Supplemental table 1A: Cox proportional hazards (OUTCOME:MACE) in patients where all quantitative measures were possible (API, PISA, VCW). N=158

ALL API, PISA, VCW	Multivariate analysis		
	RR	95% CI	p-value
API (per 10 au increase)	**1.11**	1.03-1.21	**0.007**
Age	0.99	0.982-1.017	0.931
LA vol/BSA	1.006	0.994-1.019	0.127
CMP-NI	0.563	0.340-0.932	0.119
DM	0.555	0.306-1.009	0.166
AF	0.860	0.495-1.495	0.755
LVEDV	1.002	0.998-1.006	0.092
NYHA class (per class step-up)	**1.501**	1.212-2.011	**<0.001**
RVSP (per 10 mmHg increase)	**1.288**	1.055-1.573	**<0.001**
EF (per 10% decrease)	0.904	0.675-1.209	0.688
PISA-EROA (per 10 mm² increase)	1.07*	0.862-1.329	0.54
PISA-RV (per 10 ml increase)	1.067*	0.902-1.263	0.44
VCW (per 1 mm increase)	**1.28***	1.046-1.571	**0.017**

*PISA-EROA /PISA-RV/VCW replaces API in this multivariate model as MR grading parameter; no significant changes in RR for the other variables in this model, compared to the model above including API.

Abbreviations:

See Table 1

CMP-NI: non-ischemic cardiomyopathy

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Supplemental table 1B: Cox proportional hazards (OUTCOME: Cardiovascular death/heart failure hospitalization (excluding surgical/percutaneous interventions)) N=227

	Multivariate analysis		
	RR	95% CI	p-value
API (per 10 au increase)	**1.07**	1.003-1.141	**0.039**
Age	0.998	0.981-1.015	0.793
LA vol/BSA	1.008	0.997-1.019	0.137
CMP-NI	0.729	0.454-1.171	0.191
DM	0.934	0.561-1.555	0.794
AF	1.000	0.595-1.682	0.999
LVEDV	1.002	0.999-1.006	0.165
NYHA class (per class step-up)	**1.555**	1.176-2.055	**0.002**
RVSP (per 10 mmHg increase)	**1.47**	1.217-1.775	**<0.001**
EF (per 10% decrease)	0.127	0.852-1.489	0.402
PISA-EROA (per 10 mm² increase)	1.093*	0.861-1.388	0.466
PISA-RV (per 10 ml increase)	1.06*	0.879-1.281	0.539
VCW (per 1 mm increase)	1.052*	0.847-0.306	0.646

*PISA-EROA /PISA-RV/VCW replaces API in this multivariate model as MR grading parameter; no significant changes in RR for the other variables in this model, compared to the model above including API.

Abbreviations:

See Table 1

CMP-NI: non-ischemic cardiomyopathy

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Supplemental table 2

	API	EROA20	EROA40	RV30	RV60	VCW
AUC	0.73	0.71	0.71	0.695	0.695	0.71
Sens (%)	74	56	9	58	3	22
Spec (%)	62	84	99	72	99	95
NPV (%)	74	66	54	64	53	62
PPV (%)	52	70	78	62	75	73

Abbreviations:

AUC: area under the curve; API: average pixel intensity; EROA: effective regurgitant orifice area (20 = 20 mm² cutoff, 40 = 40 mm² cut-off); RV: regurgitant volume (30 = 30 ml cut-off, 60 = 60 ml cut-off); VCW: vena contracta width; Sens: sensitivity; Spec: specificity; NPV: negative predictive value; PPV: positive predictive value

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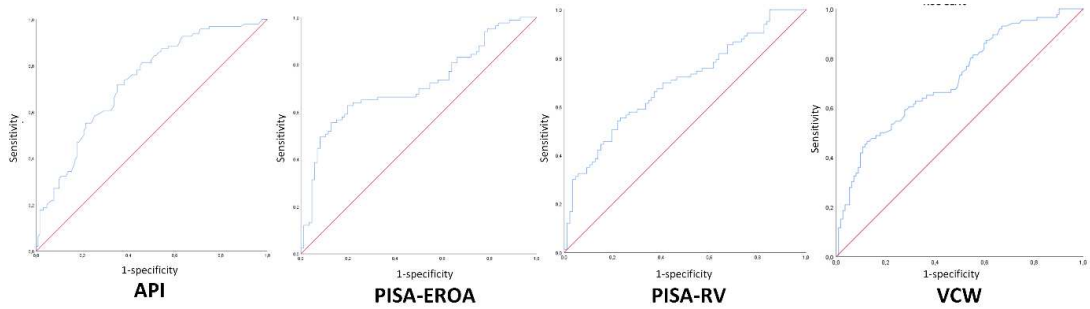
Supplemental Figure 1



