

#CardiacBiomarkers

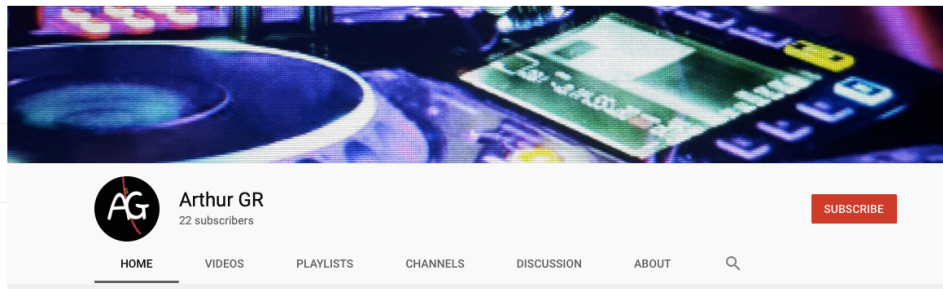
Cliniques Universitaires Saint-Luc, Brussels, Belgium



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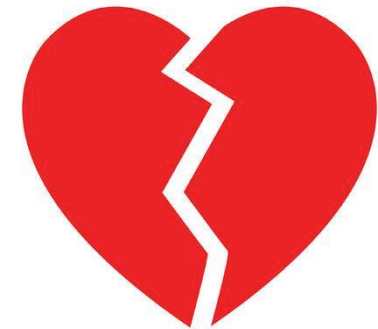
- **Unofficial declaration of interest**



Copyrights apply



Cardiovascular diseases



CVD

210

Billion a year cost the EU
economy

Diabetes

>425

Million people with
diabetes

Heart Failure

26

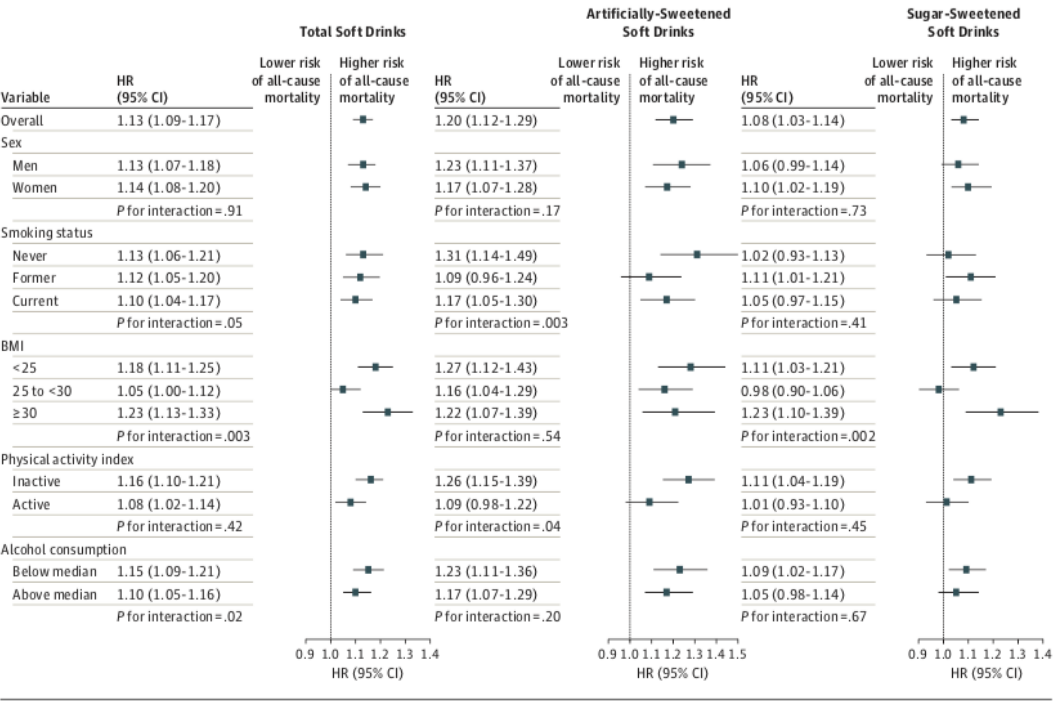
Million patients worldwide

Sources: medscape, european society of cardiology, <http://www.ehnheart.org/cvd-statistics.html>

Association Between Soft Drink Consumption and Mortality in 10 European Countries

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Figure. Subgroup Analyses of the Association Between Soft Drink Consumption and All-Cause Mortality



Association of Optimism With Cardiovascular Events and All-Cause Mortality

A Systematic Review and Meta-analysis

Alan Rozanski, MD; Chirag Bavishi, MD, MPH; Laura D. Kubzansky, PhD; Randy Cohen, MD

Figure 2. Association Between Optimism and Cardiovascular (CV) Events

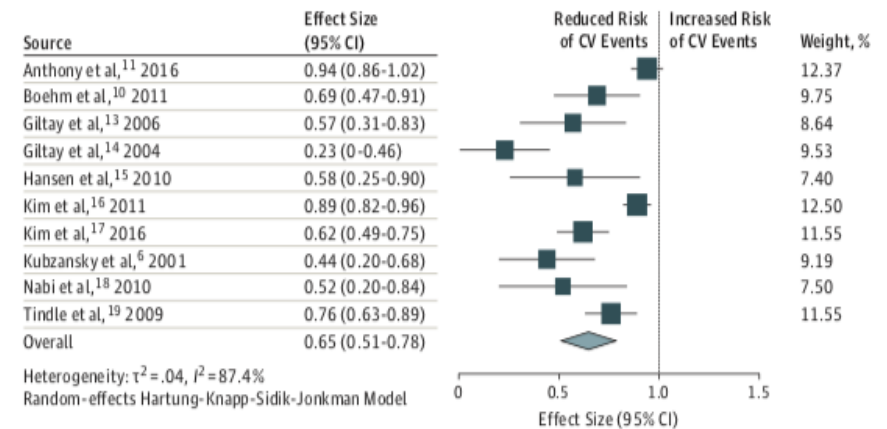
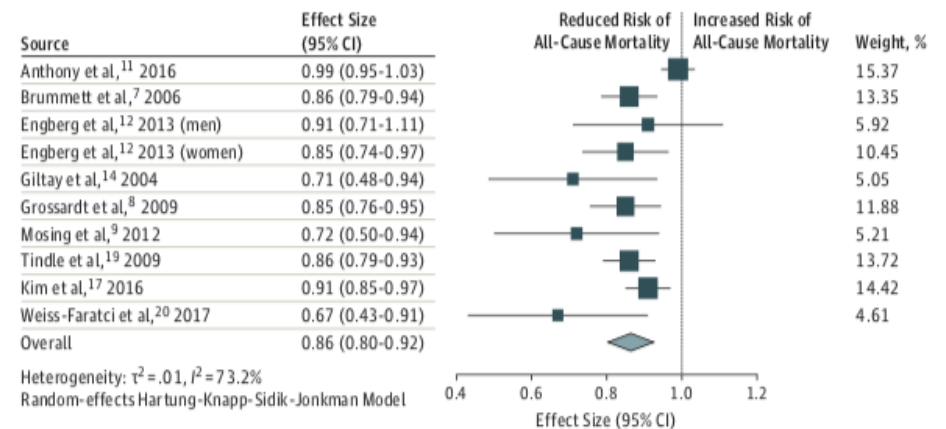
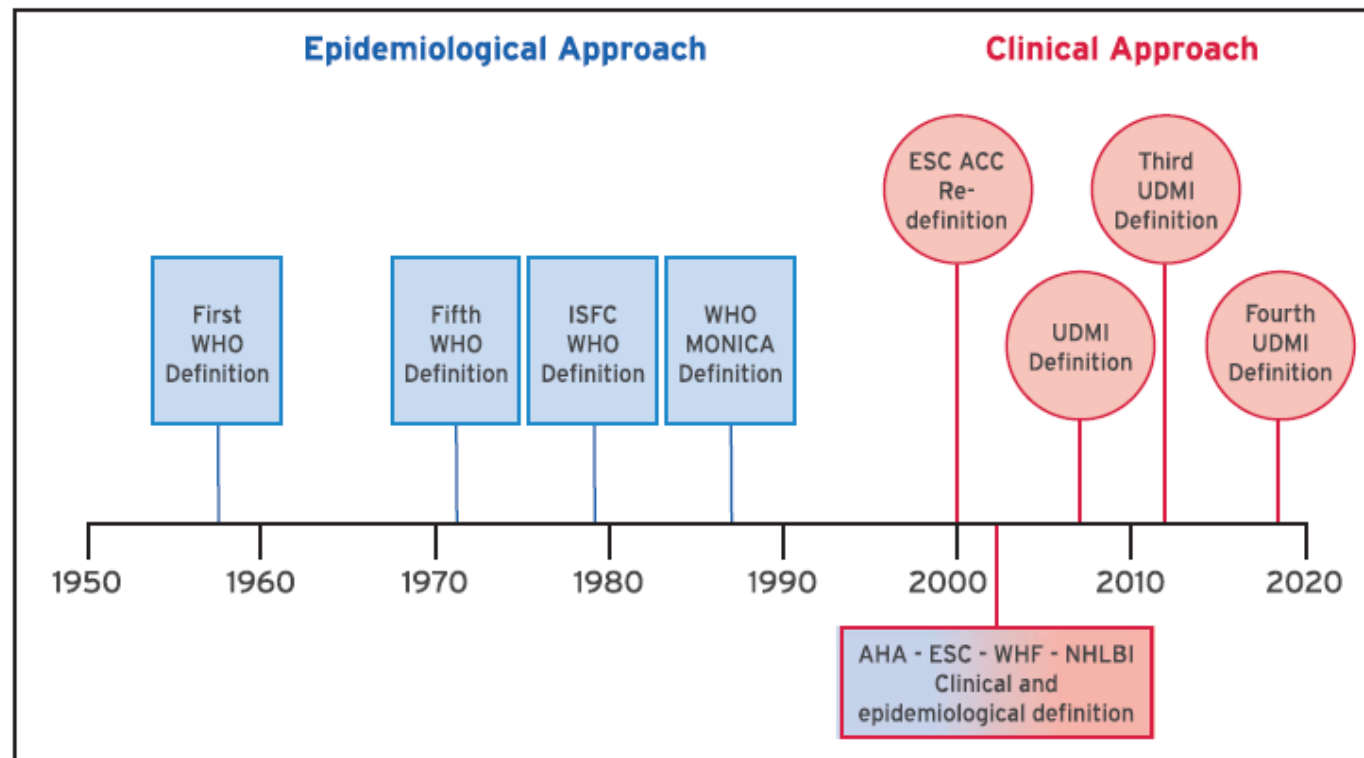


