

## Supplementary File S1

Echocardiographic assessment protocol.

*Views and acquisition requirements*

*(2 cardiac cycles in sinus rhythm, 5 cardiac cycles in atrial fibrillation)*

### 1. *Parasternal Long Axis view:*

- 2D loop at moderate (50-70/sec) frame rate
- 2D loop with colour Doppler
- 2D loop with colour tissue Doppler at high (>120/sec) frame rate
- M-mode (still frame) of aortic root/left atrium
- M-mode (still frame) of left ventricle
- 2D loop (zoomed) of aortic root for Left-ventricular outflow tract dimension
- 2D loop RV inflow view (optional)
- 2D loop RV inflow view with colour wave Doppler for TR (optional)

### 2. *Parasternal Short Axis view:*

- 2D loop at aortic valve level
- Pulse wave Doppler of right ventricular outflow tract (sweep)
- 2D loop of MV in short axis
- 2D loop with colour Doppler at MV level at high frame rate
- 2D loop at papillary muscle level at moderate frame rate
- 2D loop with colour tissue Doppler at high (>120/sec) frame rate
- 2D loop at mid left ventricular level
- 2D loop at apical left ventricular level

### 3. *Apical Four Chamber View:*

- 2D loop at moderate frame rate focusing on all 4 chambers
- 2D loop with colour flow Doppler on all 4 chambers
- 2D loop zoom at moderate frame rate focusing on left and right ventricles
- 2D loop zoom with colour tissue Doppler at high frame rate focusing on left and right ventricles
- Pulsed tissue Doppler of the lateral mitral annulus.
- Pulsed tissue Doppler of the septal mitral annulus
- Pulsed tissue Doppler of the right ventricular free wall annulus
- 2D loop with colour flow Doppler focusing on MR (must see proximal isovelocity surface area (PISA), vena contracta (VC) and jet in left atrium)
- Zoomed 2D loop with colour flow Doppler focusing on MR (must see PISA, VC and jet in LA)
- 2D loop with colour flow Doppler focusing on tricuspid regurgitation (TR)
- 2D loop at high frame rate to include both atria and pulmonary veins
- Pulsed Doppler of the mitral inflow (sweep)

- Pulsed wave Doppler of the right upper pulmonary vein (sweep)
- Continuous wave Doppler of the MR jet
- Pulsed Doppler of the left ventricular outflow (sweep)
- Continuous wave Doppler of aortic outflow
- Pulsed Doppler of the tricuspid inflow (sweep)
- Continuous wave Doppler of the TR jet

4. *Apical Two Chamber view:*

- 2D loop at moderate frame rate (LA/LV)
- 2D loop with colour flow Doppler
- 2D loop at moderate frame rate focusing on left ventricle
- 2D loop with colour tissue Doppler at high frame rate focusing on left ventricle
- 2D loop zoom at high frame rate on left atrium and pulmonary veins
- 2D loop with colour flow Doppler focusing on MR (must see PISA, VC and jet in LA)
- Zoomed 2D loop with colour flow Doppler focusing on MR (must see PISA, VC and jet in LA)

