IS OFF-CLAMP ROBOTIC PARTIAL NEPHRECTOMY BENEFICIAL FOR RENAL FUNCTION? DATA FROM THE CLOCK TRIAL

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ABSTRACT:

Objectives: to compare the functional outcomes of on- vs off-clamp robot assisted partial nephrectomy (RAPN) within a randomised controlled trial.

Materials and methods: the CLOCK (CLamp vs Off Clamp the Kidney during robotic partial nephrectomy; NCT 02287987) is a multicentre randomised controlled trial including patients with normal baseline function, two kidneys and masses with RENAL score ≤ 10. Pre- and post-operative renal scintigraphy was prescribed.

Renal defatting and hilum isolation were required in both arms; in the on-clamp, ischemia was imposed until the completion of medullary renorraphy, while in the off-clamp it was not allowed along all the procedure.

The primary endpoint was the 6-months absolute variation of eGFR (AV-GFR); secondary endpoints were: 12/18/24-months AV-GFR; rate of 6-months eGFR variation>25% (RV-GFR>25); absolute variation in ipsilateral split renal function (AV-SRF). Planned sample size was 102+102 cases, net of cross-over; a 1:1 randomization was done. AV-GFR and AV-SRF were compared with ANCOVA, RV-GFR>25 with multivariable logistic regression. Intention to treat (ITT) and per-protocol analyses (PP) were done.

Results: 160 and 164 patients were randomly assigned to on- and off-clamp RAPN; a cross-over was observed in 14% and 43% of on- and off-clamp arms, respectively. We were unable to find any statistically significant difference concerning primary (on- vs off-clamp; ITT: 6-months

AV-GFR -6.2 vs -5.1 ml/min, mean difference 0.2 ml/min [95% CI -3.1 to 3.4, p=0.8]; PP: 6-months AV-GFR -6.8 vs -4.2 ml/min, mean difference 1.6 ml/min [95% CI -2.3 to 5.5, p=0.7]) as well as all the secondary endpoints. The median warm ischemia time (WIT) was 14 vs 15 mins in the ITT analysis, 14 vs 0 mins in the PP.

Conclusions: in patients with regular baseline function and two kidneys, on-and off-clamp RAPN did not provide evidence of differences in functional outcomes.

1. Introduction

Guidelines prioritize partial over radical nephrectomy for cT1 renal cell carcinoma [1,2] and robotics (robot assisted partial nephrectomy, RAPN) is becoming the standard approach to this procedure, being equally effective but less morbid than the open and laparoscopic counterparts [3].

The major benefit of partial over radical nephrectomy is the reduced risk of chronic kidney disease, which might translate into reduced mortality at long-term, although this evidence come just from retrospective data [4-6]. The degree of functional preservation after RAPN in part depends on unmodifiable factors related to the baseline patient or tumour's features, but also on modifiable factors by adjustment of surgical technique [7,8]. Among the latter, the artery clamping strategy has been put under investigation since many years, alternatively assuming a fundamental or secondary role: to date it is well established that in presence of a normal contralateral kidney only prolonged warm ischemia time (WIT) leads to the irreversible impairment of ipsilateral renal function, as well as that the single-kidney is more exposed to the ischemic damage, lacking of contralateral compensation [9]. Conversely, it remains a matter of debate whether a limited WIT could be clinically relevant in those patients with two kidneys and normal baseline function. In fact, data from a multitude of retrospective studies remain controversial and many authors advocated well-designed prospective trials to fix this issue [10-

13].

The present paper reports the results of the CLOCK (CLamp vs Off Clamp the Kidney during robotic partial nephrectomy) trial, a multicentre randomised study designed to acquire more solid evidence on the impact of an off-clamp approach to RAPN.