Figure 3. Association Between Optimism and All-Cause Mortality

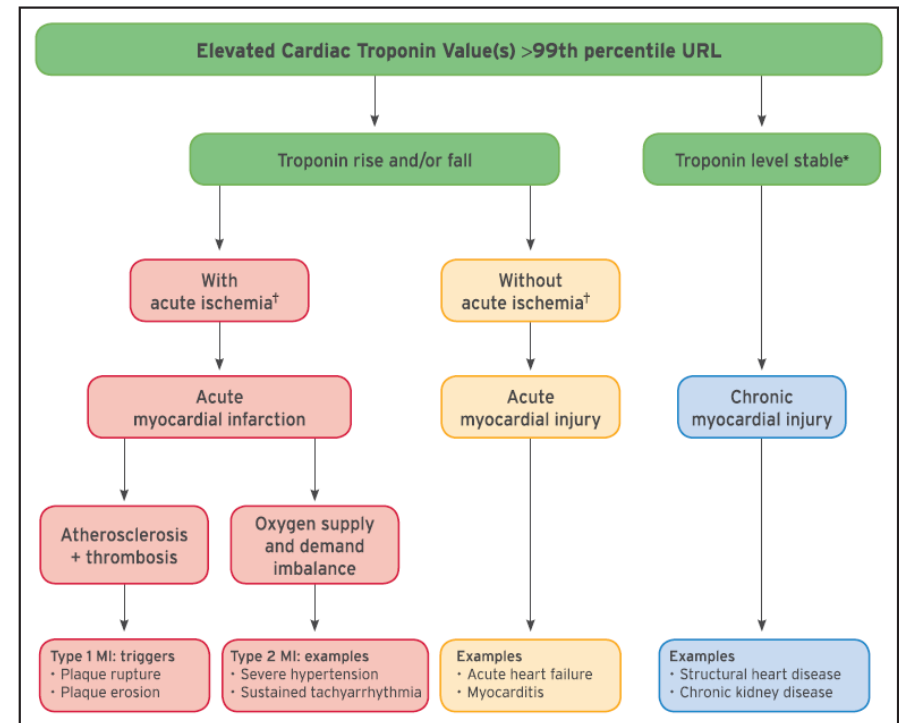
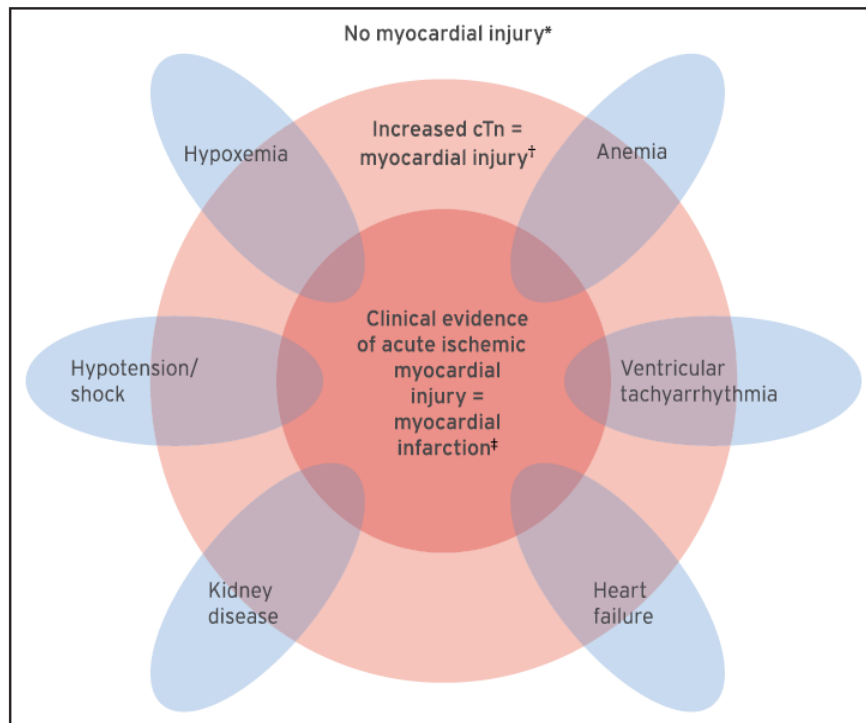


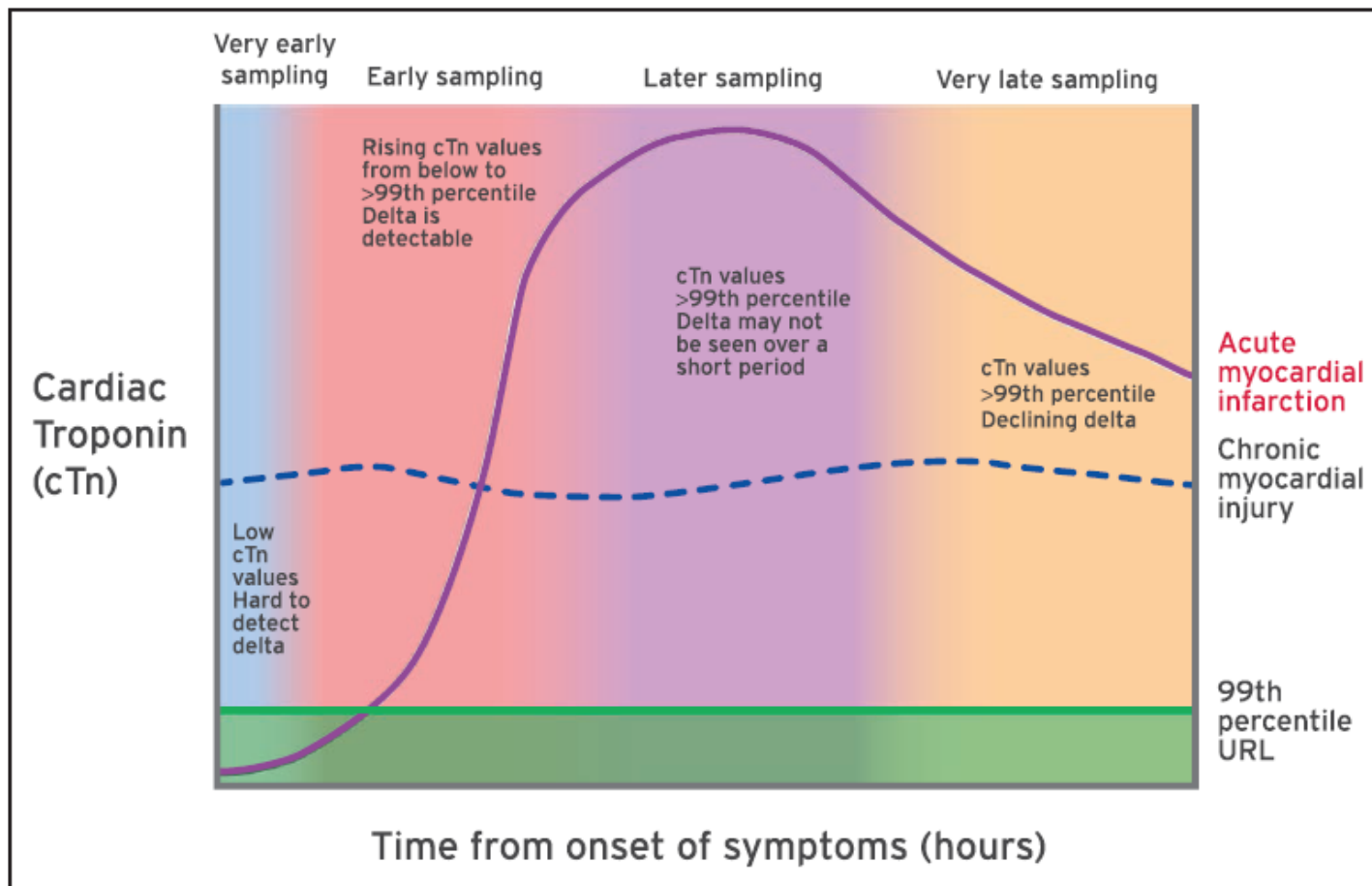
Troponin testing





Thygesen et al.; 2018





Thygesen et al.; 2018

Table 1. Summary of studies on early rule-in algorithms^{10,19–23}.

Setting	Acute non-traumatic chest pain in ED	
	0 h/1 h algorithm	0 h/2 h algorithm
Overall prevalence of AMI (%)	9–18	9–18
Inclusion criteria: onset of chest pain (h)	<12	<12
Exclusion criteria	Chronic haemodialysis	Chronic haemodialysis
Basis of gold standard diagnosis by two cardiologists	All information, including serial local cTnI (various assays) and serial hs-cTnT in the derivation and validation cohort	All information, including serial local cTnI (various assays) and serial hs-cTn in the derivation and serial s-cTnI in the validation cohort
Specificity for AMI (%)	95–97	97–99
Positive predictive value for AMI (%)	70–81	77–85
Ruled-in (%)	12–16	8–14
Observation zone (%)	23–30	26–27
Characteristics if using:		
hs-cTnT (Roche)	hs-cTnT ≥ 52 or 1 h delta ≥ 5	hs-cTnT ≥ 53 or 2 h delta ≥ 10
hs-cTnI (Abbot)	hs-cTnI ≥ 52 or 1 h delta ≥ 6	hs-cTnI ≥ 64 or 2 h delta ≥ 15
s-cTnI ultra (Siemens)	s-cTnI ≥ 166 or 1 h delta ≥ 30	s-cTnI ≥ 166 or 2 h delta ≥ 36



Drive Safely ;-)

Recommendation 4: Use a defined reference population to report 99th percentile concentrations according to sexspecific cutoffs for hs-cTn assays.

Wu et al.; 2018

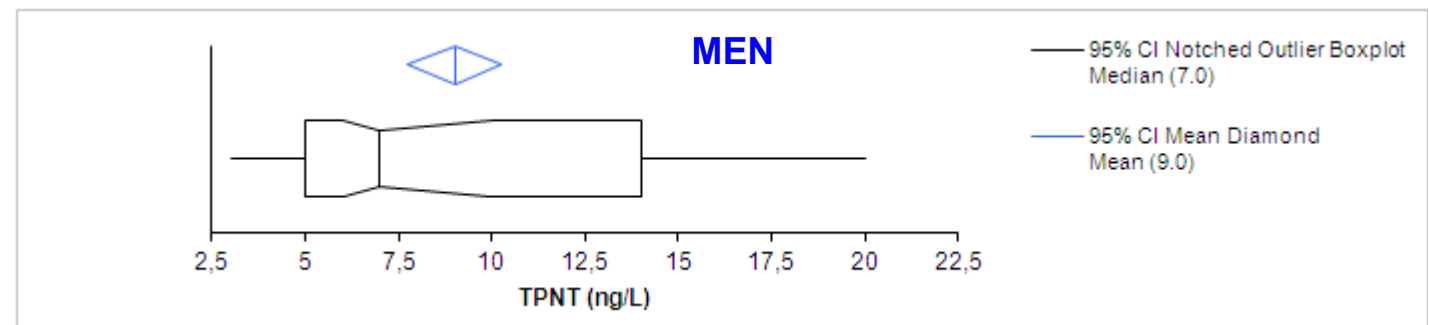
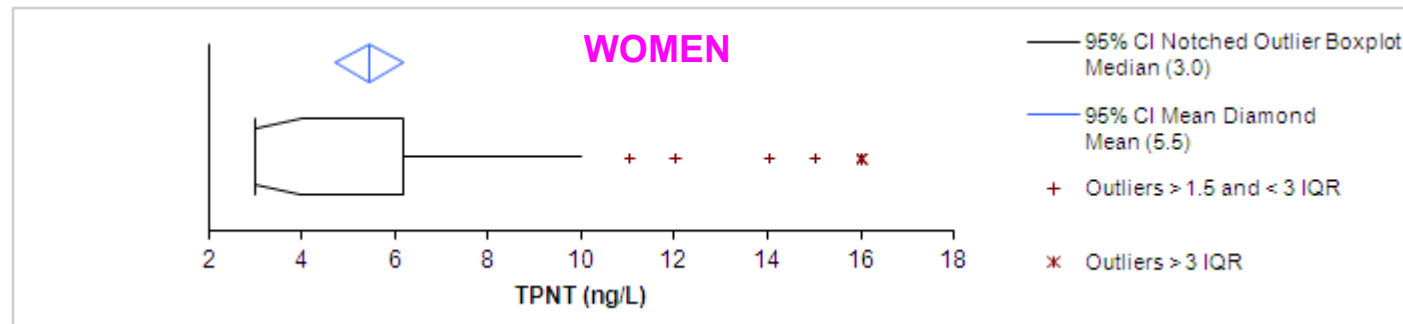
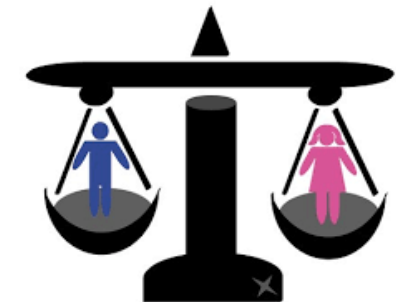


Table 2 99th Percentile Values According to the Manufacturer's Package Insert Compared with Those Reported in the Selected Peer-Reviewed Literature

Source	Instrument	99th percentiles (ng/L)		
		Overall	Men	Women
Manufacturer's package insert	Cobas e 411 and Cobas e 601	19	22	14
Apple	Cobas e 601	15	20	13
Chenevier	Cobas e 601	17.8	17.9	16.3
Collinson	Elecsys 2010	All: 29.9 Questionnaire: 20.0 Plus NTproBNP: 16.7 Plus eGFR: 14.4	All: 37.2 Questionnaire: 23.2 Plus NTproBNP: 22.8 Plus eGFR: 21.5	All: 27.7 Questionnaire: 13.6 Plus NTproBNP: 12.8 Plus eGFR: 13.8
Franzini	Cobas e 411	20.1	21.8	16.3
Giannitsis	Elecsys 2010, Cobas e 411, and Cobas e 611	13.5	14.5	10.0
Gore	Elecsys 2010	Subcohort 1 DHS: 18 ARIC: 22 CHS: 36 Subcohort 2 DHS: 14 ARIC: 21 CHS: 28	Subcohort 1 DHS: 23 ARIC: 28 CHS: 39 Subcohort 2 DHS: 17 ARIC: 26 CHS: 34	Subcohort 1 DHS: 12 ARIC: 16 CHS: 34 Subcohort 2 DHS: 11 ARIC: 15 CHS: 24
Kimenai	Cobas e 601	15	16	12
Ko	E170	13.6	15.9	10.3
Koerbin	Cobas e 411	12.5	12.9	11.0
Mingels	Elecsys 2010	16	18	8
Mueller	Modular platform	NR	13.9	11.3
Saenger	Elecsys 2010; Cobas e 601, e 411	14.2	15.5	9.0
Ungerer	Cobas e 601	15.9	18.1	9.6

