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Assessing the impact of renal artery clamping during laparoscopic partial nephrectomy (LPN) for small renal masses: the rationale and design of the CLamp vs Off Clamp Kidney during LPN (CLOCK II) randomised phase III trial

Dear Editor,

Interplay between patient- and surgery-related factors determines the functional recovery after partial nephrectomy (PN) [1]. Ischaemic injury resulting from renal arterial clamping has historically been one of the major modifiable surgical factors responsible for the functional decline after PN. As such, several techniques for minimising or even eliminating hilar clamping have been described [2].

Laparoscopic PN (LPN) with a pure off-clamp technique has been described, but the debate is still ongoing as to whether it is appropriate and beneficial with respect to safety and renal function [3]. The indication to perform an off-clamp LPN has remained mostly subjective. When opted for, the off-clamp resection is attempted to eventually clamp the artery 'on demand' in cases of bleeding. This behaviour has undoubtedly compromised the quality of the published data.

With the aim of raising the level of evidence, the CLamp vs Off Clamp Kidney during LPN (CLOCK II) randomised clinical trial was conceived. The CLOCK II is a pre–postoperative, prospective, multicentre, parallel, superiority, randomised controlled trial (RCT), supported by the Italian Group for Advanced Laparo-Endoscopic surgery (AGILE group, www.agilegroup.it).

Here we report the rationale and design of the study, a large, phase III RCT seeking to examine the role of renal artery clamping during pure LPN for small renal masses (ClinicalTrials.gov NCT02287987). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines were followed [4].

The primary aim of the study is to compare the preoperative vs postoperative (at 3 and 6 months) GFR in on-clamp vs off-clamp LPN. The secondary aim is to compare the treatment groups: (i) in terms of technical difficulties, namely the cross-over rate from off-clamp to on-clamp, the time taken for renorrhaphy, and the total operative time; (ii) in terms of morbidity, namely blood loss, haemoglobin drop, and overall and bleeding-related complications' rates; (iii) finally, in terms of oncological effectiveness, namely the positive surgical margins rate.

After accounting for exclusion criteria (Fig. 1) [[5–9]], eligible patients are randomised in a 1:1 ratio. After randomisation, the two arms are defined as follows: Arm A, on-clamp LPN (with clamping of renal artery); Arm B, off-clamp LPN (no clamping of renal artery).

The random sequence for the treatment groups is computer generated using the command *ralloc* in Stata 15 (StataCorp., College Station, TX, USA). Randomised allocation with a 1:1 ratio is assigned by a permuted block design, stratified by centre. The allocation arm is notified by the study internet-based e-form, managed by an independent software house. At any moment, from randomisation to the end of the procedure, the investigators are able to amend the indication given by randomisation and shift to the alternative clamping option, detailing the timing and the reasons of their decision. Categorical variables are summarised as absolute and relative frequencies, while numerical variables as mean and standard deviations or median and interquartile range, as appropriate. The comparison of the average estimated GFR and haemoglobin pre- vs postoperative variations in the treatment groups (off-clamp vs on-clamp LPN) is conducted using the analysis of covariance (ANCOVA). The comparison of the median values of the operative times and of the renorrhaphy times in the study groups is performed using the non-parametric Mann–Whitney test for independent samples. The complications' rates are compared by Fisher's exact test. The association between clinical features and the event of shift from off-clamp to on-clamp LPN is investigated using binary logistic regression and measured by odds ratio. All tests are two-sided.

The outcome measurements will be analysed: (i) by intention to treat, (ii) according to the actual treatment received, and (iii) per protocol (participants who actually received the treatment they were originally assigned to).

