# Human Development Index and the Efficacy and Safety of Direct Oral Anticoagulants versus Warfarin: an individual participant data analysis of 4 randomized trials across 58,015 patients from COMBINE-AF

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#ScientificSessions26

# DISCLOSURES

- I’m a member of the TIMI Study Group which has received institutional research grant support through Brigham and Women’s Hospital from Abbott, Abiomed, Inc., Amgen, Anthos Therapeutics, ARCA Biopharma, Inc., AstraZeneca, Boehringer Ingelheim, Daiichi-Sankyo, Ionis Pharmaceuticals, Inc., Janssen Research and Development, LLC, MedImmune, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Roche, Saghmos Therapeutics, Inc., Softcell Medical Limited, The Medicines Company, Verve Therapeutics, Inc., Zora Biosciences.

# Background

- Atrial fibrillation (AF) affected an estimated 52 million people worldwide, with incident cases more than doubling since 1990.
- AF is associated with a five-fold increased risk of ischemic stroke and contributes substantially to mortality, disability, and healthcare utilization
- The AF burden is shifting toward lower-income countries, with higher AF-related disability than high-income countries
- The safety and efficacy of anticoagulation may be influenced by differences in healthcare infrastructure, health literacy, access to care, and quality of warfarin management.

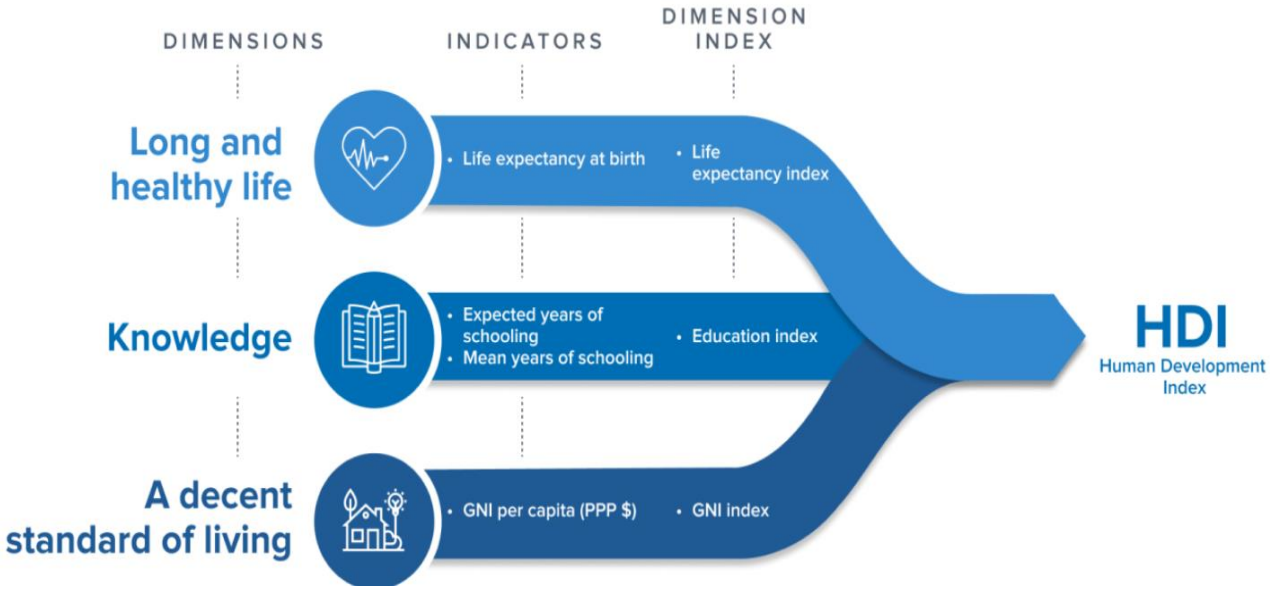
**Goal:** Using COMBINE-AF, an individual participant data analysis of 4 randomized trials in 58,015 patients, we sought to evaluate the efficacy and safety of SD DOACs vs. warfarin across Human Development Index (HDI)



