

Why there are many unmet medical needs in cardiovascular diseases and so few newly approved drugs ?

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This presentation reflects the personal opinion of the presenter
but does not reflect the position of her employers.

“...in spite of the fact that cardiovascular diseases remain the number one cause of death and morbidity in EU ... there were

[89 positive EMA’s recommendations for the authorisation, including 41 concerning new active substances]... [in...2022...but]

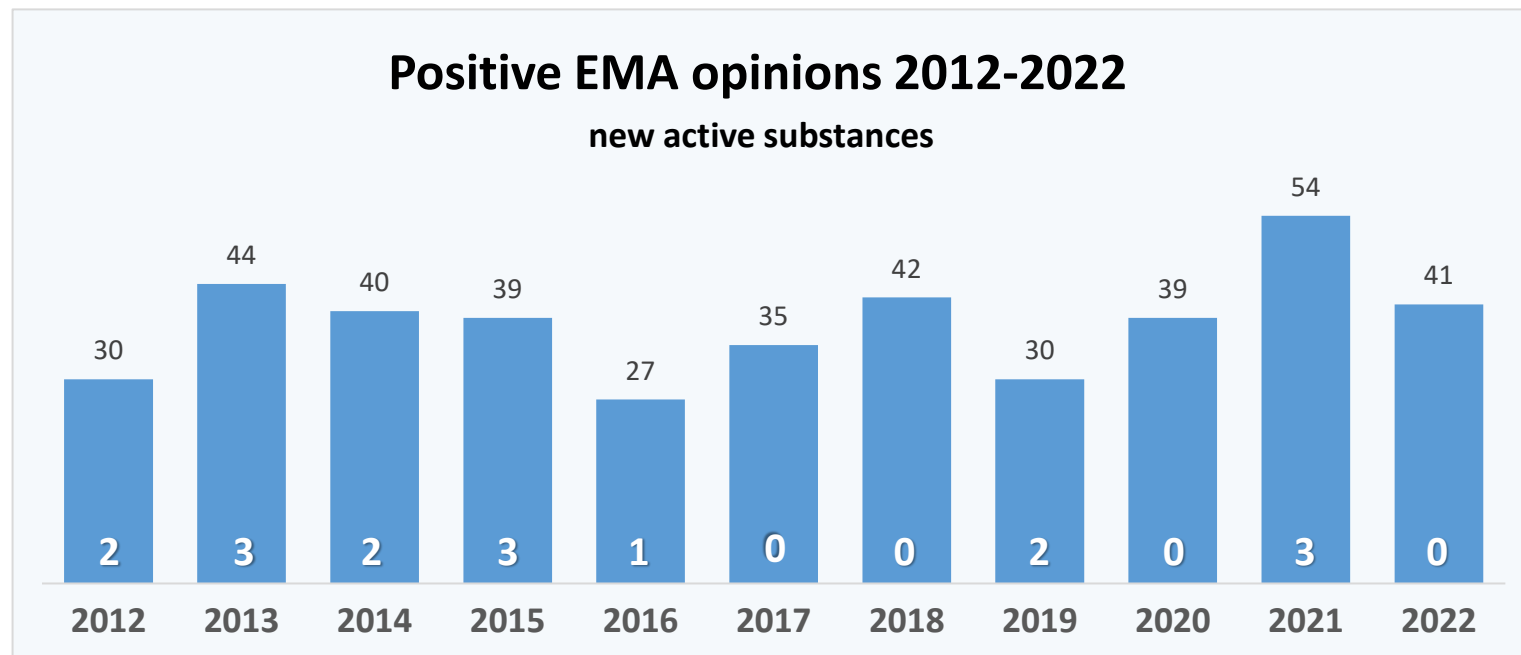
no new cardiovascular drugs recommended for marketing approval”

Meeting Agenda

Questions to consider

- 1. Do we see a mismatch between trends in CV disease burden and drug approvals?**
- 2. What are the challenges we face for drug trials in CV diseases?**
- 3. How could the CRT conversation contribute to the development of future CV drugs?**

