

Supplementary materials for:

Association of the low e' and high E/e' with long-term outcomes in patients with normal
ejection fraction: A hospital population-based observational cohort study

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Supplementary Table 1: Baseline characteristics of the study subjects with mild aortic stenosis

	Total (n=3,255)	e' \geq 7 group (n=1,384)	e' $<$ 7 and E/e' \leq 14 group (n=1,295)	e' $<$ 7 and E/e' $>$ 14 group (n=578)	P value	Cochran- Armitage trend test
The prevalence of mild AS, (%)	58 (1.8)	5 (0.4)	23 (1.8)	30 (5.2)	<0.001	<0.001
Mean PG, mmHg, mean (SD)	15.8 (2.4)	NA	17.6 (1.1)	14.6 (2.3)	0.032	

NA: not available due to the lacking data

Supplementary Table 2. Clinical outcomes of patients in cardiovascular and non-cardiovascular death and MACEs

	e'≥7 group N of patients with event/N of patients at risk (Cumulative 3-year incidence [%])	e' <7 and E/e' ≤14 group N of patients with event/N of patients at risk (Cumulative 3-year incidence [%])	e' <7 and E/e' >14 group N of patients with event/N of patients at risk (Cumulative 3-year incidence [%])	Variables	Unadjusted		Adjusted	
					HR (95% CI)	P value	HR (95% CI)	P value
Cardiovascular death	7/1384 (0.6)	14/1295 (1.2)	14/578 (1.8)	e' ≥7	reference		reference	
				e' <7 and E/e' ≤14	1.86 (0.86-4.62)	0.12	1.38 (0.63-3.47)	0.44
				e' <7 and E/e' >14	4.07 (1.95-9.92)	<0.001	2.62 (1.21-6.57)	0.013
Non cardiovascular death	94/1384 (7.3)	127/1295 (10.1)	73/578 (11.9)	e' ≥7	reference		reference	

				e' < 7 and E/e' ≤ 14	1.30 (1.03-1.65)	0.028	1.05 (0.82-1.34)	0.72
				e' < 7 and E/e' > 14	1.66 (1.31-2.12)	<0.001	1.31 (1.02-1.71)	0.038
Heart failure	10/1384 (0.9)	29/1295 (2.6)	28/578 (4.4)	e' ≥ 7	reference		reference	
				e' < 7 and E/e' ≤ 14	2.76 (1.48-5.74)	<0.001	1.70 (0.91-3.56)	0.10
				e' < 7 and E/e' > 14	5.97 (3.25-12.26)	<0.001	2.82 (1.51-5.88)	<0.001
Unstable angina pectoris	6/1384 (0.6)	10/1295 (1.0)	9/578 (1.6)	e' ≥ 7	reference		reference	
				e' < 7 and E/e' ≤ 14	1.63 (0.70-4.47)	0.27	0.88 (0.35-2.20)	0.78

				e' < 7 and E/e' > 14	3.29 (1.45-8.81)	0.0032	0.98 (0.39-2.46)	0.97
Myocardial infarction	2/1384 (0.2)	9/1295 (0.8)	5/578 (0.9)	e' ≥ 7	reference		reference	
				e' < 7 and E/e' ≤ 14	4.38 (1.26-27.51)	0.017	3.41 (0.96-21.69)	0.059
				e' < 7 and E/e' > 14	5.43 (1.53-34.44)	0.0062	2.97 (0.79-19.35)	0.11
Aorta and peripheral vascular disease	6/1384 (0.5)	16/1295 (1.2)	12/578 (2.0)	e' ≥ 7	reference		reference	
				e' < 7 and E/e' ≤ 14	2.56 (1.15-6.80)	0.019	1.74 (0.77-4.67)	0.19
				e' < 7 and E/e' > 14	4.33 (1.97-11.43)	<0.001	1.94 (0.85-5.28)	0.12

