ESC Cardiovascular Round Table

ESC European Society of Cardiology

Historically under-represented regions in cardiovascular clinical trials. Why it matters

Faiez Zannad

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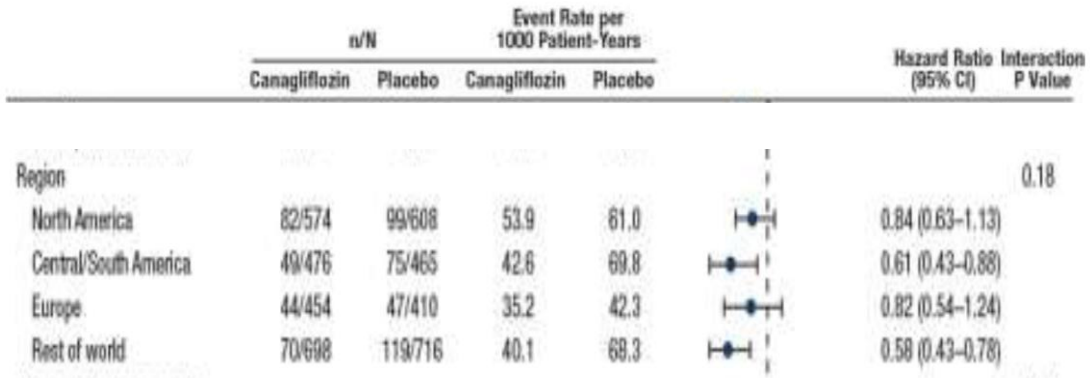
Disclosures : Personal fees from Applied Therapeutics, Bayer, Boehringer, BMS, CVRx, Cardior, Cereno pharmaceutical, Cellprothera, CEVA, KBP, Merck, Novartis, NovoNordisk, Owkin, Pfizer, Servier. Stock options at G3Pharmaceutical and equities at Cereno pharmaceutical, Cardiorenal, Eshmoun Clinical research and founder of Cardiovascular Clinical Trialists (CVCT).

Do SGLT2is NOT work in Europe?

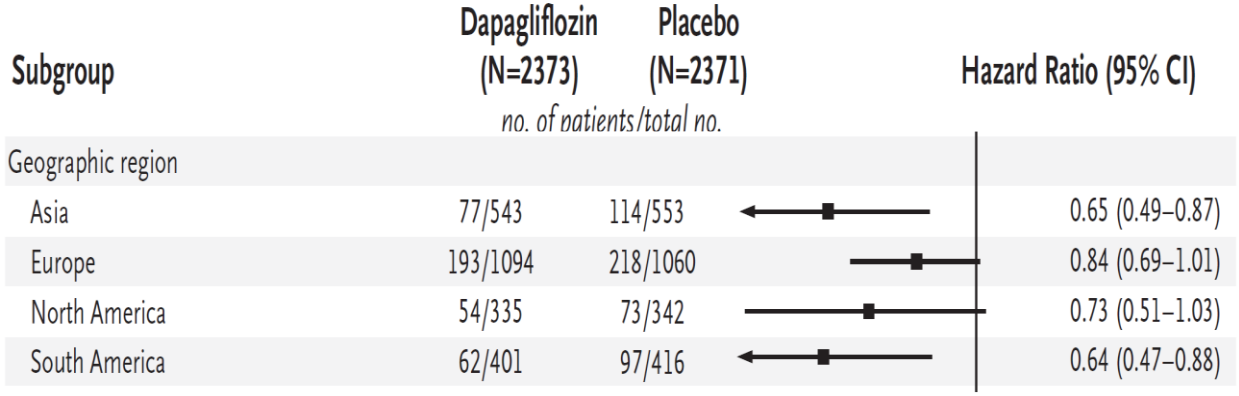
CREDENCE



	n/N		Event Rate per 1000 Patient-Years			Interaction P Value
	Canagliflozin	Placebo	Canagliflozin	Placebo	Hazard Ratio (95% CI)	
Region						0.18
North America	82/574	99/608	53.9	61.0	0.84 (0.63–1.13)	
Central/South America	49/476	75/465	42.6	69.8	0.61 (0.43–0.88)	
Europe	44/454	47/410	35.2	42.3	0.82 (0.54–1.24)	
Rest of world	70/698	119/716	40.1	68.3	0.58 (0.43–0.78)	

Europe + North America
0.83 (0.66, 1.06)

DAPA HF



Subgroup	Dapagliflozin (N=2373)	Placebo (N=2371)	Hazard Ratio (95% CI)
	no. of patients/total no.		
Geographic region			
Asia	77/543	114/553	0.65 (0.49–0.87)
Europe	193/1094	218/1060	0.84 (0.69–1.01)
North America	54/335	73/342	0.73 (0.51–1.03)
South America	62/401	97/416	0.64 (0.47–0.88)

Europe + North America
0.81 (0.69, 0.96)

EMPEROR-Reduced.
HFH and CV death.
Not effective in Europe?

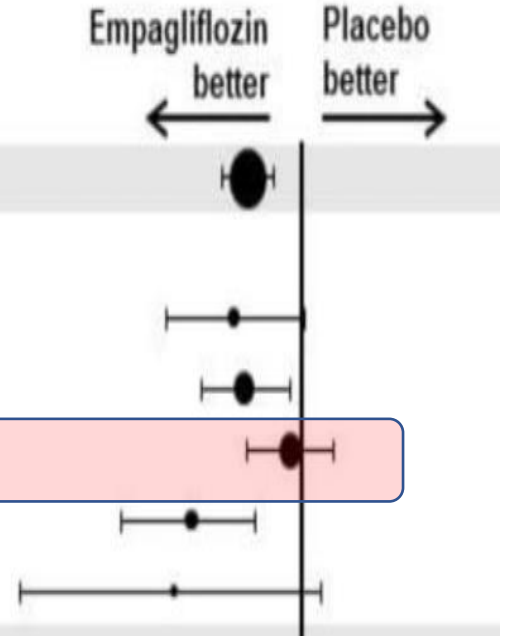
ESC European Society of Cardiology
European Heart Journal (2021) **42**, 4442–4451
doi:10.1093/eurheartj/ehab360
FASTTRACK CLINICAL RESEARCH
Heart failure and cardiomyopathies

Regional and ethnic influences on the response to empagliflozin in patients with heart failure and a reduced ejection fraction: the EMPEROR-Reduced trial

Carolyn S.P. Lam [1,2*†], João Pedro Ferreira [3†], Egon Pfarr[4], David Sim[1], Hiroyuki Tsutsui[5], Stefan D. Anker[6], Javed Butler[7], Gerasimos Filippatos[8], Stuart J. Pocock [9], Naveed Sattar [10], Subodh Verma[11], Martina Brueckmann [4,12], Janet Schnee [13], Daniel Cotton [13], Faiez Zannad [3], and Milton Packer[14,15]

A. Cardiovascular death or heart failure hospitalization

	Events / N analysed		Hazard ratio (95% CI)
	Empagliflozin	Placebo	
Overall	361/1863	462/1867	0.75 (0.65, 0.86)
Region			
North America	48/212	64/213	0.69 (0.48,1.01)
Latin America	115/641	151/645	0.73 (0.58, 0.94)
Europe	140/676	149/677	0.94 (0.74,1.18)
Asia	49/248	80/245	0.55 (0.38, 0.78)
Other	9/86	18/87	0.50 (0.22, 1.11)



Lam C et al. EHJ 2021

EMPEROR-Reduced. Extended definition of HFH and CV

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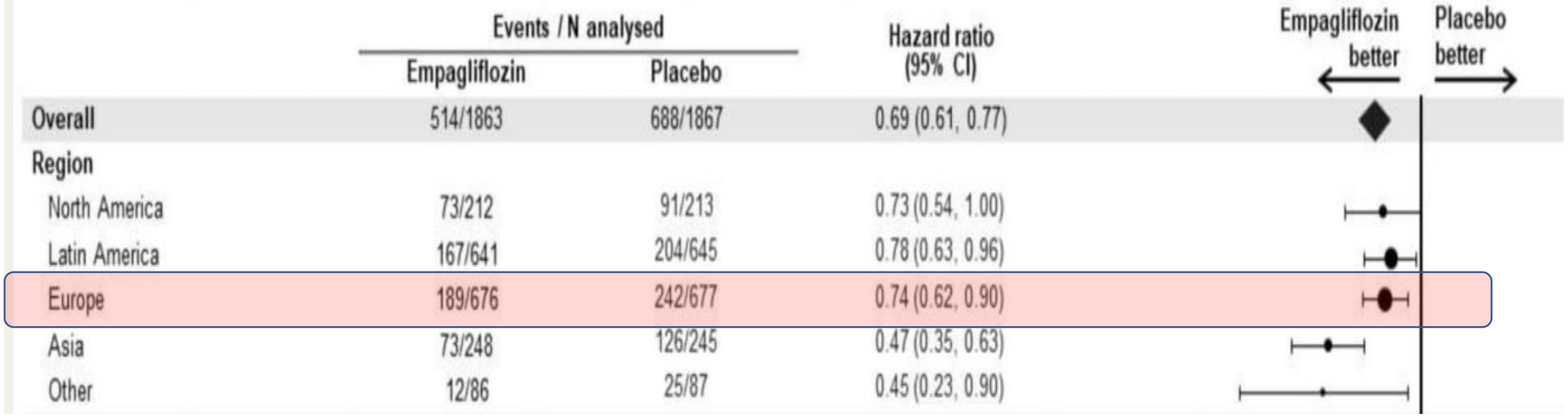
B. Extended composite of cardiovascular death and inpatient and outpatient worsening heart failure events

	Events / N analysed		Hazard ratio (95% CI)
	Empagliflozin	Placebo	
Overall	514/1863	688/1867	0.69 (0.61, 0.77)
Region			
North America	73/212	91/213	0.73 (0.54, 1.00)
Latin America	167/641	204/645	0.78 (0.63, 0.96)
Europe	189/676	242/677	0.74 (0.62, 0.90)
Asia	73/248	126/245	0.47 (0.35, 0.63)
Other	12/86	25/87	0.45 (0.23, 0.90)



Regional differences were attenuated when the definition of HF events was expanded to include outpatient worsening HF events.

