**Supplementary Material for**

**Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI-multicenter randomized controlled trial**

The PrevAKI2 Investigators

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**Collaborators**

The following persons collaborated in the trial and need to be mentioned:

Department of Critical Care, Guy's & St Thomas' NHS Foundation Hospital, Department of Critical Care, London, UK: Sara Campos, Neus Grau Novellas, Ursula Blanco-Alonso.

**Supplementary Figures**

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**Figure S1:** Hemodynamic algorithm (intervention group)

Abbreviation: CI, cardiac index; MAP, mean arterial pressure; PLRT, passive leg raising test.

**Supplementary Tables**

**Table S1:** Definition of the KDIGO bundle elements

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| **Bundle element** | **Criteria for compliance** |
| Discontinuation of all nephrotoxic agents  | Patients did not receive any nephrotoxic substances (e.g. NSAIDs, vancomycin, aminoglycosides) |
| Optimization of hemodynamics  | Patient’s lowest documented MAP was >65mmHg and no treatment had been initiated or optimized to achieve this goal |
| Close monitoring of serum creatinine, urine output and fluid balance | Serum creatinine was measured twice a day, and urine output was documented at least every 2 hours, and fluid balance was recorded twice a day |
| Avoidance of hyperglycemia | Blood glucose was not ≥150mg/dl on two consecutive samples more than 3 hours apart |
| Consideration of alternatives to radiocontrast agents | Patients did not receive radiocontrast agents for the first 72h after surgery |
| Discontinuation of angiotensin-converting-enzyme inhibitors and Angiotensin II Receptor Blockers | Patients did not receive ACEi/ARBs during the first 48h after surgery |
| Avoidance of hydroxyethyl starch (HES), gelatin, and chloride-rich solutions | Patients did not receive HES, gelatine or chloride rich solutions for 72h after surgery |

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| Table S2: Further demographic and operative data |  |
|  | **Control (n=142)** | **Intervention (n=136)** | **Standardized effect size** |
| ASA grade, No. (%) |  |  | 0.59b |
|  1 | 4 (2.8) | 2 (1.5) |  |
|  2 | 29 (20.4) | 24 (17.6) |  |
|  3 | 83 (58.5) | 86 (63.2) |  |
|  4 | 26 (18.3) | 24 (17.6) |  |
| New York Heart Association classification, No. (%) |  |  | 1.02b |
|  I | 15 (18.1) | 10 (14.5) |  |
|  II | 37 (44.6) | 31 (44.9) |  |
|  III | 31 (37.3) | 24 (34.8) |  |
|  IV | 0 (0) | 4 (5.8) |  |
| *Intraoperative volume therapy, median (Q1, Q3), ml* |
|  Crystalloids | 1000.0 (1000.0, 1500.0) | 1000.0 (1000.0, 1500.0) | 0.15c |
|  Colloids | 500.0 (400.0, 812.5) | 500.0 (400.0, 625.0) | 0.47c |
| *Intraoperative blood products, median (Q1, Q3), ml* |
|  erythrocyte concentrates  | 468.0 (300.0, 600.0) | 400.0 (300.0, 600.0) | 0.47c |
|  thrombocyte concentrates | 250.0 (196.5, 328.0) | 250.0 (187.5, 306.5) | 0.35c |
|  fresh frozen plasma | 854.0 (750.0, 900.0) | 900.0 (900.0, 1064.5) | 1.54c |

Abbreviation: ASA, American Society of Anesthesiologists Physical Classification System;

Data presented as mean (±standard deviation), median (Q1, Q3) or number (percentages).