Cerebral infarction	11/1384 (1.2)	29/1295 (2.4)	15/578 (1.9)	e'≥7	reference		reference	
				e' <7 and E/e'≤14	2.55 (1.39-5.12)	0.0017	1.55 (0.84-3.14)	0.17
				e' <7 and E/e' >14	2.92 (1.57-5.94)	<0.001	1.87 (0.98-3.88)	0.057
Cerebral hemorrhage	5/1384 (0.3)	6/1295 (0.6)	6/578 (1.1)	e'≥7	reference		reference	
				e' <7 and E/e'≤14	1.16 (0.43-3.64)	0.78	0.78 (0.29-2.49)	0.65
				e' <7 and E/e' >14	2.59 (1.04-7.86)	0.042	1.42 (0.54-4.49)	0.49

MACE=major adverse cardiac event, HR=hazard ratio, CI=confidence interval

Supplementary Table 3: Baseline characteristics of the study subjects and transthoracic echocardiography results of the patients

according to the modified classification using age- and sex- adjusted value of e' .

	Total (n=3,255)	$e' \geq$ age- and sex- adjusted value (n=564)	$e' <$ age- and sex- adjusted value and $E/e' \leq 14$ (n=2,131)	$e' <$ age- and sex- adjusted value and $E/e' > 14$ (n=562)	P value	Cochran- Armitage trend test
Age, yr, median (IQR)	68 (56-76)	74 (64-82)	65 (51-73)	75 (68-80)	<0.001	
Age>70, (%)	1417 (43.5)	340 (60.3)	690 (32.4)	387 (68.9)	<0.001	0.004
Male, (%)	1708 (52.4)	284 (50.4)	1177 (55.2)	247 (44.0)	<0.001	0.032
Body mass index (BMI), mean (SD)	23.2 (4.8)	22.2 (3.8)	23.4 (5.1)	23.4 (4.4)	<0.001	<0.001
Diabetes, (%)	969 (29.8)	137 (24.3)	590 (27.7)	242 (43.1)	<0.001	<0.001
Hypertension, (%)	1756 (53.9)	268 (47.5)	1067 (50.0)	421 (74.9)	<0.001	<0.001
Dyslipidemia, (%)	979 (30.1)	163 (28.9)	569 (26.7)	247 (44.0)	<0.001	<0.001
Ischemic heart disease, (%)	925 (28.4)	136 (24.1)	553 (26.0)	236 (42.0)	<0.001	<0.001
Chronic kidney disease, (%)	427 (13.1)	60 (10.6)	230 (10.8)	137 (24.4)	<0.001	<0.001
LVDd, cm, mean (SD)	4.61 (0.51)	4.56 (0.50)	4.63 (0.49)	4.56 (0.58)	0.002	
LVDs, cm, mean (SD)	3.03 (0.38)	2.98 (0.35)	3.05 (0.37)	3.02 (0.43)	<0.001	
IVSTd, cm, mean (SD)	0.81 (0.17)	0.76 (0.14)	0.80 (0.15)	0.90 (0.20)	<0.001	
LVPWd, cm, mean (SD)	0.79 (0.14)	0.75 (0.12)	0.79 (0.13)	0.85 (0.15)	<0.001	
RWT, mean (SD)	0.35 (0.07)	0.33 (0.06)	0.35 (0.06)	0.38 (0.07)	<0.001	

