Three-quarters of the population (73.5%) had at least one risk factor for contrast-induced nephropathy (Figure 1). The majority of patients were symptomatic (69.3%), 36 (36.7%) had angina, 25 (51.5%) had dyspnea, and 2 patients had palpitations (Table 1). Thirty-one patients (31.63%) were asymptomatic with a test for positive ischemia in 91.1% of cases (Table 1). Seventy-one (72.4%) patients had echocardiography that resulted in altered EF in 6 patients (8.4%).

All patients were hydrated as soon as they were admitted by intravenous injection with physiological saline (1 ml/kg/h); Half-dose hydration was made for subjects with an ejection fraction of less than 40%; which is an average hydration of 49.89 ml/h over an average duration of 5.35 h.

All nephrotoxic drugs (non-steroidal anti-inflammatory drugs or NSAIDs, ACE inhibitors, angiotensin II receptors antagonists, diuretics, some oral anti-diabetics, allopurinol) on the day of the test,

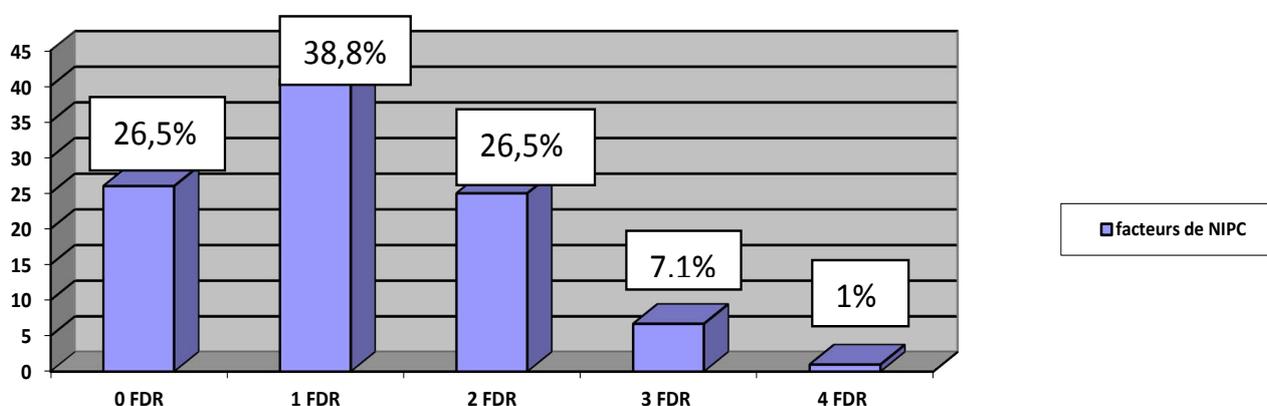


Figure 1: Cumulated risk factors for contrast-induced nephropathy. Risk factors : age older than 75 years; diabetes; hypertension; pre-existing renal failure; altered ejection function  $<40\%$ ; anemia hemoglobin  $<13 \text{ g/dl}$  in men and  $<12 \text{ g/dl}$  in women).

Variable		Number	Percentage (%)
Signs	Angina	36	36,73
	Dyspnoea	25	25,51
	Palpitations	2	2,04
	No symptoms	31	31,63
Indications	Scintigraphy	33	33,67
	Stress test	21	21,42
	Stress echocardiography	12	12,24
	Angina	14	14,28
	Others	18	18,36
EKG	Atrial fibrillation	6	6,1
	Repolarization abnormalities	25	25,5
	Q wave	14	14,3
TTE		71	72,4
	Altered left ventricle fraction	6	8,45
	Wall motions abnormalities	22	30,98

TTE: Transthoracic Echocardiography; EKG: Electrocardiogram; Altered left ventricle fraction (<40%)

Table 1 : Clinical characteristics

Variable		Number	Percentage (%)
Intra-arterial access	Radial	98	100
Amount of contrast medium	Mean dose	86	
	Minimum dose	30	
	Maximum dose	277	
Ventriculography		7	7,14
Vessel-disease	Normal arteries	42	42,85
	Single	16	16,32
	Double	25	21,42
	Triple	19	19,38
Treatment strategy	Medical treatment	60	61,22
	PCI	25	25,5
	CABG	13	13,26

PCI: Percutaneous Coronary Intervention  
CABG: Coronary Artery Bypass Graft

Table 2: Datas of the coronarography.

metformin suspended 48 h or the same day and resumed 48 h after examination and after renal function control.