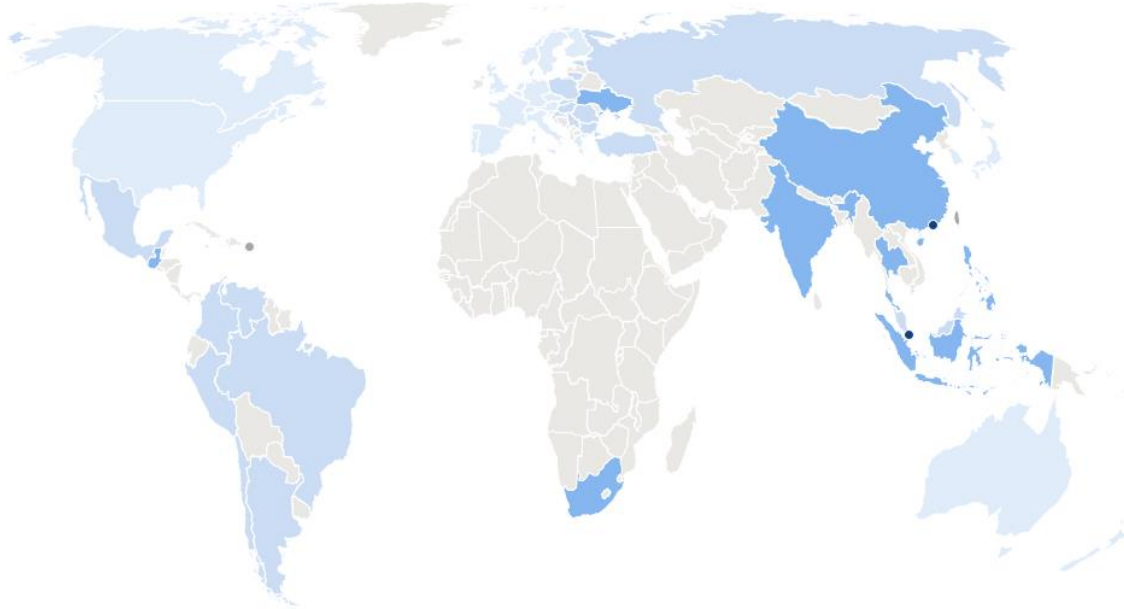
Li X, Global burden and health inequality of atrial fibrillation/atrial flutter from 1990 to 2021. *Front Cardiovasc Med*. 2025;12:1585980.

# Human development index (HDI)

## HDI Dimensions and Indicators




## Enrolling countries in COMBINE-AF by 2009 HDI




- **HDI is a composite measure of human development scaled from 0 to 1 based on 3 dimensions**
- **Countries were classified by HDI from the 2009 UNDP Human Development Report (midpoint of the four trials) using the report's standard cutpoints: very high (≥0.90), high (0.80–0.89), and medium (0.50–0.79).**

GNI: Gross national income

https://ourworldindata.org/human-development-index

# Methods

- Fifty-two countries across 6 continents from COMBINE-AF (an individual patient-level meta-analysis of 4 global RCTs) with 58,015 patients were included in our analysis