2. Material and methods

2.1 Study Design

The CLOCK trial (ClinicalTrials.gov NCT 02287987 [14]) is a phase 3 RCT conducted on behalf of the AGILE Group (Italian Group for Advanced Laparoscopic Surgery, http://www.agilegroup.it). Ethical committee approval was obtained by the coordinating centre (NP 1814). Patients were consecutively recruited at 7 Italian Institutions between September 2015 and November 2018, with approximately constant accrual rate over time. One surgeon per institution with a well-defined profile (<45 years-old, previous experience with at least 100 RAPN, done with both under on- and off-clamp approaches) performed all the procedures at his centre. All investigators were educated in detail on the study protocol, through dedicated meetings. The random sequence for the two comparison groups was computer-generated using the command ralloc in Stata 15. Randomized allocation with a 1:1 ratio was assigned by a permuted block design, stratified by center. Randomization was also stratified according to the complexity of the tumor based on the r.e.n.a.l. score (<7 vs. ≥7). Data were collected within a web-based e-form maintained by independent data-managers; only the study statistician (M.S.), had access to the datasheet. Surgeons were informed of the randomization arm just before surgery and were allowed to change the assigned approach before or during the procedure, in order to preserve patient's safety or avoid unnecessary ischemia, according to their personal opinion; in case of cross-over a dedicated report detailing the decision was required.

2.2 Study Participants

The trial screened at each Institution all the consecutive patients diagnosed of renal mass suspicious for malignancy and suitable for RAPN, according to Guidelines and treating

physician's opinion. The inclusion criteria were: age between 18 and 80 years-old; regular coagulation profile; baseline estimated glomerular filtration rate (eGFR) ≥60mL/min/1.73m^2; no abnormalities for both kidneys at medical history and imaging; cT1 renal tumour with RENAL score [15] complexity ≤10; agreement to participate to the trial and signed informed consent.

2.3 Perioperative Management and Surgical Technique

Pre- and post-operative management followed the Institutional protocols. These phases were handled by physicians/nurses not directly involved in the surgical procedures and blind of the randomization results. The CKD-EPI equation [16] was adopted to calculate eGFR from serum creatinine. Diethylene-triamine-pentacetic acid renal scan was prescribed before surgery and 6 months after to assess split renal function (SRF); nuclear medicine physicians were blinded of the randomization results. Follow-up included six-month abdominal and chest imaging and blood chemistry, up to 24 months from enrolment.

The surgical steps were strictly regulated by the study protocol: for both arms kidney defatting and renal artery isolation were mandatory. In the on-clamp arm, at least the tumour resection and the inner renorrhaphy were required to be completed under global ischemia; in the off-clamp arm the renal artery had to remain unclamped along all the procedure. Controlled hypotension during resection was not allowed. The specimens were examined according to international guidelines by experienced uro-pathologists blinded of the clamping approach.

2.4 Endpoints

The primary endpoint of the study was the absolute variation of eGFR (AV-GFR, continuous variable) at 6 months. The following secondary endpoints were addressed: the 12, 18 and 24-months AV-GFR; the 6-months rate of relative variation in eGFR over 25% (RV-GFR>25, dichotomous variable); the 6-months absolute variation in the SRF of the operated kidney at scintigraphy (AV-SRF, continuous variable).

2.5 Statistical analysis

The primary aim of the study was to compare the mean values of AV-GFR at 6 months in the on- and off-clamp groups. According to a superiority trial design, the H0 hypothesis was that no differences between groups were expected, while the alternative hypothesis H1 was that a

difference could be observed. The sample size was calculated using the formula for ANCOVA proposed by Borm, Fransen e Lemmens [17]:

$$n = \frac{2\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 (1-\rho^2)\sigma^2}{\delta^2}$$

where n is the number for each experimental group, α the statistical significance, 1-β the power of the test, σ the standard deviation of the outcome, ρ the correlation between pre- and post-operative eGFR values, and δ the effect size (absolute difference of the average outcome variation in the two experimental groups). A standard deviation σ of 20 ml/min for 1.73 m^2 was assumed, according to the best evidence available at time of study design [18]. Setting α=5%, 1-β=80%, a value of ρ^2 not less than 0.6, and a clinically significant minimum difference δ=5 ml/min for 1.73 m^2, the minimum required sample size was of 102 + 102 patients. After 12 months from the beginning of the study, investigators evaluated to continue the recruitment until the minimum sample size was reached, net of the dropout due the cross-over between groups.