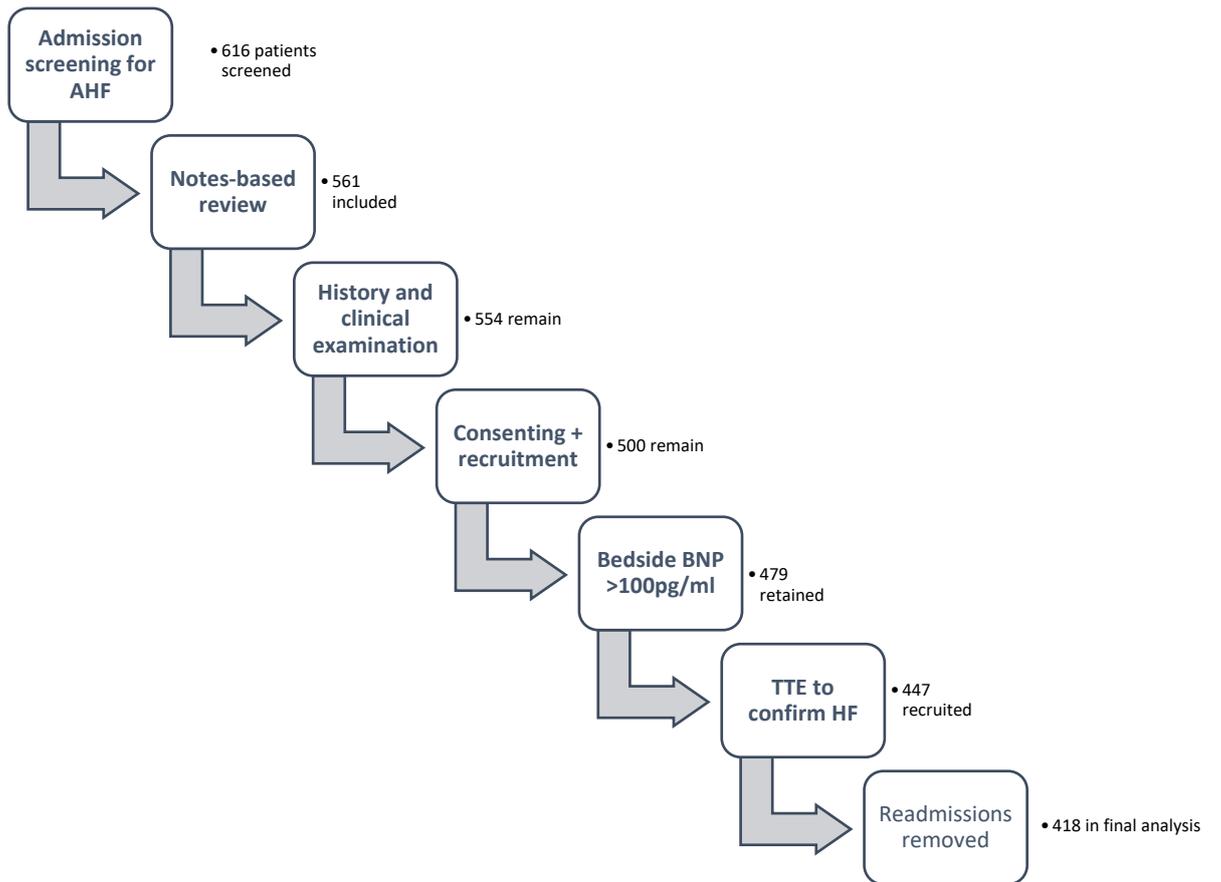
5. *Apical Long Axis view:*

- 2D loop at moderate frame rate
- 2D loop at moderate frame rate focusing on left ventricle
- 2D loop with colour Doppler
- 2D loop with colour flow Doppler focusing on MR (must see PISA, VC and jet in LA)
- Zoomed 2D loop with colour flow Doppler focusing on MR (must see PISA, VC and jet in LA)

6. *Subcostal view:*

- Inferior vena cava dimension and sniff test – 2D ± M-mode
- 2D loop of Subcostal long axis view
- 2D loop of Subcostal short axis view at papillary muscle level (optional)
- 2D loop of Subcostal short axis view at atrioventricular level (optional)

**Supplementary File S2; Flow diagram for participant exclusion**



**Supplementary Table S1:** Kaplan-Meier estimates of mild vs. >mild TR

|  | <b>Mild TR</b> | <b>Haemodynamically Significant<br/>TR (&gt;mild)</b> |
|--|----------------|---|
| <b>Regurgitant volume</b>                    |                |   |
| Number at risk, n                            | 171            | 173   |
| Mortality, n                                 | 73             | 70  |
| Hazard ratio (significant vs mild) [95% CIs] |                | 1.10 [0.78,1.54]                                      |
| p-value (Logrank)                            |                | 0.58  |
| <b>Effective Regurgitant orifice</b>         |                |   |
| Number at risk, n                            | 84             | 260   |
| Mortality, n                                 | 29             | 106   |
| Hazard ratio (significant vs mild) [95% CIs] |                | 1.25[0.85,1.84]                                       |
| p-value (Logrank)                            |                | 0.26  |
| <b>Vena contracta</b>                        |                |   |
| Number at risk, n                            | 19             | 335   |
| Mortality, n                                 | 7              | 135   |
| Hazard ratio (significant vs mild) [95% CIs] |                | 1.20[0.58,2.41]                                       |
| p-value (Logrank)                            |                | 0.61  |