a standardized mean difference (t-test statistic)

b square root of the chi-square statistic

c Wilcoxon Z statistic

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| **Table S3:** Volume and hemodynamics at different time points during the intervention period |
|  | **Control (n=142)** | **Intervention (n=136)** | **Intervention versus Control (95% CI)** |
| ***Volume therapy during intervention period, median (Q1, Q3),ml*** |
|  At randomization | 928.5 (500.0, 1394.8) | 1000.0 (537.5, 1447.0) | LS = 57.0 (-99.0, 202.0) |
|  3h | 583.0 (280.0, 985.3) | 653.5 (357.5, 1000.0) | LS = 49.0 (-50.0, 170.0) |
|  6h | 904.0 (500.0, 1447.8) | 1050.0 (550.0, 1510.0) | LS = 122.0 (0.0, 300.0) |
|  9h | 1010.0 (541.5, 1899.3) | 1351.5 (550.0, 2127.3) | LS = 140.0 (-55.0, 342.0) |
|  12h | 1340.5 (563.5, 2060.0) | 1641.0 (800.0, 2451.0) | LS = 250.0 (0.0, 500.0) |
| ***MAP, mean (± SD), mmHg*** |
|  At randomization | 73.0 (11.1) | 75.2 (11.5) | MD = 2.2 (-0.5, 4.9) |
|  3h | 73.0 (9.4) | 76.7 (11.5) | MD = 3.7 (1.2, 6.2) |
|  6h | 74.0 (10.5) | 76.4 (10.3) | MD = 2.5 (0.0, 4.9) |
|  9h | 74.8 (10.3) | 76.9 (10.1) | MD = 2.1 (-0.3, 4.5) |
|  12h | 75.3 (11.2) | 78.4 (12.6) | MD = 3.1 (0.2, 5.9) |
| ***CVP, mean (±SD), mmHg*** |  |  |  |
|  At randomization | 10.2 (4.3) | 10.1 (4.6) | MD = -0.1 (-1.2, 0.9) |
|  3h | 9.3 (4.4) | 10.0 (4.7) | MD = 0.6 (-0.5, 1.7) |
|  6h | 8.7 (4.7) | 9.9 (5.2) | MD = 1.2 (-0.0, 2.3) |
|  9h | 8.9 (4.4) | 9.9 (4.9) | MD = 1.0 (-0.1, 2.1) |
|  12h | 9.1 (4.2) | 10.1 (4.9) | MD = 1.0 (-0.1, 2.1) |

Abbreviation: CVP, central venous pressure; MAP, mean arterial pressure; OR, odds ratio with asymptotic Wald confidence limits; LS, location shift (Hodges-Lehmann estimator with confidence limits); MD, mean difference with confidence limits

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| **Table S4:** AKI outcomes |  |  |  |
|  | **Control (n=142)** | **Intervention (n=136)** | **OR****(Intervention versus Control) (95%CI)** | **RRR[[1]](#footnote-1)**  (%) **(95% CI)** | **ARR[[2]](#footnote-2)**  (%) **(95% CI)** |
| AKI within 72h, No./total No. (%) | 59/142 (41.5) | 63/136 (46.3) | 1.21 (0.76, 1.95) | -11.5 (-45.5, 14.6) | -4.8 (-16.4, 6.9) |
|  Diagnosis based on, No. (%) |  |  |  |  |
|  Creatinine | 22 (37.3) | 24 (38.1) |  |  |  |
|  Urine output | 27 (45.8) | 26 (41.3) |  |  |  |
|  Both | 10 (16.9) | 13 (20.6) |  |  |  |
| AKI stage, No./total No. patients with AKI within 72h (%) |  |  |  |  |  |
|  1 | 25 (42.4) | 44 (69.8) | 1.21 (0.76, 1.95)[[3]](#footnote-3) | -11.5 (-45.5, 14.6)[[4]](#footnote-4) | -4.8 (-16.4, 6.9)[[5]](#footnote-5) |
|  Diagnosis based on, No (%) |  |  |  |  |
|  Creatinine | 14 (56.0) | 20 (45.5) |  |  |  |
|  Urine output | 10 (40.0) | 19 (43.2) |  |  |  |
|  Both | 1 (4.0) | 5 (11.4) |  |  |  |
|  2 | 28 (47.5) | 12 (19.0) | 0.52 (0.28, 0.96)[[6]](#footnote-6) | 41.7 (2.9, 65.0)[[7]](#footnote-7) | 10.0 (0.9, 19.1)[[8]](#footnote-8) |
|  Diagnosis based on, No (%) |  |  |  |  |
|  Creatinine | 7 (25.0) | 4 (33.3) |  |  |  |
|  Urine output | 15 (53.6) | 6 (50.0) |  |  |  |
|  Both | 6 (21.4) | 2 (16.7) |  |  |  |
|  3 | 6 (10.2) | 7 (11.1) | 1.23 (0.40, 3.76)[[9]](#footnote-9) | -21.8 (-253.3, 58.0)[[10]](#footnote-10) | -0.9 (-5.9, 4.1)[[11]](#footnote-11) |
|  Diagnosis based on, No (%) |  |  |  |  |
|  Creatinine | 1 (16.7) | 0 (0) |  |  |  |
|  Urine output | 2 (33.3) | 1 (14.3) |  |  |  |
|  Both | 3 (50.0) | 6 (85.7) |  |  |  |