Lam C et al. EHJ 2021

Income level and inequality as complement to geographical differences in cardiovascular trials

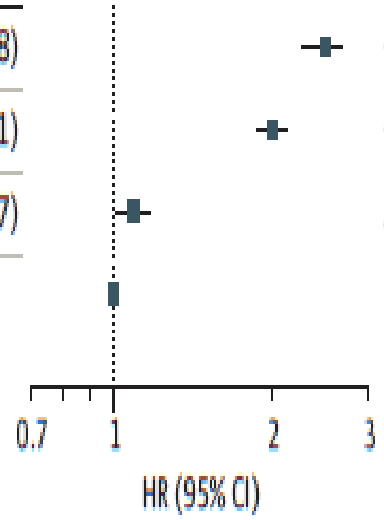
João Pedro Ferreira, MD, PhD,[a,b] Patrick Rossignol, MD, PhD,[a] Pooja Dewan, MB ChB,[c] Zohra Lamiral, Msc,[a] William B. White, MD, PhD,[d] Bertram Pitt, MD,[c] John J. V. McMurray, MD, PhD,[c] and Faiez Zannad, MD, PhD[a]

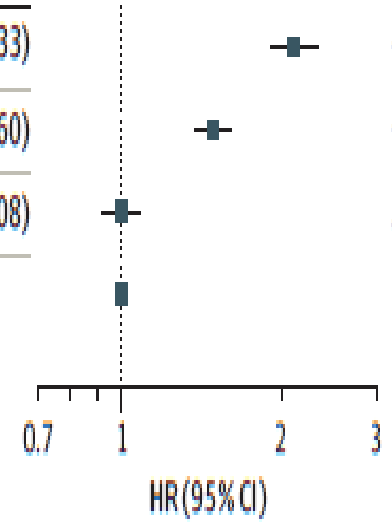
Gini-income combinations						
All-cause death						.75
Gini <28.3 & high income	6.3 (5.1-7.8)	Referent	–	Referent	–	–
Gini <28.3 & low-middle income	6.7 (4.9-9.2)	1.14 (0.78-1.67)	.67	1.45 (0.98-2.15)	.066	–
Gini ≥28.3 & high income	8.4 (7.2-9.7)	1.34 (1.03-1.75)	.028	1.23 (0.94-1.61)	.12	–
Gini ≥28.3 & low-middle income	18.0 (14.5-22.4)	2.92 (2.14-3.97)	<.001	2.38 (1.70-3.33)	<.001	–

	High income	Low-middle income	*P* value
n	2107	630	
Age, y	69.2 ± 7.8	66.9 ± 6.8	<.001
Male gender, n (%)	1656 (78.6%)	471 (74.8%)	.043
White race, n (%)	1953 (92.7%)	315 (50.0%)	<.001
Low-middle income, n (%)	–	–	–
Gini <28.3	669 (31.8%)	278 (44.1%)	<.001
28.3-34.3	757 (35.9%)	202 (32.1%)	
>34.3	681 (32.3%)	150 (23.8%)	
BMI, kg/m^2	27.7 ± 4.7	26.8 ± 5.4	<.001
LVEF, %	26.1 ± 4.8	26. ± 4.1	.44
SBP, mm Hg	123.8 ± 16.9	125.1 ± 16.9	.085
Heart rate, beat/min	71.1 ± 12.3	74.1 ± 12.6	<.001
eGFR, mL/min/1.73 m^2	70.0 ± 21.3	73.3 ± 23.1	<.001
NYHA III/IV, n (%)	196 (9.3%)	33 (5.2%)	<.001
Ischemic HF, n (%)	1382 (65.7%)	504 (80.4%)	<.001
Atrial fibrillation, n (%)	721 (34.2%)	123 (19.5%)	<.001
Diabetes, n (%)	646 (30.7%)	213 (33.8%)	.13
Hypertension, n (%)	1403 (66.6%)	416 (66.0%)	.80
Prior stroke, n (%)	203 (9.7%)	59 (9.5%)	.88
Cardiac device, n (%)	597 (28.9%)	18 (2.9%)	<.001
PCI/CABG, n (%)	823 (39.1%)	105 (16.7%)	<.001
ACE/ARB, n (%)	1988 (94.4%)	569 (90.3%)	<.001
β-Blocker, n (%)	1876 (89.5%)	498 (79.8%)	<.001
Lipid-lowering drug, n (%)	1386 (66.1%)	327 (52.4%)	<.001
Digoxin, n (%)	524 (24.9%)	216 (34.3%)	<.001
Loop diuretics, n (%)	1773 (84.5%)	553 (88.6%)	.011

LIC = Lower rate of Hospitalization and Higher rate of Death

	Hospitalizations[a] per total person-years	Age- and sex-standardized hospitalization rate per 100 person-years (95% CI)	Deaths per total person-years	Age- and sex-standardized mortality rate per 100 person-years (95% CI)	Relative risk of death, model 1[b] HR (95% CI)	*P* value	Relative risk of death, model 2[c] HR (95% CI)	*P* value
Low-income countries	434/3682	11.7 (10.5-12.9)	716/4092	19.1 (17.6-20.7)	2.49 (2.25-2.68)	<.001	2.10 (1.90-2.33)	<.001
Lower-middle-income countries	2177/12 954	17.3 (16.5-18.1)	2205/15 847	15.7 (15.0-16.4)	1.98 (1.85-2.11)	<.001	1.48 (1.37-1.60)	<.001
Upper-middle-income countries	2238/9784	22.6 (21.7-23.6)	1188/12 638	9.3 (8.8-9.9)	1.09 (1.01-1.17)	.02	1.00 (0.92-1.08)	.91
High-income countries	4429/14 340	29.9 (28.9-30.8)	1926/21 511	7.8 (7.5-8.2)	1 [Reference]		1 [Reference]	