Sandoval and Jaffe 2017

Gender



Age



1414 men and 1082 women with estimated glomerular filtration rate (eGFR) ≥ 60 mL/min/1.73 m² were assumed as non-AMI

Age (yrs)	18 - 50	51 - 70	71 - 98
Hs TnT 99th URLs (M/W - ng/L)	18 / 16	33 / 30	66 / 84

Monneret et al.; 2018

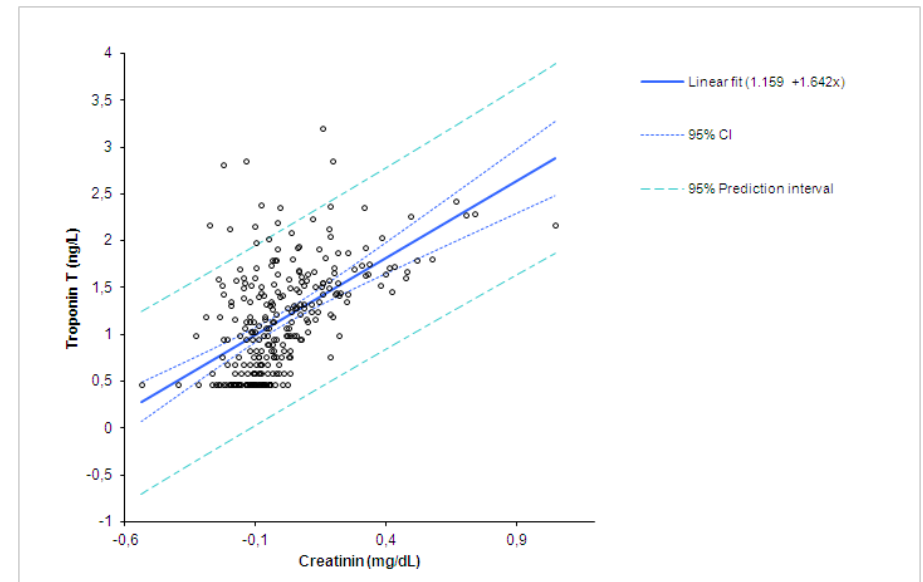
Data of 4118 consecutive emergency department (ED) patients who underwent a routine TnT measurement between 11 October 2012 and 30 November 2013

There were significant differences in hsTnT concentrations between age-groups ($p < 0.001$) in all patients

72.2% of all patients ≥ 75 years of age (583/808) without NSTEMI had hsTnT concentrations above the 99th percentile of a healthy reference population

Riedlinger D et al 2018

Kidney function



Dialysis

	Total	Men	Women	Diabetes	No Diabetes
n	98	57	41	50	48
hsTnT median (min - max), ng/L	63.1 (10.1-314.5)	66.2 (16.5-314.5)	52.9 (10.1-181.9)	68.7 (23.3-314.5)	58.2 (10.1-140.1)

Poux et al.; 2018



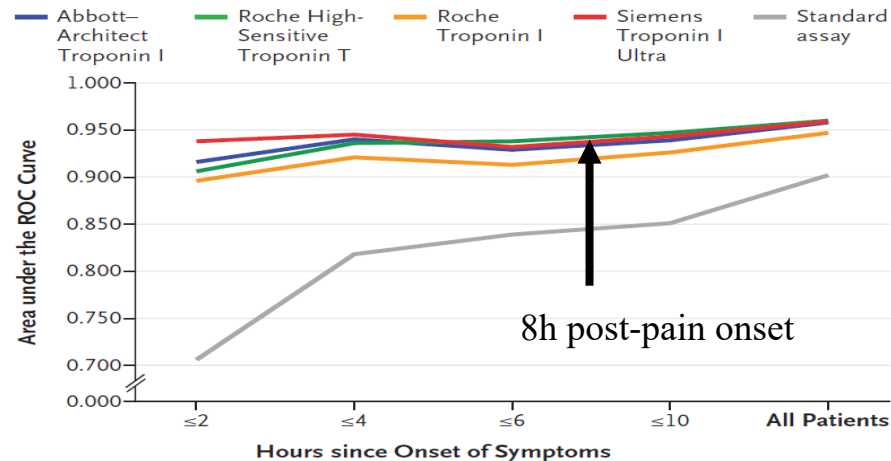
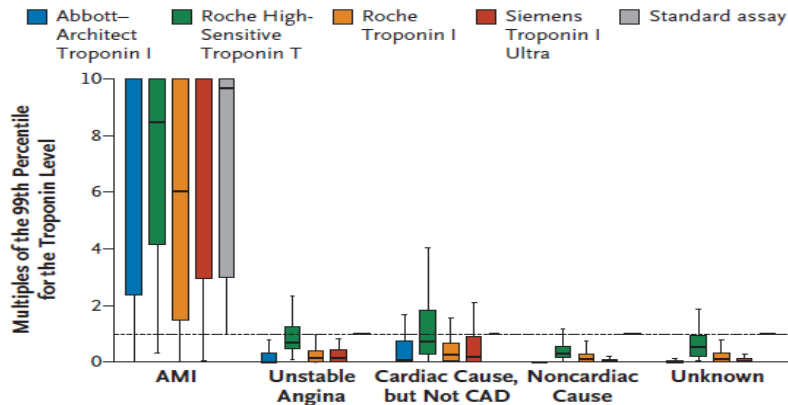
	Ensemble des patients	SCA	Non SCA
Nombre total de patients (%)	98 (100)	24 (25)	74 (75)
Hommes (%)	72 (74)	19 (80)	53 (72)
Femmes (%)	26 (26)	5 (20)	21 (28)
Age médian (ans) (mimumum-maximum)	74 (39-95)	74 (47-87)	75 (39-95)
Médiane créatinine (mg/dl) (Q1-Q3)	1,65 (1,4-2,36)	1,63 (1,45-1,98)	1,79 (1,39-2,48)
Médiane GFR (glomerular filtration rate) (ml/min) (Q1-Q3)	35 (22-49)	41 (24-50)	34 (22-49)
Médiane hsTnT H0 (ng/l) (Q1-Q3)	41 (21-123)	130 (28-252)	36 (18-69)
Médiane hsTnT H3 (ng/l) (Q1-Q3)	50 (28-159)	178 (59-615)	36 (23-90)
Médiane Δ hsTnT 0/3h (ng/l) (Q1-Q3)	6 (2-36)	37 (16-480)	3 (1-8)
Médiane hsTnT H0 (ng/l) IR Stade 2 (GFR entre 60 et 90ml/min) (Q1-Q3)	7 (5-21)	121	6 (4-11)
Médiane hsTnT H0 (ng/l) IR Stade 3 (GFR entre 30 et 59ml/min) (Q1-Q3)	29 (17-88)	129 (25-187)	29 (15-45)
Médiane hsTnT H0 (ng/l) IR Stades 4 et 5 (GFR $\leq$ 29ml/min) (Q1-Q3)	76 (38-160)	132 (104-710)	43 (29-87)

Data from
Caroline Moureau

ORIGINAL ARTICLE

Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays

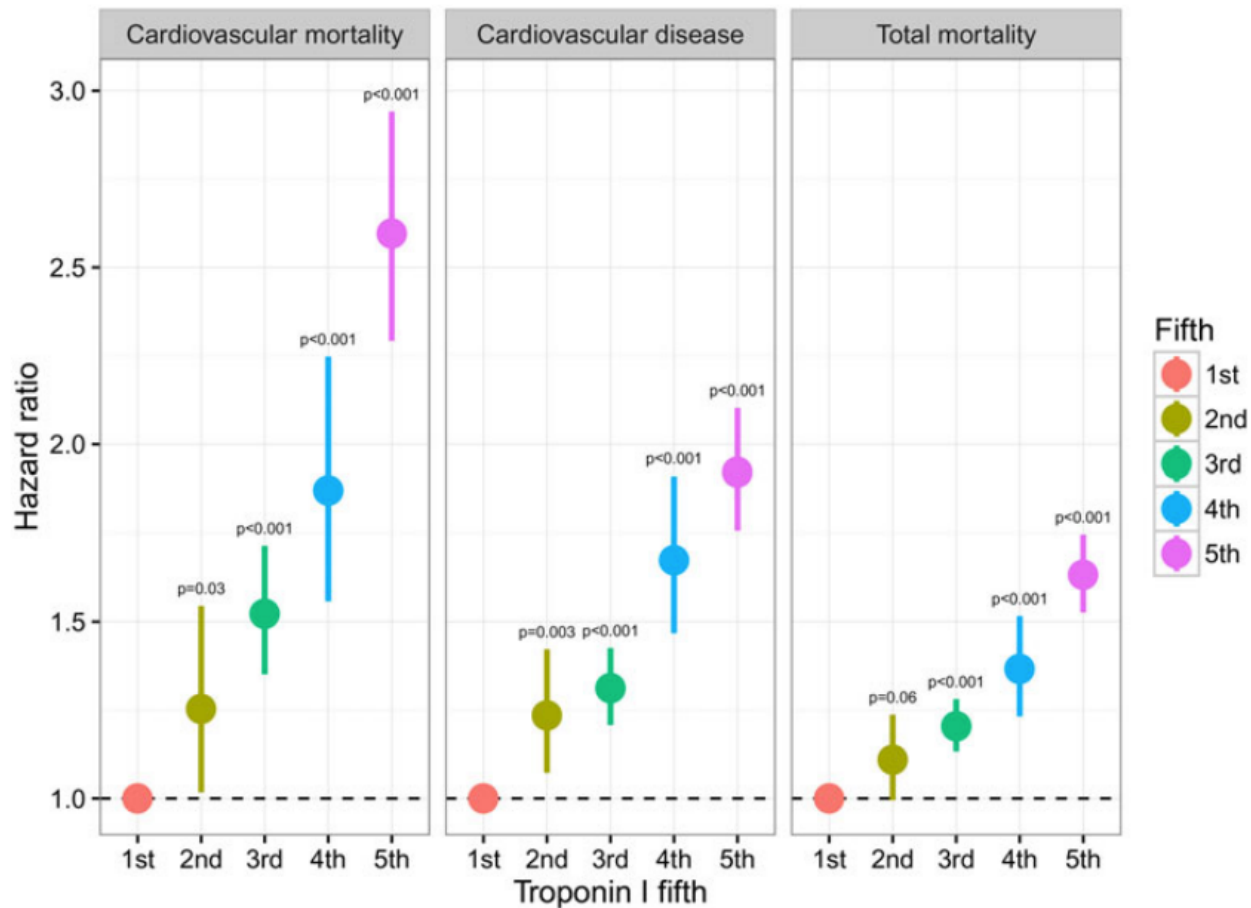
Samples obtained in the emergency department from 718 consecutive patients who presented with symptoms suggestive of acute myocardial infarction



The diagnostic performance of sensitive cardiac troponin assays is excellent, and these assays can substantially improve the early diagnosis of acute myocardial infarction, particularly in patients with a recent onset of chest pain



Risks...