Descriptive analysis reported median and interquartile range (IQR) for continuous variables, frequencies and proportions for dichotomous ones.

The mean values of the AV-GFR and AV-SRF outcomes at 6 months in the on- and off-clamp groups were compared using ANCOVA, statistically controlling for the effects of gender, age, tumour dimension, RENAL score, and the outcome observed at the baseline. The adjusted mean difference between the two study groups (with 95% confidence intervals) was reported.

The comparison of RV-GFR>25 rates in the on- and off-clamp groups was performed by multivariable logistic regression and the odd ratio (OR) (adjusted by gender, age, tumour dimension, RENAL score, and preoperative eGFR) was estimated (on-clamp as the reference group).

An explorative (ITT and PP) subgroup analysis was also performed and heterogeneity of AV-GFR differences between on- and off-clamp was analysed, considering some potential confounders (diabetes, hypertension, ECOG score o vs >0, CCI 0-1 vs >1, and RENAL score 4-6 vs >6). A test of interaction and rainforest plot were used to investigate heterogeneity.

A p value <0.05 was considered statistically significant. Analysis was performed using

Stata® 16.1 (StataCorp 2019, College Station, TX, USA).

3. Results

Over 353 patients screened, 324 were enrolled and randomly allocated either in the on-clamp (160) or off-clamp (164) arm. A cross-over was observed in 23/160 (14%) patients allocated into the on-clamp arm and in 69/164 (43%) randomised to the off-clamp (Figure 1). According to surgeon's reports, such events were due to: "no need for ischemia due to the low complexity of the tumour" in the 23 cases shifted to off-clamp; "presumptive need for ischemia due to high complexity of the tumour" and "excessive bleeding" in 14 and 55 of the cases shifted to on-clamp, respectively.

3.1 Intention-to-treat Analysis

Baseline features were well-balanced, with median eGFR equal to 87.3 vs 86.9 mL/min, operated kidney SRF 48% vs 49%, tumour diameter 3 vs 2.7 cm and RENAL score 7 vs 6, respectively in the on- and off-clamp arms (Table 1).

Given the rate of cross-over, on the whole 137/160 (86%) patients in the on-clamp arm and 69/164 (43%) in the off-clamp arm underwent artery clamping with WIT equal to 14 (IQR 11 to 18) and 15 (IQR 13 to 19) mins (p=0.09), respectively.

No statistically significant differences were found concerning the primary endpoint. Indeed, the 6-month AV-GFR was -6.2 (IQR -18 to 0.5) ml/min for the on-clamp group and -5.1 (IQR -14 to 0.1) ml/min for the off-clamp group, with a mean difference between groups of 0.2 (95% CI -3.1 to 3.4, p=0.8). No statistically significant differences were noted also in secondary endpoints. In detail, in the off- vs on-clamp groups: the AV-GFR at 12, 18 and 24 months, was -6.4 (IQR -14.1 to -0.7) vs -5.8 (IQR -17 to -1.5), -5.2 (IQR -16.1 to 0.2) vs -5.3 (IQR -13.4 to 1.0), -5.3 (-13.9 to 0.3) vs -6.3 (IQR -15.9 to 0.1); the 6-month RV-GFR>25 rate was 17% and 10% (adjusted OR 1.2, p=0.8); the 6-month AV-SRF was -2.5% vs -2% (mean difference of -1%, p=0.3). (Table 2, Figure 2).

Subgroup analysis did not evidence any significant heterogeneity between subgroups based on diabetes, hypertension, ECOG score, CCI and RENAL score (Supplementary Material).

3.2 Per-protocol Analysis

This analysis includes the 232/324 patients (137 on-clamp, 95 off-clamp) who effectively underwent the surgery originally assigned by randomization, net of drop out. The median WIT was 14.3 (IQR 11 to 18) mins for the on-clamp group, 0 mins for the off-clamp group.

