UNIVERSITY OF BIRMINGHAM | INSTITUTE OF CARDIOVASCULAR SCIENCES

Universitäres Herz- und Gefäßzentrum Hamburg

How and when surrogate endpoints may help in cardiovascular drug approval trials?

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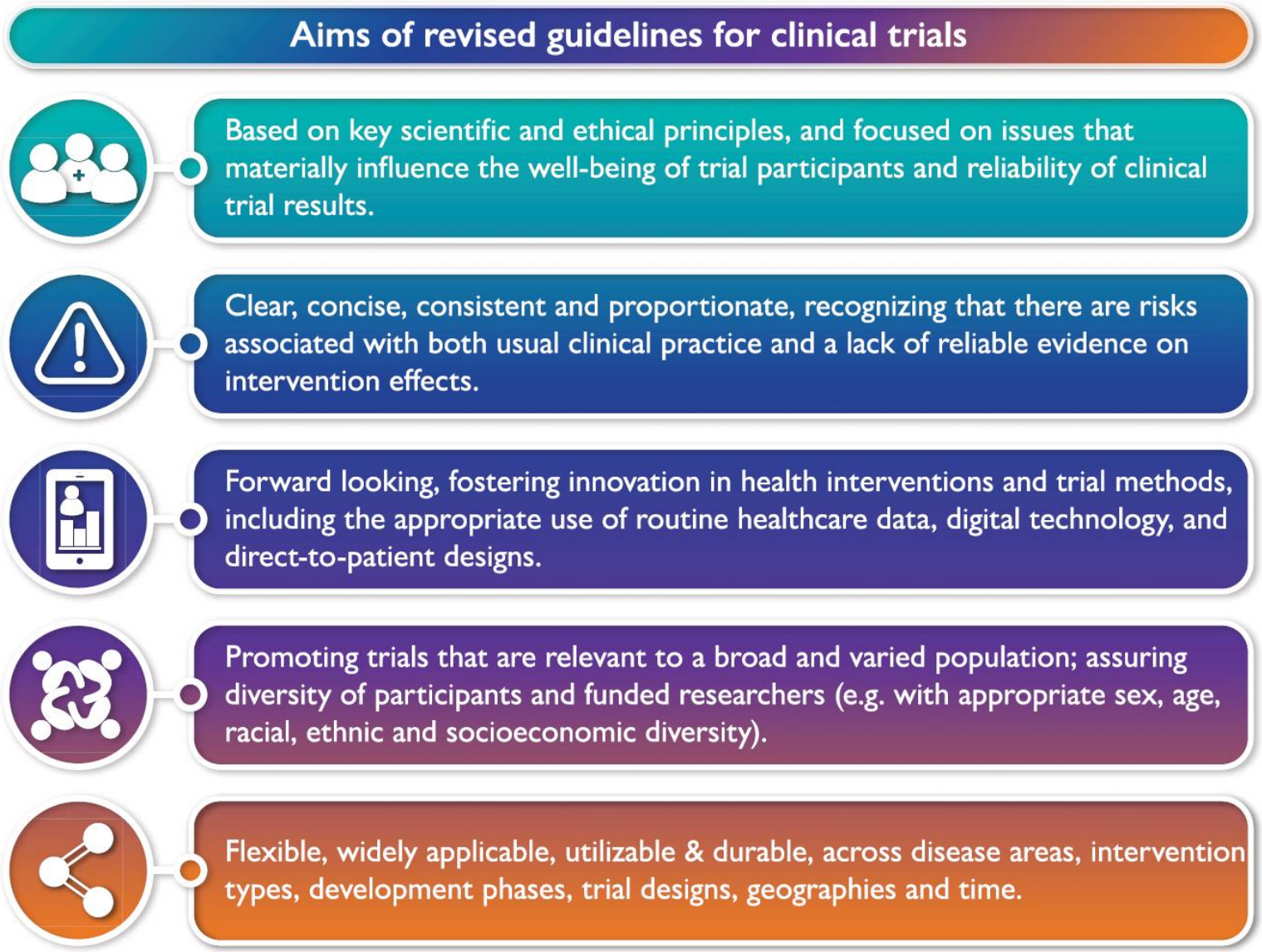
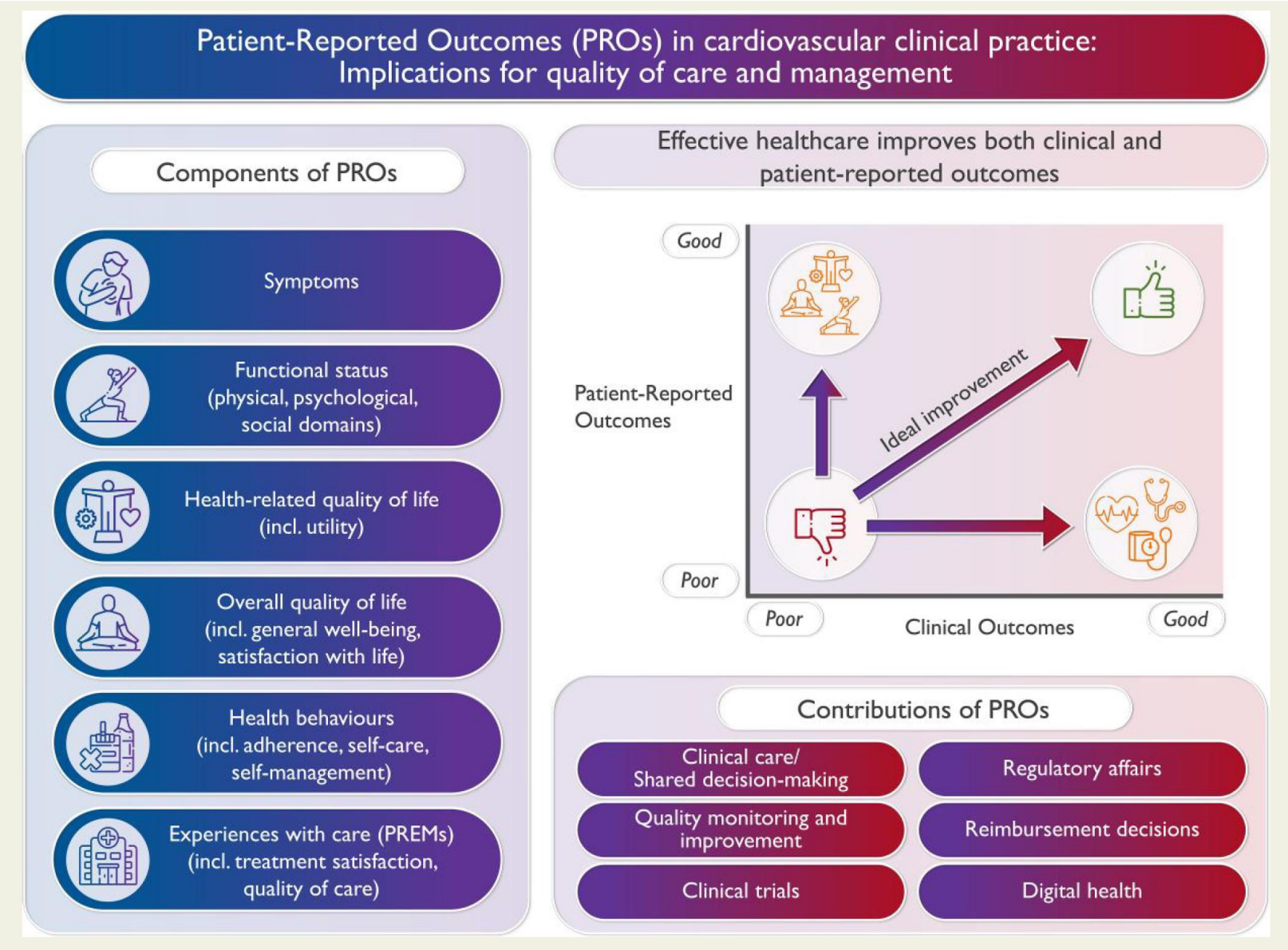
The future of clinical trials in cardiovascular medicine