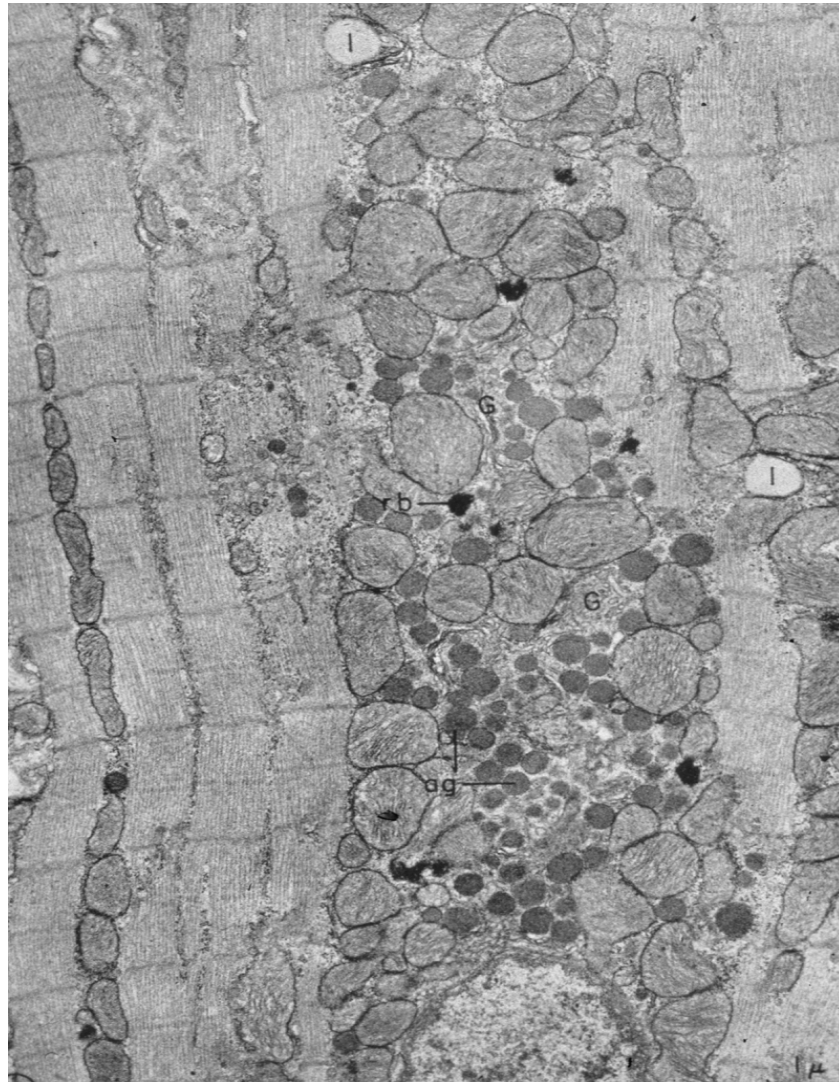


Hazard ratios according to fifths of the troponin I distribution in the study population

The BiomarCaRE consortium, European Heart Journal (2016)

Natriuretic Peptides Testing





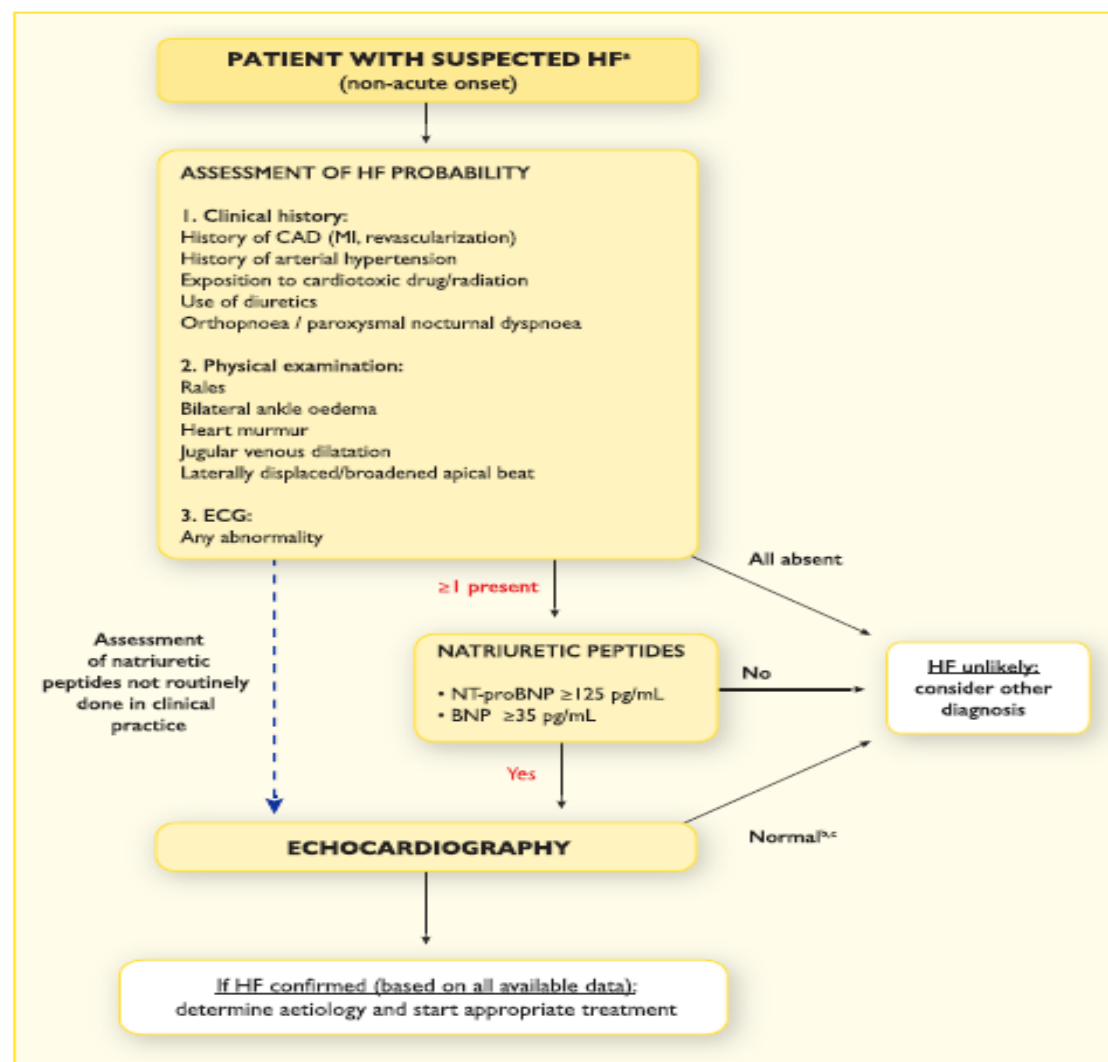
Endocrine Heart[≡]

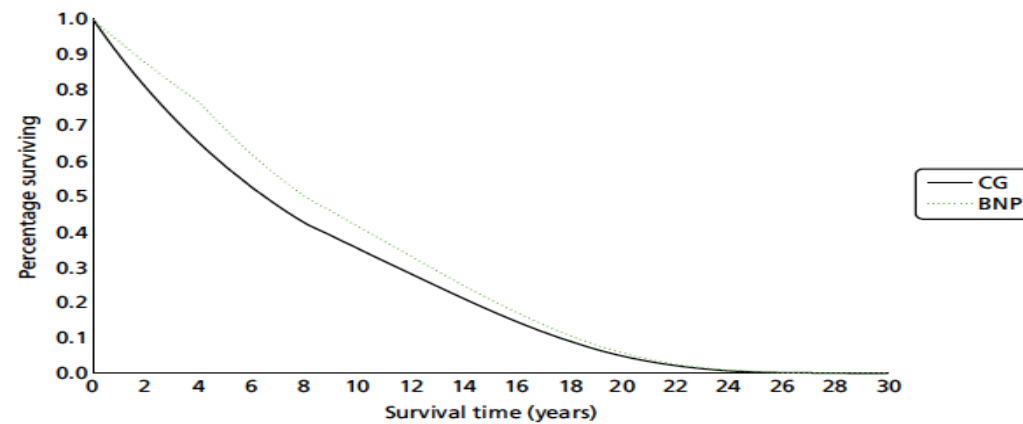
**Secretory granules in atrial
cardiocytes**

Jamieson and Palade, 1962

De Bold et al., 1980

**Atria extracts strongly stimulate
sodium excretion and diuresis, when
injected to rats**





Subgroup	CG		BNP		iNMB (95 % CI) ^b (£)
	Cost ^a (£)	QALYs ^a	Cost ^a (£)	QALYs ^a	
Patients aged < 75 years					
All HF	58,139	5.02	64,777	5.68	6426 (2401 to 10,075)
HFrEF	58,139	5.02	63,527	5.57	5424 (987 to 9469)
HFpEF	67,694	5.86	71,097	6.23	3155 (−10,307 to 11,613)
Patients aged ≥ 75 years					
All HF	26,093	2.20	25,802	2.23	869 (−2814 to 4606)
HFrEF	26,093	2.20	27,676	2.39	2267 (−1524 to 6074)

a

Deterministic SAs.

b

PSA.

Pufulete et al.; 2017

Valeurs de référence pour le N-terminal du peptide natriurétique de type B, NT-proBNP.

❖→ Les valeurs de références (97.5^{ème} percentiles en ng/L) sont ajustées en fonction de l'âge et du sexe (source°: insert Roche 2018-07-V13)°

Age (en années)	Hommes	Femmes
18—44	85.8	130
45—54	121	249
55—64	210	287
65—74	376	301
>75	486	738

❖→ Valeur cible ESC (Ponikowski 2016) pour l'exclusion d'une insuffisance cardiaque:

○→ Situation non aigue: 125 pg/mL

○→ Situation aigue: 300 pg/mL

❖→ Insuffisance rénale: «°When the GFR was less than 60 mL/min/1.73m², the NT-proBNP cut-off point should be raised to 750 pg/mL°» (Gergei et al.; 2019)

Note pour le risque d'interférence avec la biotine°:

Biological variation?

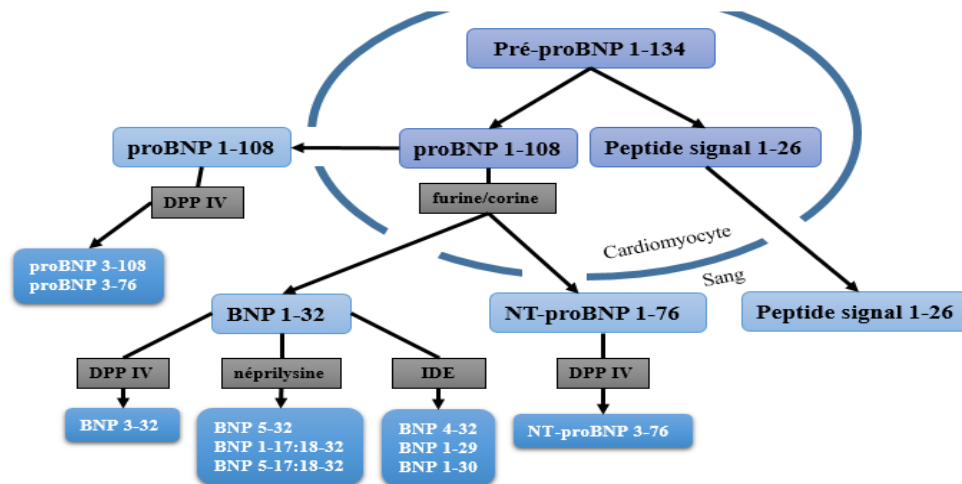
Table 5 Biological variation indices for all biomarkers in chronic heart failure patients

	CV _a	CV _i	CV _g	II	RCV (%)	Log normal RCV up	RCV down
Established biomarkers							
NT-proBNP	3.3	21.8	116.3	0.2	61.7	104.9	−40.1
hsTnT	1.5	11.1	96.6	0.1	31.4	42.6	−22.1
Novel biomarkers							
Galectin-3	3.2	8.1	21.2	0.4	25.0	30.2	−20.1
GDF-15	15.2	16.6	77.1	0.3	64.3	78.2	−38.3
ST2	2.9	15.0	36.9	0.4	42.9	62.7	−31.4
Renal/neurohormonal biomarkers							
Creatinine	1.6	5.0	19.6	0.3	15.0	16.5	−13.3
Plasma renin concentration	2.3	32.6	222.2	0.1	90.8	180.6	−51.2
Aldosterone	6.2	27.7	91.1	0.3	80.2	139.3	−48.9
Phosphate	1.3	10.7	17.4	0.6	30.0	38.7	−24.3
PTH	1.1	22.5	49.2	0.5	62.4	93.0	−43.3
hsTnT (n = 49)	4.4	13.4	70.4	0.1	37.6	52.1	−28.3
Electrolytes							
Calcium	1.5	1.6	3.3	0.7	6.3	5.4	−5.0
Sodium	0.7	0.8	1.3	0.9	3.1	2.7	−2.6

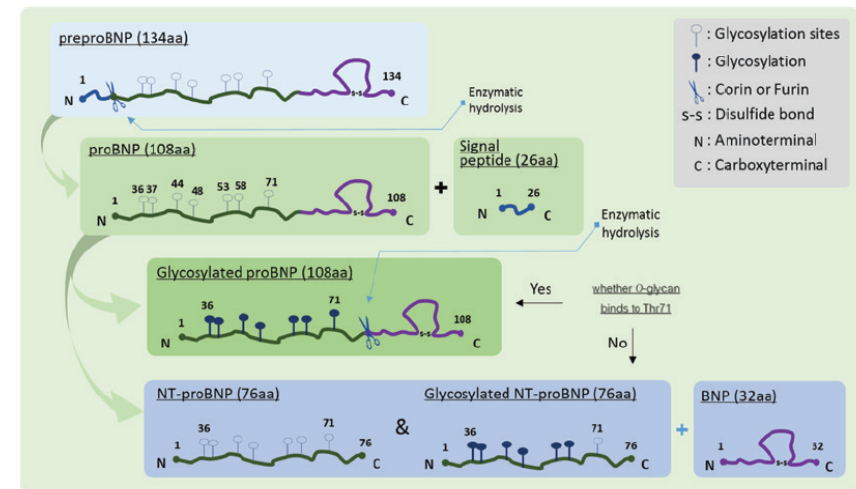
CV_a, analytical coefficient of variation; CV_g, interindividual coefficient of variation; CV_i, intraindividual coefficient of variation; GDF-15, growth differentiation factor 15; hsTnT, high-sensitivity troponin T; II, index of individuality; PTH, parathyroid hormone; RCV, reference change value; ST2, suppression of tumorigenicity 2.