Baseline of on- vs off-clamp groups was similar, with eGFR 86.2 vs 87 ml/min, operated kidney SRF 48% vs 49%, median tumour 3 vs 2.2 cm and RENAL score 7 vs 6 points, respectively (Table 1).

No statistically significant differences were noted in the 6-month AV-GFR, equal to -6.8 (IQR -18 to 0.6) ml/min for the on-clamp group vs -4.2 (IQR -12 to 1.7) ml/min for the off-clamp group, for a mean difference between groups of 1.6 (95% CI -2.3 to 5.5 ml/min, p=0.7). Concerning secondary endpoints, again, no statistically significant differences were noted between the on- and off-clamp group: the AV-GFR at 12, 18 and 24 months, was -3.6 (IQR -14.1 to -0.7) vs -6.5 (IQR -17.1 to 0.1), -3.9 (IQR -10.1 to 1.0) vs 6.4 (IQR -16.1 to 0.0), -5.1 (IQR -11.9 to 0.7) vs -6.4 (-16.5 to 0.1); the 6-month rate of RV-GFR>25 was 15% vs 10% (adjusted OR 1, p=1); the 6-month median AV-SRF was -3% vs -2% (mean difference -0.6%, p=0.7) (Table 2, Figure 2).

Subgroup analysis did not find any significant heterogeneity between subgroups (Supplementary Material).

4. Discussion

The CLOCK trial was designed to address whether clamping or not the artery during RAPN influences the post-operative renal function. The prospective and randomised design, the availability of pre- and post-operative renal scintigraphy and the rigorous data-management represent some distinctive strengths of this project. Moreover, the study was conducted within a "real-life scenario" involving multiple surgeons in order to improve the generalizability of our results.

The main finding is that we cannot show differences between on- and off-clamp RAPN in terms of functional endpoints, both at the intention-to-treat and per-protocol analyses. Indeed, at 6-12-18 and 24 months after surgery the groups were comparable in terms of absolute decrease in eGFR, rate of eGFR decrease>25% and extent of variation in ipsilateral renal function at renal scan. Overall, these data provide new evidence that no detrimental functional effects should be

attributed to the artery clamping in patients with two normal kidneys, regular baseline function, masses with RENAL score ≤10 and experiencing a limited WIT.

Such a conclusion offers a valuable contribution to the debate on the functional impact of on- vs off-clamp approaches for RAPN. To date, the evidence is mostly based on a large amount of retrospective studies, however reaching conflicting conclusions [10-12], reasonably owing to selection bias.

A few more studies tried to fill this gap by means of statistical matching, but results were again not univocal. From a multi-institutional dataset with 886 cases operated by 5 surgeons, Kaczmarek et al. [18] could match 49 off- and on-clamp procedures, showing a significant lower eGFR decrease for the first (-2% vs -6%, p=0.0008). Conversely, Rosen et al. [19], from another multi-institutional dataset including 351 cases treated by 5 surgeons, matched 41 off-clamp and 82 on-clamp RAPNs, finding no differences in early and late functional endpoints. Mari et al. [20], over 491 cases treated by multiple surgeons at a single Institution, matched 120 on- vs 120 off-clamp RAPN done by pure enucleation, and reported better short-term outcomes for the off-clamp approach (30-day eGFR drop -2.5 vs -9%, p=0.01), but this was not the case at 6 months. Bertolo et al. [21] compared the experience of 2 high-volume surgeons, each one devoted to one clamping approach, matching 200 off-clamp cases with 400 on-clamp (WIT of 22 mins). They found a larger early eGFR drop for the on-clamp group, but no differences at longer follow-up. Simone et al. [22] matched 472 off-clamp procedures from the same surgeon with 157 on-clamp (WIT 16 mins) performed at an Institution different from the previous study. On the contrary, they found an advantage for the off-clamp group in terms of long-term probability to maintain an unmodified eGFR (8-year probability, 58% vs 4%, p=0.02) and risk of eGFR<45 ml/min (risk at 2, 5 and 8 years for off-clamp 0.8% vs 0.6%, 4.9% and 15.5% for the on-clamp).