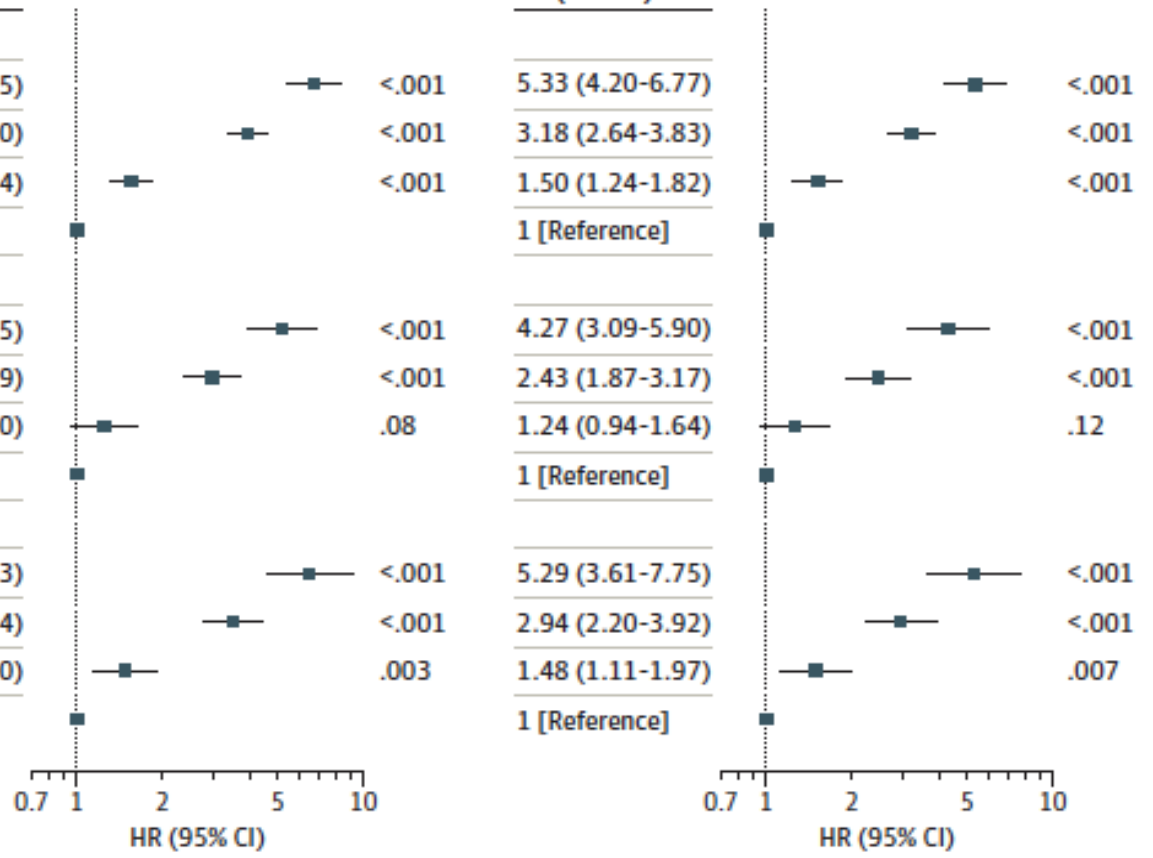




Yusuf S et al. JAMA. 2023;329(19):1650-1661

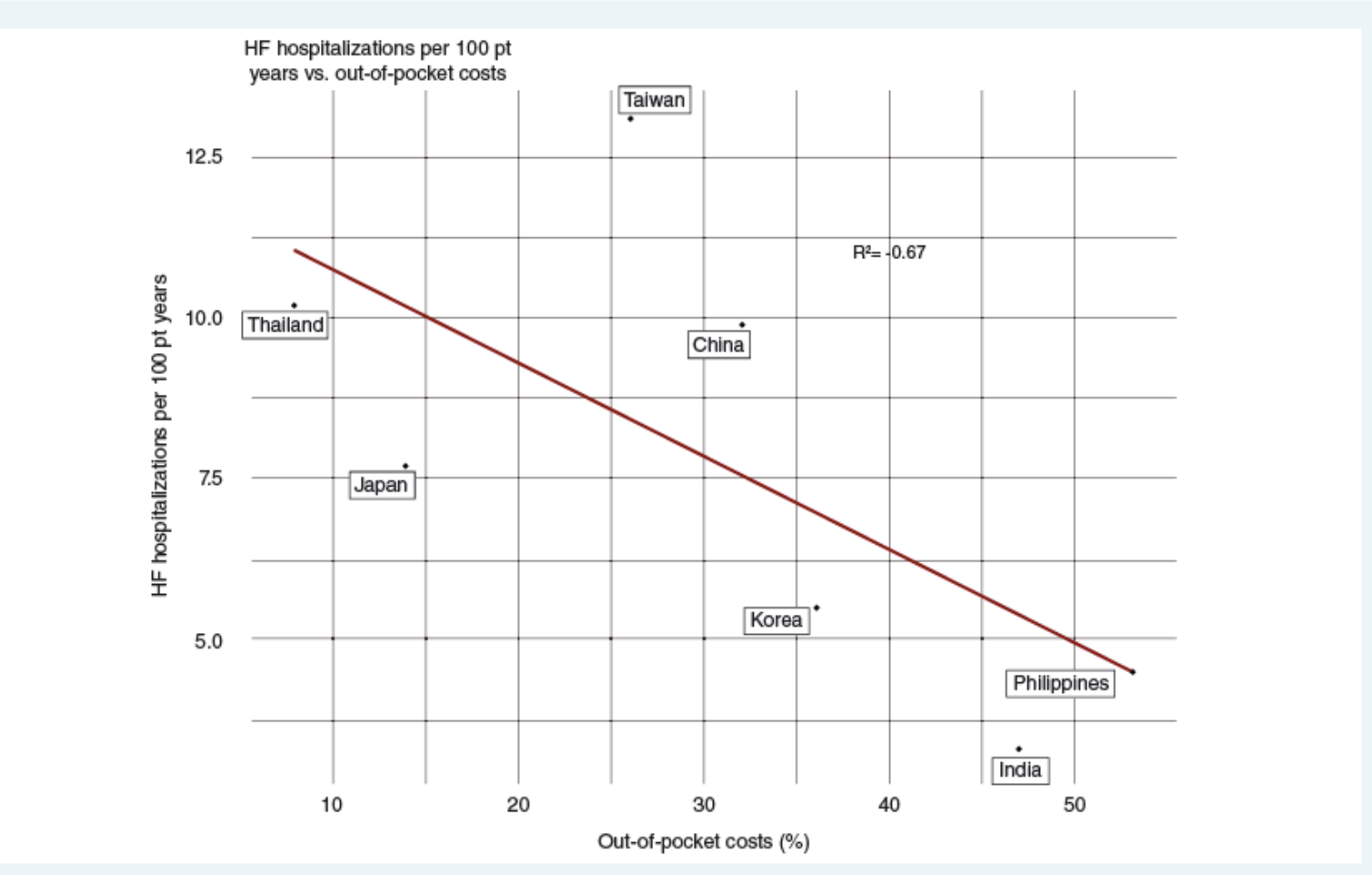
LIC : Excessive risk of Death Within 30 Days of the First Hospital Admission by Country Income Level

	Proportion of deaths occurring within 30 days of the first hospital admission[a] (%)	Relative risk of death, model 1[b] HR (95% CI)	*P* value	Relative risk of death, model 2[c] HR (95% CI)	*P* value
First hospitalization for any cause					
Low-income countries	137/434 (31.6)	6.69 (5.43-8.25)	<.001	5.33 (4.20-6.77)	<.001
Lower-middle-income countries	456/2177 (21.1)	3.95 (3.39-4.60)	<.001	3.18 (2.64-3.83)	<.001
Upper-middle-income countries	218/2238 (9.7)	1.54 (1.29-1.84)	<.001	1.50 (1.24-1.82)	<.001
High-income countries	296/4429 (6.7)	1 [Reference]		1 [Reference]	
Heart failure as the cause for the first hospitalization					
Low-income countries	93/235 (39.6)	5.19 (3.93-6.85)	<.001	4.27 (3.09-5.90)	<.001
Lower-middle-income countries	331/1313 (25.2)	2.96 (2.37-3.69)	<.001	2.43 (1.87-3.17)	<.001
Upper-middle-income countries	130/1044 (12.5)	1.24 (0.97-1.60)	.08	1.24 (0.94-1.64)	.12
High-income countries	118/1120 (10.5)	1 [Reference]		1 [Reference]	
Other cause for the first hospitalization					
Low-income countries	44/199 (22.1)	6.48 (4.61-9.13)	<.001	5.29 (3.61-7.75)	<.001
Lower-middle-income countries	125/864 (14.5)	3.50 (2.76-4.44)	<.001	2.94 (2.20-3.92)	<.001
Upper-middle-income countries	88/1194 (7.4)	1.47 (1.14-1.90)	.003	1.48 (1.11-1.97)	.007
High-income countries	178/3309 (5.3)	1 [Reference]		1 [Reference]	



Yusuf S et al. JAMA. 2023;329(19):1650-1661

Association between heart failure (HF) hospitalizations per 100 patient-years and out-of-pocket costs in Asian countries from PARADIGM-HF.



Dewan P et al Eur J Heart Fail 2019

Income level and inequality as complement to geographical differences in cardiovascular trials

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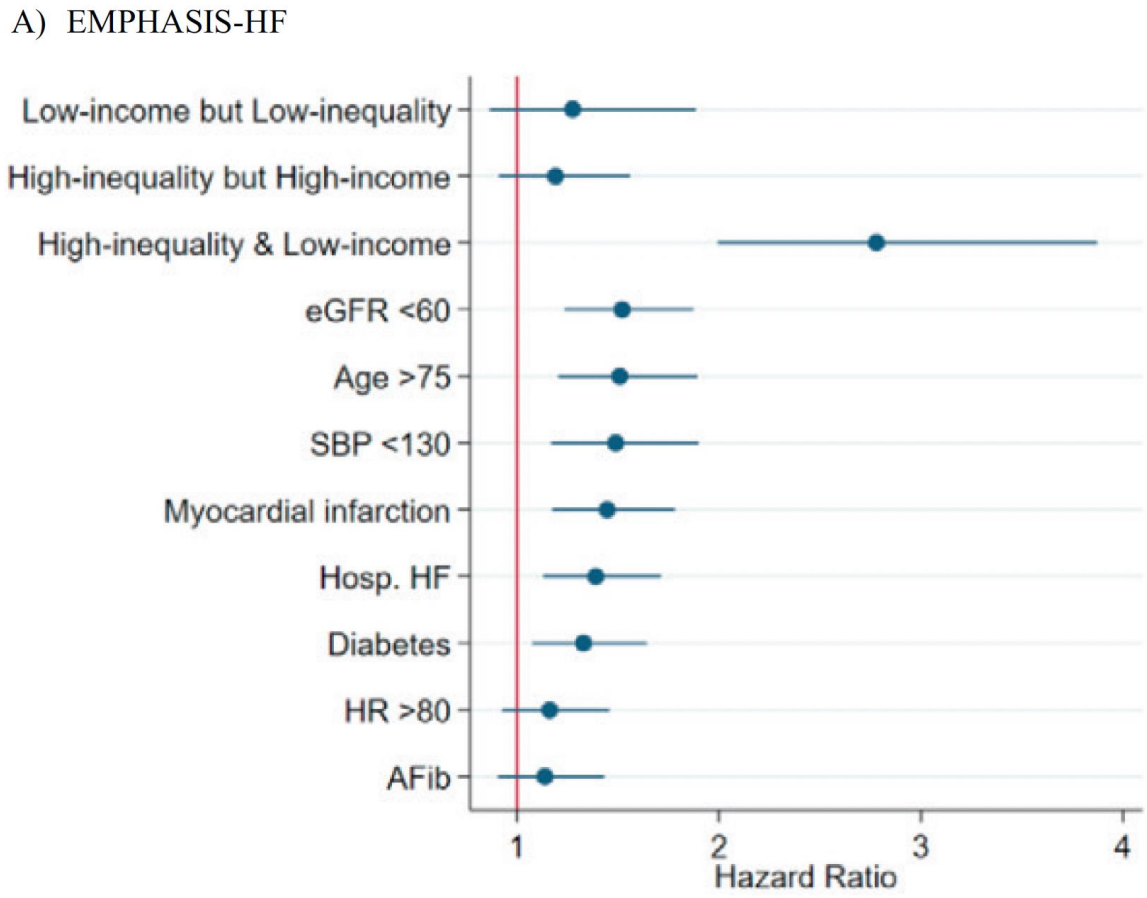
Compared to common risk factors, low + high-inequality income is the best predictor of all cause death in HF patients enrolled in EMPHASIS-HF