Meijers et al.; 2017

Circulating forms and assay specificity?



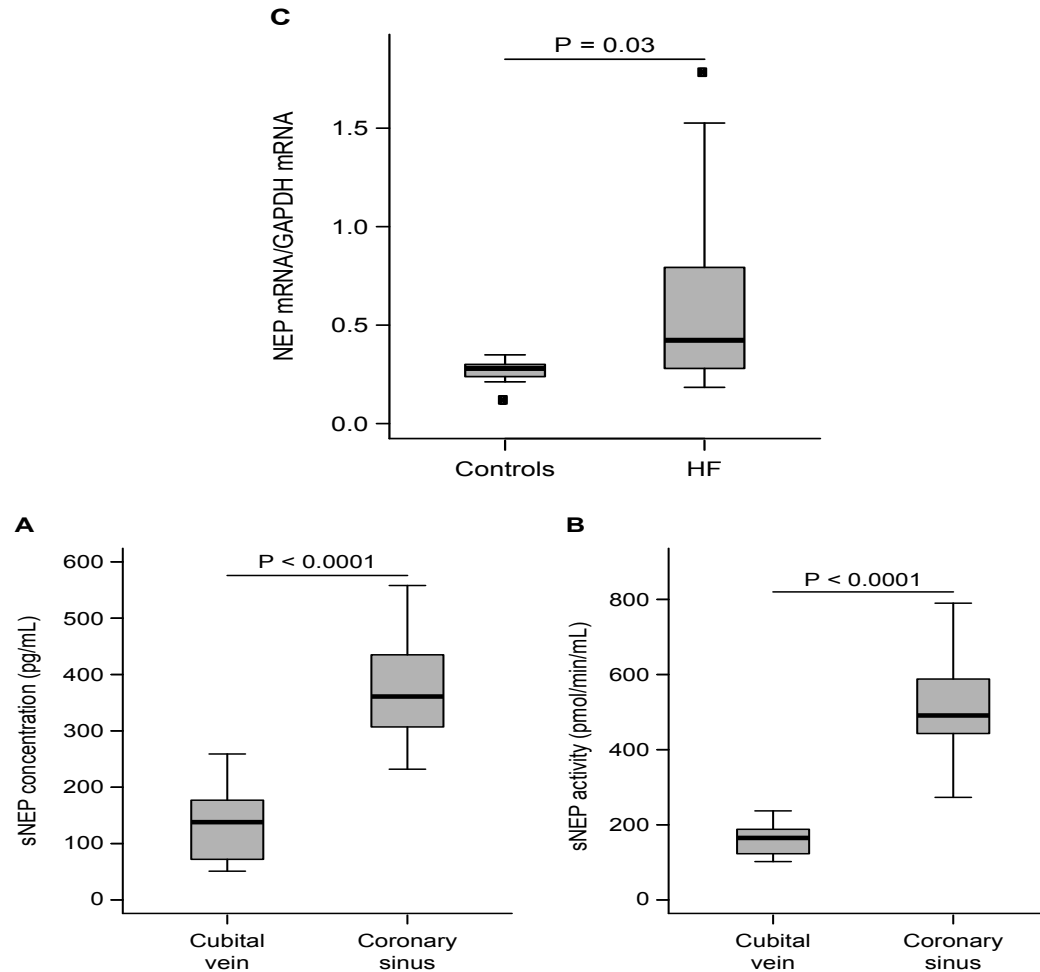
Favresse J., ABC 2017



Xiao et al.; 2019

The heart regulates the endocrine response to heart failure: cardiac contribution to circulating neprilysin

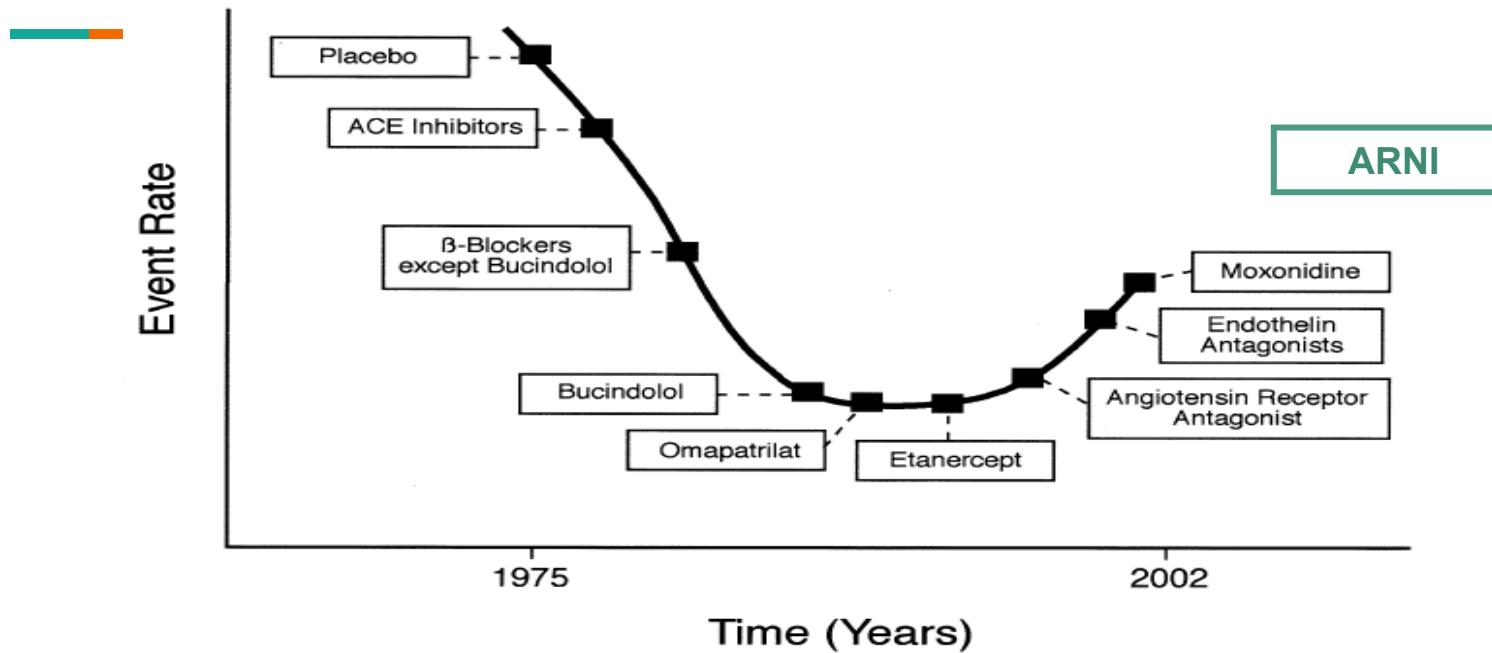
**Mattia Arrigo^{1,2†}, Nicolas Vodovar^{1†}, H          ^{1,3}, Malha Sadoune¹,
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Christian Latremouille^{6,9}, Jane-Lise Samuel¹, Jean-Marie Launay^{1,16},
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and Alexandre Mebazaa^{1,3,12*}**



In patients with reduced cardiac systolic function the heart becomes a source of sNEP, which will in turn modulate the plasma concentrations of sNEP substrates.

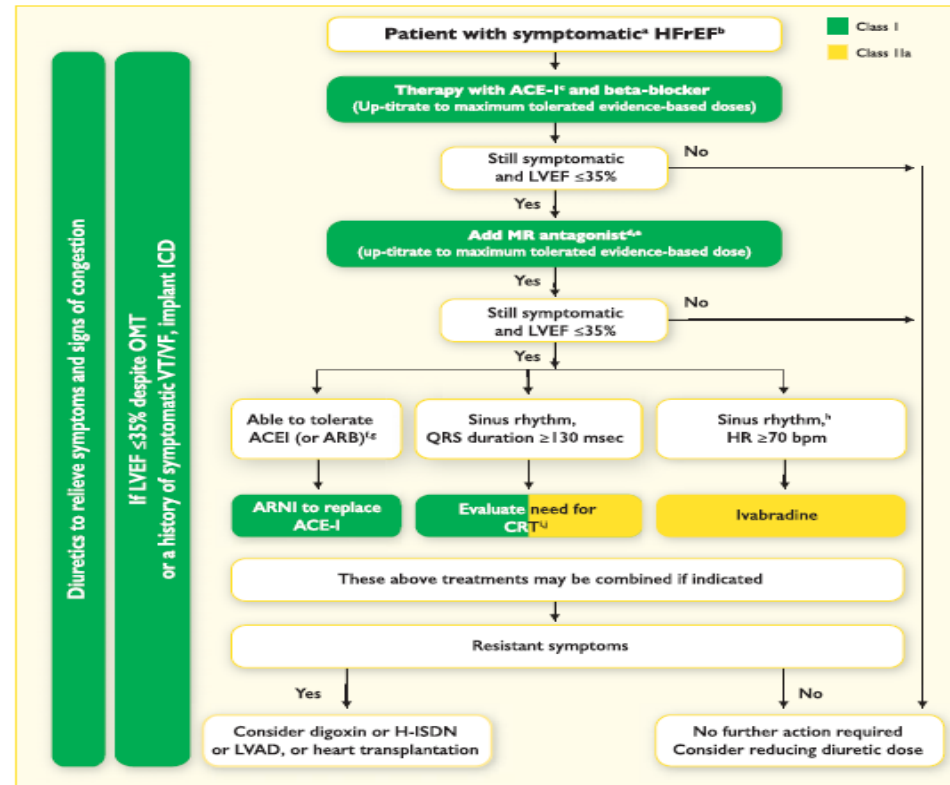
Regional differences in sNEP in patients with reduced systolic function

New therapeutic strategies and molecular targets



Mehra et al.; 2003

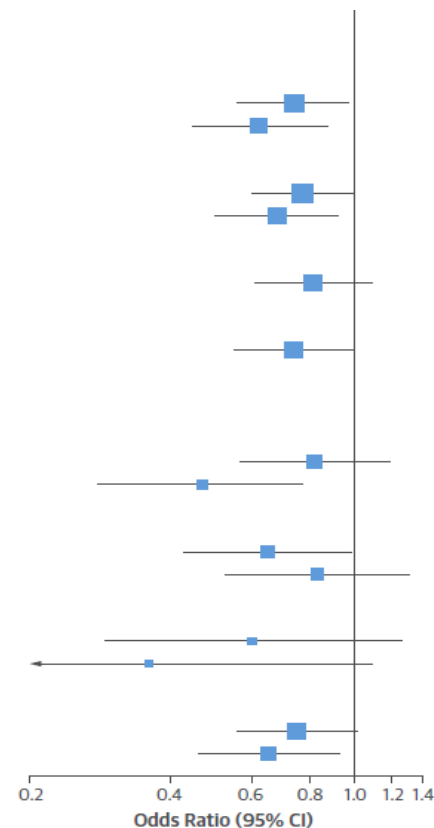
ARNI Angiotensin Receptor Neprilysin Inhibitor