Drug approvals in Europe

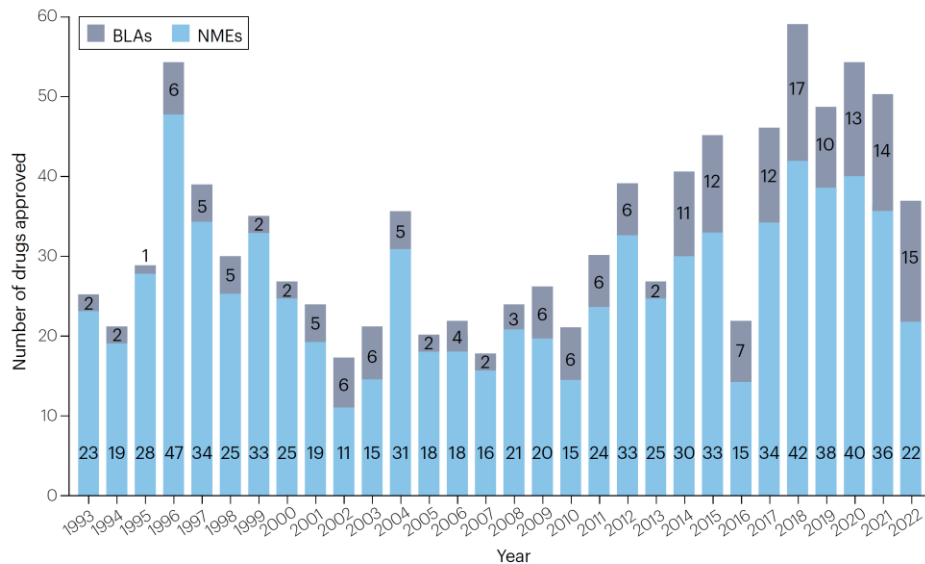


Cardiovascular

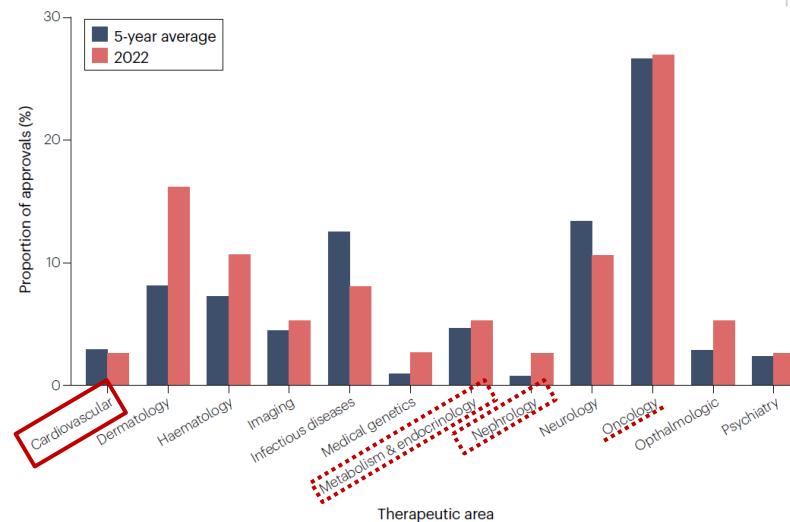
Drug approvals in the US

- Similarities with Europe

FDA approvals 1993-2022



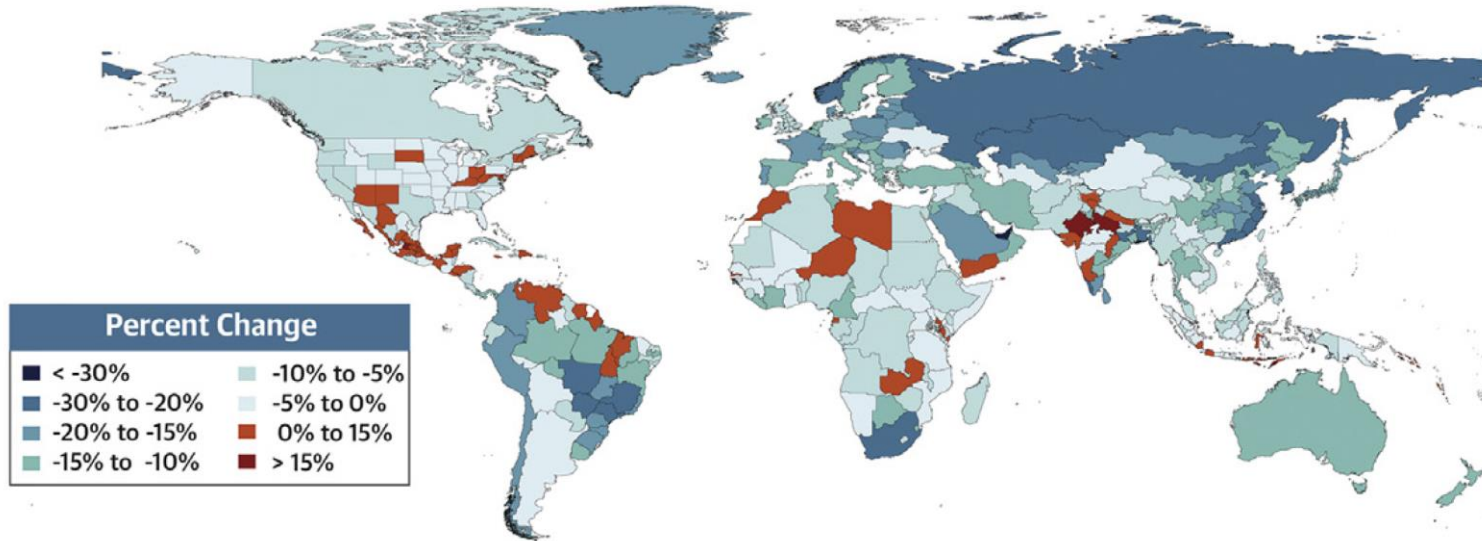
FDA approvals by indications



Trend in Cardiovascular Mortality Rates

Globally 1990-2019