The prognostic impact of income and inequality is substantial and should be considered when looking into subgroup differences in CV trials



DAPA-HF - A global trial

4,744 patients 20 countries

North America

Canada	223
USA	454

Western Europe

Denmark	99
Germany	186
Netherlands	135
Sweden	68
UK	62

Central/Eastern Europe

Bulgaria	266
Czech Rep.	210
Hungary	250
Poland	290
Slovakia	166
Russia	422

Latin America

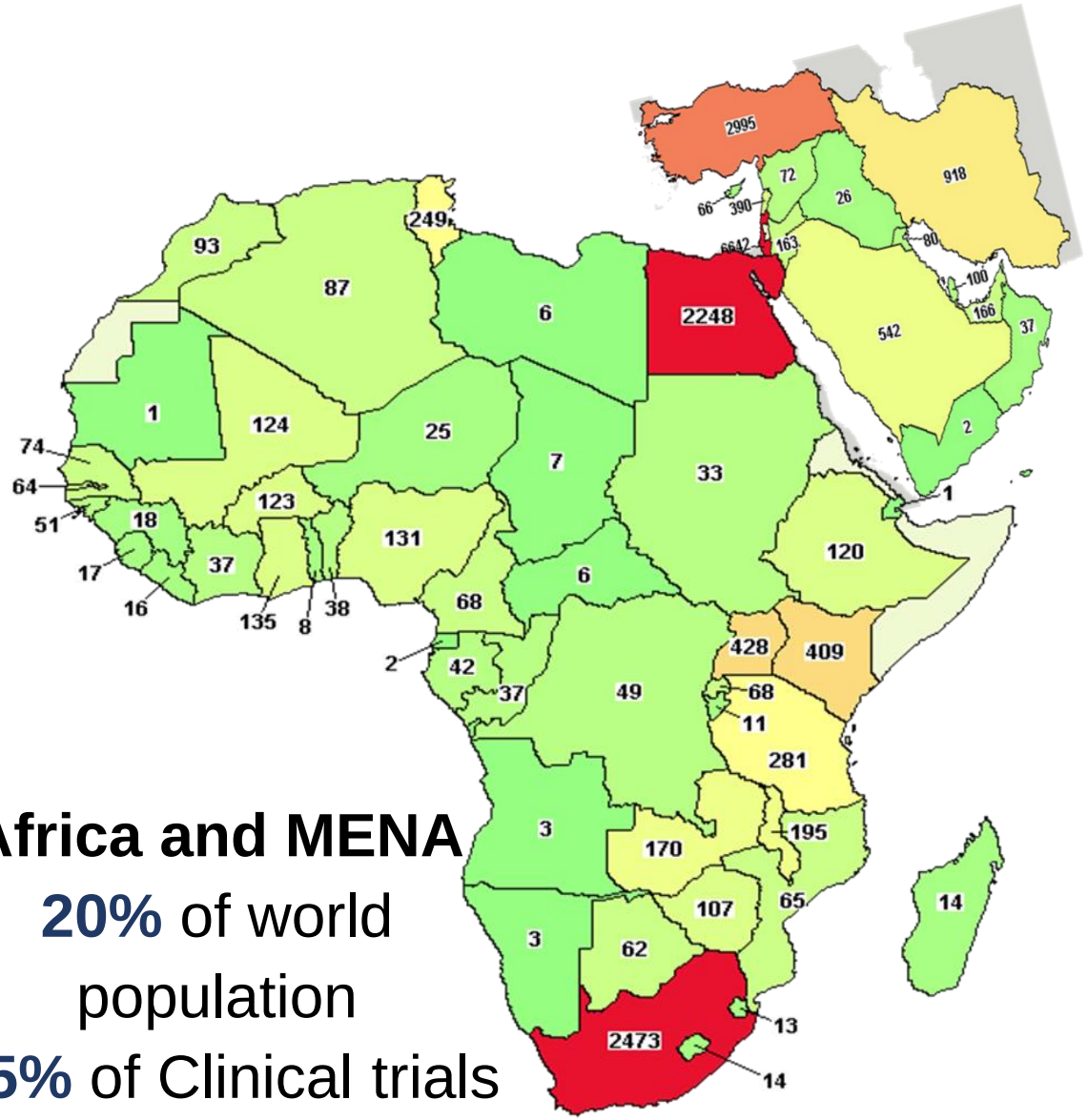
Argentina	297
Brazil	520

Asia-Pacific

China	237
India	237
Japan	343
Taiwan	141
Vietnam	138

The “EMRO” (East Mediterranean Region) : one of the six geographical areas created by the WHO. Stretching from Morocco to Pakistan, and if we add Algeria, it covers **22 countries** and represents a **population of nearly 630 million. > NA > SA, only second to EU**

