I, Tan SH, declare no conflict of interest.

# Real-World Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants (NOAC) in Patients with Non-Valvular Atrial Fibrillation (NVAF):

# A Retrospective Cohort Study in Singapore

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ACE
agency for
care effectiveness

# Background - Disease burden and treatment options for AF in Singapore

- In Singapore, the overall population prevalence of atrial fibrillation (AF) in Chinese adults aged 55 years and above was estimated at 1.5%, with higher prevalence (5.8%) in those aged 80 years or older[1]
- The risk of thromboembolic complications, namely ischemic strokes, increased 3 to 5 times in AF patients[2]

## Oral anticoagulant treatment options

### Warfarin

- Mainstay treatment and subsidized for decades
- Frequent drug-drug interactions, dietary restrictions and the need for regular monitoring

### Non-vitamin K antagonist oral anticoagulation agents (NOACs)

- Acceptable cost-effectiveness and favorable safety profile compared to warfarin
- Rivaroxaban and Apixaban were recommended for subsidy listing in 2017 and 2018 respectively

[1] Yap KB, Ng TP, Ong HY. Low prevalence of atrial fibrillation in community-dwelling Chinese aged 55 years or older in Singapore: a population-based study. Journal of electrocardiology. 2008;41(2):94-8.
[2] Kannel WB, Wolf PA, Benjamin EJ, et al. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates 1. American Journal of Cardiology.82(7):2N-9N.

# Background - Technology guidance on subsidy listing of drugs

ACE agency for care effectiveness

## Non-vitamin K antagonist oral anti-coagulation agents (NOACs)

*for preventing stroke and systemic embolism in non-valvular atrial fibrillation*

**Technology Guidance from the MOH Drug Advisory Committee**

### Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

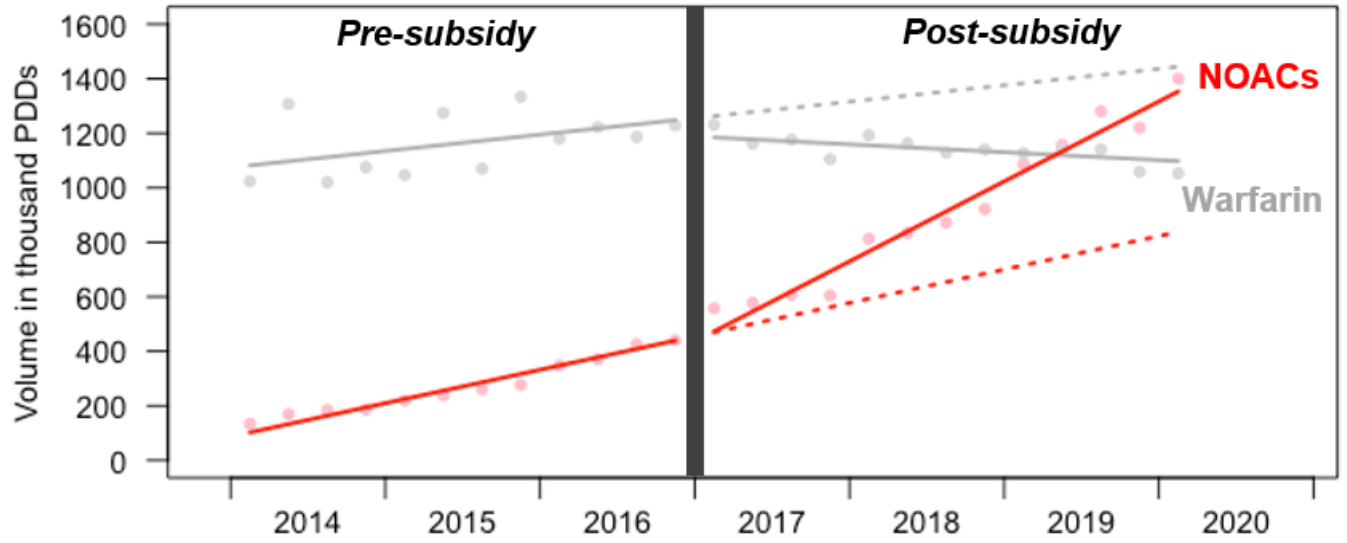
- ✓ Rivaroxaban 15 mg and 20 mg tablets, and apixaban 2.5 mg and 5 mg tablets for preventing stroke and systemic embolism in patients with non-valvular atrial fibrillation (NVAF) and:
  - $CHA_2DS_2$-VASc score of 1 or more for men; and
  - $CHA_2DS_2$-VASc score of 2 or more for women.