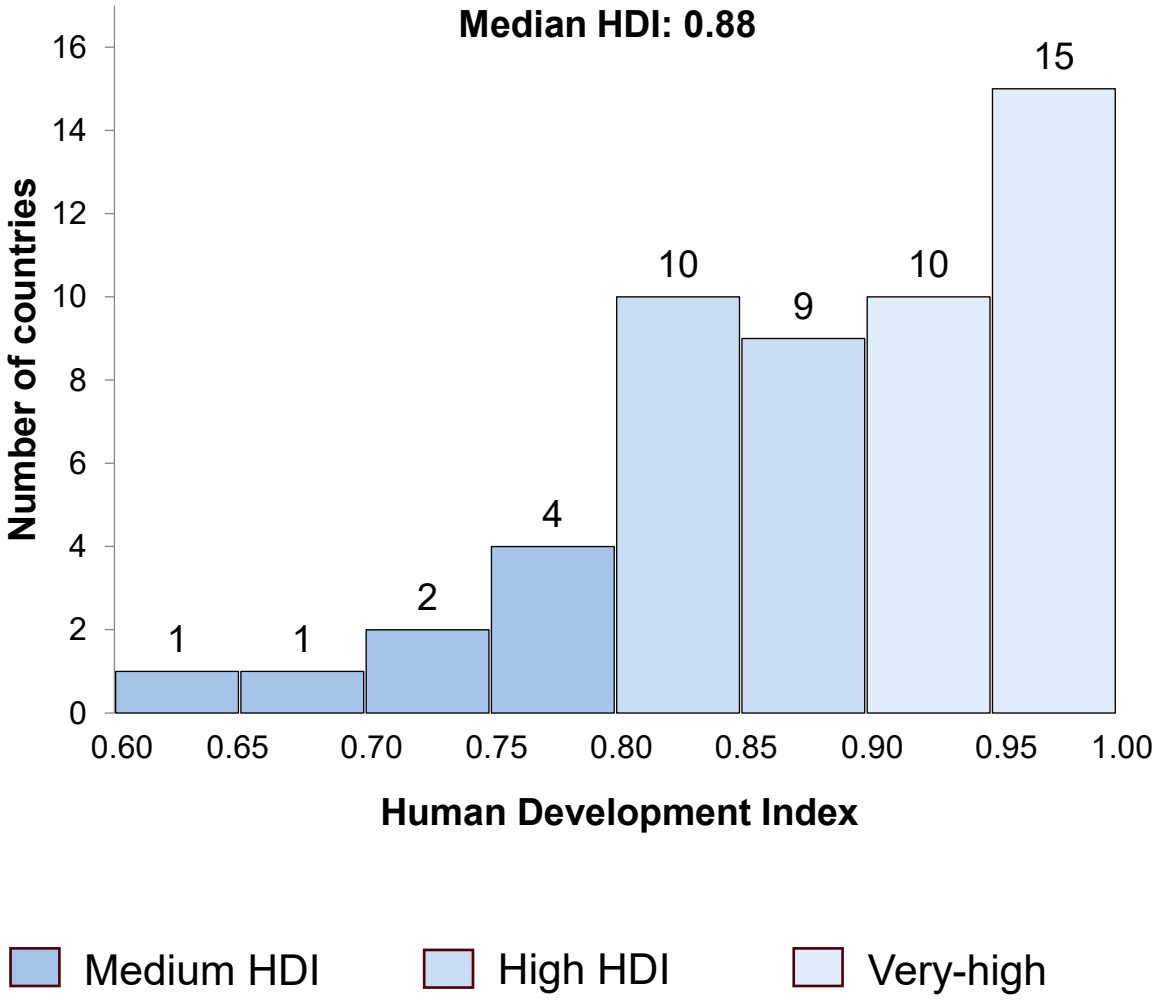
- Primary outcomes included
  - Stroke / systemic embolism (SSE)
  - Major bleeding
  - All-cause death
  - Net clinical outcome (NCO) of (SSE, Major Bleeding, and Death)

- All Outcomes were adjudicated by independent blinded CEC during the time of the included trials.

- Models were adjusted for Age, BMI, CrCl, prior stroke, DM, HTN, antiplatelet use, and country-based TTR

- Adjusted Cox models included a treatment-by-HDI interaction term, with HDI modeled as a continuous variable (primary analysis) and as a categorical variable (secondary analysis).