Clinical Trials in Africa – Middle East

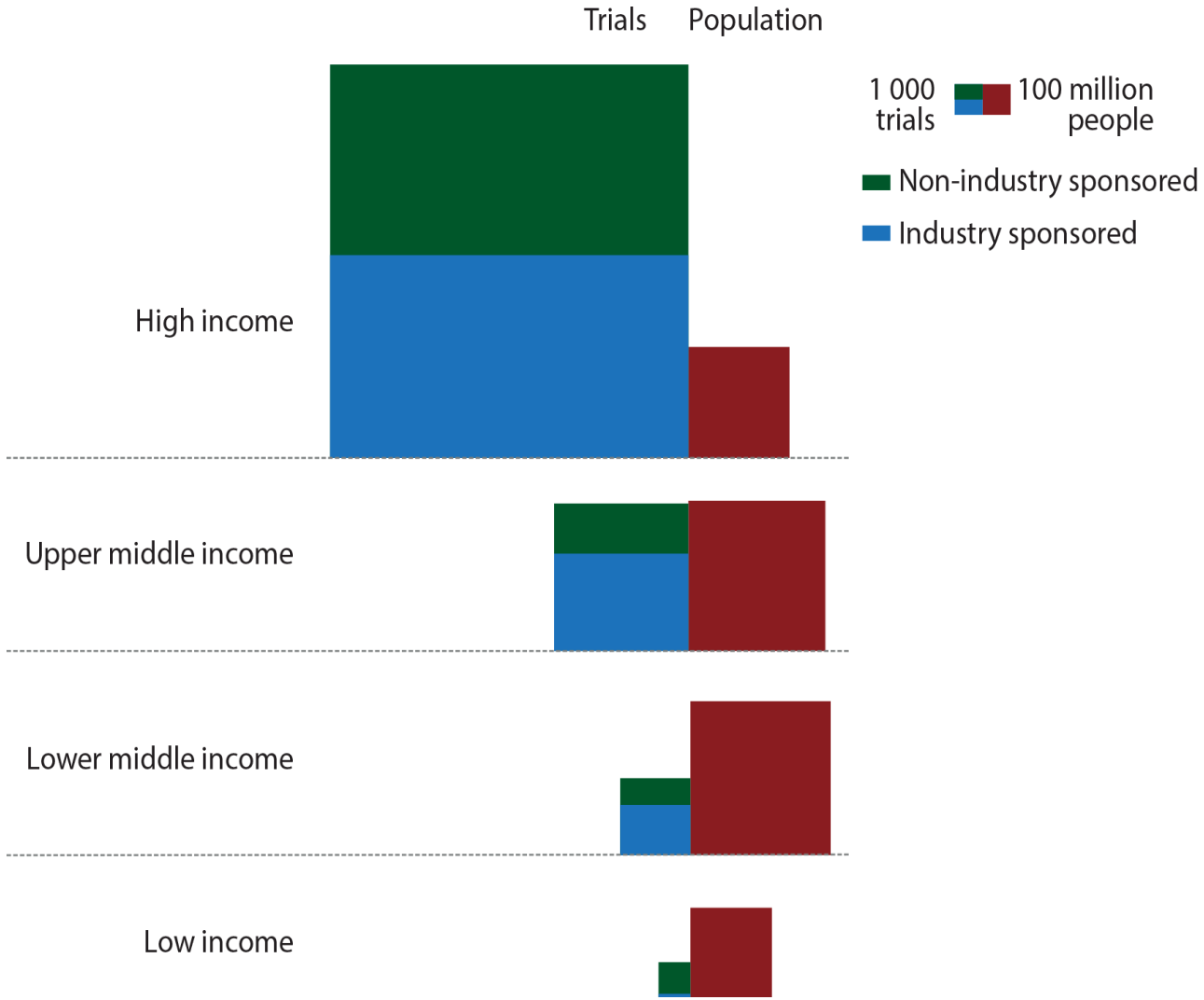


Africa and MENA

20% of world population

6,5% of Clinical trials

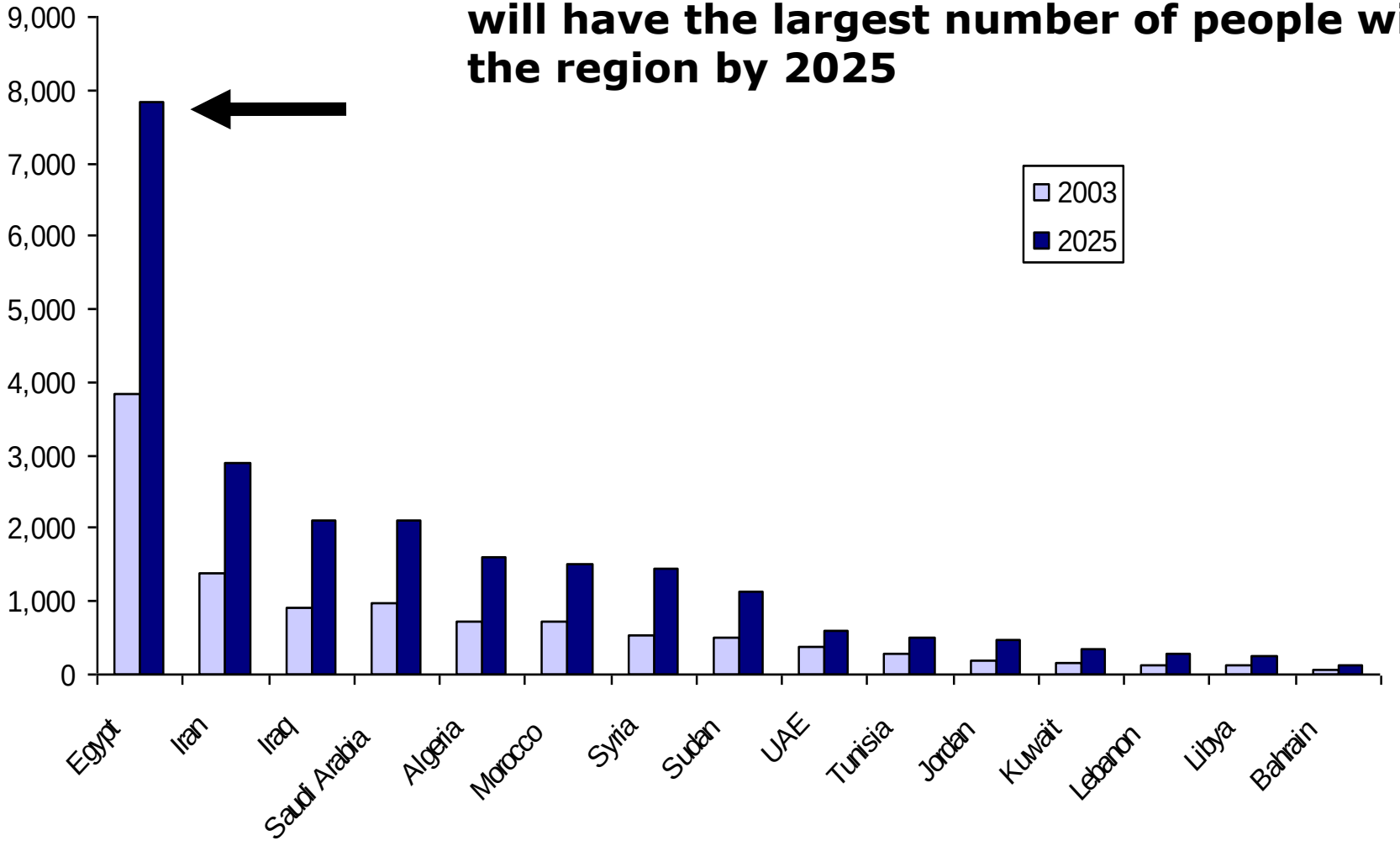
More people but fewer trials in middle income countries



Source: Clinicaltrials,gov

Egypt will face explosive growth of diabetes

Due to a rapidly increasing & ageing population, Egypt will have the largest number of people with diabetes in the region by 2025



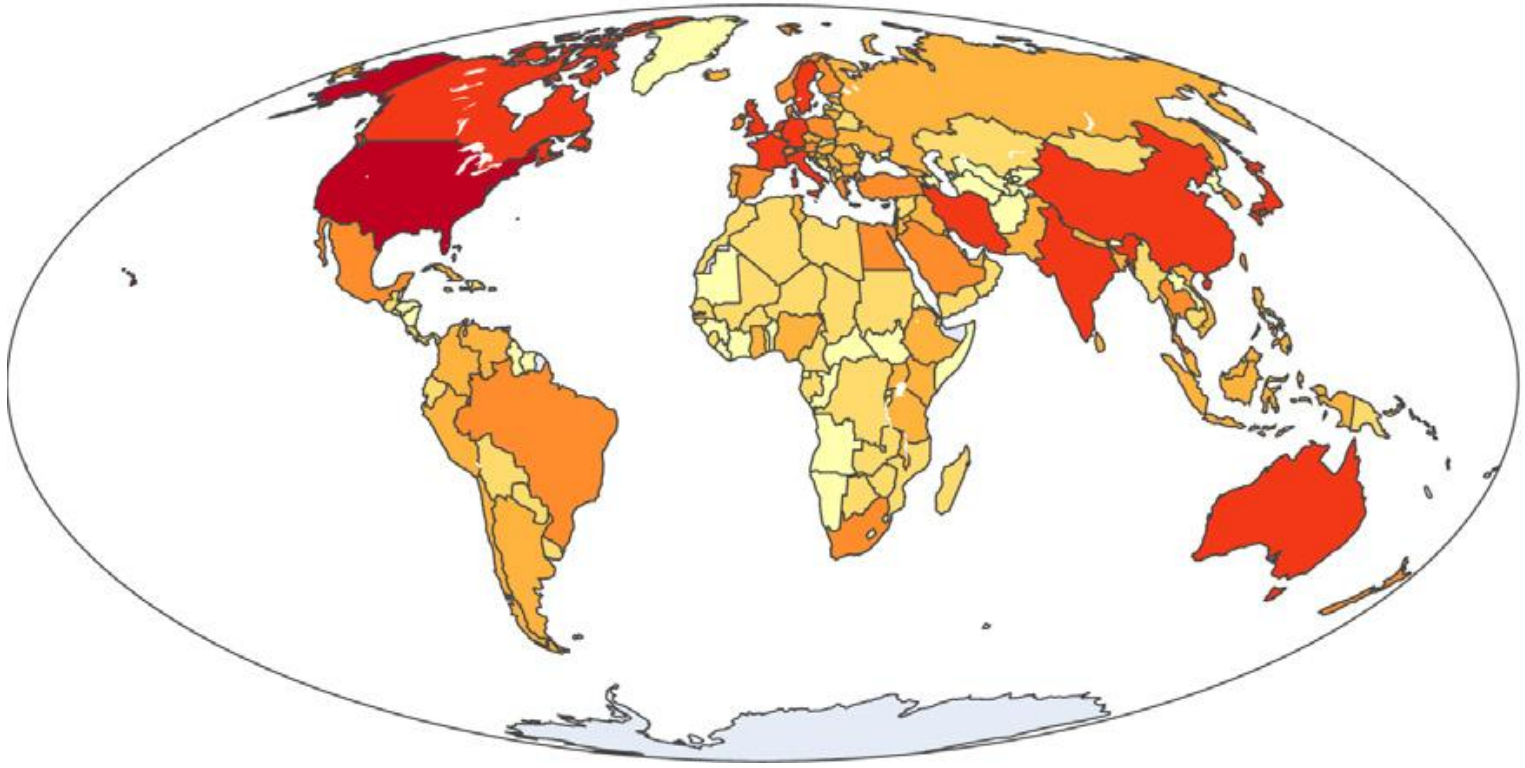
Source: Diabetes Atlas, 2nd edition, IDF

Original research

BMJ Global Health

State of the evidence: a survey of global disparities in clinical trials

Iain James Marshall ,[1] Veline L'Esperance,[1] Rachel Marshall,[2] James Thomas,[3] Anna Noel-Storr,[4] Frank Soboczenski,[1] Benjamin Nye,[5] Ani Nenkova,[6] Byron C Wallace[5]



Global clinical trial publications by first author location, 1990–2017

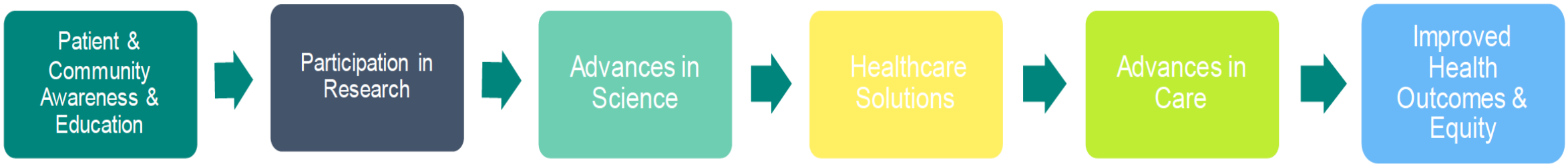
Marshall IJ, et al. BMJ Global Health 2021

Why geopraphical diversity matters?