Rivaroxaban or apixaban should not be used in patients with valvular AF (especially rheumatic mitral stenosis), or patients with prosthetic heart valves.

# Background - Utilization of NOACs increased post subsidy

- After subsidy listing, the share of NOACs increased from 26% in Q4 2016 (pre-subsidy) to 55% in Q1 2020 (post-subsidy) (Figure 1)
- From prescribing data, it is noted that AF was the most common indication among prescribing of oral anticoagulants for new initiators

**Figure 1. Quarterly utilisation of NOACs and warfarin from Q1 2017 to Q1 2020**




*Solid lines: Modelled trends pre- and post-subsidy*
*Dotted line: Expected trend if pre-subsidy trend continues*

# Objectives

- With increasing use of NOACs over warfarin for stroke prevention in AF patients and limited studies on clinical outcomes of NOACs in a multi-ethnic Asian country such as Singapore, this study aims to answer the following questions:

**1. Real-world clinical effectiveness (e.g. stroke) and safety outcomes (e.g. bleeding) associated with NOACs**

**2. Long-term effect on healthcare costs post-subsidy listing**

# Methodology - Real-world outcomes

| | |
|---|---|
| **Study type** | ▪ Retrospective cohort study |
| **Data Sources** | ▪ National Electronic Health Record prescribed drugs data (2015 – 2018)<br>▪ Chronic diseases management system and hospitalization data (up to 2019)<br>▪ Death registry data (up to 2019) |
| **Inclusion** | ▪ Patients (aged ≥ 18 years) newly prescribed with anticoagulant treatment from 2015 – 2018, with AF diagnosis in the Singapore public healthcare institutions<br>▪ Newly prescribed: one year washout period |
| **Exclusion** | ▪ Patients with less than 2 prescriptions of a particular oral anticoagulant in 1 year or were prescribed with 2 different oral anticoagulants on the index date<br>▪ Patients with severe to end-stage chronic kidney disease, rheumatic mitral stenosis or prosthetic heart valve procedure done prior to the index date<br>▪ Patients who switched from warfarin to NOAC and vice versa within 7 days |

The follow-up period was from the day after the index date to 6 months after the last warfarin or NOAC prescription date, switch date, death, or the end of study period (31 December 2019), whichever occurred first

# Methodology - Real-world outcomes

| | |
|---|---|
| **Study type** | ▪ Retrospective cohort study |
| **Analyses** | ▪ Using propensity score matching (1:1), patients from NOAC and warfarin group were matched based on 31 variables on demographics and clinical characteristics (with a caliper of 0.01)<br>▪ Primary efficacy outcomes: time to first stroke/systemic embolism (SE)<br>▪ Primary safety outcomes: time to first intracranial hemorrhage (ICH)/Gastrointestinal (GI) bleed<br>▪ Secondary efficacy outcomes: time to first myocardial infarction (MI) and all-cause mortality<br>▪ Hazard ratio (HR) and 95% CI was estimated using cox proportional hazard models with robust variance estimates |

The follow-up period was from the day after the index date to 6 months after the last warfarin or NOAC prescription date, switch date, death, or the end of study period (31 December 2019), whichever occurred first