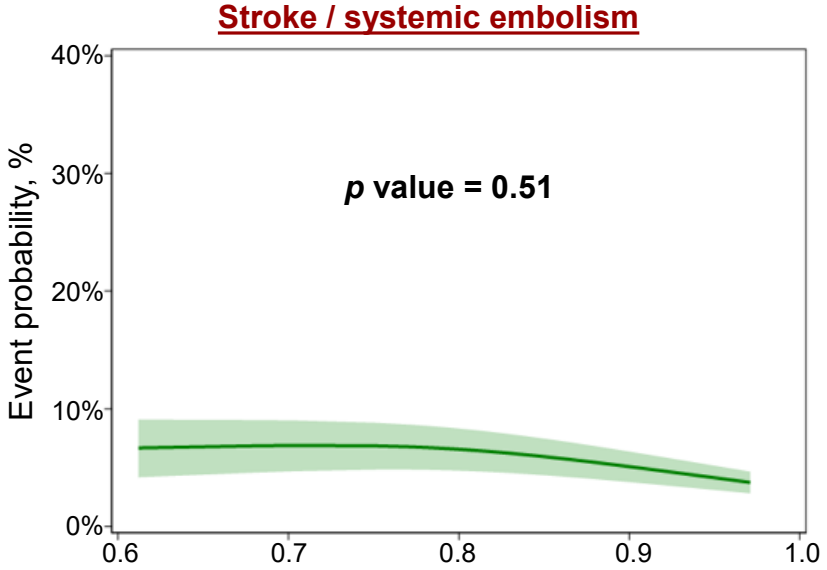
# Baseline Characteristics

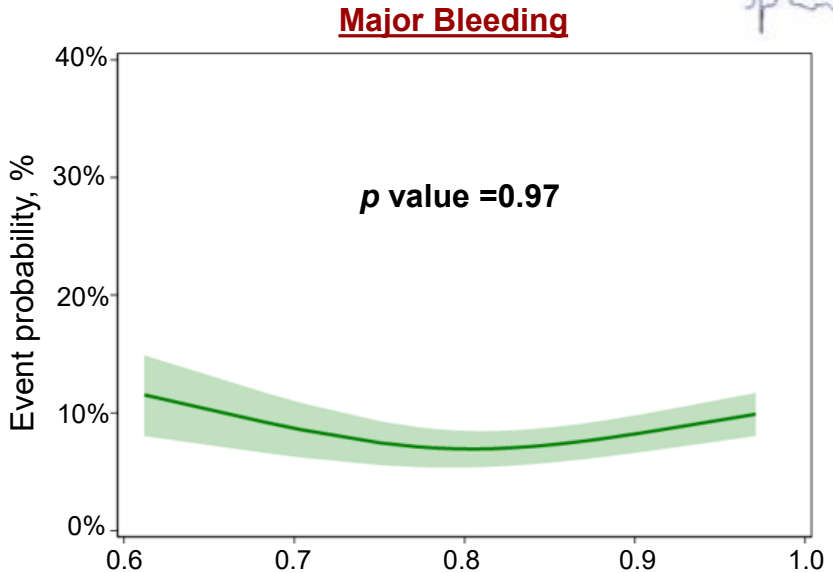


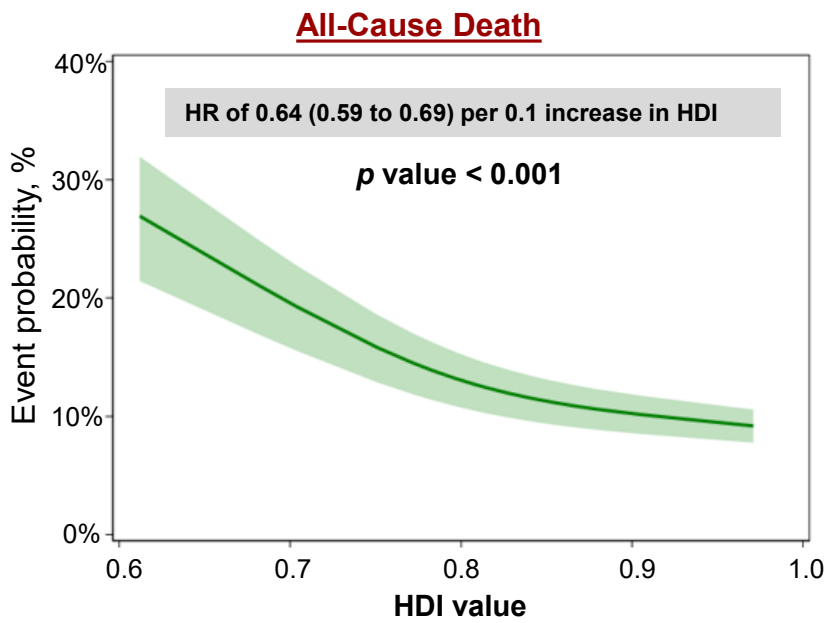

| Clinical Characteristics | N=8358 14.4 % | N=18997 32.7 % | N=30660 52.9 % |
|---|---|---|---|
| Age, median, y | 67 | 70 | 74 |
| Female, % | 39 | 42 | 34 |
| Creatinine clearance mL/min, median | 70 | 72 | 70 |
| Time in therapeutic range, Median, % | 56 | 61 | 70 |
| Prior ischemic stroke, % | 27 | 21 | 15 |
| VKA experience, % | 22 | 36 | 61 |
| Concomitant Antiplatelet therapy, % | 43 | 36 | 33 |
| $CHA_2DS_2$-VASc ≥ 4 | 59 | 65 | 58 |
| HAS-BLED ≥ 3 | 39 | 42 | 49 |
| DOAC Score ≥ 5 | 54 | 61 | 71 |