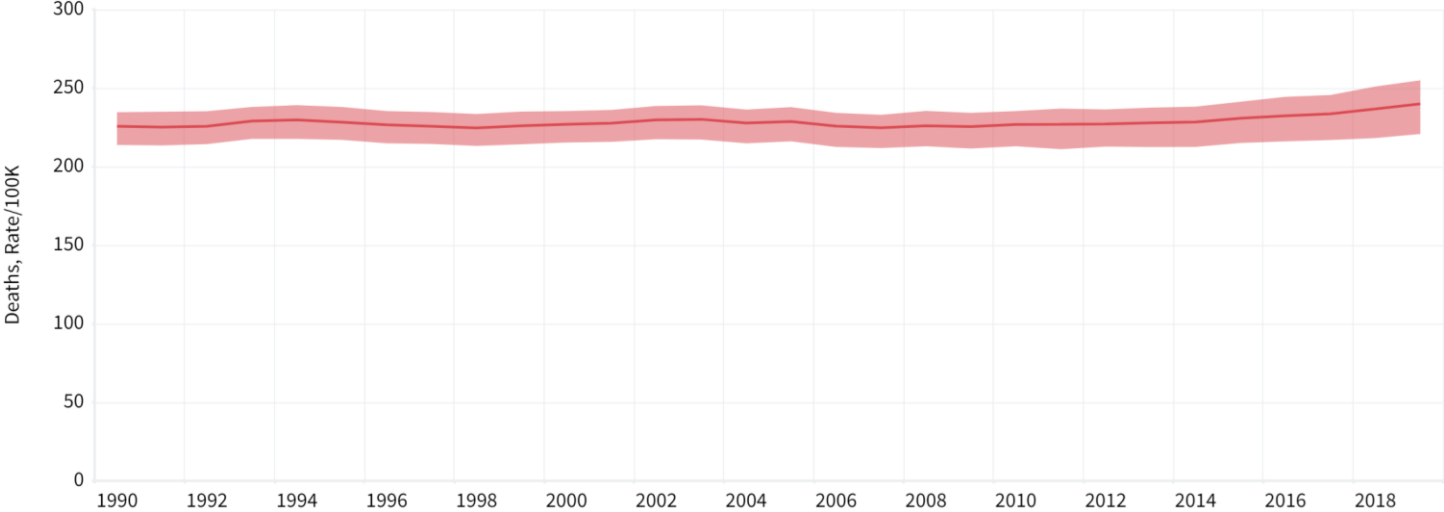
Percent Change in Age-Standardized CVD Death Rate from 2010-2019



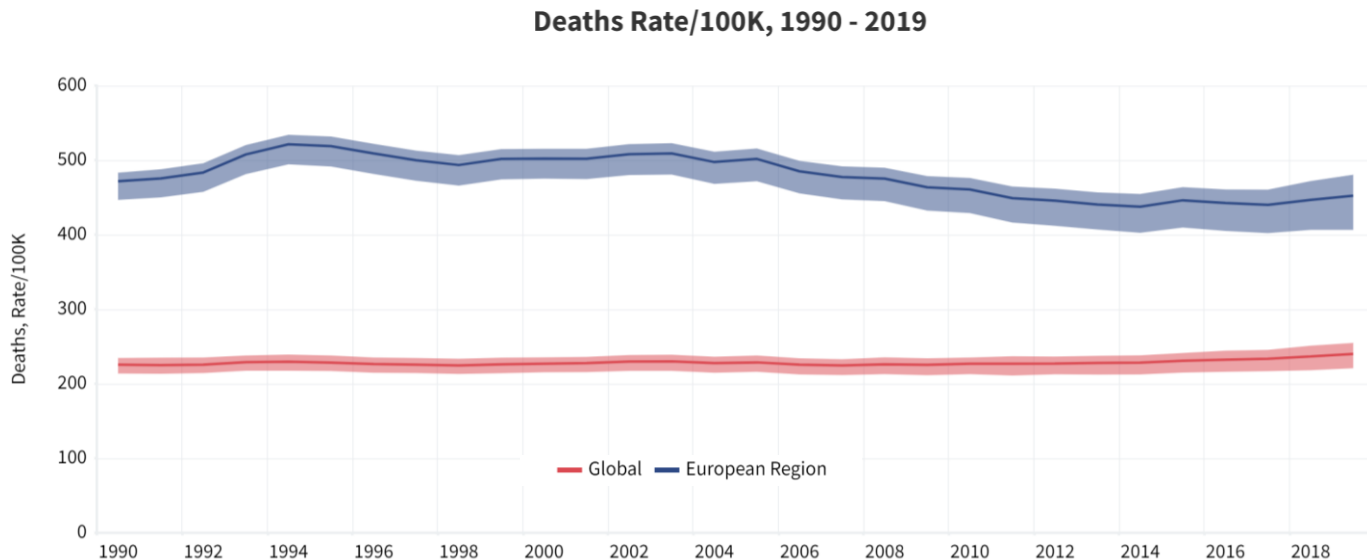
Trend in Cardiovascular Mortality Rates / 100K Globally



Deaths Rate/100K, 1990 - 2019



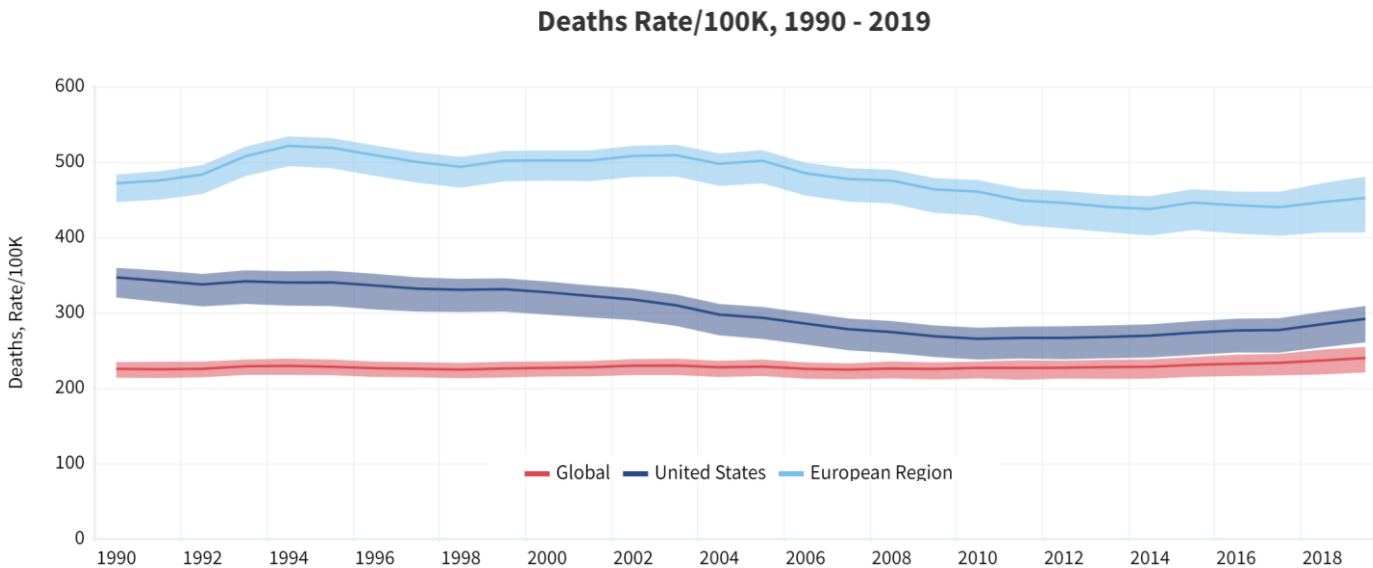
Trend in Cardiovascular Mortality Rates / 100K Globally, in Europe