# Baseline characteristics before propensity score (PS) matching

## Table 1. Comparison of baseline characteristics before PS matching

| Patient characteristics | | Unmatched cohorts | | |
|---|---|---|---|---|
| | | Warfarin (n = 3,393) | NOAC (n = 7,702) | d |
| **Demographics at initiation** | | | | |
| Age*, n(%) | Mean ± SD | 70.0 ± 10.9 | 70.8 ± 10.7 | 0.069 |
| | 18 – 64 years | 994 (29.4%) | 2,005 (26.0%) | 0.074 |
| | 65 – 74 years | 1,095 (32.3%) | 2,588 (33.6%) | |
| | ≥ 75 years | 1,297 (38.3%) | 3,104 (40.3%) | |
| Duration with AF (years)*, mean ± SD | | 2.6 ± 4.1 | 2.5 ± 3.9 | 0.007 |
| Gender (male)*, n(%) | | 2,029 (59.9%) | 4,387 (57.0%) | 0.059 |
| Ethnicity*, n(%) | Chinese | 2,526 (74.6%) | 6,033 (78.4%) | **0.128** |
| | Malay | 505 (14.9%) | 826 (10.7%) | |
| | Indian | 137 (4.0%) | 293 (3.8%) | |
| | Others | 218 (6.4%) | 545 (7.1%) | |
| Residential status, n(%) | Singapore citizen | 3,278 (96.8%) | 7,430 (96.5%) | 0.016 |
| | Permanent resident | 108 (3.2%) | 267 (3.5%) | |
| SES category*, n(%) | Maximum subsidy | 2,329 (68.8%) | 4,377 (56.9%) | **0.249** |
| | Some subsidy | 49 (1.4%) | 134 (1.7%) | |
| | Minimum subsidy | 86 (2.5%) | 275 (3.6%) | |
| | NA | 922 (27.2%) | 2,911 (37.8%) | |
| Setting*, n(%) | Hospitals | 3,257 (96.2%) | 7,542 (98.0%) | **0.107** |
| | Polyclinics | 129 (3.8%) | 155 (2.0%) | |
| **Comorbidities, n(%)** | | | | |
| Heart failure* | | 1,315 (38.8%) | 1,984 (25.8%) | **0.282** |
| Hypertension* | | 2,887 (85.3%) | 6,540 (85.0%) | 0.008 |
| Diabetes mellitus* | | 1,563 (46.2%) | 3,225 (41.9%) | 0.086 |
| Coronary heart disease | | 1,786 (52.7%) | 3,499 (45.5%) | **0.146** |
| Myocardial infarction* | | 850 (25.1%) | 1,398 (18.2%) | **0.169** |
| Peripheral vascular disease* | | 183 (5.4%) | 243 (3.2%) | **0.111** |
| Malignancy* | | 143 (4.2%) | 382 (5.0%) | 0.035 |
| Liver disease* | | 41 (1.2%) | 66 (0.9%) | 0.035 |
| Alcohol abuse* | | 35 (1.0%) | 73 (0.9%) | 0.009 |