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Supplemental Figure 2

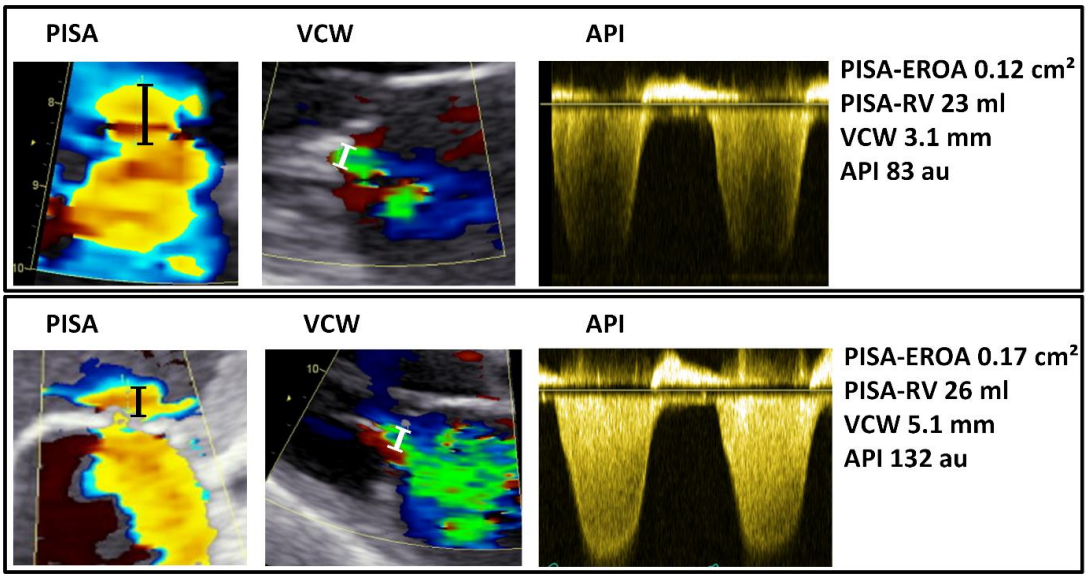

Figure legend:

In the panel above, a case of non-severe SMR is shown with concordance between all grading. The 'urchinoid' flow convergence zone (FCZ) is 0.5 cm resulting in a PISA-EROA and PISA-RV value of 0.12 cm² and 23 ml, respectively. The vena contracta is 3.1 mm, which is mild. The API value is 83 au, which is rather mild. The CW Doppler envelope shows the typical flow pattern encountered in SMR, with a highest flow/pixel intensities at proto- and telesystole, and a midsystolic decrease of API, which indicates reduced MR flow at midsystole.

The panel below illustrates a typical case with flattening of the FCZ zone (0.48 cm). In this patient, the calculated PISA-EROA and PISA-RV were 0.17 cm² and 26 ml, indicating non-severe MR. As such, the flattened FCZ probably leads to underestimation of MR severity using the PISA method. Vena contracta width was moderate (5.1 mm). However, the CW Doppler has an intense signal with an API value of 132 au, indicating severe MR.

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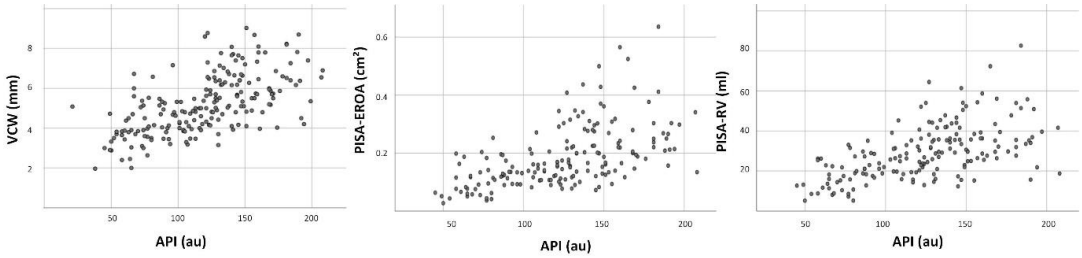
Statistics

Continuous variables were expressed as mean±SD (or median with interquartile range for non-normal distributions) and dichotomous variables as percentage. Normality of data distribution was tested with Shapiro-Wilk test. Student t-test or Mann-Whitney U-test (for continuous variables) and $\chi 2$ test (for dichotomous variables) were used to evaluate group differences.

Correlations were calculated using Spearman's correlation coefficient. Correlations of the API method with other direct MR grading methods:

- PISA-EROA: 0.615 ($p<0.001$)
- PISA-RV: 0.594 ($p<0.001$)
- VCW: 0.642 ($p<0.001$)



For outcome analysis, proportional hazard assumption tests was tested prior to Cox proportional hazards analysis using Schoenfeld residuals test (time dependent covariates in the Cox Model): $p = 0.40$, thus proportional hazards can be assumed.

Receiver operating curves (ROC) curves were constructed to determine cut-off values. Areas under the curve were calculated with MACE defined as a binary outcome and the API value (and other grading parameters) as continuous test variable, using the non-parametric (distribution-free) method. For ROC, events were analyzed at the end of the study. Besides ROC curves, a principal component analysis was performed for discrimination. For all analyses performed, KOM – Bartlett tests were significant ($p <0.001$). When only considering API, VCW and PISA-based methods, only one single Eigenvector could be generated that grouped all these grading parameters with similar loading factors. This indicates that all these parameters

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have equal variance in this model. Also, when considering a model with multiple variables, these four variables remain grouped in the principal component vector.

For calibration, on logistic regression analysis Nagelkerke R^2 was 0.29 and Hosmer-Lemeshow test was non-significant (p 0.19). For survival analysis, Cox proportional hazard model (time to first event) was used to calculate hazard ratios and Kaplan Meier curves were constructed with log-rank tests.

All statistical analyses were performed in SPSS Statistics V.25 (IBM, New York, USA), including plotting of Kaplan-Meier graphs and ROCs. P values <0.05 were considered statistically significant (2-tailed).

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