- Clinical trials provide a crucial base of evidence for evaluating whether a medical product is safe and effective
- Enrollment in clinical trials should reflect the diversity of the population that will ultimately use the product
- Generalizability of the results of western trials to other geographies is risky
  - Results may depend on ethnicity
  - Genetic background
  - Co-moribidities
  - « Usual care »
  - Access to care, Socio-economic status and health care systems

Potential Benefits of geographical diversity

- Generalizability of findings since CV trials show geographical-based differences
  - Outcome rate and type are variable across geographies
  - Patient-reported outcomes responses are variable
  - Specific safety considerations and efficacy afe variable
- Increase trust in new recommendations
- ESC guidelines are followed (adapted? Adopted?) in many non-EU, non-Western geopgarphies



Few tips for successfully involving MOW countries in CV trials

- Focus on sustainability, systems development, and capacity building
- Share: Ideas, Money/Resources, Data, Power
- Insist on having transparent discussions about power
- Seek to identify opportunities for co-creation and co-learning
- Protect the well-being and interests of underserved communities
- Build on global community strengths but highly respect local knowledge

LMIC regions attractiveness

- Population’s sheer size, large pool of eligible patients
- the least trial saturated of all regions
- Diversity: genetic profile, lifestyle, eating habits
- Large medication-naive patient populations

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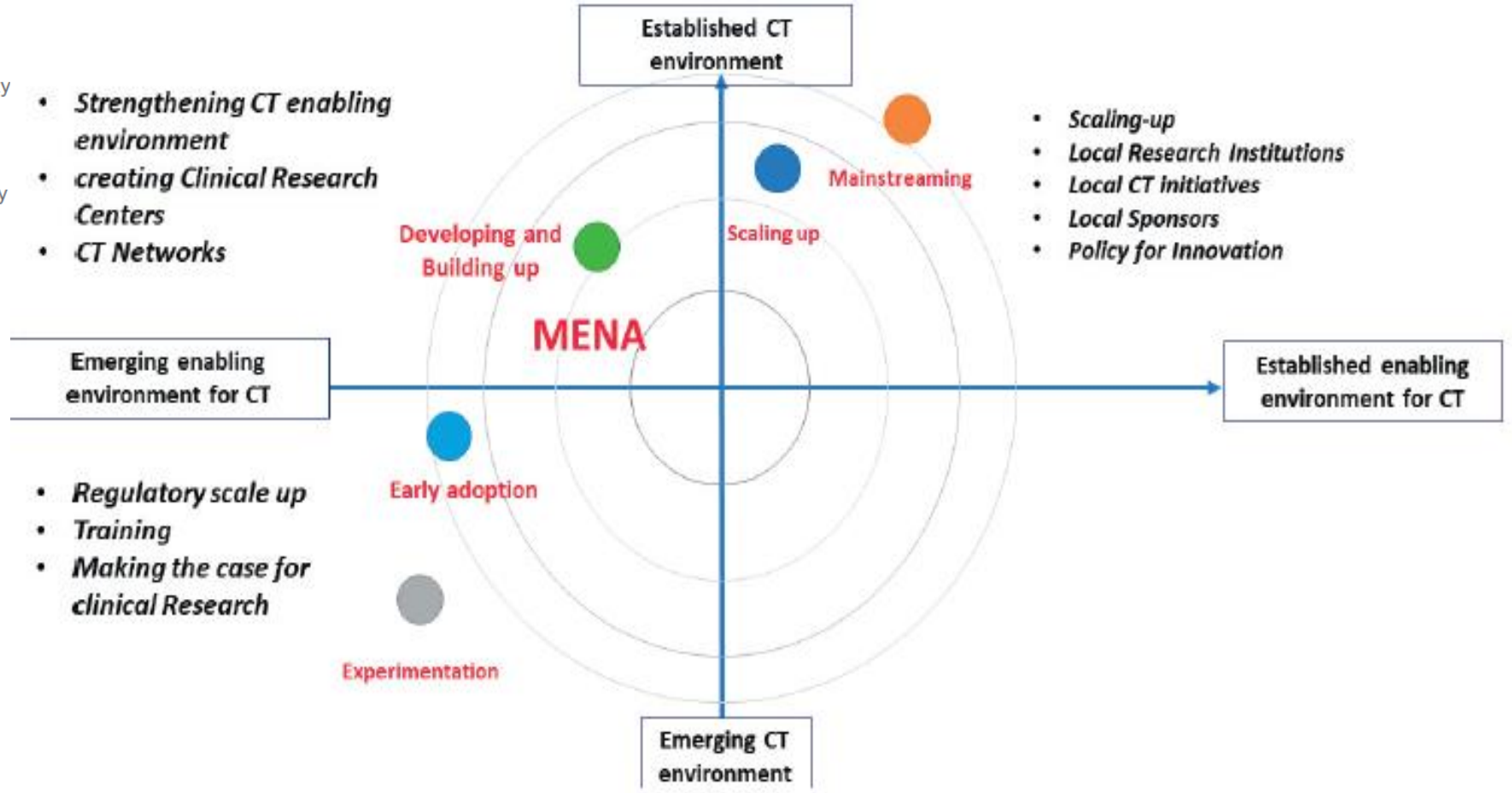
Promoting clinical research capacity building in non-EU/NA countries

Clinical research in Africa and Middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development

Faiez Zannad[1], Mohamed Sobhy[2], Wael Almahmeed[3], Mohamed Balghith[4], Javed Butler[5], Souad Dziri[6], Sahar Ebrahim[7], Ashraf El Fiky Ahmed Elshal[9], Ines Fradi[10], Ziyad Ghazzal[11], Chokri Jeribi[12], Zainab Samad[13], Maciej Kostrubiec[14], Manal Milhem[15], Mossad Morsi[16], Ali Oto[17], Hany Ragy[18], Georges Saade[19], Rana Malkawi[20], Azza Saleh[21], Dina Shokri[21], Karen Sliwa[22], Habib Gamra[23], for the CVCT Regulatory summit Think Tank*



The Challenges of international collaboration with LMICs.

- Industry view the Region as the next frontier in global health business, but not necessarily in global health research.

Conclusion : What the Industry-Sponsored Research Enterprise Can Do to Increase Global Diversity in Clinical Trial Leadership?

Level 5: Diversity-transformative

Level 4: Diversity-specific

Level 3: Diversity-sensitive

Level 2: Diversity-blind

Level 1: Diversity-unequal

Adapted from WHO Gender Responsive Assessment Scale

CVCT MEMA 2018

MIDDLE EAST, MEDITERRANEAN & AFRICA
CARDIOVASCULAR CLINICAL TRIALISTS FORUM
13-14 September 2018
InterContinental Semiramis, Cairo - Egypt

THURSDAY, 13 SEPTEMBER 2018

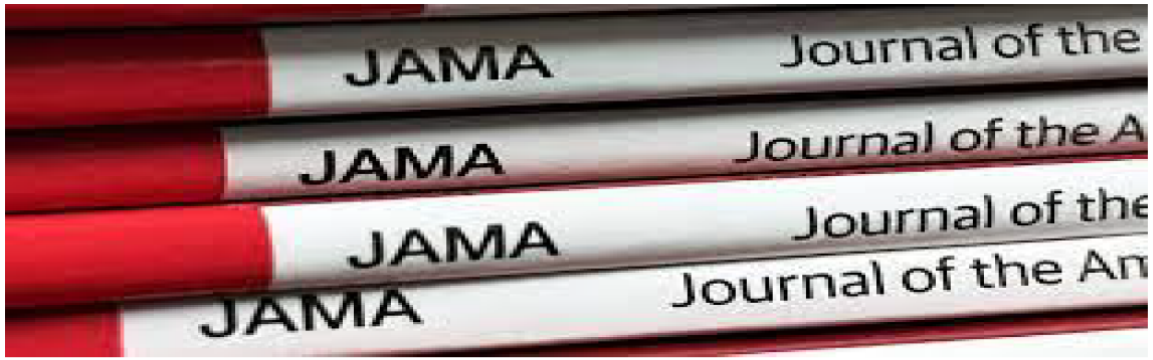
DAY 1: CVCT Forum REGULATORY SUMMIT
Pavilion Meeting Room
Closed workshop – on invitation only
(Running simultaneously to the CVCT Forum)

Experts/representatives from

- regulatory bodies
- competent authorities
- ministries of health

Objective: Discuss ways to scale up local regulations to international standards.