**Supplementary Table S2:** Kaplan-Meier estimates of non-severe vs. severe TR

|  | <b>Non-Severe TR<br/>(≤moderate)</b> | <b>Severe TR</b> |
|--|--------------------------------------|------------------|
| <b>Regurgitant volume</b>                      |                                      |                  |
| Number at risk, n                              | 214                                  | 130              |
| Mortality, n                                   | 84                                   | 51               |
| Hazard ratio (severe vs non-severe) [95% CIs]  | 1.03 [0.72,1.46]                     |                  |
| p-value (Logrank)                              | 0.87                                 |                  |
| <b>Effective Regurgitant orifice</b>           |                                      |                  |
| Number at risk, n                              | 175                                  | 169              |
| Mortality, n                                   | 69                                   | 66               |
| Hazard ratio (severe vs non-severe) [95% CIs]  | 1.01[0.72,1.41]                      |                  |
| p-value (Logrank)                              | 0.97                                 |                  |
| <b>Vena contracta</b>                          |                                      |                  |
| Number at risk, n                              | 173                                  | 181              |
| Mortality, n                                   | 67                                   | 76               |
| Hazard ratio (severe vs. non-severe) [95% CIs] | 1.14[0.82,1.58]                      |                  |
| p-value (Logrank)                              | 0.44                                 |                  |

**Supplementary Table S3.** Univariate analysis of the full cohort

| <b>Variable</b>                    | <b>Hazard Ratio (95% CIs)</b> | <b>p *</b>         |
|------------------------------------|-------------------------------|--------------------|
| <u>Age</u> (n=414)                 | <u>1.056(1.038-1.074)</u>     | <u>&lt;0.0001*</u> |
| Gender (n=414)                     | 1.093(0.802-1.489)            | 0.574              |
| <u>BMI</u> (n=411)                 | <u>0.970(0.949-0.992)</u>     | <u>0.0077*</u>     |
| Coronary artery disease (n=414)    | 1.240(0.905-1.699)            | 0.181              |
| Hypertension (n=414)               | 1.286(0.938-1.763)            | 0.119              |
| Diabetes (n=414)                   | 1.141(0.8224-1.582)           | 0.430              |
| <u>CKD</u> (n=414)                 | <u>1.931(1.411-2.641)</u>     | <u>&lt;0.0001*</u> |
| <u>COPD</u> (n=414)                | <u>1.924(1.322-2.800)</u>     | <u>0.0006*</u>     |
| Previous CVA (n=414)               | 0.861(0.549-1.351)            | 0.516              |
| Right atrial size (n=412)          | 1.006(0.988-1.023)            | 0.543              |
| Left atrial size (n=414)           | 1.001(0.991-1.028)            | 0.313              |
| <u>Moderate+MR</u> (n=414)         | <u>1.396(1.023-1.903)</u>     | <u>0.0354*</u>     |
| <u>SPAP</u> (n=401)                | <u>1.012(1.012-1.028)</u>     | <u>&lt;0.0001*</u> |
| TAPSE (n=411)                      | 0.793(0.578-1.090)            | 0.153              |
| LVEF (n=411)                       | 1.002(0.992-1.013)            | 0.699              |
| <u>LVEDV</u> (n=411)               | <u>0.997(0.994-0.100)</u>     | <u>0.0314*</u>     |
| <u>Urea</u> (n=414)                | <u>1.060(1.040-1.082)</u>     | <u>&lt;0.0001*</u> |
| <u>Sodium</u> (n=414)              | <u>0.947(0.923-0.973)</u>     | <u>0.0001*</u>     |
| <u>BNP</u> (n=414)                 | <u>1.0003(1.0002-1.0004)</u>  | <u>&lt;0.0001*</u> |
| <u>Hb</u> (n=414)                  | <u>0.990(0.984-0.997)</u>     | <u>0.004*</u>      |
| <u>eGFR</u> (n=413)                | <u>0.977(0.967-0.987)</u>     | <u>&lt;0.0001*</u> |
| RVA diastole index (n=383)         | 1.042(0.998-1.087)            | 0.059              |
| <u>Disproportionate TR</u> (n=352) | <u>1.481 (1.064-2.061)</u>    | <u>0.020*</u>      |

Data was analysed using a cox-proportional hazards model to generate survival estimates between the subgroups of each variable.