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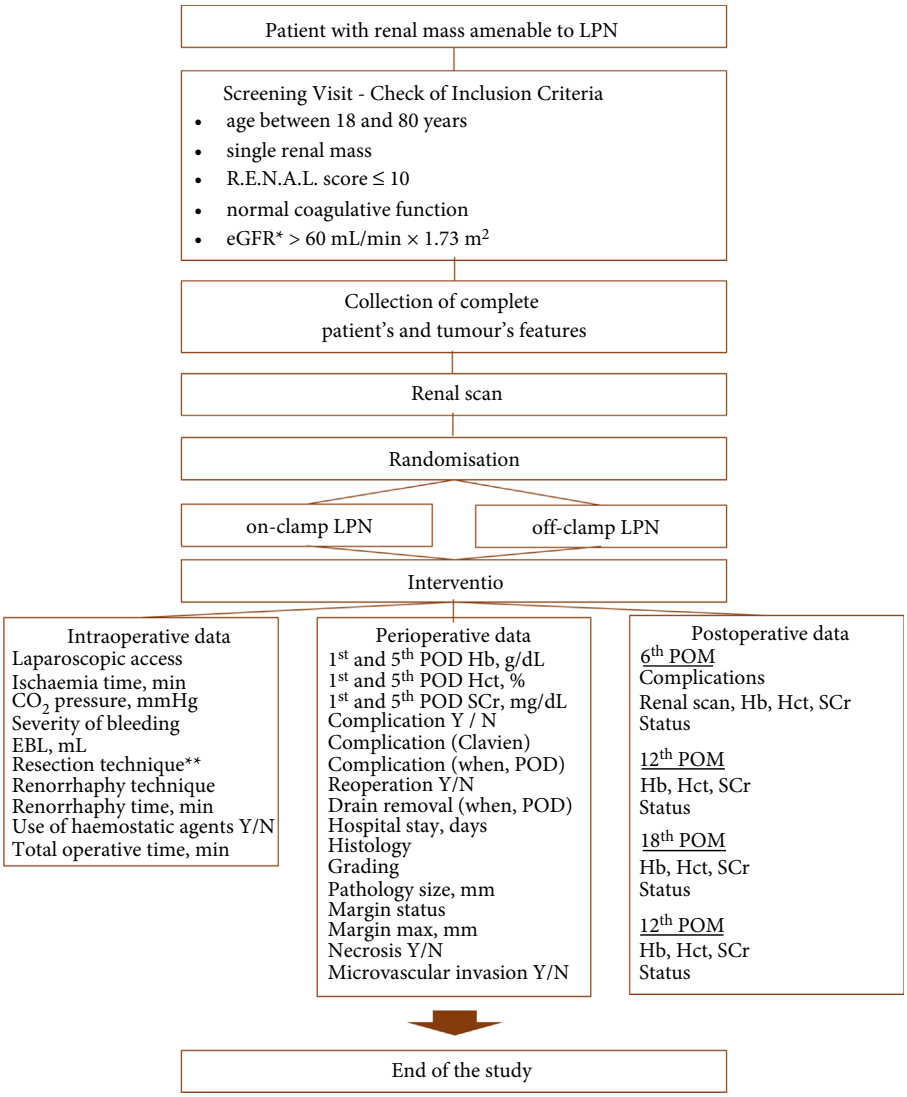
Fig. 1 The Clock II RCT flowchart. Patients demographics (body mass index, hypertension, diabetes, vascular disease, cardiac disease, comorbidities classified according to Charlson Comorbidity Index [5] and Eastern Cooperative Oncology Group [ECOG] performance status), baseline characteristics (tumour size, R.E.N.A.L. [Radius; Exophytic/Endophytic; Nearness; Anterior/Posterior; Location] score [6], renal scan data, serum creatinine [SCr], estimated GFR [eGFR] – calculated by the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI) from SCr [7], haemoglobin [Hb] and haematocrit [Hct]), perioperative, and postoperative data are collected. The resection technique is classified by the validated Surface-Intermediate-Base margin (SIB) score [8]. Intraoperative bleeding severity is quantified on a scale from 0 (no bleeding) to 5 (bleeding faster than can be removed by suction); postoperative complications are classified according to the Clavien–Dindo system [9]. The surgical procedure is determined by the study protocol and includes kidney defatting, and renal artery isolation and suspension in all patients. In the on-clamp LPN arm, tumour resection and inner renorrhaphy are mandatorily done under ischaemia, whereas in the off-clamp arm the artery is left unclamped throughout the entire procedure. Neither preoperative trans-arterial embolisation nor intraoperative controlled deep systemic hypotension is allowed. EBL, estimated blood loss; POD, postoperative day; POM, postoperative month.



All adverse and serious adverse events that might be related to the study procedures are collected, fully investigated and documented during the whole study period. An online dataset is generated (web sites: https://www.agilegroup.it/progetti-scientifici/rene/ and http://agilegroup.scientificnetwork.org/user/login). The datasets generated and/or analysed during the present study are available from the corresponding author on reasonable request. The target sample size has been calculated

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using the Borm, Fransen and Lemmens formula for ANCOVA:

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

where n is the number for each experimental group, α the statistical significance, $1-\beta$ the power of the test, σ the standard deviation of the outcome, ρ the correlation between pre- and postoperative GFR values, and δ the effect size (absolute difference of the average outcome variation in the two experimental groups) [10].

Based on previous reports, we assumed a standard deviation σ of 20 mL/min/1.73 m^2 [11]. For α = 5%, $1-\beta$ = 80%, a ρ^2 of 0.6, and a clinically significant minimum difference δ = 5 mL/min/1.73 m^2, the minimum required sample size was calculated to equal 102 patients per arm. Finally, after adjusting for a 10% chance of dropouts, 113 patients per arm were considered the target enrolment. The study will be completed 24 months after the last enrollment, including a 6-, 12-, 18- and 24-month follow-up.

To the best of our knowledge, the CLOCK II study is noteworthy because it will be the first prospective RCT comparing the perioperative and functional outcomes of off-clamp vs on-clamp LPN. Interestingly, the data obtained will be cross-analysed with those of the CLOCK I randomised study [12] comparing off-clamp to on-clamp robot-assisted PN.

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Conflict of Interest

All authors declare that they have no conflict of interests.

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