The radial pathway was used in all patients. The contrast agent used in our center is Xenetix 300 (iobitridol) which is a product with low osmolality (695 mOsm/Kg H<sub>2</sub>O).

The injected dose of contrast agent varies between (30 and 277 ml) with an average dose of 86 (standard deviation: 37.48) (Table 2). Ventriculography was performed in seven patients (7.14%). Within our population; eight patients (6.7%) had a clearance of less than 60 ml/min, only one patient (1%) had a clearance of 35 ml/min. Mean serum creatinine before coronary angiography was 81.08 µmol/L (standard deviation: 16.23); after examination, it did not vary (80.95 µmol/l). Mean serum creatinine varied between 45 and 133 µmol/l in pre-angiography; And between 44 and 143 µmol/l in post-angiography (Table 3).

The creatinine variation ranged from -12 to +21 µmol/l. The values

of the clearances went in the same direction; with very little difference between before and after angiography as illustrated in Table 3. Eight patients (7.6%) had anemia defined by a hemoglobin level below 13 g/dl for men and 12 g/dl for women [5]. No subject had a history of myeloma. Mean serum creatinine before coronary angiography in diabetics was slightly higher than that of non-diabetic subjects (84.88 µmol/l versus 83.12 µmol/l), but no significant variation was observed after contrast injection (P: 0.36). There is also an improvement in renal function after coronary angiography in diabetics. In patients with renal insufficiency (2 patients); we note a slight increase of +5 µmol/l not significant (p: 0.42) after angiography as illustrated in Table 4.

This relationship remains constant in elderly patients with a minimal creatinine variation of + 0.1 µmol/l, not significant (p: 0.9); with a mean creatinine value (84.48 µmol/l) slightly higher than in young patients (79.99 µmol/l) as shown in Table 4.

There was no significant change in creatinine in hypertensive subjects and an improvement in renal function was observed in patients with impaired FE after contrast injection.

We took more precaution for known renal insufficiency where a very little amount of contrast medium was used (contrast agent average

Variable (µmol/l)	Values prior to ICM	Values after ICM
Mean creatinine	81,08	80,95
Mean clearance	88,19	88,42
Minimum creatinine	45	44
Maximum creatinine	133	143
Minimum clearance	35	35
Maximum clearance	162	155

ICM : Iodinated Contrast Media

Table 3: Comparison of renal function before and after injection of iodinated contrast media

Comorbidities	Creatinine	Clearance		Creatinine at 48 h	Variation of creatinine
		(MDRD)			
Diabetes					
Yes	84,88	83,84	83,12	86,72	-0,96
No	79,63	89,92	79,96	89,31	0,40
p	0,2	0,26	0,41	0,4	0,36
Pre-existing renal impairment					
Yes	131	42,5	136	40,5	5
No	80,05	89,15	79,80	89,48	0,11
p	0,001	0,001	0,001	0,001	0,42
Elderly patients					
Yes	84,81	78,24	84,48	80,57	0,10
No	80,06	90,91	79,99	90,56	0,13
p	0,23	0,01	0,26	0,02	0,9
Hypertension					
Yes	83,82	84,64	83,64	84,74	0,18
No	77,7	92,48	78,07	92,80	0,37
p	0,17	0,11	0,25	0,09	0,29
Left ventricle ejection fraction altered					
Yes	80,19	89,81	82,42	86,9	2,23
No	80,67	86,83	79,5	87,83	-1,17
p	0,9	0,84	0,83	0,84	0,02

Table 4: Variations of renal function according to comorbidities

amount of 40 ml). If the risk factors for nephropathy induced by the contrast media are cumulative, we find an increase in serum creatinine with the number of factors, But without significant variation in renal function after injection of contrast agent (Table 5).