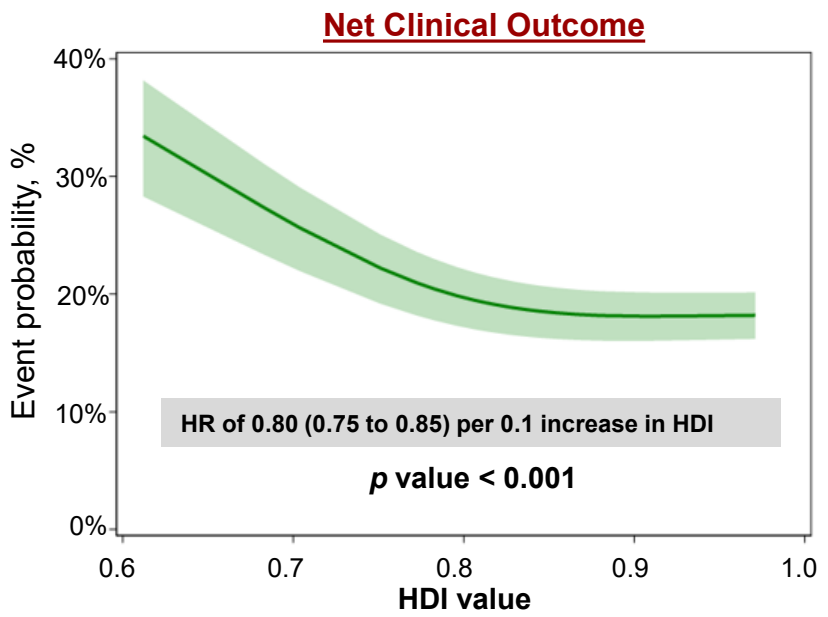
All *p*-trend <0.001 except creatinine clearance, *p*-trend = 0.11