| Patient characteristics (con't) | | Unmatched cohorts | | |
|---|---|---|---|---|
| | | Warfarin (n = 3,393) | NOAC (n = 7,702) | d |
| **Comorbidities, n(%)** | | | | |
| Previous stroke or systemic embolism* | Any | 1,044 (30.8%) | 2,332 (30.3%) | 0.012 |
| | Ischemic stroke | 696 (20.5%) | 1,430 (18.6%) | 0.050 |
| | Hemorrhagic stroke | 150 (4.4%) | 315 (4.1%) | 0.017 |
| | Unspecified | 966 (28.5%) | 2,100 (27.3%) | 0.028 |
| | TIA | 287 (8.5%) | 653 (8.5%) | 0.000 |
| | Systemic embolism | 35 (1.0%) | 39 (0.5%) | 0.060 |
| Previous ICH or GI bleed in past 1 year* | Any | 118 (3.5%) | 243 (3.2%) | 0.018 |
| | ICH bleed | 78 (2.3%) | 165 (2.1%) | 0.011 |
| | GI bleed | 45 (1.3%) | 87 (1.1%) | 0.018 |
| Mild to moderate CKD (stage 1 to 3)* | | 1,001 (29.6%) | 1,980 (25.7%) | 0.086 |
| Valvular heart disease*^ | | 376 (11.1%) | 348 (4.5%) | **0.247** |
| $CHA_2DS_2$-VASc score | Mean ± SD | 4.4 ± 1.8 | 4.2 ± 1.9 | **0.103** |
| | 0 – 1 | 174 (5.1%) | 557 (7.2%) | **0.100** |
| | 2 – 3 | 951 (28.1%) | 2,281 (29.6%) | |
| | ≥ 4 | 2,261 (66.8%) | 4,859 (63.1%) | |
| Charlson Comorbidity Index score* | Mean ± SD | 4.5 ± 3.0 | 4.0 ± 2.9 | **0.145** |
| | 0 – 2 | 937 (27.7%) | 2,350 (30.5%) | **0.198** |
| | 3 – 4 | 799 (23.6%) | 1,878 (24.4%) | |
| | ≥ 5 | 1,296 (38.3%) | 2,316 (30.1%) | |
| | NA | 354 (10.5%) | 1,153 (15.0%) | |
| **Concomitant drugs*, n(%)** | | | | |
| Proton pump inhibitors | | 2,048 (60.5%) | 4,437 (57.6%) | 0.058 |
| Low-dose aspirin | | 1,656 (48.9%) | 3,070 (39.9%) | **0.183** |
| $P2Y_{12}$ inhibitors | | 776 (22.9%) | 1,426 (18.5%) | **0.109** |
| NSAIDs | | 209 (6.2%) | 577 (7.5%) | 0.052 |
| SSRIs | | 143 (4.2%) | 379 (4.9%) | 0.034 |
| Glucocorticoids | | 276 (8.2%) | 540 (7.0%) | 0.043 |
| Polypharmacy (≥ 10 ATC classes) | | 2,300 (67.9%) | 4,462 (58.0%) | **0.207** |

*Variables included in the PSM logistic models
^Excludes rheumatic mitral stenosis and presence of artificial heart valves

# No significant differences in baseline characteristics were observed after propensity score (PS) matching

## Table 2. Comparison of baseline characteristics after PS matching

| Patient characteristics | | Matched cohorts Warfarin (n = 3,315) | NOAC (n = 3,315) | d |
|---|---|---|---|---|
| **Demographics at initiation** | | | | |
| Age*, n(%) | Mean ± SD | 70.2 ± 10.8 | 70.2 ± 11.0 | 0.007 |
| | 18 – 64 years | 961 (29.0%) | 918 (27.7%) | 0.038 |
| | 65 – 74 years | 1,074 (32.4%) | 1,128 (34.0%) | |
| | ≥ 75 years | 1,280 (38.6%) | 1,269 (38.3%) | |
| Duration with AF (years)*, mean ± SD | | 2.6 ± 4.2 | 2.6 ± 3.9 | 0.000 |
| Gender (male)*, n(%) | | 1,982 (59.8%) | 1,986 (59.9%) | 0.002 |
| Ethnicity*, n(%) | Chinese | 2,488 (75.1%) | 2,464 (74.3%) | 0.019 |
| | Malay | 479 (14.4%) | 495 (14.9%) | |
| | Indian | 133 (4.0%) | 132 (4.0%) | |
| | Others | 215 (6.5%) | 224 (6.8%) | |
| Residential status, n(%) | Singapore citizen | 3,208 (96.8%) | 3,218 (97.1%) | 0.017 |
| | Permanent resident | 107 (3.2%) | 97 (2.9%) | |
| SES category*, n(%) | Maximum subsidy | 2,260 (68.2%) | 2,400 (72.4%) | 0.093 |
| | Some subsidy | 49 (1.5%) | 46 (1.4%) | |
| | Minimum subsidy | 86 (2.6%) | 74 (2.2%) | |
| | NA | 920 (27.8%) | 795 (24.0%) | |
| Setting*, n(%) | Hospitals | 3,199 (96.5%) | 3,197 (96.4%) | 0.003 |
| | Polyclinics | 116 (3.5%) | 118 (3.6%) | |
| **Comorbidities, n(%)** | | | | |
| Heart failure* | | 1,254 (37.8%) | 1,314 (39.6%) | 0.037 |
| Hypertension* | | 2,831 (85.4%) | 2,636 (85.6%) | 0.004 |
| Diabetes mellitus* | | 1,524 (46.0%) | 1,559 (47.0%) | 0.021 |
| Coronary heart disease | | 1,737 (52.4%) | 1,839 (55.5%) | 0.062 |
| Myocardial infarction* | | 821 (24.8%) | 858 (25.9%) | 0.026 |
| Peripheral vascular disease* | | 168 (5.1%) | 177 (5.3%) | 0.012 |
| Malignancy* | | 141 (4.3%) | 131 (4.0%) | 0.015 |
| Liver disease* | | 39 (1.2%) | 39 (1.2%) | 0.000 |
| Alcohol abuse* | | 35 (1.1%) | 38 (1.1%) | 0.009 |