LVMI, g/m, mean (SD) ²	74.9 (21.0)	69.8 (19.7)	73.4 (19.1)	85.8 (25.5)	<0.001	
High LVMI, (M>115, F>95) (%)	272 (8.4)	30 (5.3)	130 (6.1)	112 (20.0)	<0.001	<0.001
LAD, cm, mean (SD)	3.42 (0.58)	3.35 (0.59)	3.37 (0.55)	3.69 (0.60)	<0.001	
LAVI, ml/m, mean (SD) ²	20.9 (9.5)	21.9 (15.3)	19.4 (6.6)	25.7 (9.8)	<0.001	
High LAVI, (>34) (%)	180 (6.1)	38 (7.6)	58 (3.0)	84 (16.1)	<0.001	<0.001
EF, %, mean (SD)	63.3 (4.1)	64.0 (3.9)	63.2 (4.0)	63.0 (4.4)	<0.001	
E, cm/s, mean (SD)	70.4 (18.8)	77.3 (19.8)	66.1 (16.2)	79.8 (21.2)	<0.001	
A, cm/s, mean (SD)	79.1 (27.0)	80.5 (44.3)	73.7 (18.7)	98.7 (22.2)	<0.001	
E/A ratio, mean (SD)	0.97 (0.43)	1.06 (0.49)	0.97 (0.42)	0.85 (0.36)	<0.001	
Dec time, mean (SD)	228.6 (60.3)	221.5 (58.5)	225.7 (56.4)	246.8 (71.9)	<0.001	
e' velocity, mean (SD)	7.0 (2.6)	9.4 (2.9)	7.0 (2.3)	4.6 (1.1)	<0.001	
a' velocity, mean (SD)	9.3 (2.2)	10.4 (2.5)	9.3 (2.1)	8.4 (2.0)	<0.001	
E/e', mean (SD)	11.0 (4.2)	8.9 (3.3)	9.8 (2.3)	17.8 (3.8)	<0.001	
HR, bpm	69.8 (13.5)	69.6 (13.2)	69.8 (13.5)	70.1 (14.0)	0.78	

p values were calculated using the χ^2 test or Fisher's exact test for categorical variables, and 1-way ANOVA or Kruskal-Wallis test for continuous variables. Values are number (%), mean (SD), or median (IQR). SD=standard deviation, BMI=body mass index, LVDd=left ventricular diastolic dimension, LVDs=left ventricular systolic dimension, BSA=Body surface area, LAVI=left atrial volume index,

EF=ejection fraction, AF=atrial fibrillation, LVMI=left ventricular mass index, RWT=relative wall thickness, HR=heart rate,

IVSTd=diastolic interventricular septal wall thickness, LVPWd=diastolic left ventricular posterior wall thickness.

Supplementary Table 4. Results of IDI and NRI (conventional criteria and modified criteria using age- and sex- adjusted value of e')

	IDI (CI 95%)	P value	NRI (CI 95%)	P value
Conventional criteria vs modified criteria.	10.9 (4.7 – 16.2)	<0.001	74.0 (69.4 – 79.5)	<0.001

IDI= integrated discrimination improvement, NRI= net reclassification improvement