## Discussion

Patients admitted to the cardiac catheterization room are at particular risk of developing induced nephropathy due to their comorbidities. In our series, Two out of three patients had at least one risk factor. In addition, prevention remains the most effective strategy for combating nephropathy induced by the contrast medium.

In our center, we take the precaution not to carry out an outpatient with a contrast agent injection within 48 h of the coronary examination.

All patients were hydrated once intravenously (1 ml/kg/h), Half-dose (0.5 ml/kg/hr for subjects with an ejection fraction (EF) of less than 40%). Continued oral hydration was recommended on the days following the examination.

Most published studies show the decreased incidence of ARI after iodine injection [6] in patients admitted for outpatient coronary angiography with preventive measures. Similarly, no post-coronary angiography was noted in our series, the maximum increase in serum creatinine is 21  $\mu\text{mol/L}$ , lower than the value of 44  $\mu\text{mol/L}$  defining the post-PCI acute renal failure.

Hypovolemia correction and volume expansion is the best-established measures to prevent the toxicity of iodinated contrast media [7].

Hydration also reduces the direct toxic effects of the contrast agent on the kidney by diluting and decreasing its viscosity in the renal tubules [8,9]. A meta-analysis of six trials demonstrated that oral hydration with a pre-specified expansion volume is as effective as intravenous for the prevention of contrast-induced nephropathy. Hydration with isotonic saline (SSI, 0.9% NaCl) is superior to hypotonic saline (0.45% NaCl) (0.7% % Versus 2%,  $p=0.04$ ), due to a better ability to expand the intravascular volume [7,10].

Therefore, current recommendations recommend hydration with 0.9% NaCl at 12 h before and 24 h after exposure to PC at a rate of 1-1.5 ml/kg/h [10].

For patients receiving an iodinated contrast agent in an outpatient setting, oral hydration is an alternative to avoid hospitalization; however, it should be associated with increased sodium intake [11].

There is currently no pharmacological strategy approved by European or American drug agencies for the prevention of acute renal failure following iodine injection [12,13].

Although popular since the study of Tepel et al. [13], N-acetylcysteine is not considered effective by most experts. NAC appears

to decrease creatinine by a tubular effect and a reduction in muscle production, without exerting any nephron-protective effect [14].

Despite the absence of specific studies, the temporary abolition of all drugs with nephrotoxic potential (NSAID, ACE inhibitors, diuretic, metformin) appears reasonable. These measures are well applied in our center, metformin was suspended on the day of the examination, and the recovery was only made after the renal function was returned to the previous values or its stability [1], and this in order to avoid the direct nephrotoxicity of the lactic acid released in case of imbalance.

Martinez [15] has shown that the risk is almost nil in a population with a strictly normal renal function and no other risk factor and will grow gradually to exceed 50% in a population characterized by advanced or even severe renal failure associated with sweetened diabetes or heart failure.

Known renal impairment patients, diabetics, hypertensive patients, elderly subjects and those with impaired EF (EF<40%) have a slightly higher risk [1]. In our study, more than 30% had at least 2 cumulative factors without there being an acute renal failure post contrast injection.

This lack of impairment of renal function in this at-risk population is due to preventive measures such as IV and oral hydration, use of low-osmolality contrast agents, cessation of nephrotoxic drugs, the use of radial approach and the limitation of the amount of contrast.

It appears that diabetes mellitus without nephropathy is not a significant risk factor [5].

However, diabetes is such a risk factor for nephropathy that caution should be exercised in this population [5]. In the diabetics of our series, No significant increase in serum creatinine was noted.

Pre-existing renal insufficiency is a sufficient and almost necessary condition for the development of renal failure by IBD [5].

A slight increase in serum creatinine (+5 micromoles) was noted in the two patients studied. The volume of contrast agent injected, its viscosity and its osmolality and its route of administration are strongly involved in induced nephrotoxicity [16,17].

