*Appendix 3: Stepwise calculations for adjusted outcomes*

**Primary Analysis**

1. What is the excess risk of adverse events in patients with low eGFR undergoing RRC?

*Causal risk difference*. This is the excess risk of AE as a result of RRC administration in patients with low versus normal eGFR after adjustment for the presumed overall greater illness of the low eGFR population. Expressed another way, this is the AE rate if all AFF patients, dichotomized into low- and normal-eGFR groups, received RRC, minus the AE rate if no AFF patients received RRC.

*Population attributable risk.* The population attributable risk is the excess AE risk due to RRC use, compared to no RRC use, in patients with both low and normal eGFR after adjustment for comorbidities; or alternatively, the proportion of AEs that would not have occurred had RRC not been attempted. While similar to (1) this only measures patients who actually had RRC, rather than if “all” patient had RRC.

*Exposure effect in the exposed.* The exposure effect is the excess AE risk when RRC is used in patients with low versus normal eGFR. This only applies to patients who received RRC.

A low GFR was defined as < 60, and assumed all patients without GFR had a normal GFR. For each patient group (low, normal GFR), we fit the logistic regression model for risk of AE as a function of use of RRC, sex, age, initial systolic blood pressure, hypertension, prior atrial flutter, and diabetes. We used the fitted model to estimate standardized (to the covariate distribution) risks under different exposure assumptions (actual exposure, everyone exposed, no one exposed) and subpopulations (all patients, only recipients of RRC) to calculate the 3 measures of effect in each patient group and compare these effect measures between the two patient groups. We used the percentile method bootstrap to obtain 95% CIs.

2. In patients who received RRC, does the success rate of RRC differ in patients with low GFR versus patients with normal GFR?

In patients who received RRC, we fit the logistic regression model for successful control as a function of GFR (low versus normal), adjusted for sex, age, initial blood pressure, hypertension, atrial flutter, and DM.

*Secondary analysis:*

We included patients with initial heart rate > 100 or those who received RRC.

*Sensitivity analysis*:

We included patients with a GFR and all covariates.

**Results**

*Crude analysis*

In normal GFR group:

AE rate in those who did not receive RRC = 7/462 = 1.5%

AE rate in those who received RRC = 27/238 = 11.3%

Difference = 9.8%

In low GFR group:

AE rate in those who did not receive RRC = 13/309 = 4.2%

AE rate in those who received RRC = 26/103 = 25.2%

Difference = 21.0%

RRC success rate:

In normal GFR group = 173/238 = 72.7%

In low GFR group = 47/103 = 45.6%

*Primary adjusted analysis*

N = 1031; exclude 81 patients due to missing covariate values.

*1. Adverse event rates (95% CI)*

*In normal GFR group:*

Observed AE rate = 5.1% (3.5%, 6.9%)

AE rate if everyone received RRC = 7.1% (4.4%, 11.0%)

AE rate if no one received RRC = 2.6% (0.8%, 5.0%)

Causal risk difference = 4.5% (0.5%, 9.4%)

Population attributable risk = 1.9% (0.2%, 5.1%)

AE rate in RRC recipients = 11.4% (7.4%, 15.7%)

AE rate in RRC recipients if they had not received RRC = 4.3% (1.1%, 8.9%)

Exposure effect in the exposed = 7.1% (0.9%, 12.6%)

*In low GFR group:*

Observed AE rate = 9.8% (7.0%, 12.9%)

AE rate if everyone received RRC = 20.0% (12.2%, 31.6%)

AE rate if no one received RRC = 4.5% (2.1%, 7.7%)

Causal risk difference = 16.3% (6.4%, 27.8%)

Population attributable risk = 11.0% (3.5%, 20.7%)

AE rate in RRC recipients= 26.3% (17.8%, 35.3%)

AE rate in RRC recipients if they had not received RRC = 5.5% (1.7%, 12.5%)

Exposure effect in the exposed = 20.8% (10.2%, 30.4%)

*Excess AE risk in low vs normal GFR groups:*

Excess causal risk difference = 11.8% (0.7%, 23.9%)

Excess population attributable risk = 9.0% (1.0% 18.8%)

Excess exposure effect in the exposed = 13.7% (1.7%, 25.1%)

*2. Failure of RRC treatments*

Adjusted odds ratio for low vs normal GFR = 3.11 (1.79, 5.57)

*Secondary analysis*

N = 581; exclude 18 patients due to missing covariate values.