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WorldHeartObservatory/trends

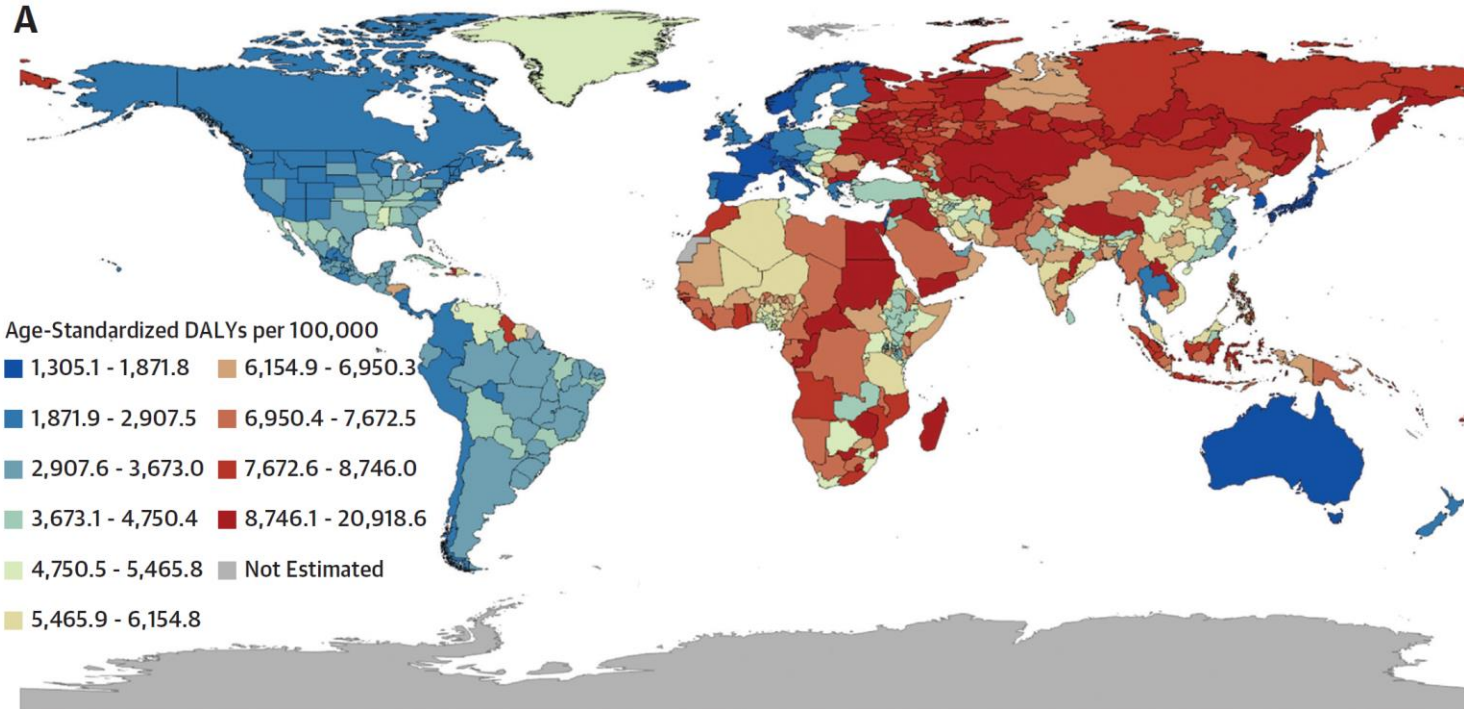
Trend in Cardiovascular Mortality Rates / 100K Globally, in Europe and US



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WorldHeartObservatory/trends