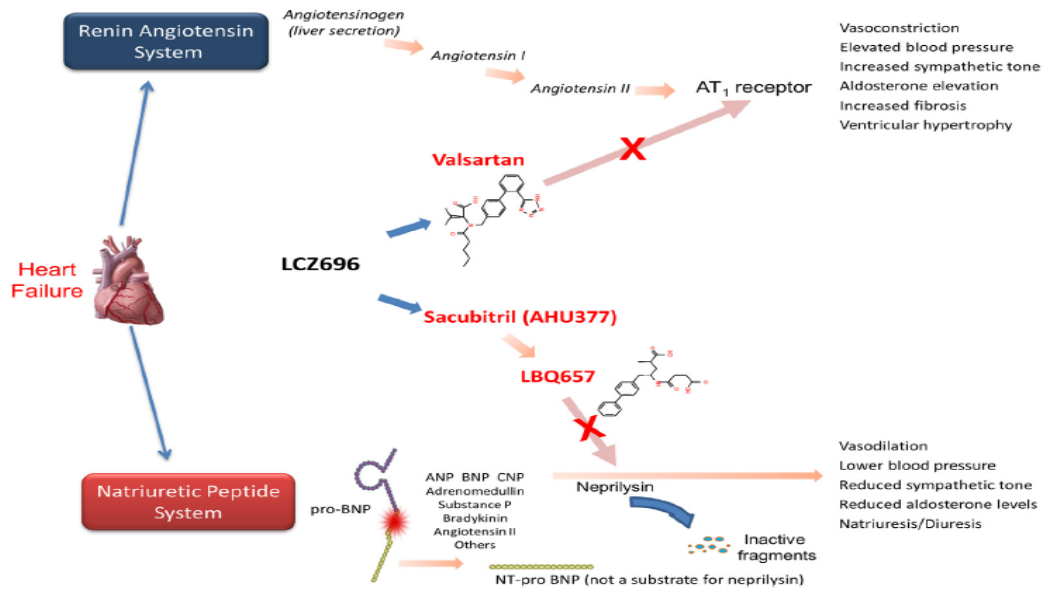


COR	LOE	RECOMMENDATIONS
I	ACE: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors (Level of Evidence: A) (9-14), OR ARBs (Level of Evidence: A) (15-18), OR ARNI (Level of Evidence: B-R) (19) in conjunction with evidence-based beta blockers (20-22), and aldosterone antagonists in selected patients (23,24), is recommended for patients with chronic HFrEF to reduce morbidity and mortality.

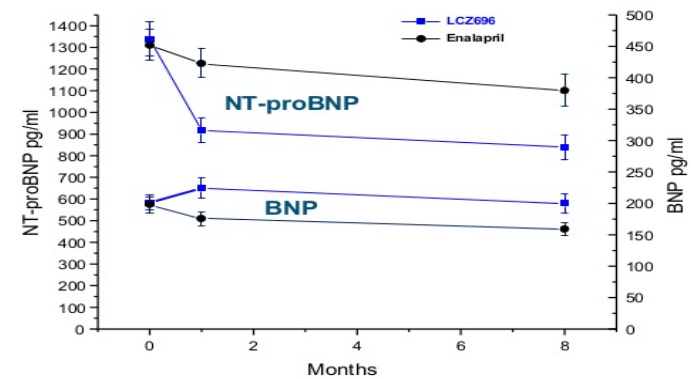
Influence of Sacubitril/Valsartan (LCZ696) on 30-Day Readmission After Heart Failure Hospitalization

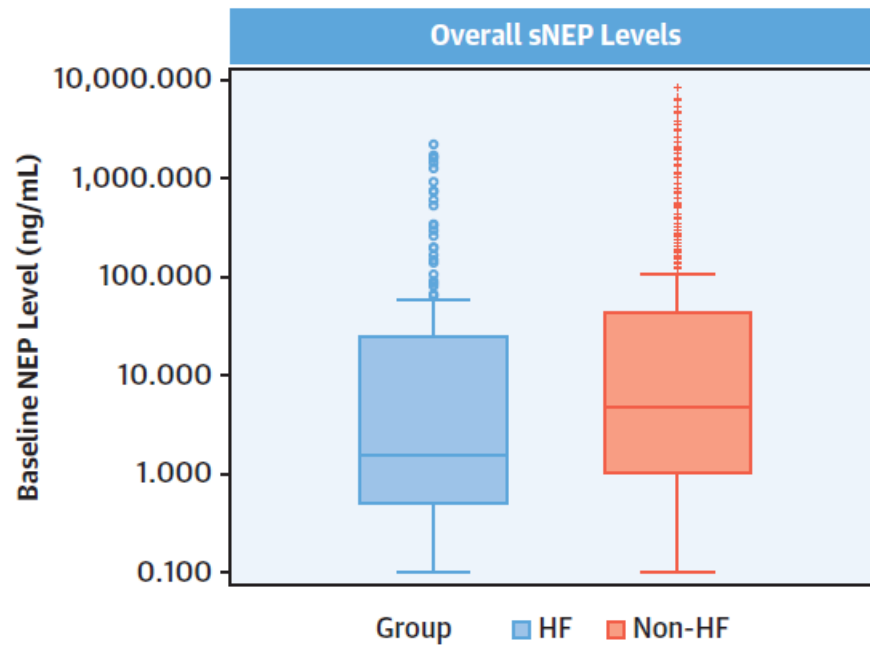
Analysis	LCZ696	Enalapril	Odds Ratio	P-Value
30-day (after any investigator-reported HF Hosp)				
All-cause readmission	192/1076 (17.8%)	275/1307 (21.0%)	0.74 (0.56-0.97)	0.031
HF readmission	104/1074 (9.7%)	175/1302 (13.4%)	0.62 (0.45-0.87)	0.006
60-day (after any investigator-reported HF Hosp)				
All-cause readmission	294/1059 (27.8%)	391/1283 (30.5%)	0.77 (0.60-0.99)	0.045
HF readmission	180/1055 (17.1%)	259/1275 (20.3%)	0.68 (0.50-0.92)	0.013
30-day (after first investigator-reported HF Hosp)				
All-cause readmission	92/666 (13.8%)	125/760 (16.4%)	0.81 (0.61-1.09)	0.17
30-day (after any CEC-confirmed HF Hosp)				
All-cause readmission	171/967 (17.7%)	243/1172 (20.7%)	0.74 (0.55-0.99)	0.043
30-day (after any investigator-reported HF Hosp):				
Subgroup: Patients at least 65 years				
All-cause readmission	101/567 (17.8%)	133/644 (20.7%)	0.82 (0.57-1.19)	0.30
HF readmission	47/565 (8.3%)	94/643 (14.6%)	0.47 (0.28-0.77)	0.003
Subgroup: Patients less than 65 years				
All-cause readmission	91/509 (17.9%)	142/663 (21.4%)	0.65 (0.43-0.98)	0.041
HF readmission	57/509 (11.2%)	81/659 (12.3%)	0.83 (0.53-1.31)	0.42
Subgroup: US Patients				
All-cause readmission	18/104 (17.3%)	34/131 (26.0%)	0.60 (0.29-1.26)	0.18
HF readmission	6/104 (5.8%)	21/131 (16.0%)	0.36 (0.12-1.09)	0.07
Subgroup: non-US Patients				
All-cause readmission	174/972 (17.9%)	241/1176 (20.5%)	0.75 (0.56-1.01)	0.06
HF readmission	98/970 (10.1%)	154/1171 (13.2%)	0.65 (0.46-0.93)	0.018





Vardeny et al.; 2014





Lyle, M.A. et al. J Am Coll Cardiol HF. 2019;■(■):■-■.

TABLE 4A Soluble Neprilysin (ng/ml) Levels in HFpEF Patients Compared With Community-Based Controls Without HFpEF

Adjustment	HF Adjusted Mean (CI) (n = 242)	Non-HF Adjusted Mean (CI) (n = 891)	p Value
None	3.5 (2.5–4.8)	8.5 (7.2–10.0)	<0.001
Smoking history	3.6 (2.6–5.0)	8.4 (7.1–9.8)	<0.001
Age, gender, BMI, smoking history	4.0 (2.7–5.9)	8.2 (6.8–9.7)	0.002
Age, gender, BMI, smoking history, ACE-I	4.3 (2.8–6.4)	8.1 (6.7–9.8)	0.009
Age, gender, BMI, Smoking history, ACE-I, hyperlipidemia	4.5 (2.9–7.0)	8.0 (6.6–9.7)	0.04
Age, gender, BMI, smoking history, hypertension	4.2 (2.8–6.4)	8.0 (6.7–9.6)	0.01

Lyle et al.; 2019

Transforming Ecosystem

Precision care



Prevention

Data

Technologies

Early diagnosis

Multidisciplinary

Well being

Care pathways

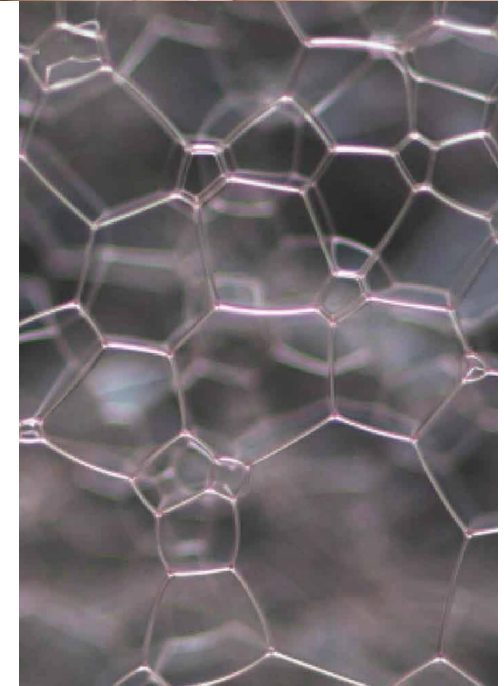
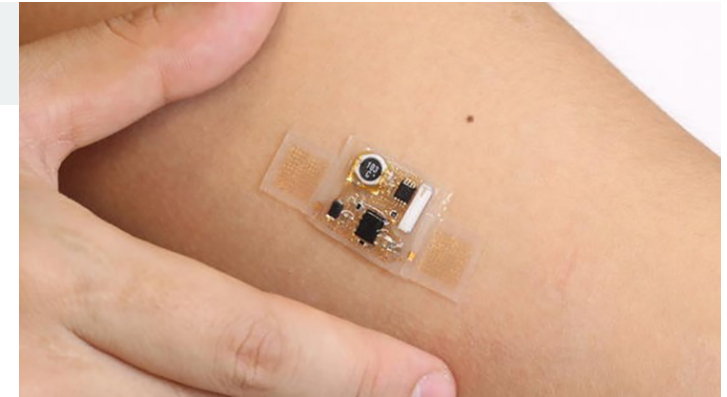
<http://med.stanford.edu/news/all-news/2015/06/precision-health-predicting-and-preventing-disease.html>

Trends: Sensors

An Aptamer-based Biosensor for Troponin I Detection in Diagnosis of Myocardial Infarction

Negahdary M.^{1,2}, Behjati-Ardakani M.¹, Sattarahmady N.^{2,3},
Heli H.^{2*}

Aptamer sequence	Detection Techniques	Transducer	Detection Range	LOD	Ref
1	Electrochemiluminescence	Gold	8.0×10^{-13} – 1.0×10^{-11} g mL ⁻¹	0.3 pg mL ⁻¹	(Liu et al., 2017)
2	DPV, Cyclic voltammetry	Gold	0.05–500 ng mL ⁻¹	8.0 pg mL ⁻¹	(Negahdary et al., 2017)
3, 4	Cyclic voltammetry, Impedance spectroscopy	Carbon	0.024–2.4 ng mL ⁻¹	24 pg mL ⁻¹	(Jo et al., 2017)
5	Impedance spectroscopy	Gold	0–10 µg mL ⁻¹	0.34 µg mL ⁻¹	(Wu et al., 2010)
6–11	Square wave voltammetry	Gold	1–10 000 pmol L ⁻¹	1.0 pM	(Jo et al., 2015)
12	DPV	Gold	0.03 to 2.0 ng mL ⁻¹	10 pg mL ⁻¹	This work