1. Adverse event rates (95% CI**)**

*In normal GFR group:*

Observed AE rate = 8.7% (6.0%, 11.6%)

AE rate if everyone received R/RC = 10.7% (6.9%, 15.0%)

AE rate if no one received R/RC = 5.2% (1.8%, 9.3%)

Causal risk difference = 5.5% (-0.3%, 11.1%)

Population attributable risk = 2.0% (-0.1%, 4.3%)

AE rate in R/RC recipients = 11.4% (7.4%, 15.7%)

AE rate in R/RC recipients if they had not received R/RC = 5.6% (1.9%, 10.2%)

Exposure effect in the exposed = 5.8% (-0.3%, 11.5%)

*In low GFR group:*

Observed AE rate = 17.4% (12.0%, 23.1%)

AE rate if everyone received R/RC = 27.3% (17.7%, 36.5%)

AE rate if no one received R/RC = 6.4% (1.9%, 12.9%)

Causal risk difference = 20.9% (8.7%, 31.4%)

Population attributable risk = 9.9% (3.7%, 16.0%)

AE rate in R/RC recipients= 26.3% (17.6%, 35.2%)

AE rate in R/RC recipients if they had not received R/RC = 5.9% (1.4%, 13.3%)

Exposure effect in the exposed = 20.4% (9.0%, 30.1%)

*Excess AE risk in low vs normal GFR groups:*

Excess causal risk difference = 15.4% (1.8%, 27.3%)

Excess population attributable risk = 7.9% (1.2%, 14.2%)

Excess exposure effect in the exposed = 14.6% (1.8%, 25.9%)

*2. Failure of RRC treatment*

Adjusted odds ratio for low vs normal GFR = 3.07 (1.71, 5.52)

*Sensitivity analysis*

N = 885; exclude 180 patients missing eGFR + 47 patients missing other covariates

*1. Adverse event rates*

*In normal GFR group:*

Observed AE rate = 4.6% (2.8%, 6.5%)

AE rate if everyone received RRC = 6.7% (3.6%, 11.8%)

AE rate if no one received RRC = 1.9% (0.3%, 4.4%)

Causal risk difference = 4.8% (0.4%, 10.9%)

Population attributable risk = 2.1% (0.1%, 6.5%)

AE rate in RRC recipients = 10.2% (6%, 14.8%)

AE rate in RRC recipients if they had not received R/RC = 2.9% (0.2%, 7.9%)

Exposure effect in the exposed = 7.3% (0.7%, 12.9%)

*In low GFR group:*

Observed AE rate = 9.8% (7.0%, 12.9%)

AE rate if everyone received RRC = 20.8% (12.1%, 31.6%)

AE rate if no one received RRC = 4.5% (2.1%, 7.7%)

Causal risk difference = 16.3% (6.2%, 27.8%)

Population attributable risk = 11.0% (3.6%, 20.7%)

AE rate in RRC recipients= 26.3% (17.9%, 35.3%)

AE rate in RRC recipients if they had not received R/RC = 5.5% (1.7%, 12.9%)

Exposure effect in the exposed = 20.8% (9.9%, 30.2%)

*Excess AE risk in low vs normal GFR groups:*

Excess causal risk difference = 11.5% (-0.4%, 23.7%)

Excess population attributable risk = 8.9% (0.1% 18.5%)

Excess exposure effect in the exposed = 13.5% (1.1%, 24.8%)

*2. Failure of RRC treatments*

Adjusted odds ratio for low vs normal GFR = 3.08 (1.72, 5.53)