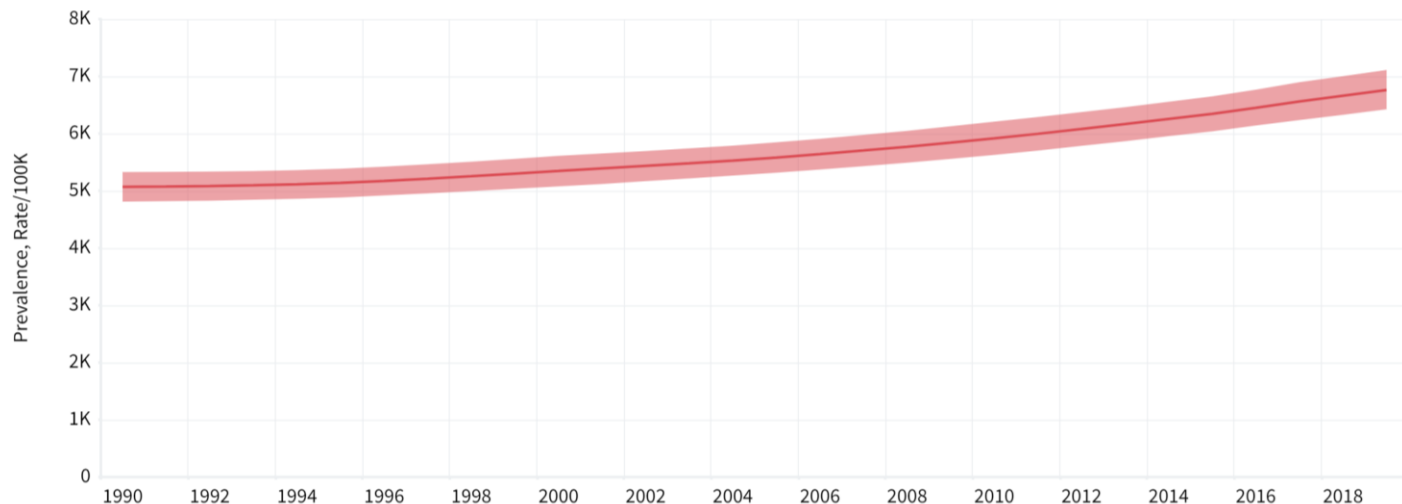
Cardiovascular Disease Burden 2021



DALYs: disability adjusted life years are the sum of years of life lost due to premature mortality and years lived with disability (based on standardized disability weights for each health state)

Trend in Cardiovascular Disease Burden / 100K – globally

Prevalence Rate/100K, 1990 - 2019

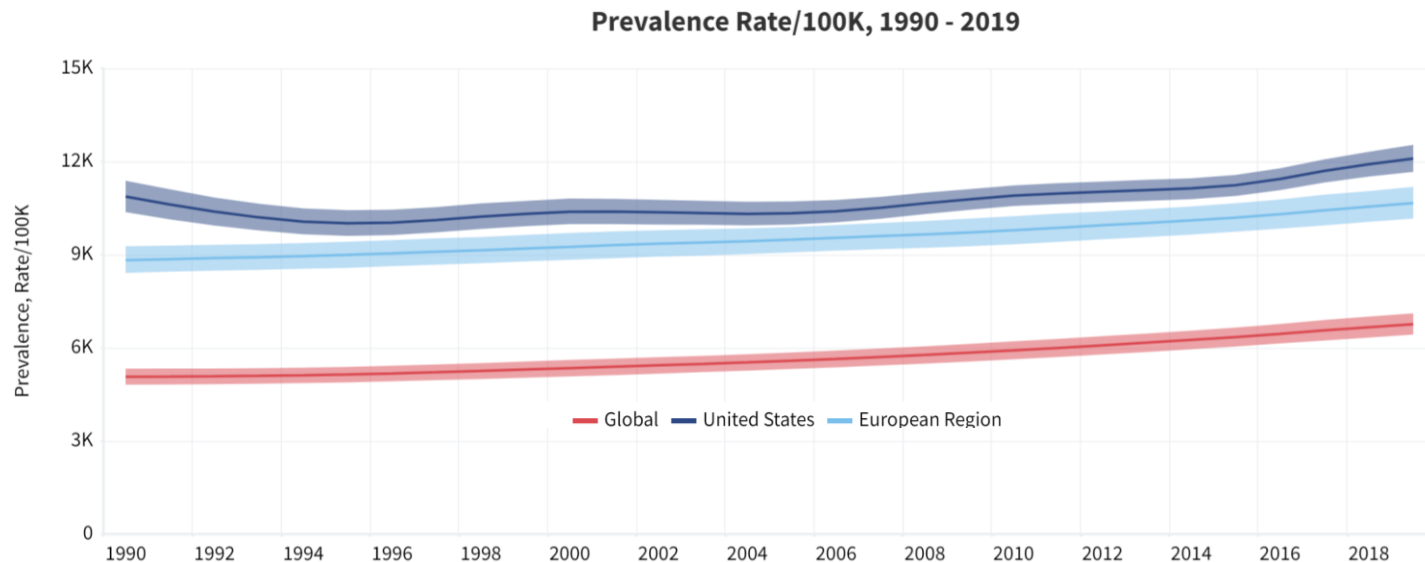


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WorldHeartObservatory/trends

Trend in Cardiovascular Disease Burden / 100K

– globally, in Europe and US



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WorldHeartObservatory/trends