ESC/AHA/ACC/WHF joint opinion *Eur Heart J* 44:931-4.(2023) doi:10.1093/eurheartj/ehac633

Streamline, but also collect more information



Moons P, et al. *Eur Heart J* 44:3405-22.(2023) doi:10.1093/eurheartj/ehad514

1. Established surrogates
2. Better detection of events, composite primary outcomes
3. New, quantitative, disease process-related surrogates
    1. Arrhythmia burden, LV function
    2. the potential of circulating biomolecules

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Ciani O, et al, SPIRIT-SURROGATE/CONSORT-SURROGATE consortium *EClinicalMedicine* 65:102283.(2023)

Cardiovascular surrogate outcomes 25 years ago

Blood pressure

LDL cholesterol / non-HDL cholesterol

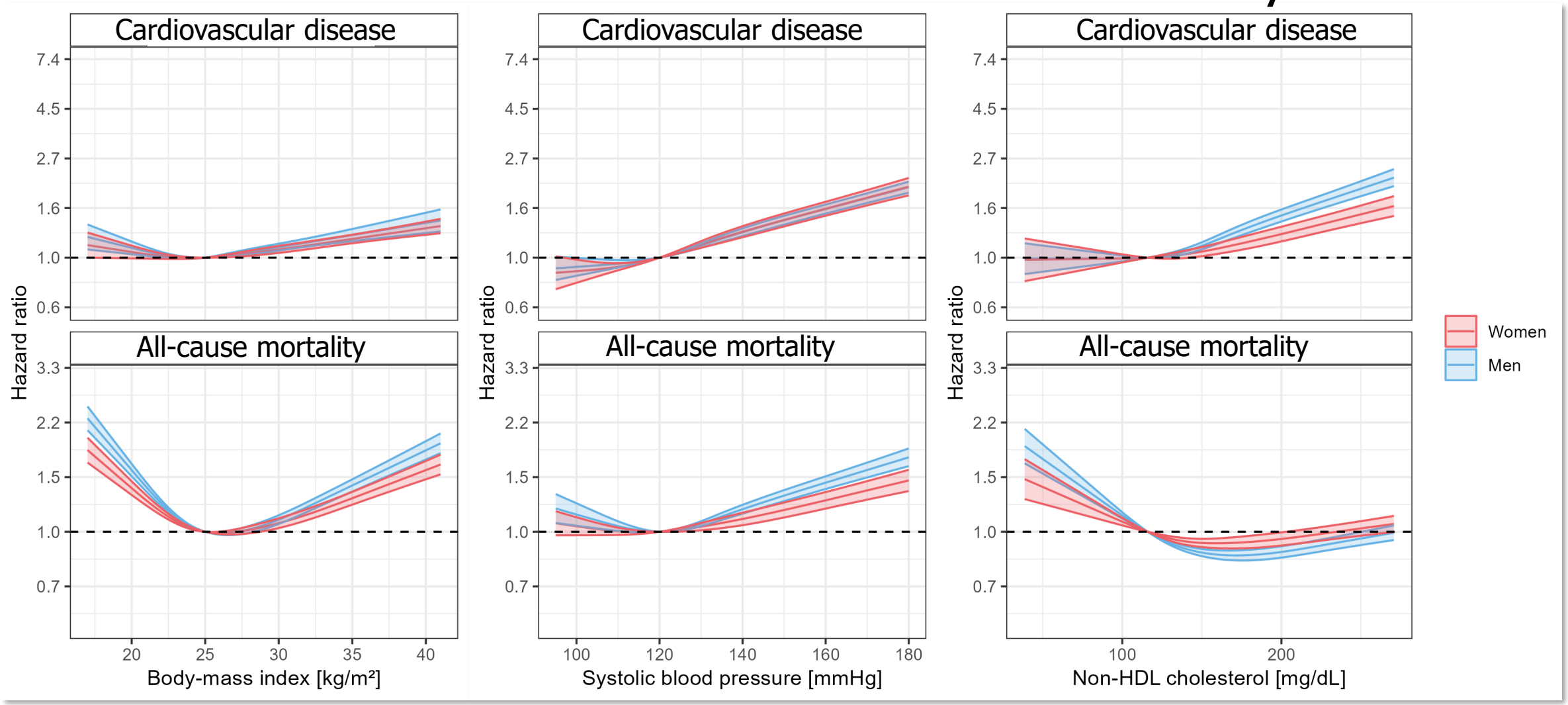
Blood glucose

Recurrent atrial arrhythmia

All are quantitative, objectively measurable, and disease process-related

Temple R. *JAMA* 282:790-5.(1999)