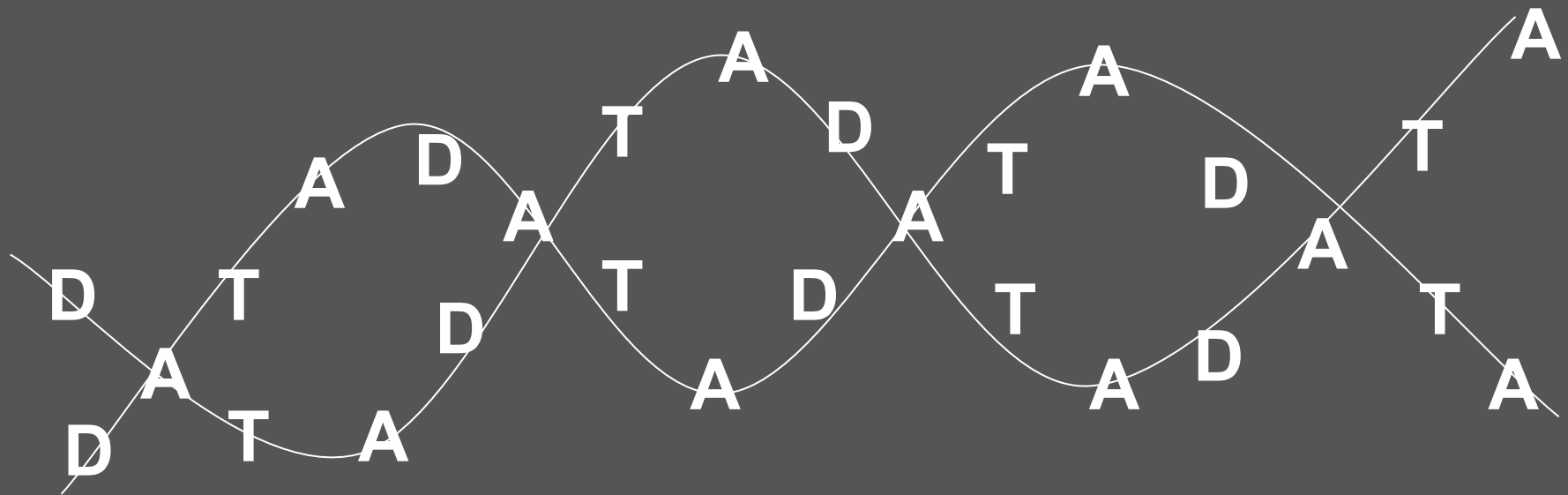
The power of data



Several sources

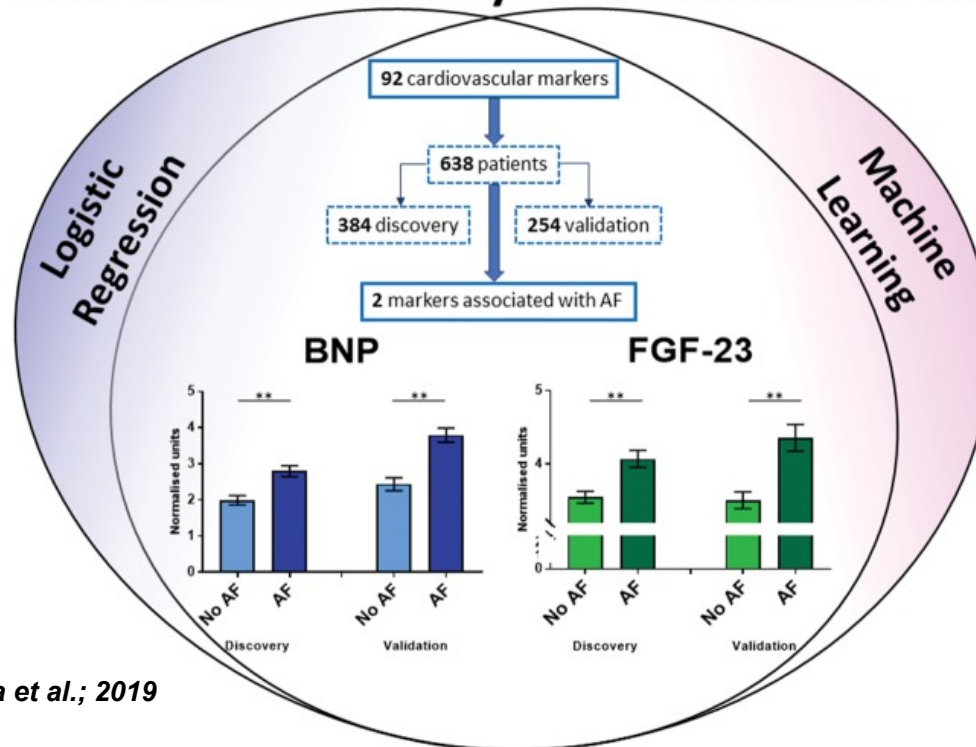


- LIS
- EMR
- Advanced imaging
- Omics
- Digital health



Data driven modeling

Data-Driven Discovery of Biomarkers for AF

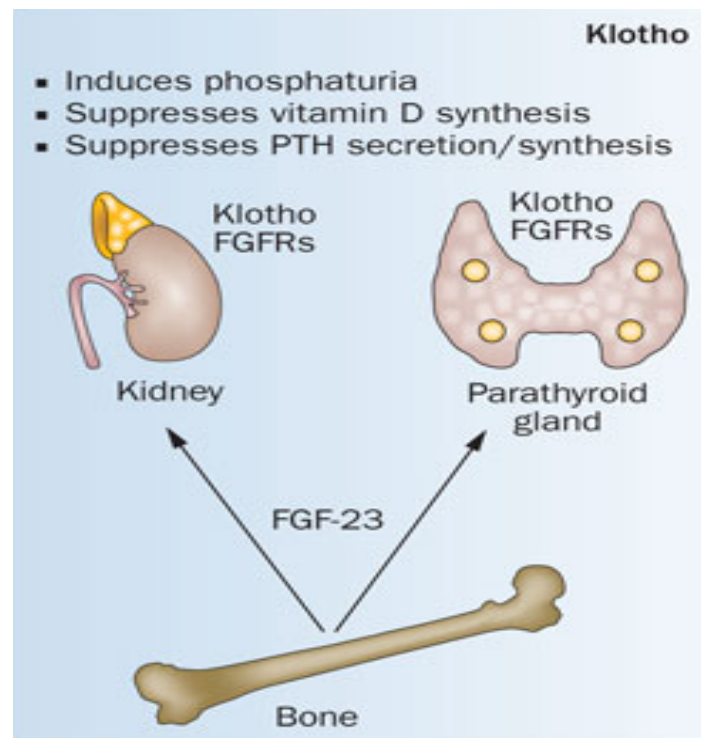


Chua et al.; 2019

Three simple clinical risk factors (age, sex, and BMI) and two biomarkers (elevated BNP and elevated FGF-23) identify patients with AF.

« Combining routine measures with new measures »

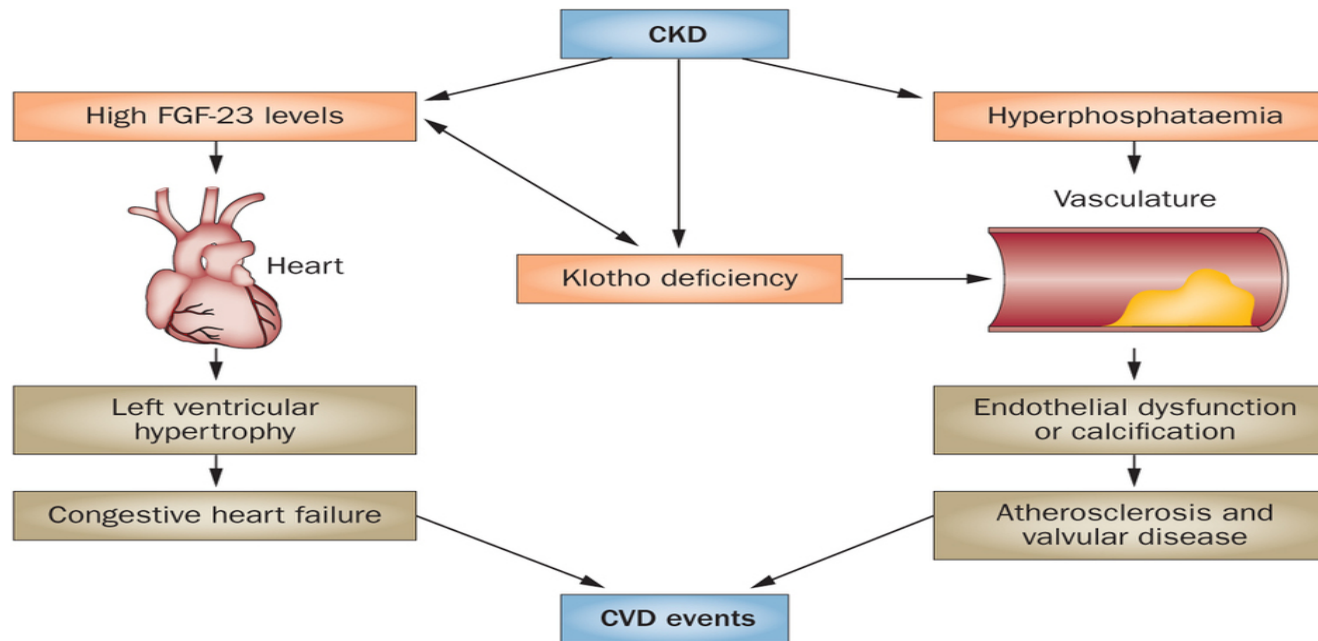
« *The most exciting advance in the understanding of mineral metabolism in the last decade was the discovery of the phosphate-regulating hormone, FGF23. »*



Kronenberg, JCEM, 2016

Relation Between Serum Phosphate Level and Cardiovascular Event Rate in People With Coronary Disease

Marcello Tonelli, MD, SM; Frank Sacks, MD; Marc Pfeffer, MD, PhD; Zhiwei Gao, MSc; Gary Curhan, MD, ScD; for the Cholesterol And Recurrent Events (CARE) Trial Investigators

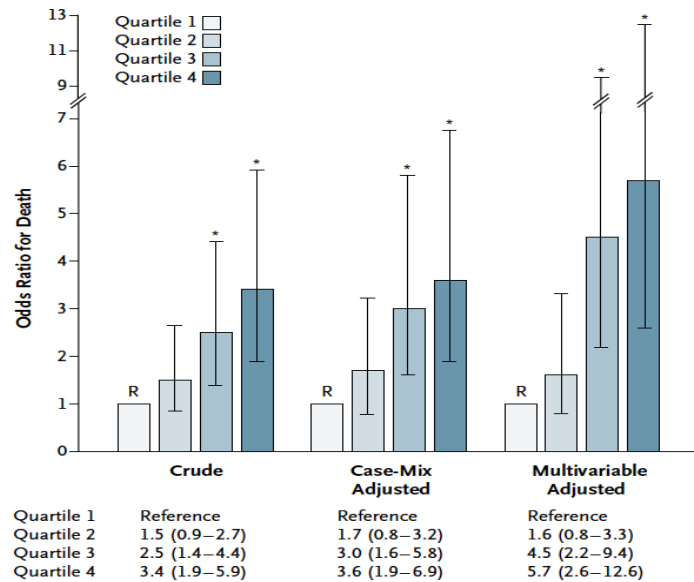


Julia J. Scialla and Myles Wolf; 2014

ORIGINAL ARTICLE

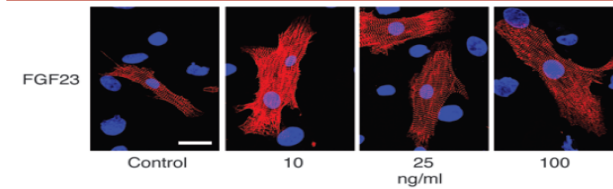
Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis