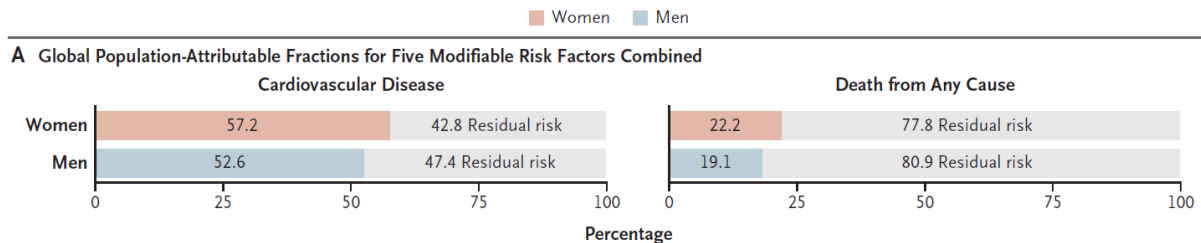
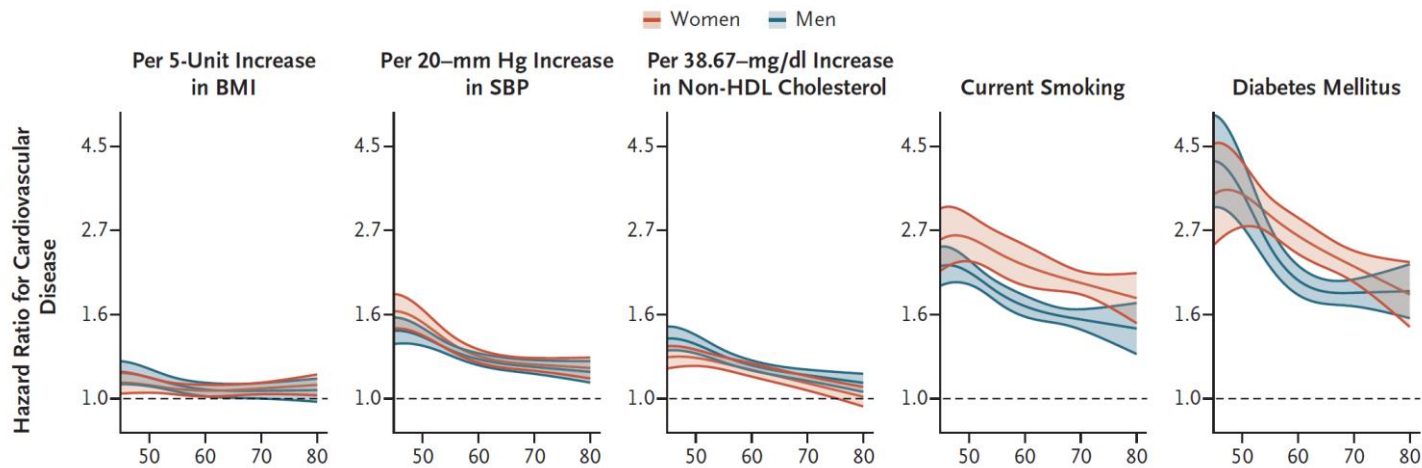
What is the burden of CV disease attributed to?

– many modifiable cardio-renal-metabolic risk factors among top ten, known to be underdiagnosed/under-treated

TABLE 2 Global Ranking of Attributable Burden of Cardiovascular Diseases Due to Selected Modifiable Risk Factors

Rank	Cause of Death	Number of Deaths in 2021 (95% UI)	Number of DALYs (95% UI)
1	High systolic blood pressure	10,800,000 (9,150,000-12,100,000)	209,000,000 (172,000,000-236,000,000)
2	Dietary risks	6,580,000 (2,270,000-9,520,000)	142,000,000 (45,300,000-200,000,000)
3	High low-density lipoprotein cholesterol	3,810,000 (2,170,000-5,420,000)	86,300,000 (54,100,000-115,000,000)
4	Ambient particulate matter pollution	3,130,000 (2,310,000-3,930,000)	62,500,000 (45,700,000-78,400,000)
5	Smoking	2,370,000 (498,000-4,410,000)	59,600,000 (13,100,000-107,000,000)
6	High fasting plasma glucose	2,300,000 (2,030,000-2,650,000)	41,200,000 (36,600,000-47,600,000)
7	High body mass index	1,950,000 (1,120,000-2,910,000)	43,900,000 (23,800,000-65,400,000)
8	Kidney dysfunction	1,870,000 (1,440,000-2,340,000)	38,200,000 (30,700,000-45,900,000)
9	Household air pollution from solid fuels	1,610,000 (904,000-2,820,000)	36,200,000 (21,200,000-61,100,000)
10	Lead exposure	1,570,000 (-139,000-3,170,000)	29,700,000 (-2,780,000-61,200,000)
11	Low temperature	1,020,000 (915,000-1,100,000)	17,700,000 (15,900,000-19,200,000)
12	Secondhand smoke	743,000 (297,000-1,070,000)	16,700,000 (6,870,000-24,300,000)
13	High alcohol use	407,000 (179,000-708,000)	9,260,000 (3,830,000-16,300,000)
14	Low physical activity	397,000 (122,000-684,000)	7,220,000 (2,870,000-11,500,000)
15	High temperature	164,000 (114,000-205,000)	3,440,000 (2,370,000-4,300,000)