The main reason of the discrepancies found in all these few retrospective studies is, reasonably, the unaccounted selection bias. Actually, the small proportion of procedures that could be extracted for matching from larger datasets unveil how stringent was the selection to the off-clamp approach. Additionally, all studies omitted to report if cases were converted from the off- to the on-clamp approach, although we found that this is a frequent event and depends on tumours complexity [23].

To address these limitations, “well designed prospective trials” have been eagerly invoked. To date only Anderson et al. [24] commendably conducted a RCT with this aim.

Compared to the CLOCK trial, their cohort was smaller (71 patients) and all the procedures were done by a single surgeon devoted to the off-clamp approach, having previously performed more than 300 procedures. With similar baseline patient and tumours features, as well as comparable WIT (19 mins), at a median of 3-months of follow-up they observed in the on- vs off-clamp a decrease in eGFR of -10.2 vs -9.8 ml/min, and a decrease in SRF of -5.4% vs -5.4%. Hence and notably, this and our RCTs reached perfectly aligned conclusions showing no statistically significant differences in the functional outcomes of the off- and on-clamp approaches. It should be remarked that the two approaches proved to be equivalently safe, in terms of both intra- and peri-operative courses, as well as positive surgical margins rate [25].

Although randomised and perspective, the present study is not devoid of limitations to be acknowledged. Firstly, it could be argued that the results coming from the specific setting of a RCT could be less generalizable because patients could have received some additional care: this concern can be mitigated by the fact that the pre- and post-operative phases were handled following standard protocols, and by physicians not directly involved in the trial. Secondly, the study was powered on a mid-term endpoint, i.e the 6-months variation of eGFR. However, it should be noted that at this interval functional compensation is almost complete [26] and that this new-baseline eGFR well predicts long term renal function [27]. Thirdly and mostly, we observed a not negligible rate of cross-over that could have reduced reliability of the ITT analysis. In randomised superiority trials, it is well established that data analysis should be performed based on the ITT principle, although this should be considered as a conservative approach that tends to produce diluted treatment effect estimates. In addition, heterogeneity might be introduced when noncompliant, dropouts and compliant subjects are mixed together in the final analysis [28, 29]. Considering the higher rate of cross-over in the off-clamp arm, mostly related to tumour's complexity, it could be assumed that the ITT analysis might have "favoured" the on-clamp arm. On the other hand, it should be remarked that crossover should be expected in any RCT focused on a surgical procedure. For example, in a recent RCT on pelvic lymphadenectomy for prostate cancer that compared arms differing just for the template of dissection, noteworthily 9% of cases did not receive the assigned treatment [30]. It could be shared that the greater are the differences in the perceived risk between study arms, the higher the expected cross-over rate: reasonably, resecting a tumour from a kidney perfused or not makes some differences and explain the cross-over rate we noted.

The present RCT did not show evidence of different functional outcomes between on- and off-clamp RAPN, in patients with two kidneys, normal baseline renal function and exposed to a limited warm ischemia time. Surgeons should adopt their preferred approach, regardless the intention to improve functional preservation.

Legends to illustrations:

Figure 1: CONSORT flow diagram for the CLOCK trial concerning the intention-to-treat (Figure 1a) and per protocol (Figure 1b) analysis.

Figure 2: Box plots describing the variation between baseline and 6-months after surgery of eGFR and ipsilateral scintigraphic contribute, in the intention-to-treat (left boxes) and per protocol analyses (right boxes) (AV-GFR, absolute variation of estimated glomerular filtration rate; AV-SRF, absolute variation of split renal function).

Tables and their legends:

Table 1: Baseline features according to the intention to treat and per protocol analysis - numbers represent frequency (percentage) and median (IQR - interquartile range).