Abbreviation: AKI, acute kidney injury; ARR, absolute risk reduction; RRR, relative risk reduction; asymptotic Wald confidence limits;

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| **Table S5:** Further outcomes |  |  |  |
|  | **Control (n=142)** | **Intervention (n=136)** | **OR****(Intervention versus Control) (95%CI)** | **RRR[[12]](#footnote-12)**  (%) **(95% CI)** | **ARR[[13]](#footnote-13)**  (%) **(95% CI)** |
| ***Persistent renal dysfunction, No./total No. (%)*** |
| PRD on day 30 | 0 (0) | 3 (3.2) | 7.70 (0.39, 151.04) |  | -3.2 (-6.8, 0.4) |
| PRD on day 60 | 0 (0) | 0 (0) |  |  |  |
| PRD on day 90 | 0 (0) | 0 (0) |  |  |  |
| ***Renal replacement therapy, No./total No. (%)*** |
| RRT on day 30 | 1 (0.7) | 3 (2.3) | 3.14 (0.32, 30.56) | -209.0 (-2833.6, 67.4) | -1.5 (-4.4, 1.4) |
| RRT on day 60 | 0 (0) | 3 (2.3) | 10.24 (0.55, 192.14) |  | -2.3 (-5.0, 0.3) |
| ***Mortality, No./total No. (%)*** |
| Mortality at hospital discharge | 3/142 (2.1) | 2/136 (1.5) | 0.69 (0.11, 4.20) | 30.4 (-310.2, 88.2) | 0.6 (-2.5, 3.8) |
| 30-day all cause mortality | 4/138 (2.9) | 2/133 (1.5) | 0.51 (0.09, 2.84) | 48.1 (-178.5, 90.3) | 1.4 (-2.1, 4.9) |
| 60-day all cause mortality | 4/134 (3.0) | 4/129 (3.1) | 1.04 (0.25, 4.25) | -3.9 (-306.6, 73.5) | -0.1 (-4.3, 4.0) |
| ***Major adverse kidney events, No./total No. (%)*** |
| MAKE30 | 2/99 (2.0) | 5/93 (5.4) | 2.76 (0.52, 14.57) | -166.1 (-1238.4, 47.1) | -3.4 (-8.7, 2.0) |
| MAKE60 | 1/79 (1.3) | 2/73 (2.7) | 2.20 (0.20, 24.76) | -116.4 (-2236.9, 80.0) | -1.5 (-6.0, 3.0) |
| MAKE90 | 1/71 (1.4) | 3/67 (4.5) | 3.28 (0.33, 32.35) | -217.9 (-2881.5, 66.1) | -3.1 (-8.7, 2.6) |

Abbreviation: MAKE, major adverse kidney events; PRD, persistent renal dysfunction; RRT, renal replacement therapy