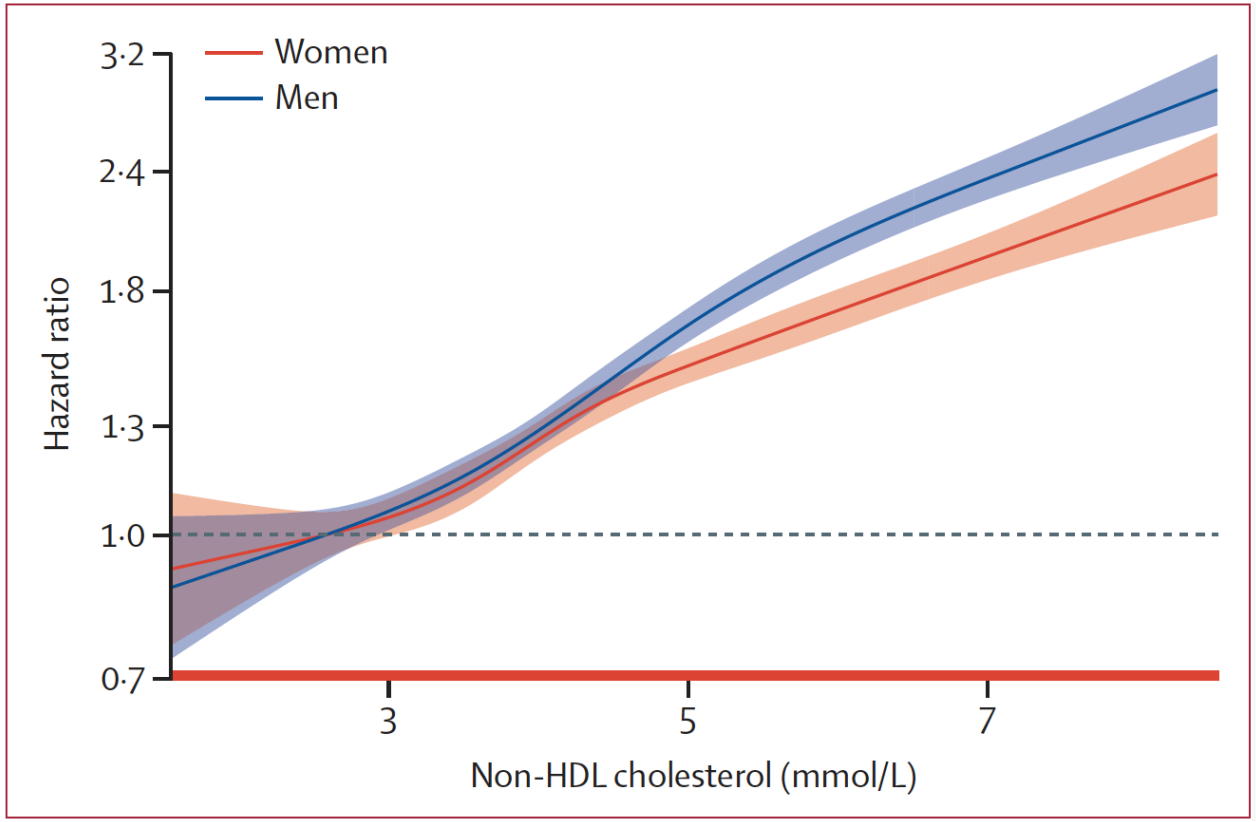
Association of body mass index, systolic blood pressure and non-HDL cholesterol with CVD and all-cause mortality