- **Move at the speed of trust**
- Prove ourselves trustworthy
- Be transparent about adverse effects; potential risks; benefits of research
- Always, always tell the truth



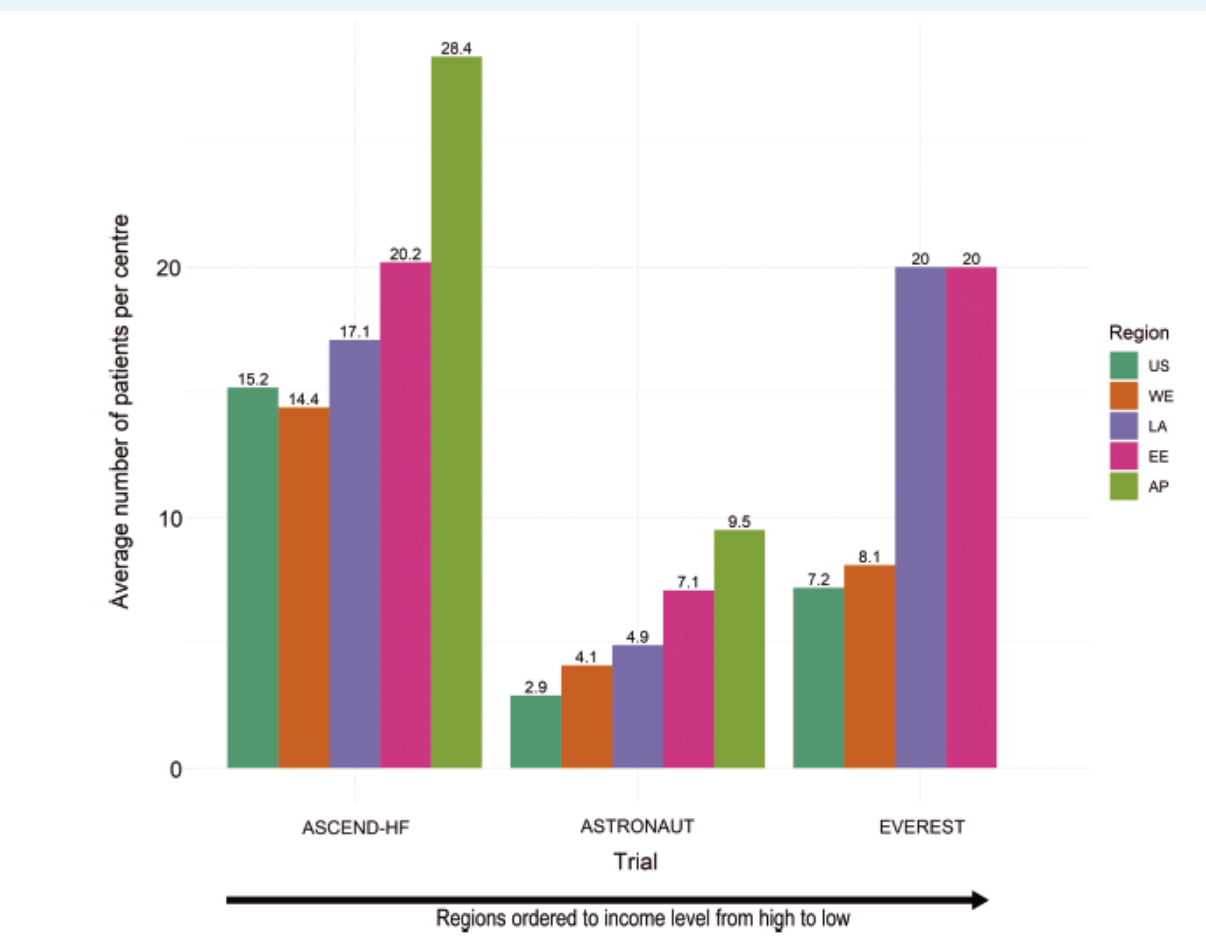
Viewpoint

October 4, 2016

Toward a New Era of Trust and Transparency in Clinical Trials

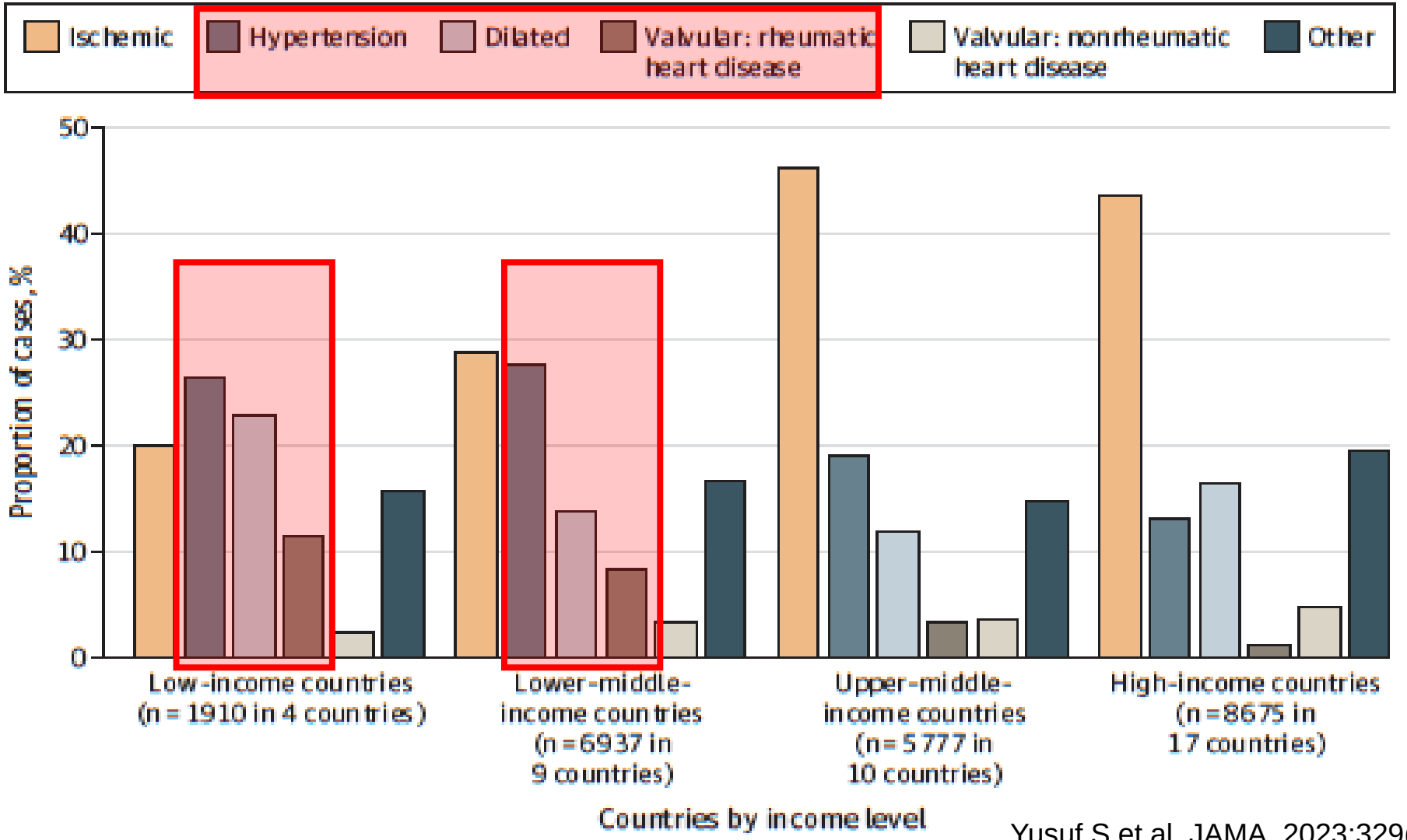
Hudson, Lauer, Collins. *JAMA* 2016;316:1353-1354

Enrolment per region, per trial,. Average number of pts/site



Tromp J et al. European Journal of Heart Failure 2019

Causes of HF



Yusuf S et al. JAMA. 2023;329(19):1650-1661

Baseline Characteristics of the Study Population

Yusuf S et al. JAMA. 2023;329(19):1650-1661

	Overall	Low-income countries	Lower–middle-income countries	middle-income countries	Upper– High-income countries
LVEF					
No.	19 237	1853	5896	4818	6670
≤40	11 642 (60.5)	1140 (61.5)	3685 (62.5)	2554 (53.0)	4263 (63.9)
41-49	2909 (15.1)	273 (14.7)	710 (12.0)	969 (20.1)	957 (14.3)
≥50	4686 (24.4)	440 (23.7)	1501 (25.5)	1295 (26.9)	1450 (21.7)
Stage 4-5 kidney	963 (4.1)	74 (3.9)	151 (2.2)	192 (3.3)	546 (6.3)
NYHA					
No.	23 227	1910	6946	5786	8585
I	2658 (11.4)	261 (13.7)	497 (7.2)	690 (11.9)	1210 (14.1)
II	11 347 (48.6)	508 (26.6)	3325 (47.9)	2875 (49.7)	4639 (54.0)
III	7395 (31.8)	670 (35.1)	2504 (36.0)	1743 (30.1)	2478 (28.9)
IV	1827 (7.9)	**471 (24.7)**	620 (8.9)	478 (8.3)	258 (3.0)