Table 2: Descriptive statistics and mean differences between groups for primary (AV-GFR) and secondary endpoints (RV-GFR>25 and AV-SRF). P is the p-value of the test of equal means performed by ANCOVA. Model1 is a multivariable regression model with treatment (on-clamp vs off-clamp) and eGFR at diagnosis as covariates; Model2 is a multivariable regression model with treatment, eGFR at diagnosis, sex, age, tumor dimension, and RENAL score as covariates.

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Conflict of interest statement:

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	Intention to treat analysis		Per-protocol analysis	
	On-Clamp (n=160)	**Off-Clamp (n=164)**	**On-Clamp (n=137)**	**Off-Clamp (n=95)**
Gender, male	86 (60)	99 (60)	83 (61)	56 (59)
Age, years	63 (54 – 70)	66 (55 – 71)	63 (54 – 70)	66 (55 – 70)
BMI, Kg/m^2	26.4 (24.6 – 28.7)	26.1 (24.2 – 28.4)	26 (24.2 – 28.4)	26.2 (23.9 – 29)
Platelets count, n	220,500 (180,000 – 271,500)	216,000 (186,500 – 259,000)	221,000 (181,000 – 271,000)	214,000 (185,000 – 254,000)
Hemoglobin, g/dl	14 (12.9 – 15)	14.3 (13.3 – 15.3)	14 (12.9 – 14.9)	14.3 (13.3 – 15.2)
Hematocrit, %	42.6 (40 – 45)	43 (40.2 – 45.7)	42 (40 – 44.7)	42.8 (40 – 45)
PT, %	98 (94 – 100)	99 (93 – 100)	97 (93 – 100)	99 (95 – 100)
PTT, sec	29.9 (27.9 – 32.1)	29.6 (27.2 – 32.4)	30 (27.9 – 32.1)	29.4 (27.1 – 32)
GFR, ml/min	87.3 (75.5 – 96.2)	86.9 (76.2 – 98.5)	86.2 (73.1 – 96)	87.0 (77.5 – 99.8)
Operated Kidney % SRF	48.1 (46 – 51)	49 (47 – 52)	48 (46 – 51)	49 (47 – 52)
Hypertension	85 (53)	95 (58)	71 (52)	51 (54)
Diabetes	21 (13)	17 (10)	16 (12)	11 (12)
Vascular Disease	28 (17)	25 (15)	23 (17)	12 (13)
Cardiac Disease	40 (25)	29 (18)	33 (24)	12 (13)
Urinary Obstruction	2 (1.3)	1 (0.7)	2 (1.6)	1 (1.1)
ECOG Performance Status				
0	116 (73)	136 (83)	101 (74)	82 (86)
1	35 (22)	25 (15)	28 (21)	11 (12)
>2	8 (5)	3 (1.8)	7 (5.1)	2 (2.1)
CCI				
0	91 (58)	98 (61)	80 (60)	55 (60)
1	39 (25)	43 (27)	31 (23)	23 (25)

2	13 (8.3)	10 (6.3)	12 (9)	8 (8.8)
>2	13 (8.3)	9 (5.6)	10 (7.5)	5 (5.5)
Clinical tumor dimension, cm	3.0 (2.2 – 4)	2.7 (2 – 3.8)	3 (2.3 – 4)	2.2 (2 – 3)
R.E.N.A.L. Score	7.0 (5 – 8)	6.0 (5 – 7)	7 (6 – 8)	6 (4 – 7)

BMI=body mass index; GFR=glomerular filtration rate; ECOG=Eastern Cooperative Oncology Group; SRF=split renal function; CCI=Charlson comorbidity index

Table 1. Baseline features according to the intention to treat and per protocol analysis - numbers represent frequency (percentage) and median (IQR - interquartile range).