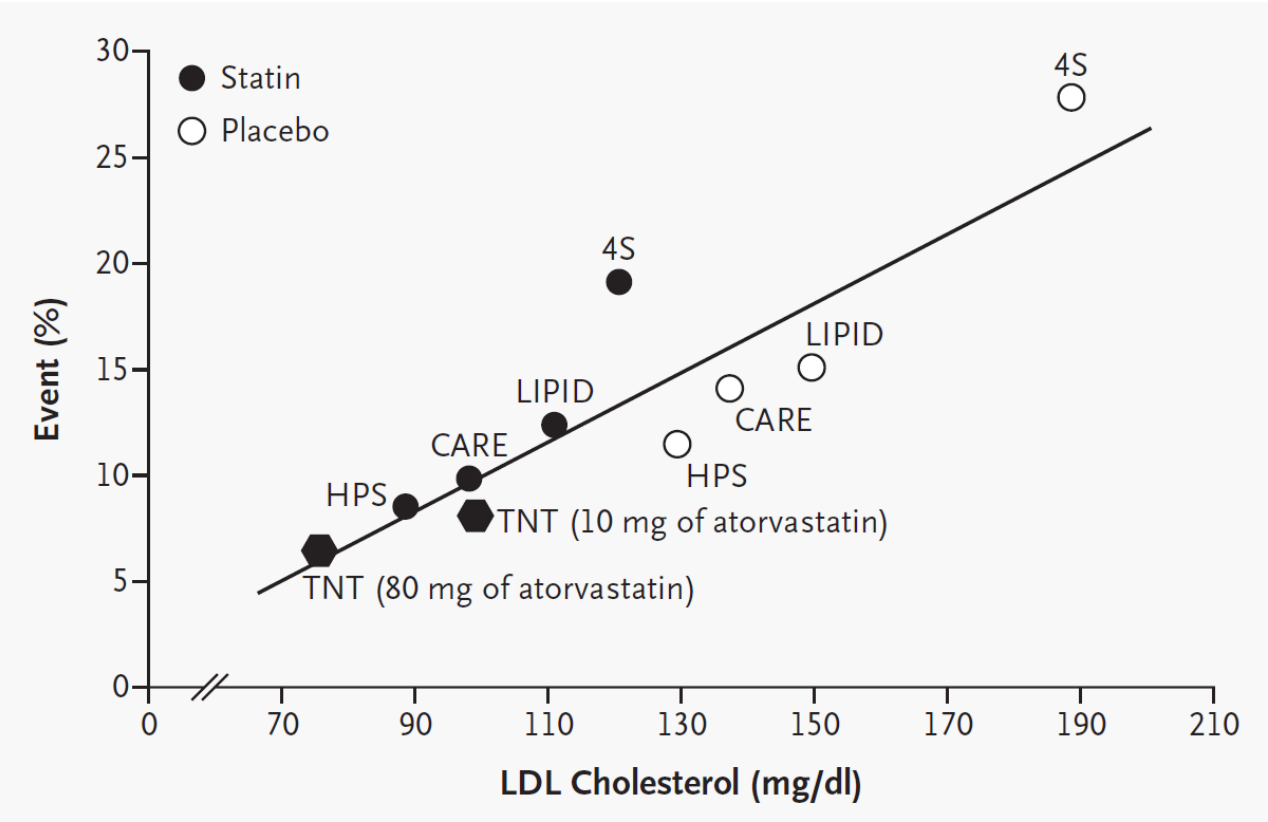


Individuals with CVD at baseline were excluded. Age was used as the time scale. All five risk factors were included in the models together with use of antihypertensive medications.

Magnussen C, et al Global Cardiovascular Risk Consortium*N Engl J Med* 389:1273-85.(2023) doi:10.1056/NEJMoa2206916

Association of LDL cholesterol and CVD, treatment effect of statins





Brunner FJ, et al. *Lancet* 394:2173-83.(2019) doi:10.1016/S0140-6736(19)32519-X
LaRosa JC, et al. *N Engl J Med* 352:1425-35.(2005)

The FDA-NIH Perspective: Response Biomarker

Definition

A biomarker used to show that a biological response, potentially beneficial or harmful, has occurred in an individual who has been exposed to a medical product or an environmental agent.

- Pharmacodynamic biomarker: A response biomarker that indicates biologic activity of a medical product or environmental agent without necessarily drawing conclusions about efficacy or disease outcome or necessarily linking this activity to an established mechanism of action. Potential uses of a pharmacodynamic biomarker include establishing proof-of-concept, assisting in dose selection or measuring a response to medical products or environmental agents, including the use as a measure of potential harm. In some cases, such measures may be secondary endpoints in clinical trials and may be described in labeling.
- Surrogate endpoint biomarker: A response biomarker that is an endpoint used in clinical trials as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint does not measure the clinical benefit of primary interest in and of itself, but rather is expected to predict that clinical benefit or harm based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence.

BEST (Biomarkers, EndpointS, and other Tools) Resource - NCBI Bookshelf (nih.gov) accessed on 14 Nov 2023

Surrogate outcomes for cardiovascular drug development

Surrogate (response) outcomes can be used

- to guide clinical development (target populations, early termination) and
- to accelerate limited approval with continued safety evaluation.

Cardiovascular surrogates accepted by FDA 2023

Reduction of GL-3 inclusions in renal biopsies (Fabry Disease)

Blood pressure reduction (mechanism-agnostic)

Serum LDL cholesterol cholesterol reduction

Serum HbA1c reduction

Serum phosphate, potassium, and sodium

All are quantitative, objectively measurable, and disease process-related

https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure, accessed on 14 Nov 2023
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-medicinal-products-treatment-hypertension_en.pdf