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| **Table S6:** Primary and secondary outcomes (Subgroup of patients with NC≤2) |
|  | **Control (n=135)** | **Intervention (n=123)** | **OR****(Intervention versus Control) (95%CI)** | **RRR[[14]](#footnote-14)**  (%) **(95% CI)** | **ARR[[15]](#footnote-15)**  (%) **(95% CI)** |
| **Primary outcome** |  |  |  |  |  |
| Patients treated according to CT surgery bundle, No./total No. (%) | 6/135 (4.4) | 78/123 (63.4) | 37.27 (15.20, 91.39) | 61.7 (51.5, 69.7) | 59.0 (49.8, 68.2) |
| **Secondary outcomes** |  |  |  |  |
| AKI within 72h, No./total No. (%) | 53/135 (39.3) | 56/123 (45.5) | 1.29 (0.79, 2.12) | -16.0 (-54.3, 12.8) | -6.3 (-18.3, 5.8) |
| Moderate to severe AKI, No./total No. (%) | 29/135 (21.5) | 16/123 (13.0) | 0.55 (0.28, 1.06) | 39.4 (-5.9, 65.4) | 8.5 (-0.7, 17.6) |

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| **Table S7:** Primary and secondary outcomes (Subgroup of patients with NC>2) |
|  | **Control (n=7)** | **Intervention (n=13)** | **OR****(Intervention versus Control) (95%CI)** | **RRR[[16]](#footnote-16)**  (%) **(95% CI)** | **ARR[[17]](#footnote-17)**  (%) **(95% CI)** |
| **Primary outcome** |  |  |  |  |  |
| Patients treated according to CT surgery bundle, No./total No. (%) | 0/7 (0) | 11/13 (84.6) | 69.00 (2.89, 1647.08) | 84.6 (45.0, 95.7) | 84.6 (65.0, 100.0) |
| **Secondary outcomes** |  |  |  |  |
| AKI within 72h, No./total No. (%) | 6/7 (85.7) | 7/13 (53.8) | 0.19 (0.02, 2.10) | 37.2 (-13, 65.1) | 31.9 (-5.6, 69.4) |
| Moderate to severe AKI, No./total No. (%) | 5/7 (71.4) | 3/13 (23.1) | 0.12 (0.01, 0.97) | 67.7 (3.2, 89.2) | 48.4 (7.8, 88.9) |

1. RRR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-1)
2. ARR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-2)
3. OR, RRR and ARR refer to the risk of AKI stage ≥ 1 versus No AKI [↑](#footnote-ref-3)
4. OR, RRR and ARR refer to the risk of AKI stage ≥ 1 versus No AKI [↑](#footnote-ref-4)
5. OR, RRR and ARR refer to the risk of AKI stage ≥ 1 versus No AKI [↑](#footnote-ref-5)
6. OR, RRR and ARR refer to the risk of AKI stage ≥ 2 versus stage < 2 (incl. No AKI) [↑](#footnote-ref-6)
7. OR, RRR and ARR refer to the risk of AKI stage ≥ 2 versus stage < 2 (incl. No AKI) [↑](#footnote-ref-7)
8. OR, RRR and ARR refer to the risk of AKI stage ≥ 2 versus stage < 2 (incl. No AKI) [↑](#footnote-ref-8)
9. OR, RRR and ARR refer to the risk of AKI stage 3 versus stage < 3 (incl. No AKI) [↑](#footnote-ref-9)
10. OR, RRR and ARR refer to the risk of AKI stage 3 versus stage < 3 (incl. No AKI) [↑](#footnote-ref-10)
11. OR, RRR and ARR refer to the risk of AKI stage 3 versus stage < 3 (incl. No AKI) [↑](#footnote-ref-11)
12. RRR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-12)
13. ARR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-13)
14. RRR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-14)
15. ARR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-15)
16. RRR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-16)
17. ARR>0 indicate treatment effects in favor of the interventional treatment group. [↑](#footnote-ref-17)