>50% of CVD risk attributed to 5 modifiable factors

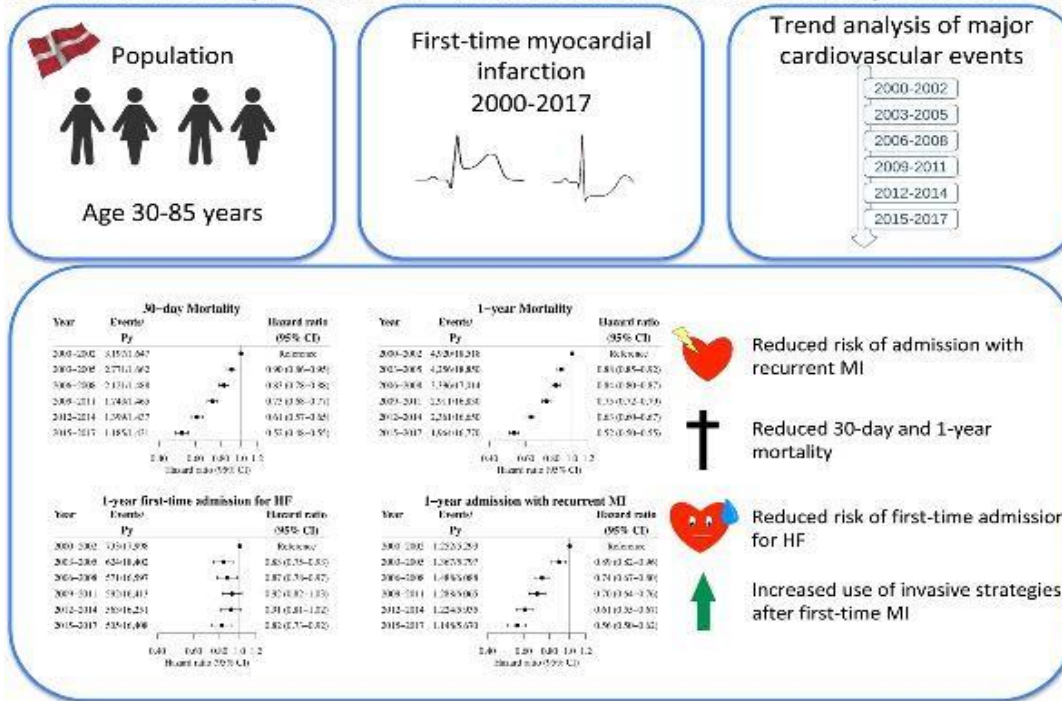


What are the challenges we face with drug trials in CV diseases?

- **Trial design: The bar has risen – do we need ever larger trials?**
- ...
- **Trial design: Can novel trial designs bring the ultimate solution?**
- ...
- **Endpoint definitions: What should we evaluate?**
- ...
- **Endpoint evaluation: What's the statistical method of choice?**
- ...
- **Endpoint adjudication: Are CECs always essential?**

Trend in MACE Rates Following first MI

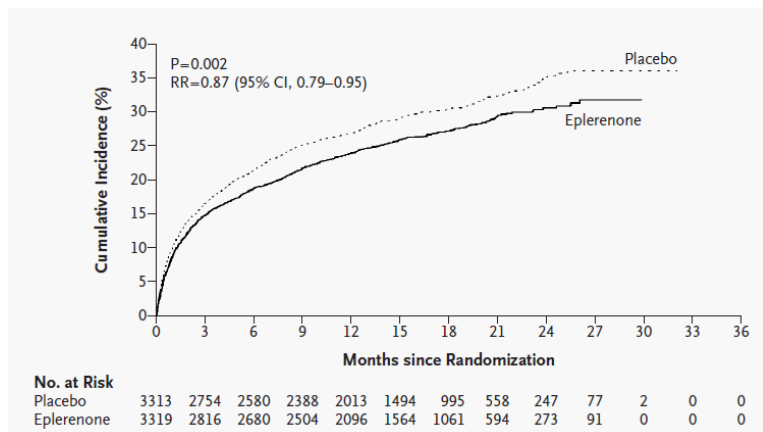
Temporal trends in major cardiovascular events following first-time myocardial infarction in the reperfusion era – a Danish nationwide cohort study from 2000-2017



Event rates in patients following AMI

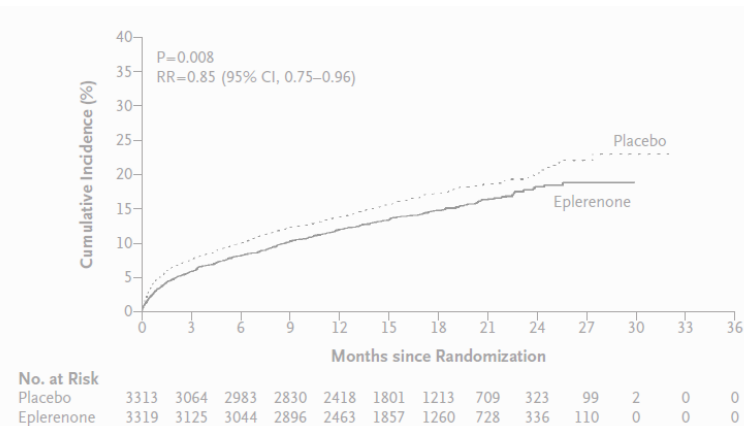
EPHESUS (2003)

CV death or CV hospitalization



PBO: 993 patients (**30%**)
 Eplerenone: 885 patients (26.%)
 with CV death or CV hospitalization

All-cause Mortality

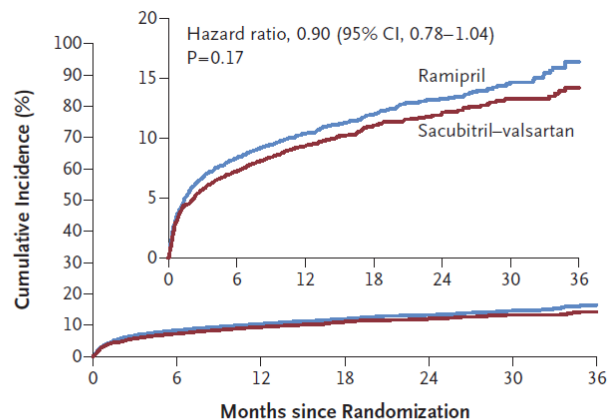


PBO: 554 patients (**16.7%**)
 Eplerenone: 478 patients (14.4%)
 died

Event rates in patients following AMI

PARADISE-MI (2021)

CV death or HF event



No. at Risk

Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril-valsartan	2830	2614	2342	1732	1101	568	280