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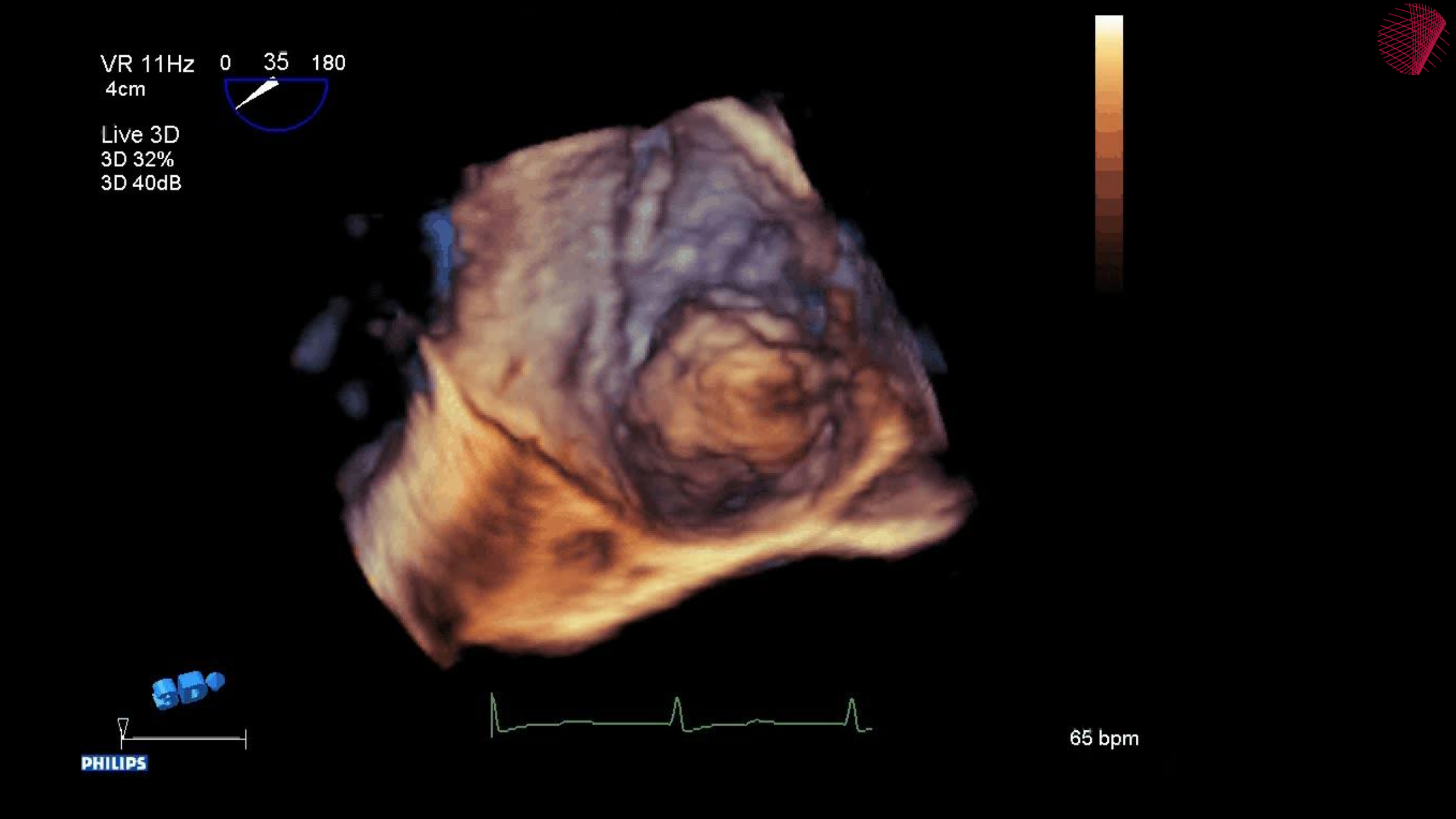
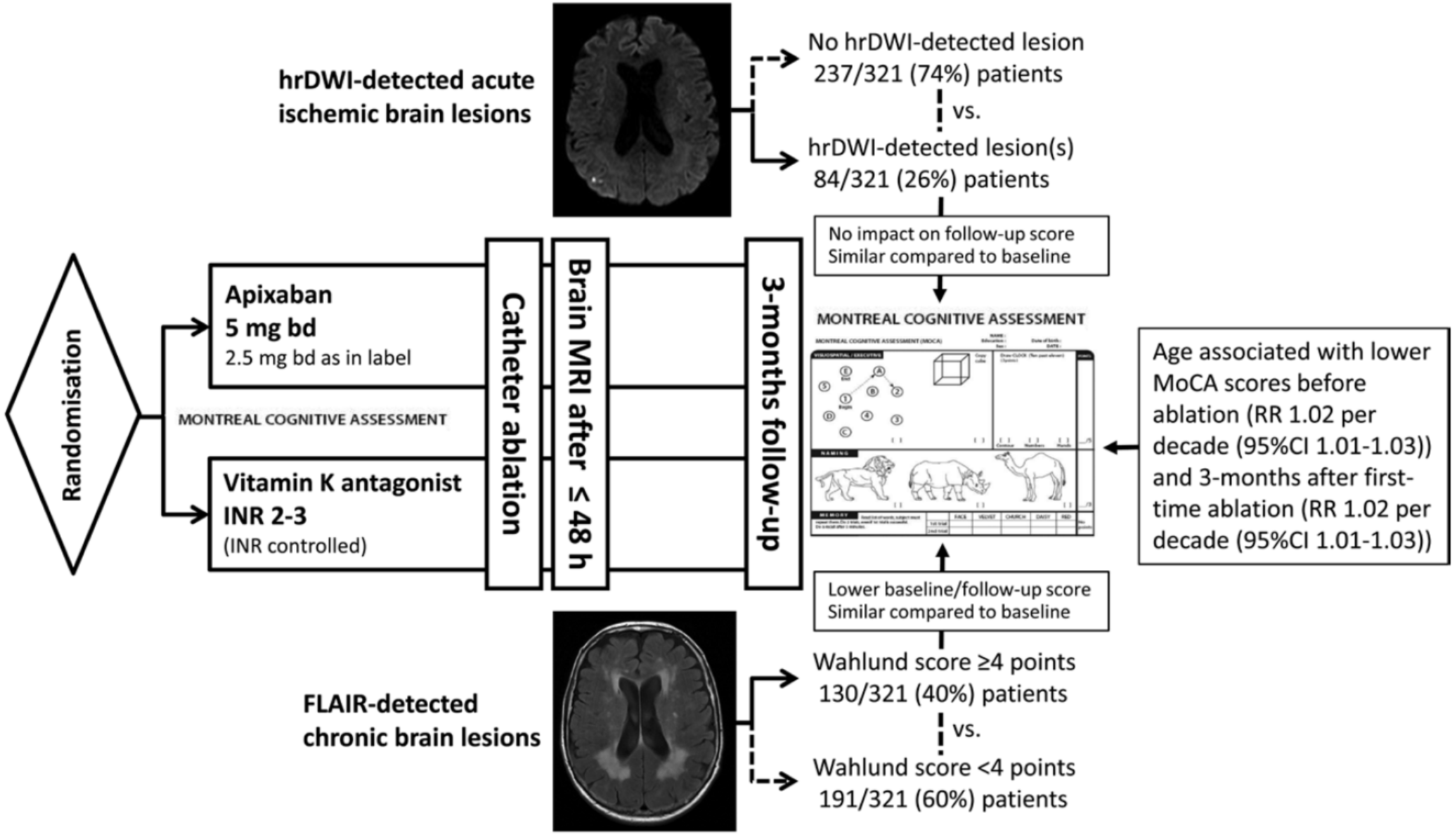
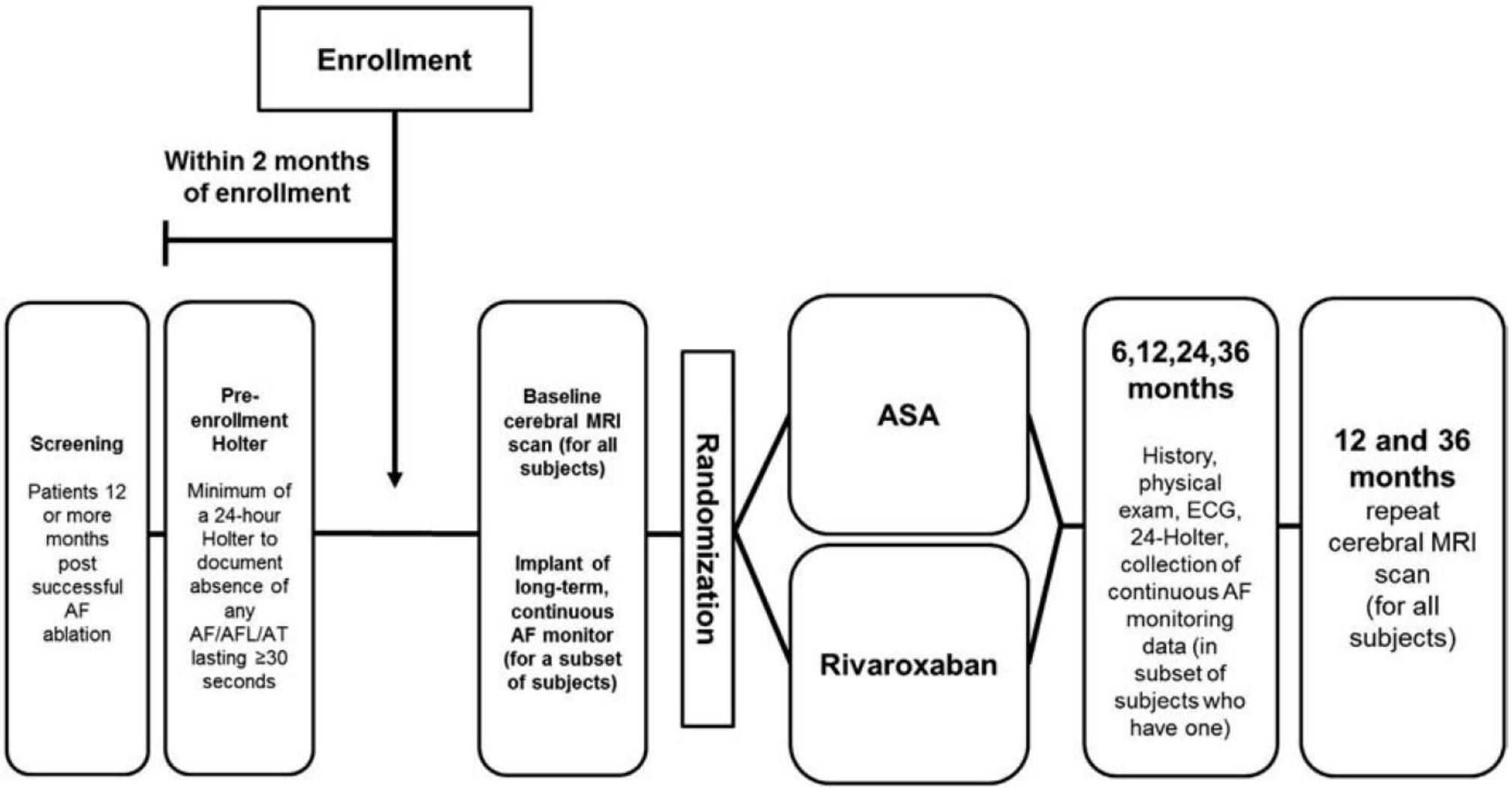