**Supplementary Table S4.** Univariate analysis of the Fortuni cohort

| <b>Variable</b>                             | <b>Hazard Ratio (95% CIs)</b> | <b>p *</b>         |
|---|-------------------------------|--------------------|
| <i>Age (n=59)</i>                           | 1.028(0.981-1.077)            | 0.236              |
| <i>Gender (n=59)</i>                        | 1.135(0.501-2.568)            | 0.762              |
| <i>BMI (n=59)</i>                           | 0.976(0.936-1.017)            | 0.247              |
| <i>Coronary artery disease (n=59)</i>       | 0.631(0.237-1.681)            | 0.357              |
| <i>Hypertension (n=59)</i>                  | 0.729(0.331-1.605)            | 0.432              |
| <i>Diabetes (n=59)</i>                      | 0.990(0.445-2.205)            | 0.981              |
| <u><i>Chronic kidney disease (n=59)</i></u> | <u>3.055(1.313-7.108)</u>     | <u>0.00953*</u>    |
| <u><i>COPD (n=59)</i></u>                   | <u>3.067(1.316-7.147)</u>     | <u>0.0094*</u>     |
| <i>Previous CVA (n=59)</i>                  | 0.290(0.068-1.232)            | 0.0935             |
| <u><i>Right atrial size (n=59)</i></u>      | <u>1.043(1.010-1.079)</u>     | <u>0.0116*</u>     |
| <i>Left atrial size (n=59)</i>              | 1.026(0.991-1.063)            | 0.141              |
| <i>Moderate+MR (n=59)</i>                   | 0.871(0.364-2.085)            | 0.756              |
| <u><i>SPAP (n=59)</i></u>                   | <u>1.023(1.003-1.043)</u>     | <u>0.0252*</u>     |
| <i>TAPSE (n=59)</i>                         | 0.848(0.384-1.873)            | 0.684              |
| <i>LVEF (n=59)</i>                          | 1.015(0.943-1.093)            | 0.686              |
| <i>LVEDV (n=59)</i>                         | 0.997(0.985-1.010)            | 0.689              |
| <u><i>Urea (n=59)</i></u>                   | <u>1.154(1.079-1.236)</u>     | <u>&lt;0.0001*</u> |
| <i>Sodium (n=59)</i>                        | 0.971(0.910-1.035)            | 0.365              |
| <i>BNP (n=59)</i>                           | 1.000(1.000-1.001)            | 0.0782             |
| <i>Hb (n=59)</i>                            | 0.984(0.963-1.006)            | 0.157              |
| <u><i>eGFR (n=59)</i></u>                   | <u>0.967(0.945-0.990)</u>     | <u>0.00525*</u>    |
| <i>RVA diastole index (n=59)</i>            | 1.060(0.991-1.135)            | 0.094              |
| <i>Disproportionate TR (n=59)</i>           | 2.034(0.869-4.751)            | 0.102              |

Data was analysed using a cox-proportional hazards model to generate survival estimates between the subgroups of each variable. The Fortuni cohort is a subgroup of patients who had greater than mild TR and an LVEF value of  $\geq 55$ .

**Supplementary Table S5.** Multivariate analysis of the Fortuni cohort

| <b>Variable</b>                         | <b>B</b>     | <b>Se</b>    | <b>Wald</b>  | <b>Exp b</b> | <b>95% CI</b>      | <b>p*</b>     |
|---|--------------|--------------|--------------|--------------|--------------------|---------------|
| <i>Chronic Kidney disease</i><br>(n=59) | 0.863        | 0.632        | 1.365        | 2.370        | 0.686-8.188        | 0.172         |
| <u><i>COPD</i></u> (n=59)               | <u>1.286</u> | <u>0.529</u> | <u>2.429</u> | <u>3.618</u> | <u>1.282-10.21</u> | <u>0.015*</u> |
| <i>Right atrial size</i> (n=59)         | 0.031        | 0.018        | 1.754        | 1.032        | 0.996-1.069        | 0.079         |
| <i>SPAP</i> (n=59)                      | 0.012        | 0.012        | 1.025        | 1.012        | 0.989-1.036        | 0.305         |
| <u><i>Urea</i></u> (n=59)               | <u>0.151</u> | <u>0.060</u> | <u>2.558</u> | <u>1.163</u> | <u>1.036-1.305</u> | <u>0.011*</u> |
| <i>eGFR</i> (n=59)                      | 0.018        | 0.018        | 0.997        | 1.018        | 0.983-1.055        | 0.319         |

Data was analysed using a cox-proportional hazards model to generate survival estimates between subgroups of each variable and with respect to the covariates selected. The covariates listed were selected for posthoc, multivariate analysis if demonstrating statistical significance in the univariate analysis reported in table 3. The Fortuni cohort is a subgroup of patients who greater than mild TR and an LVEF value of  $\geq 55$ .