Supplementary Figure legends

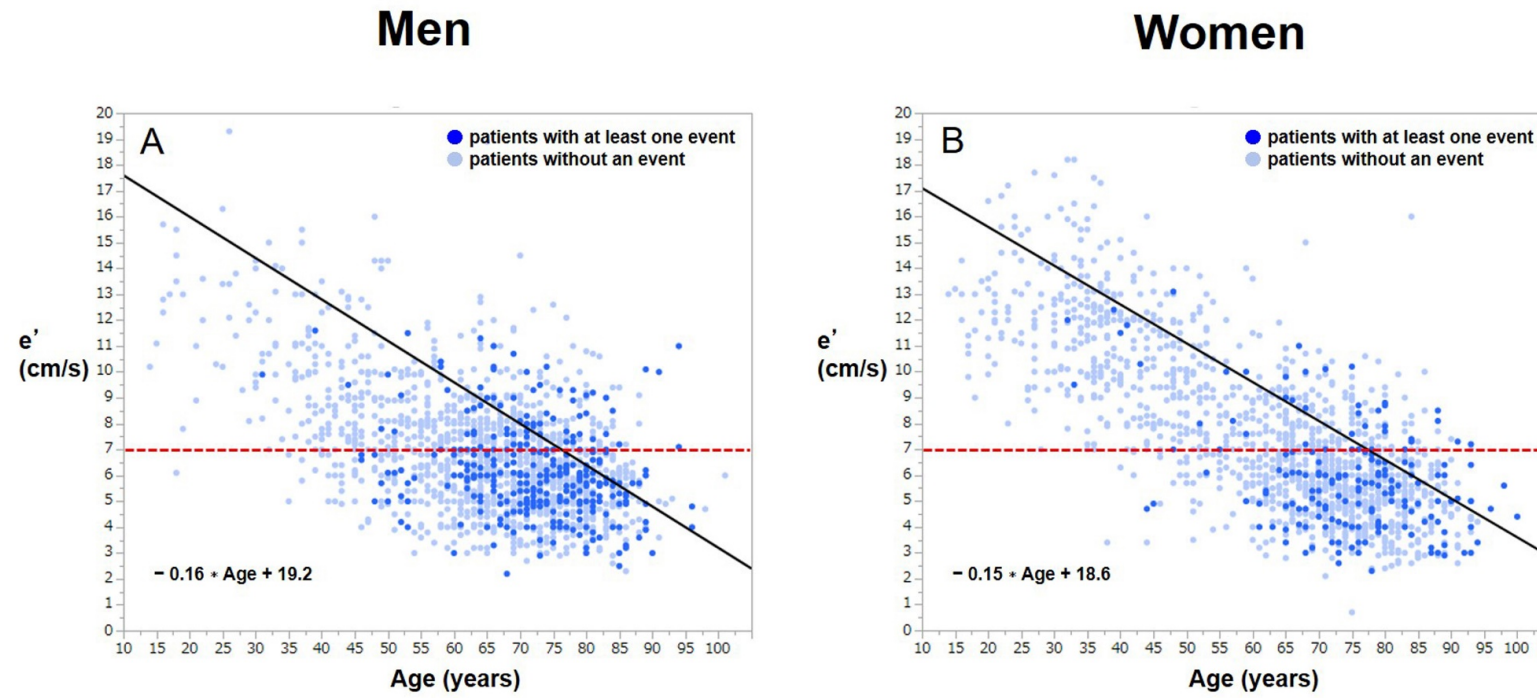
Supplementary Figure 1. Scattered plots of age and e' . The red line indicates the conventional cutoff values ($e'=7$).

Supplementary Figure 2. Cumulative incidence of the primary outcome measure (a composite of all-cause death and MACE) and secondary outcomes measure (all cause death, MACE)

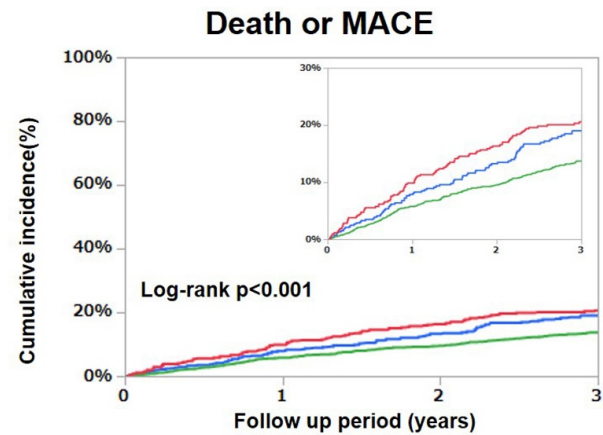
A; a composite of all cause death and MACE, B; all cause death, C; MACE. MACE defined as acute heart failure, acute myocardial infarction, unstable angina pectoris, cerebral infarction, cerebral hemorrhage, aortic dissection, and treatment of aortic aneurysm.

Abbreviations: MACE=Major adverse cardiac event

Supplementary Figure 1.



Supplementary Figure 2.



Interval (Years)	0	1	2	3
$e' <$ age- and sex- adjusted value and $E/e' > 14$ group				
N of patients with at least 1 event		50	80	98
N of patients at risk	562	431	372	321
Cumulative incidence		9.9%	16.3%	20.6%
$e' <$ age- and sex- adjusted value and $E/e' \leq 14$ group				
N of patients with at least 1 event		103	164	225
N of patients at risk	2131	1587	1373	1181
Cumulative incidence		5.8%	9.6%	13.8%
$e' \geq$ age- and sex- adjusted value group				
N of patients with at least 1 event		39	63	86
N of patients at risk	564	434	362	303
Cumulative incidence		7.9%	13.3%	19.0%