VR 11Hz
0
35
180
4cm
Live 3D
3D 32%
3D 40dB
65 bpm
PHILIPS

MRI-detected brain lesions and silent strokes



Haeusler KG, et al. *Circulation* 145:906-15.(2022)

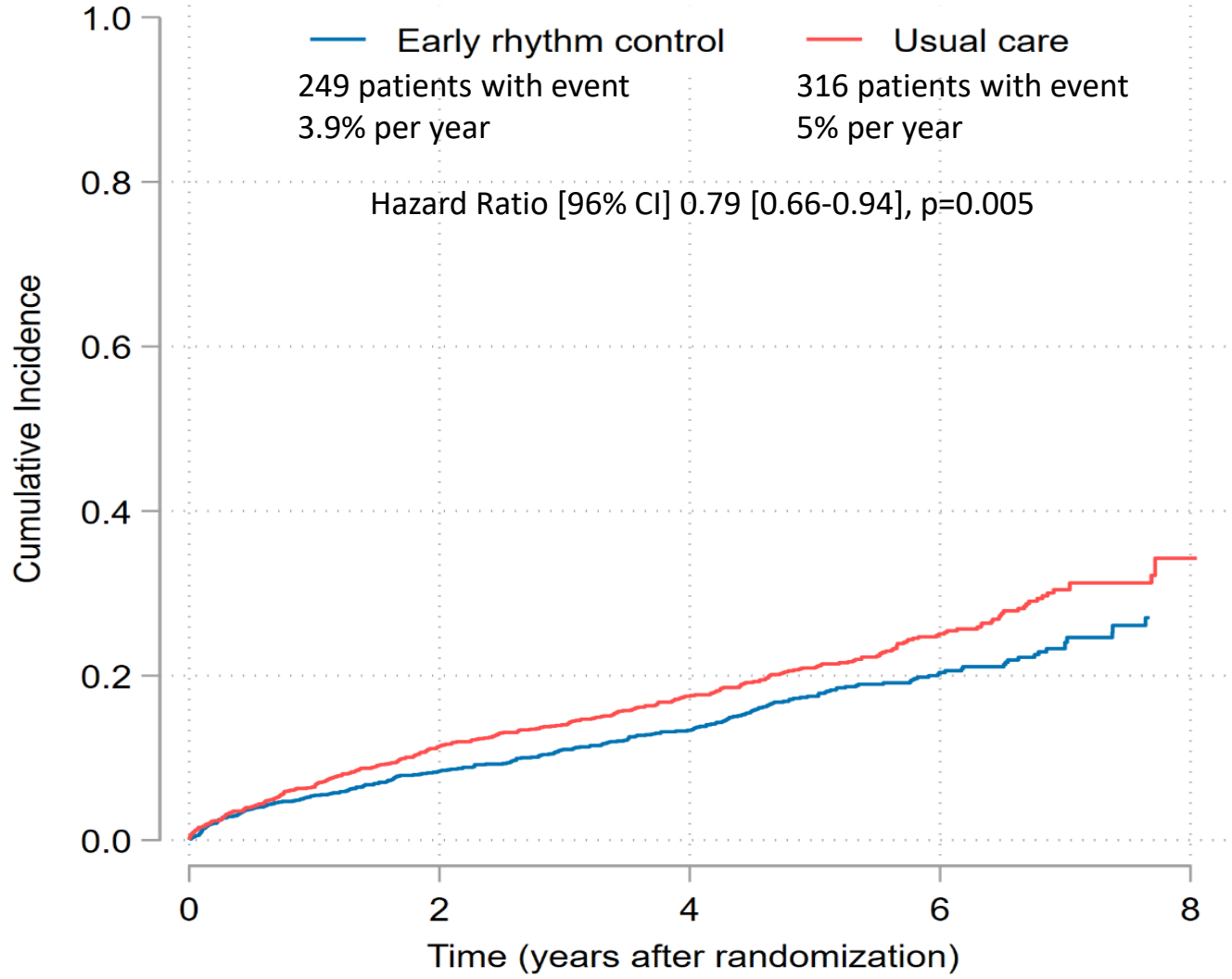
MRI-detected brain lesions as part of an enhanced stroke outcome



Study flow diagram for the OCEAN trial.