Orlando M. Gutiérrez, M.D., M.M.Sc., Michael Mannstadt, M.D.,

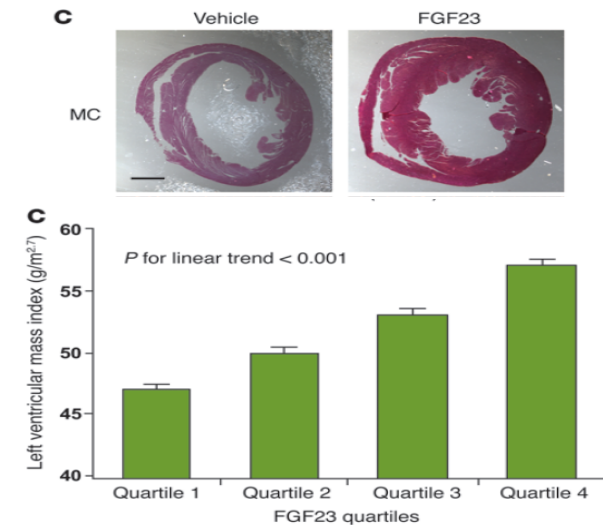


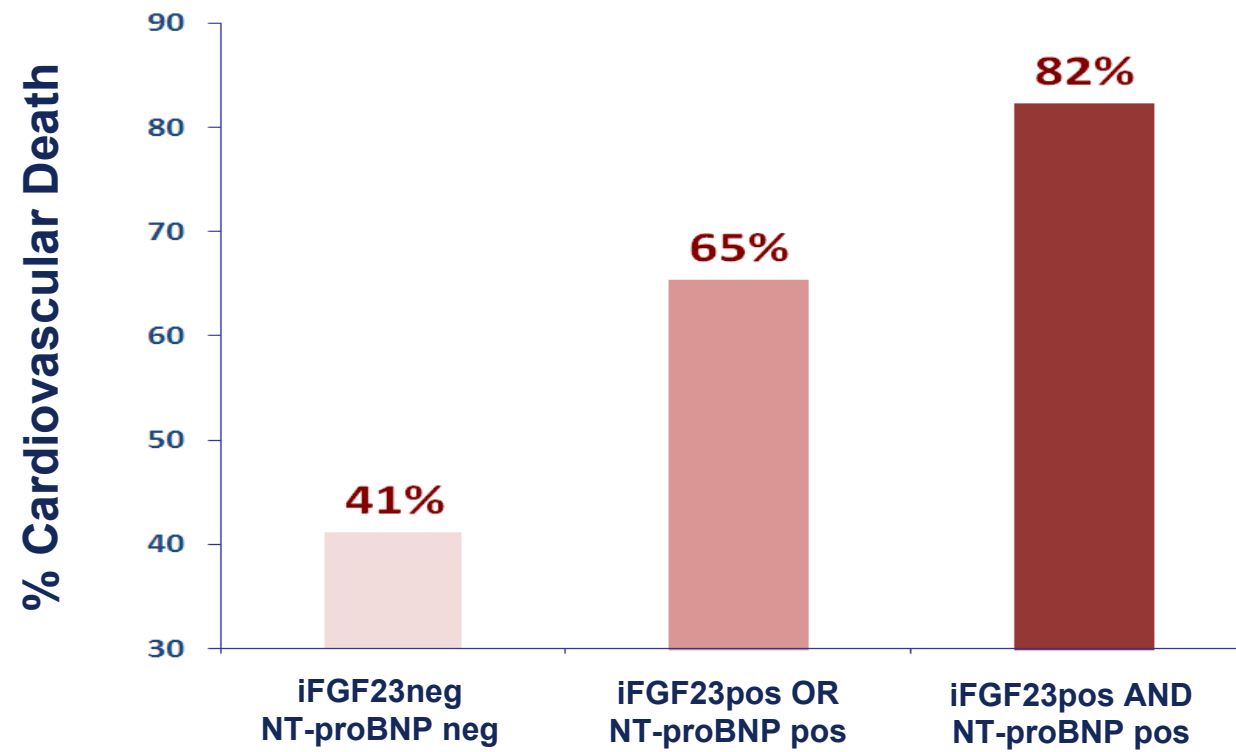
Faul et al., 2011

Cardiomyocytes Hypertrophy and Activation of Hypertrophic gene programs



Intramyocardial or intravenous injection of FGF23 in wild-type mice resulted in LVH



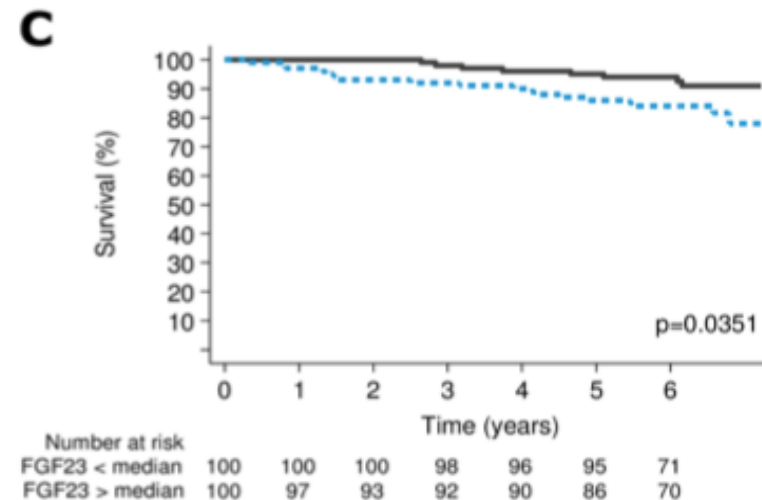
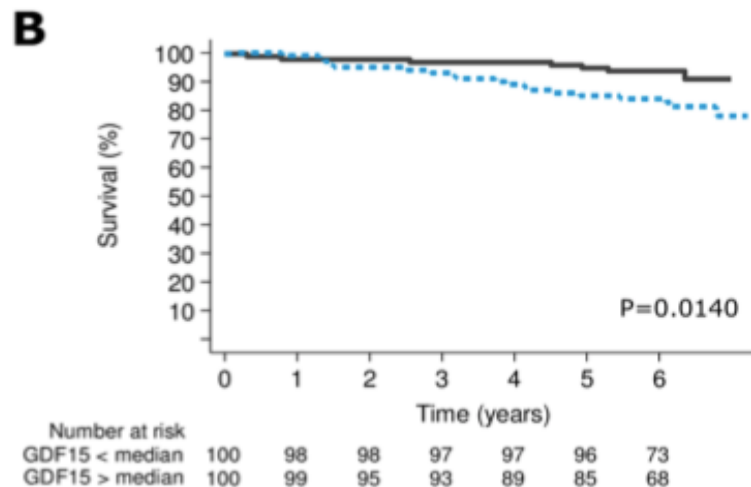


Gruson et al.; 2018

Early sub-phenotyping of high-risk populations

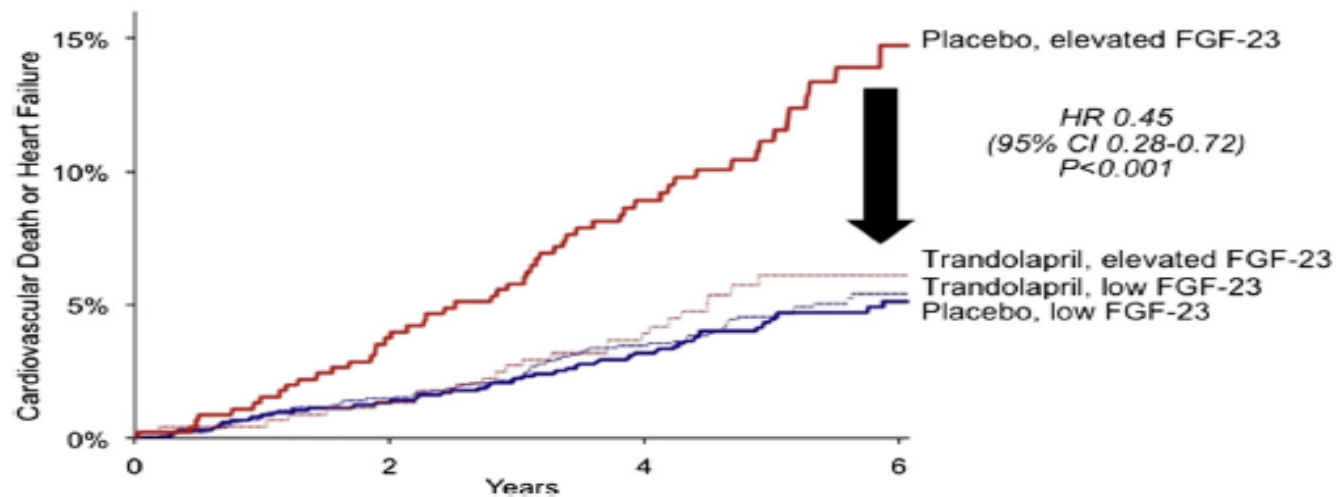
Growth differentiation factor-15 and fibroblast growth factor-23 are associated with mortality in type 2 diabetes – An observational follow-up study

Marie Frimodt-Møller^{1*}, Bernt Johan von Scholten¹, Henrik Reinhard¹, Peter Karl Jacobsen², Tine Willum Hansen¹, Frederik Ivar Persson¹, Hans-Henrik Parving^{3,4}, Peter Rossing^{1,4}



Tailored therapy for heart failure: the role of biomarkers

Fibroblast Growth Factor-23, Cardiovascular Prognosis, and Benefit of Angiotensin-Converting Enzyme Inhibition in Stable Ischemic Heart Disease

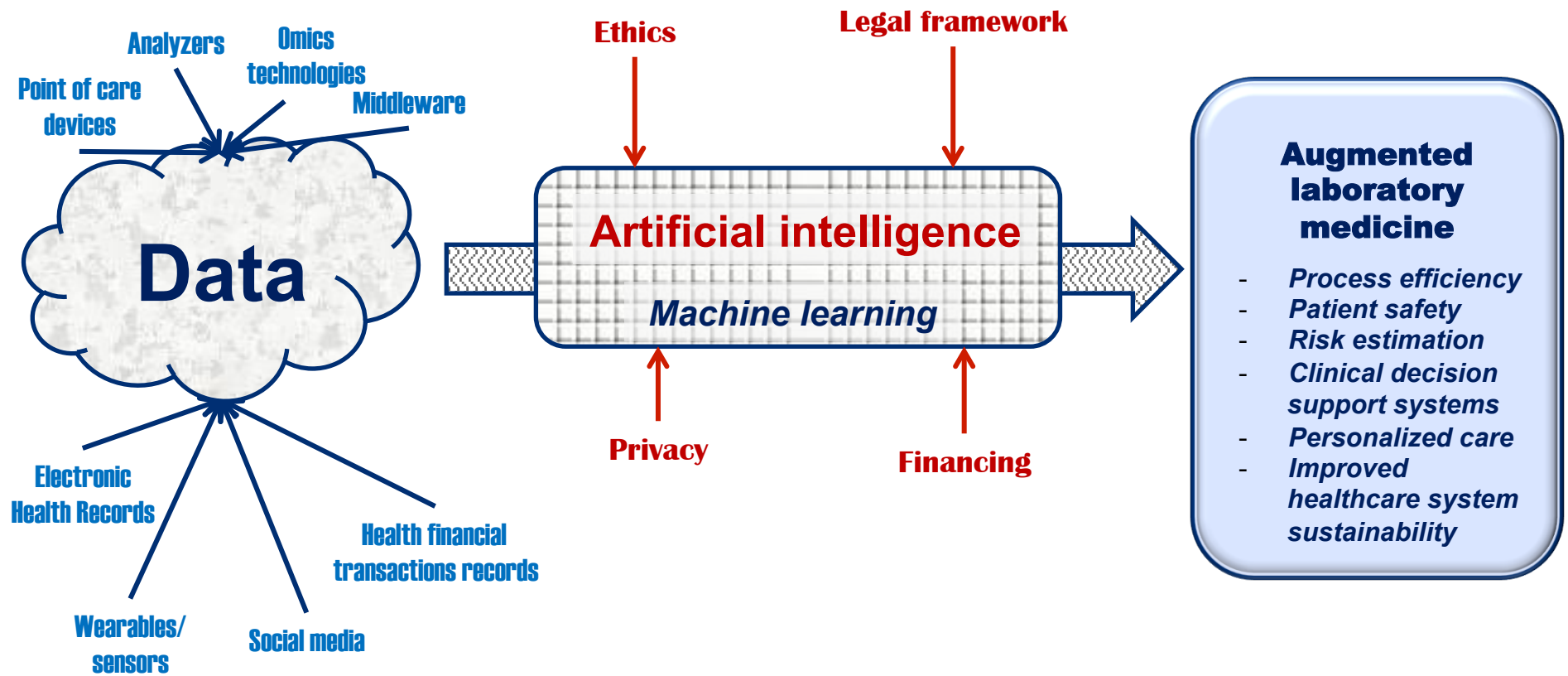


Udell et al. 2014

Control centre – Specialist in laboratory data medicine



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