# Adjusted Results: Warfarin arm across HDI range



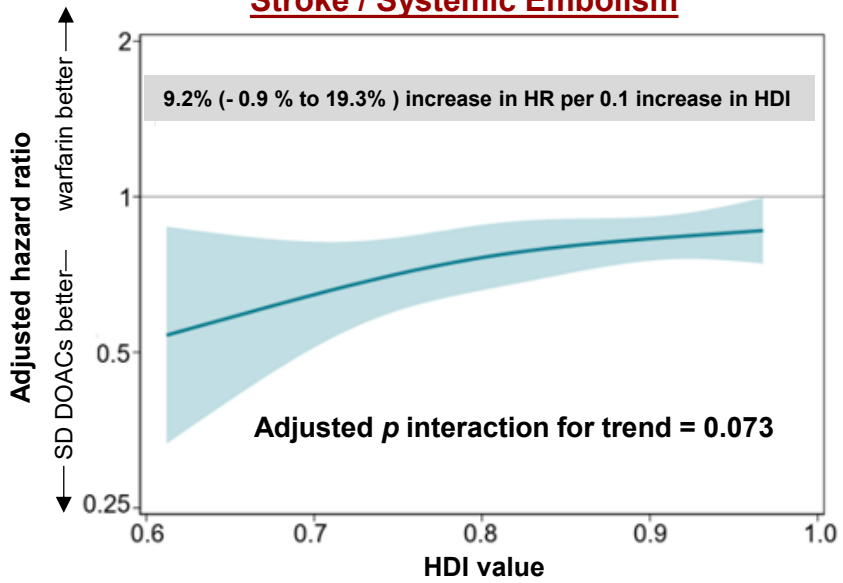



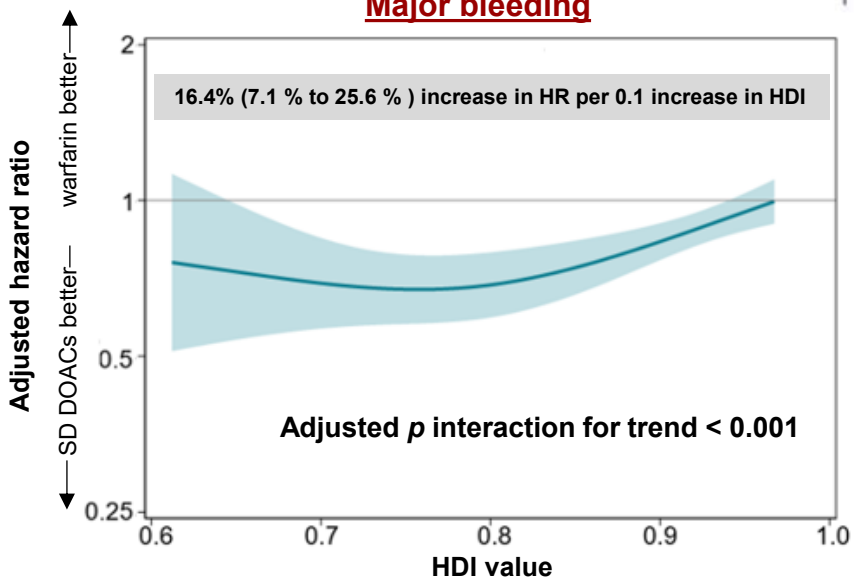



# Adjusted Results : SD DOACs vs. warfarin across HDI range

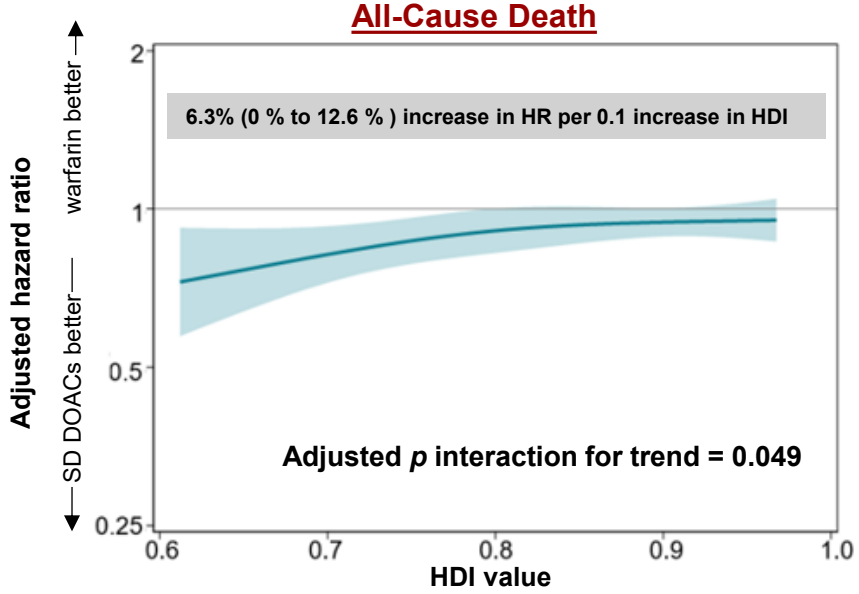
## Stroke / Systemic Embolism



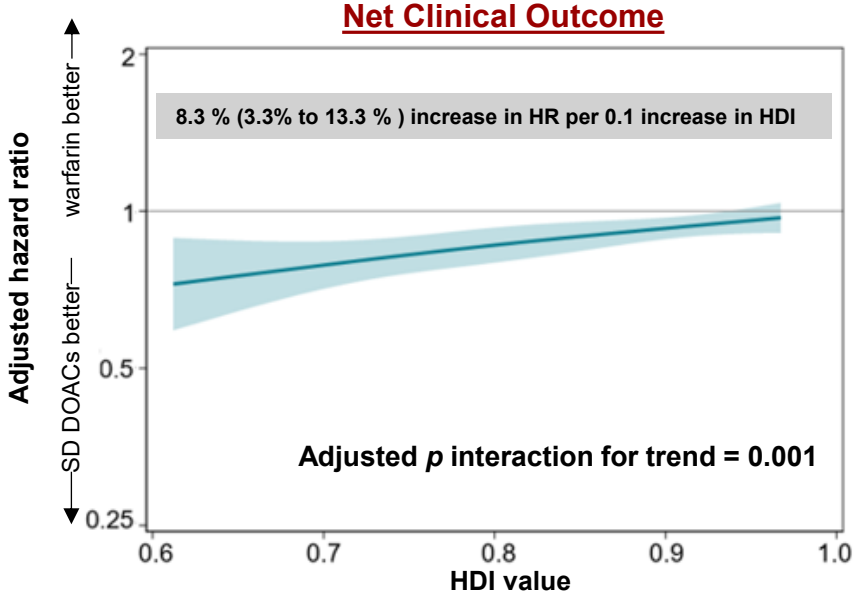

## Major bleeding



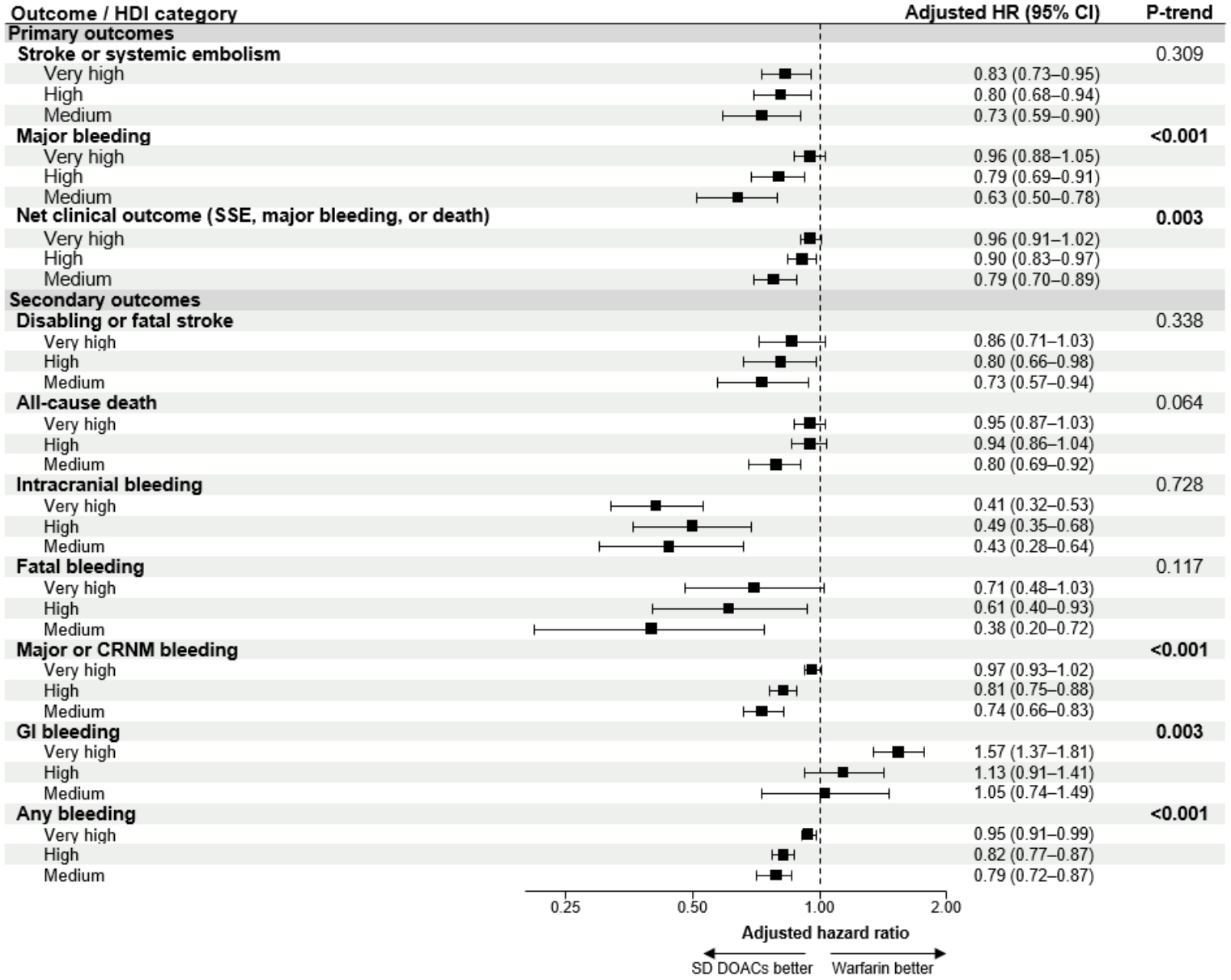

## All-Cause Death




## Net Clinical Outcome



# Outcomes by HDI in Categories



# Conclusion

- In Warfarin arm, Lower HDI was significantly associated with higher risk of all-cause death, and net clinical outcomes (SSE, major bleeding, and death).
- SD DOACs consistently reduced the risk of SSE across HDI strata compared to warfarin
- The reduction in major bleeding, all-cause death and Net Clinical Outcome with SD DOACs were significantly greater among patients from lower HDI countries
- Importantly, GI bleeding which is the most common type of bleeding from oral anticoagulation, was not increased with SD DOACs in lower HDI countries
- This analysis provides evidence that SD DOACs shows a greater clinical benefit over warfarin in lower HDI countries and suggests that their actual clinical value may be higher in these settings.