Verma A, et al. *Am Heart J* 197:124-32 (2018)

Combine outcomes that are modified by intervention



Patients at risk

Early rhythm control	1395	1193	913	404	26
Usual care	1394	1169	888	405	34

	Patients with event in Early Rhythm Control (n=1395)	Patients with event in Usual Care (n=1394)	Uncorrected Hazard Ratio [95% CI]
Cardiovascular death	67	94	0.72 [0.52-0.98]
Stroke	40	62	0.65 [0.44-0.97]
Hospitalization with worsening of heart failure	139	169	0.81 [0.65-1.02]
Hospitalization with acute coronary syndrome	53	65	0.83 [0.58-1.19]

Kirchhof P, et al. *N Engl J Med* 383:1305-16.(2020) doi:10.1056/NEJMoa2019422

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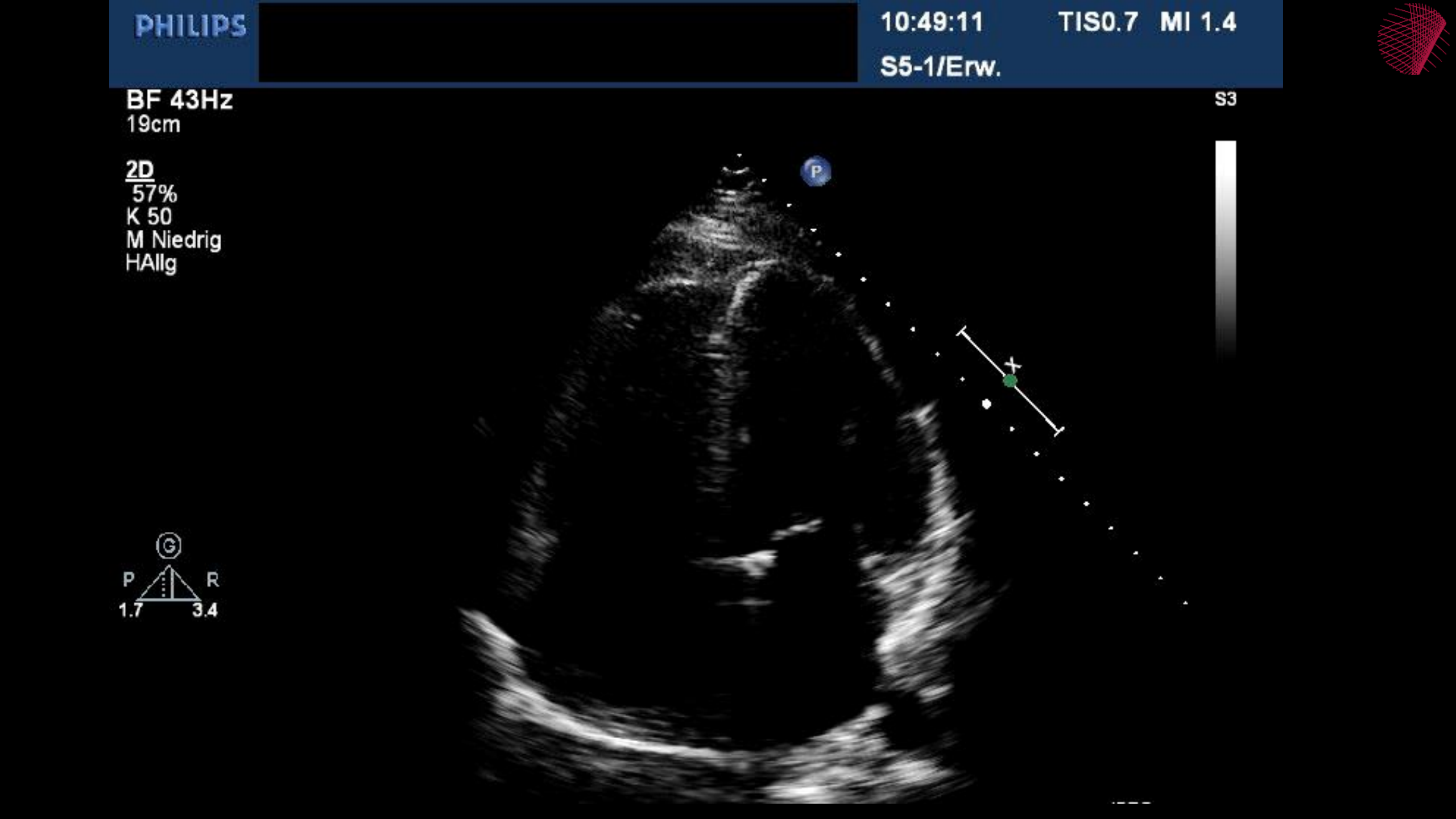
PHILIPS
10:49:11
TIS0.7
MI 1.4
S5-1/Erw.
BF 43Hz
19cm
2D
57%
K 50
M Niedrig
HAllg
S3
P
G
P
R
1.7
3.4

Left ventricular function as a surrogate outcome

Can only improve in patients with reduced ejection fraction („HFrEF“)
Quantifiable (with 5%-10% variability) by echocardiogram or magnetic resonance tomography
Directly affected by some interventions (CRT, inotropic and myofilament drugs, AF ablation)
Indirectly affected by established heart failure medications (RAAS + b blockers, SGLT2i)

LVEF is quantitative, objectively measurable, and related to some disease processes

Relation of AF burden with outcomes

	AF burden (estimated)	Stroke rate without anticoagulation	Stroke rate with anticoagulation	Concomitant Heart Failure, Reduction in HF events
Persistent and permanent AF	70 – 100%	3%/year	1.5%/year	30-50% of patients
Paroxysmal AF	11-20%	2%/year	1%/year	
AF on early rhythm control therapy	0.4 – 5%	?	0.6%/year	30% reduction
Device-detected AF	0.2 – 0.5%	1%/year	0.7%/year	?