Overall, the risk of acute renal failure after PCI is proportional to the osmolality of the PDCs used [15,16]. Most studies, but not all, as well as most meta-analyses, indicate that the risk of post-PCI acute renal failure is lower with iso-osmolar PCI (Iodixanol: Visipaque) as used in our center [16,17].

Current recommendations of the American College of Cardiology and the American Heart Association advocate the use of iso-osmolar PCI for the evaluation of acute coronary syndromes (grade A recommendations) [9].

The best way is to use the minimum contrast product for an exam. This amount is even more limited in subjects at risk. The average dose of contrast was 92 ml, and with very low dose of the order of 30 ml, we were able to carry out quality examinations.

The volume of PCI is a major risk factor for post-PCI acute renal failure, with the risk increasing in proportion to the dose [13,18].

It is therefore generally important to inject only the minimum contrast product without disregarding the rules of good practice for obtaining a good quality examination. The amount of contrast agent injected should not exceed twice the value of the clearance but this does not prevent a small amount of 30 ml of the contrast agent can

Numbers of cumulated risk factors	Mean creatinine prior to angiography	Mean creatinine after angiography	Variations of creatinine
0	78,12	75,84	-2,28
1	81,08	80,08	-1
2	87,11	88,26	1,15
3	91,42	89,14	-2,28
4	88	79	-9
	p : 0,24	p : 0,53	

**Table 5:** Variation of creatinine ( $\mu\text{mol/l}$ ) according to cumulated risk factors of contrast-induced nephropathy.

induce acute renal failure.

Angiographic techniques of rotational coronary angiography reduce the amount of iodine contrast agent [19] but are not used in our center.

The almost exclusive use of the radial artery (98% in our series) on an outpatient basis allows patients to get up early and wander in order to limit contact time between contrast agent and nephrons and to stimulate urination. This early diuresis is essential and allows limiting the contact time of the contrast product with the nephrons, which is the main physiopathological mechanism of nephrotoxicity. PCI stasis in the renal tubular lumen is responsible for direct cell damage [20]. The degree of renal tubular cytotoxicity is directly related to the duration of exposure of these cells to the iodinated contrast agent.

The effect of risk factors is additive and the likelihood of developing post-PCI acute renal failure increases rapidly with the number of risk factors. This has led to the development of prognostic models of risk, but none of these models has been prospectively validated in all populations at risk, so that these models, despite their conceptual interest, are not currently recommended in daily practice [3,4]. Overall, we can note that in a patient with chronic renal insufficiency, diabetes and other comorbidities, the estimated risk of post-PCI acute renal failure and emergency dialysis approaches 50 and 15% respectively.

In our prospective series, for patients who cumulated several risk factors for contrast-induced nephropathy, the well-conducted preventive hydration surrounding the injection avoided degradation of renal function.

Moreover, in view of the results of our study, we questioned the relevance of performing 48 h creatinine levels after angiography in very low-risk subjects and who benefited from measures to prevent nephropathies induced by the contrast agent as recommended.

## Recommendations

The identification of subjects at risk of post-PCI acute renal failure is paramount with strict monitoring of renal function.

Beforehand, it is necessary to study all the alternatives to injection of the contrast product. Nephrotoxic drugs are discontinued, and intravenous and oral hydration to all patients is recommended. A contrast agent of low osmolality is chosen and the intervening physician should use the lowest possible amount of contrast agent to perform a quality examination. The use of the radial pathway which would allow for earlier ambulation may be of interest in reducing the exposure of nephrons to the iodinated contrast agent.

## Limits of the Study

This is a monocentric trial with a population limited to 98 patients. Other studies of larger scale, multicentrics with greater population size will support better our conclusions.

## Conclusion

Despite significant progress in understanding the risk factors and pathophysiological mechanisms of post-PCI acute renal failure, the incidence of this complication is still high due to the multiplication of interventional procedures and procedures increasingly in high-risk patients and elderly.

The identification of subjects at risk and the implementation of appropriate measures to prevent renal toxicity make it possible to

avoid a large number of iatrogenic accidents. The two main recognized measures are the intravenous volume expansion of the procedure and the elimination of nephrotoxic drugs.

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