	Intention to treat analysis					
	On-clamp (N=160)	**Off-clamp (N=164)**	**Model1: difference Off- vs On-Clamp**		**Model2: difference Off- vs On-Clamp**	
AV-GFR at 6 months (ml/min)	Median (IQR)	Median (IQR)	Mean (95% CI)	P	Mean (95% CI)	P
	-6.2 (-18 to 0.5)	-5.1 (-14 to 0.1)	0.1 (-3.1 to 3.4)	0.9	0.2 (-3.1 to 3.4)	0.8
RV-GFR>25 at 6 months	N (%)	N (%)	Unadjusted OR	P*	Adjusted OR	P*
	32/186 (17%)	10/98 (10%)	1 (0.5 to 2)	0.9	1.2 (0.6 to 2.4)	0.6
AV-SRF at 6 months (%)	Median (IQR)	Median (IQR)	Mean (95% CI)	P	Mean (95% CI)	P
	-2.5 (-6.1 to 0.8)	-2 (-6 to 0)	-0.3 (-2.1 to 1.5)	0.7	-1 (-2.7 to 0.8)	0.3
	Per-protocol analysis					
	On-clamp (N=137)	**Off-clamp (N=95)**	**Model1: difference Off- vs On-Clamp**		**Model2: difference Off- vs On-Clamp**	
AV-GFR at 6 months (ml/min)	Median (IQR)	Median (IQR)	Mean (95% CI)	P	Mean (95% CI)	P
	-6.8 (-18 to 0.6)	-4.2 (-12 to 1.7)	1.6 (-2.3 to 5.5)	0.4	1.6 (-2.3 to 5.5)	0.7
RV-GFR>25 at 6 months	N (%)	N (%)	Unadjusted OR	P*	Adjusted OR	P*
	19/124 (15%)	8/79 (10%)	0.6 (0.3 to 1.5)	0.3	1 (0.4 to 2.9)	1
AV-SRF at 6 months (%)	Median (IQR)	Median (IQR)	Mean (95% CI)	P	Mean (95% CI)	P

	-3 (-7 to 0)	-2 (-6 to 0)	0.5 (-1.4 to 2.3)	0.6	-0.4 (-2.2 to 1.5)	0.7

Table 2. Descriptive statistics and mean differences between groups for primary (AV-GFR) and secondary endpoints (RV-GFR>25 and AV-SRF). P is the p-value of the test of equal means performed by ANCOVA. Model1 is a multivariable regression model with treatment (on-clamp vs off-clamp) and eGFR at diagnosis as covariates; Model2 is a multivariable regression model with treatment, eGFR at diagnosis, sex, age, tumor dimension, and RENAL score as covariates.