Ramipril: 373 patients (**13.2%**)

LCZ696 : 338 patients (**11.9%**)

with CV death or HF event

Design Challenge: Event Rates

Declining event rates

Population	Trial	Year	Composite outcome	Participants	Ptps w/ event*	Mortality**
Post compl. MI	EPHESUS	2003	CV death or CVH	6,632	30%	16.7%
post compl. MI	PARADISE-MI	2021	CV death or HFE	5,661	13.2%	8.5% (6.7%†)

* Comparator/Placebo arm; **all-cause mortality in comparator/Placebo arm; all-cause mortality; † CV death

Design Challenge: Event Rates

Declining event rates across various endpoints and populations

Population	Trial	Year	Composite outcome	Participants	Ptps w/ event*	Mortality**
Post compl. MI	EPHESUS	2003	CV death or CVH	6,632	30%	16.7%
post compl. MI	PARADISE-MI	2021	CV death or HFE	5,661	13.2%	8.5% (6.7%†)
CVD + T2D	EMPA-REG Outcome	2015	3-MACE	7,020	12.1%	8.3% (5.9%†)
CVD + Obesity	SELECT	2023	3-MACE	17,604	8.0%	5.2% (3.0%†)
HFrEF (EF<35%)	SOLVD	1991	death or HHF	2,569	57.3%	39.7% (31.1%)
HFrEF (EF<40%)	PARADIGM-HF	2014	CV death or HHF	8,399	26.5%	19.8% (16.5%†)
HL in CHD	4S	1994	Major coronary event	4,444	28%	12% (9%†)
HL in CVD	FOURIER	2017	5-MACE	27,564	11.3%	3.1% (1.7%†)

→ Can novel concepts like adaptive trials / Platform trials / real-world / registry-based trials / use of AI for patient identification provide solutions?

Design Challenge: Endpoint Evaluation

What and how to assess?

Population	Trial	Year	Composite outcome	Participants	Ptps w/ event*	Mortality**
Post compl. MI	EPHESUS	2003	CV death or CVH	6,632	30%	16.7%
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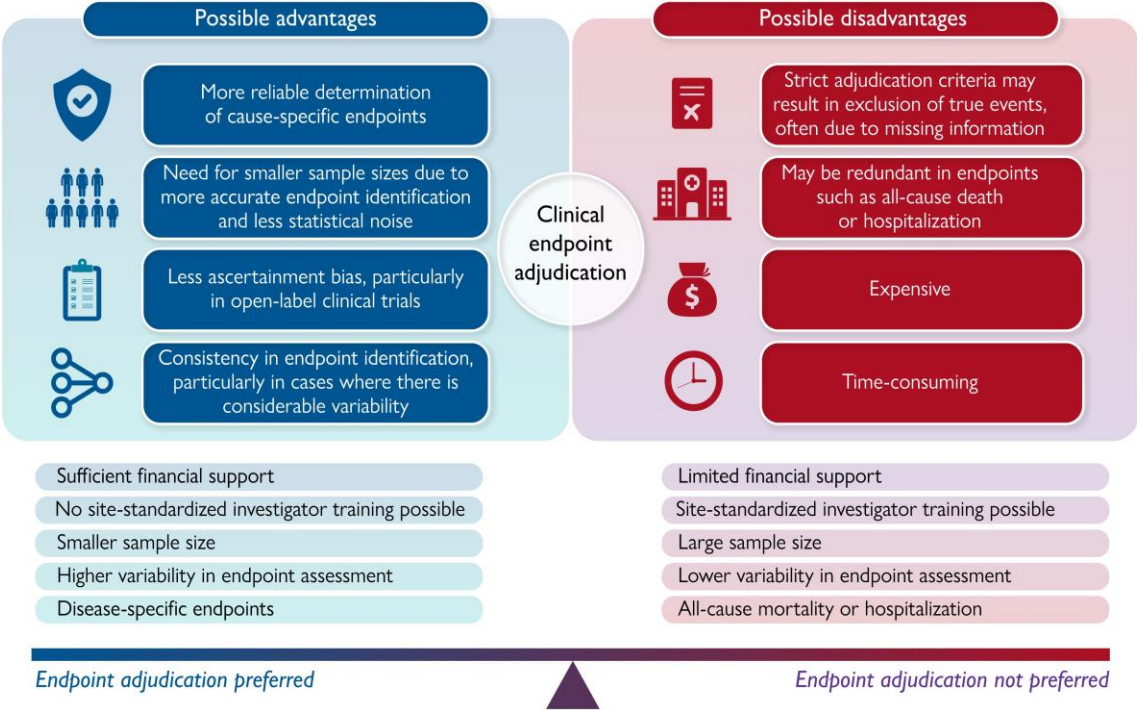
→ Are time-to-first event proportional HRs still the optimal method to evaluate patient benefit?

How about hierarchies or total events?

→ Are we assessing relevant endpoints to evaluate patient benefit?

Design Challenge: Endpoint Adjudication

Is endpoint adjudication required to ensure reliable trial results?



Summary

- **Number of drugs approved for CV diseases in Europe and US has been stable on a very low level in the past decade**
- **Despite advances in treatment options over the last decades, the global burden of CV disease is continuously growing**
- **CV disease burden is driven by modifiable risk factors known to be under-diagnosed and/or under-treated**
- **Contemporary CV outcomes trials face a number of challenges that require multi-disciplinary approaches**

Why there are many unmet medical needs in cardiovascular diseases and so few newly approved drugs ?

Thank you

Bettina Kraus

Nov 21st 2023