Goette A, et al. *Circ Arrhythm Electrophysiol* 5:43-51.(2012)
Vanassche T, et al. Eur Heart J 36:281-7a. (2015)
Charitos EI, et al. *J Am Coll Cardiol*. 63:2840-2848 (2014)
Diederichsen SZ, et al. *J Am Coll Cardiol* 74:2771-81.(2019)
Kirchhof P, et al. *N Engl J Med* 383:1305-16.(2020)

Eckardt L, et al. Eur Heart J 43:4127-4144 (2022)
Andrade JG, et al. *N Engl J Med* (2022)
Kirchhof P, et al. *N Engl J Med* 389:1167-79 (2023)
Healey JS, et al. N Engl J Med, published 12 Nov (2023)
Becher N, et al. *Eur Heart J* (2023) doi:10.1093/eurheartj/ehad771
McIntyre WF, et al. Circulation.(2023) doi:10.1161/CIRCULATIONAHA.123.067512

AF burden, and its reduction on treatment, could be a new surrogate parameter for drug with effects on heart rhythm (antiarrhythmic drugs, heart failure drugs, also metabolic and antiinflammatory drugs).

AF burden is quantitative, objectively measurable, and potentially disease process-related

Pictograms taken from ESC AF guidelines, Hindricks G, et al. *Eur Heart J* 42:373-498.(2021)

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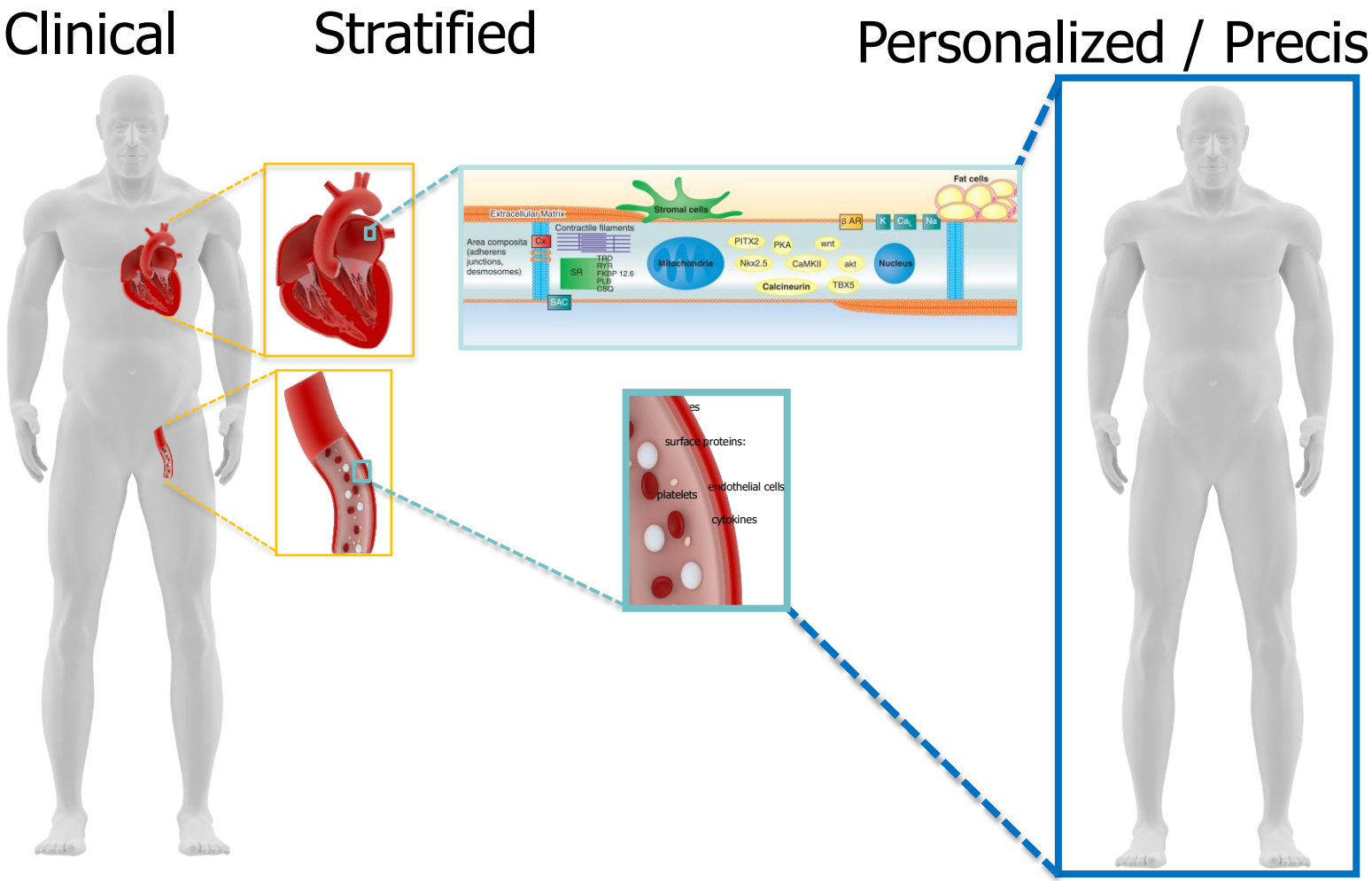
From Clinical to Personalised Cardiovascular Medicine



Clinical diseases and risk factors

Imaging of heart and vessels

Molecular disease processes in heart tissue and blood (molecular imaging, biomarkers, genetics)

Integration into personalized disease management

ESC CRT position paper. *Eur Heart J*. 35:3250-7 (2014)

Biomolecules and their combination as surrogates

Biomolecule	Potential for Patient Selection	Potential as Surrogate (Response) Outcome
Troponin I and T	Chronic elevations identify patients at riks of cardiovascular events	ACS / mycardial damage (integral over several measurements)

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Genetic defects (mutations, polygenic risk scores)	Good prognostic information for myocardial infar´ction, stroke, AF, heart failure	

Surrogate outcomes for cardiovascular drug development

Useful surrogates are quantitative, objectively measurable, and related to disease processes.

They can be used

- to guide clinical development (target populations, early termination) and
- to accelerate limited approval with continued safety evaluation.

Cardiovascular surrogates have not changed much since 1999.

New disease mechanisms invite evaluation of additional surrogates, including

- atrial fibrillation burden,
- left ventricular function, and
- circulating biomolecules.

There is no surrogate for safety.