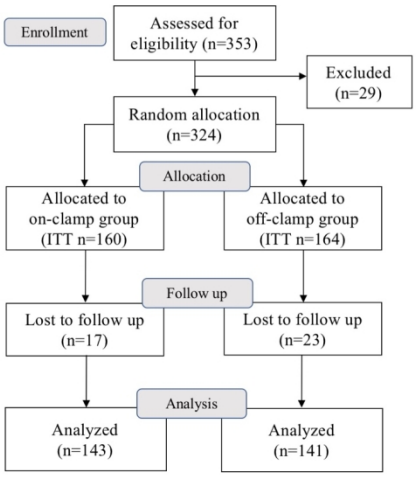

Figure 1a

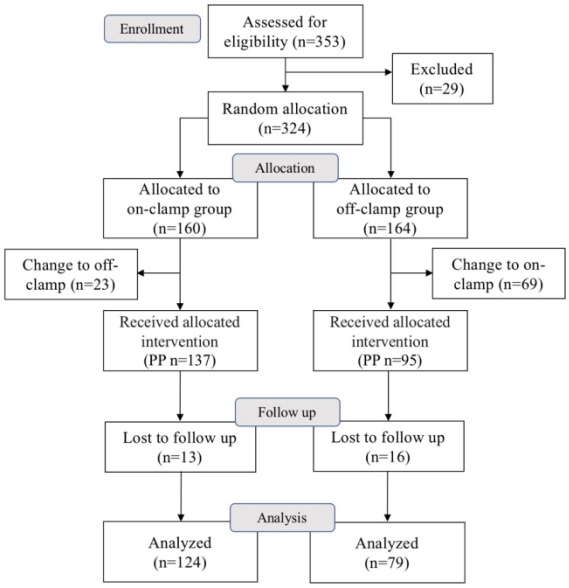

Figure 1b

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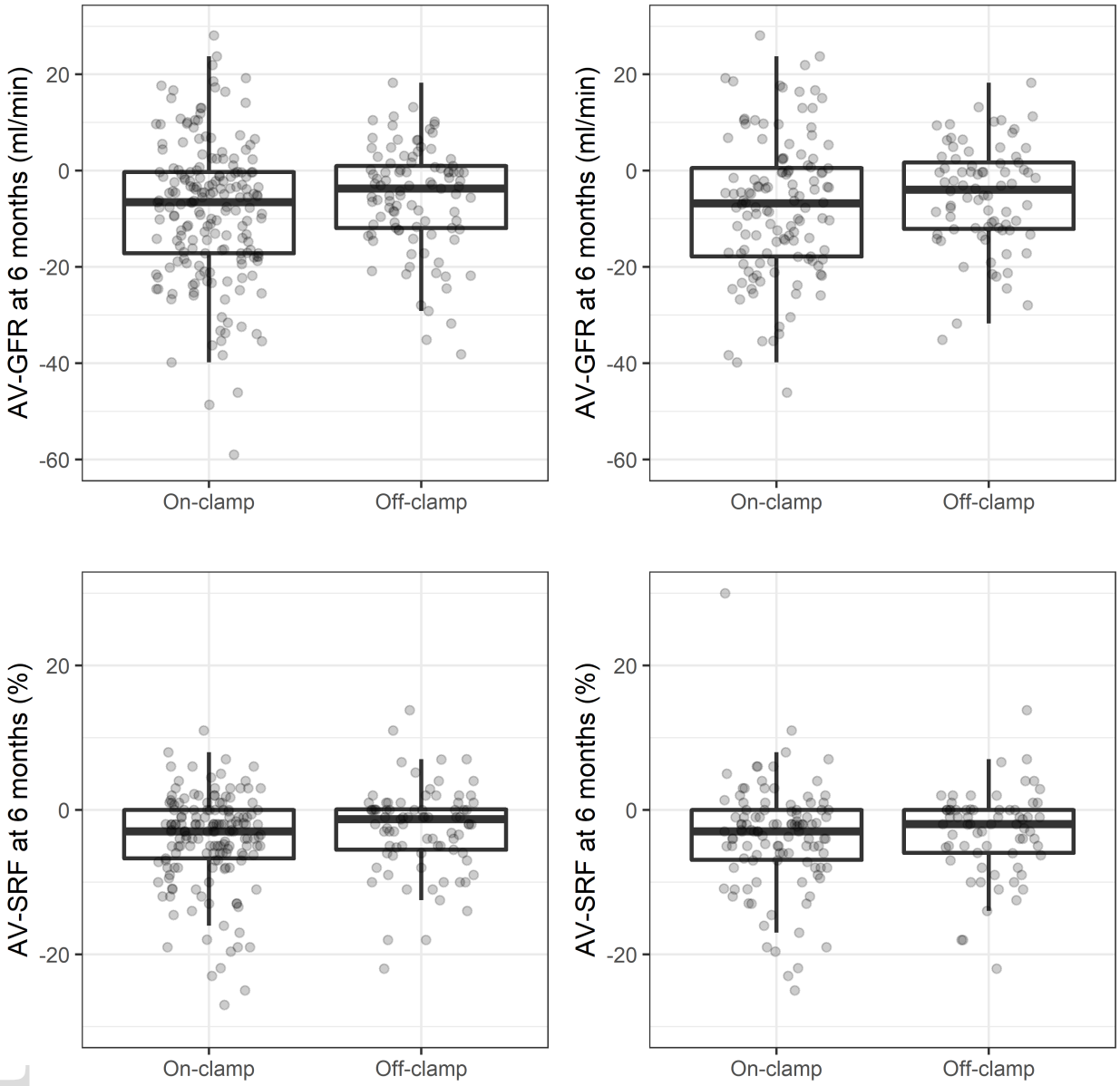

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