Review

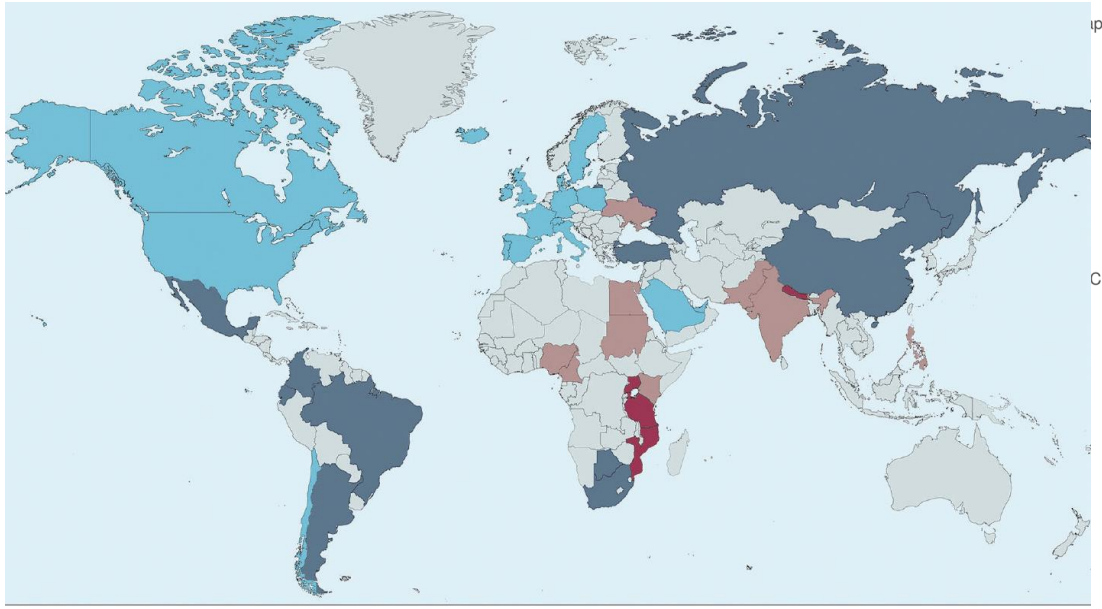
Prevalence, incidence and survival of heart failure: a systematic review

Sophia Emmons-Bell,[1] Catherine Johnson,[1] Gregory Roth [1,2]

Research

JAMA | Original Investigation Yusuf S et al. JAMA. 2023;329(19):1650-1661

Global Variations in Heart Failure Etiology, Management, and Outcomes



High-income countries
Canada, United States, Chile, Iceland, Sweden, Ireland, United Kingdom, Denmark, Germany, Poland, France, Switzerland, Italy, Portugal, Spain, Saudi Arabia, United Arab Emirates

Upper-middle-income countries
Mexico, Colombia, Ecuador, Brazil, Argentina, Russia, Türkiye, China, Botswana, South Africa

Lower-middle-income countries
Ukraine, Egypt, Sudan, Nigeria, Cameroon, Kenya, Pakistan, India, Philippines

Low-income countries
Uganda, Tanzania, Mozambique, Nepal

Reported incidence of heart failure in 41 studies identified in systematic review.

Emmons-Bell S, Johnson C, Roth G. *Heart* 2022;**108**:1351–1360.

Baseline Characteristics of the Study Population

	Overall	Low-income countries	Lower–middle-income countries	middle-income countries	Upper– High-income countries
Total No.	23 341	**1910**	6947	5793	8691
Age, median (IQR), y	65 (54-74)	**59** (45-70)	**60** (48-69)	67 (57-75)	69 (59-77)
Age, mean (SD), y	63.1 (14.9)	57.1 (17.1)	57.8 (15.4)	65.3 (13.9)	67.2 (12.9)
Female sex	9119 (39.1)	**1027 (53.7)**	**3094 (54.5)**	2232 (38.5)	2766 (31.8)
Enrollment from the inpatient hospitalization setting	7371 (31.6)	**600 (31.4)**	**2917 (42.0)**	1733 (29.9)	2121 (24.4)

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Offline: Global health has forgotten the Arab World

Richard Horton The Lancet April 6th 2019

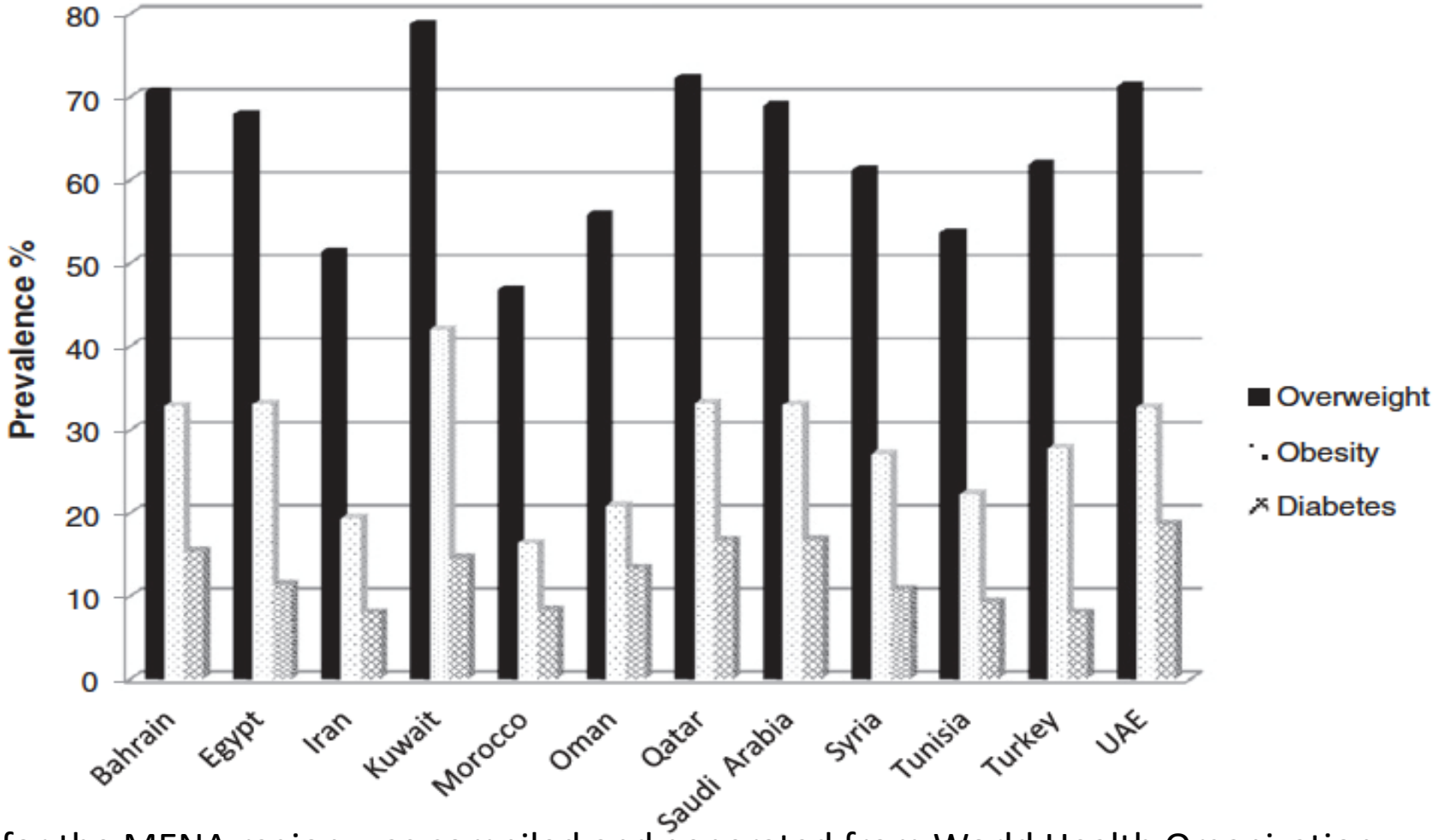
- What can be done?
- Instead of waiting for governments to act, the health and medical research communities could do more to encourage collaborations.
- By forging bilateral educational, clinical, and research partnerships, possibilities for a transformational shift in opportunities for a new Arab generation are palpable.
- Arab countries are an illuminatingly rich arena for health action.
- The Qur'an underlines the importance of knowledge (20.114), reflection (45.13), and education (96.5). Scaling up programmes of scientific and professional exchange

The burden of the CV disease in the MENA region

- 54% of deaths from noncommunicable diseases are due to CVD
- Sedentary lifestyles and common risk factors
- Up to 70% overweight/obesity in Bahrain, Kuwait, United Arab Emirates, and Saudi Arabia, particularly among women.
- Higher rates of physical inactivity than other regions.
- About 50% of women and more than a third of men are insufficiently active.
- The prevalence of smoking among adult men ranges from between 7% and 57%... and rising

http://www.emro.who.int/health-topics/cardiovascular-diseases/index.html

Prevalence of overweight, obesity and diabetes in MENA countries.



Data for the MENA region was compiled and generated from World Health Organization Non-communicable Diseases, Country profiles 2011 [18]. Body mass index: 25–29.9 (overweight) and >30 (obese).

Future trialists fellowship

https://www.globalcvctforum.com/young-trialists

- CVCT – Industry (and now also NHLBI) Future trialists Fellowships program supports the development of young trialists (Early and mid-career) with diversity background.
- Awardees serve as full (junior) members of large outcome trials' steering committees

What (if any) are the unmet gaps in biomedical research in the MENA region?

Clinical research in Africa and Middle East: roadmap for reform and harmonisation of the regulatory framework and sustainable capacity development

Faiez Zannad[1], Mohamed Sobhy[2], Wael Almahmeed[3], Mohamed Balghith[4], Javed Butler[5], Souad Dziri[6], Sahar Ebrahim[7], Ashraf El Fiky[8], Ahmed Elshal[9], Ines Fradi[10], Ziyad Ghazzal[11], Chokri Jeribi[12], Zainab Samad[13], Maciej Kostrubiec[14], Manal Milhem[15], Mossad Morsi[16], Ali Oto[17], Hany Ragy[18], Georges Saade[19], Rana Malkawi[20], Azza Saleh[21], Dina Shokri[21], Karen Sliwa[22], Habib Gamra[23], for the CVCT Regulatory summit Think Tank*

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