| Patient characteristics (con't) | | Matched cohorts Warfarin (n = 3,315) | NOAC (n = 3,315) | d |
|---|---|---|---|---|
| **Comorbidities, n(%)** | | | | |
| Previous stroke or systemic embolism* | Any | 1,019 (30.7%) | 1,036 (31.3%) | 0.011 |
| | Ischemic stroke | 676 (20.4%) | 713 (21.5%) | 0.027 |
| | Hemorrhagic stroke | 144 (4.3%) | 142 (4.3%) | 0.003 |
| | Unspecified | 944 (28.5%) | 956 (28.8%) | 0.008 |
| | TIA | 278 (8.4%) | 270 (8.1%) | 0.009 |
| | Systemic embolism | 32 (1.0%) | 34 (1.0%) | 0.006 |
| Previous ICH or GI bleed in past 1 year* | Any | 116 (3.5%) | 111 (3.3%) | 0.008 |
| | ICH bleed | 77 (2.3%) | 76 (2.3%) | 0.002 |
| | GI bleed | 44 (1.3%) | 41 (1.2%) | 0.008 |
| Mild to moderate CKD (stage 1 to 3)* | | 972 (29.3%) | 1,045 (31.5%) | 0.048 |
| Valvular heart disease*^ | | 331 (10.0%) | 315 (9.5%) | 0.016 |
| $CHA_2DS_2$-VASc score | Mean ± SD | 4.4 ± 1.8 | 4.4 ± 1.9 | 0.042 |
| | 0 – 1 | 171 (5.2%) | 183 (5.5%) | 0.056 |
| | 2 – 3 | 933 (28.1%) | 851 (25.7%) | |
| | ≥ 4 | 2,211 (66.7%) | 2,281 (68.8%) | |
| Charlson Comorbidity Index score* | Mean ± SD | 4.5 ± 3.0 | 4.5 ± 3.0 | 0.010 |
| | 0 – 2 | 920 (27.8%) | 910 (27.5%) | 0.064 |
| | 3 – 4 | 788 (23.8%) | 778 (23.5%) | |
| | ≥ 5 | 1,255 (37.9%) | 1,329 (40.1%) | |
| | NA | 352 (10.6%) | 298 (9.0%) | |
| **Concomitant drugs*, n(%)** | | | | |
| Proton pump inhibitors | | 2,004 (60.5%) | 2,021 (61.0%) | 0.011 |
| Low-dose aspirin | | 1,601 (48.3%) | 1,667 (50.3%) | 0.040 |
| $P2Y_{12}$ inhibitors | | 752 (22.7%) | 797 (24.0%) | 0.032 |
| NSAIDs | | 208 (6.3%) | 198 (6.0%) | 0.013 |
| SSRIs | | 141 (4.3%) | 130 (3.9%) | 0.017 |
| Glucocorticoids | | 265 (8.0%) | 278 (8.4%) | 0.014 |
| Polypharmacy (≥ 10 ATC classes) | | 2,237 (67.5%) | 2,294 (69.2%) | 0.037 |

A standardized difference, d of less than 0.1 indicates negligible differences between groups

*Variables included in the PSM logistic models

^Excludes rheumatic mitral stenosis and presence of artificial heart valves

# NOAC was more effective than warfarin in reducing stroke and death

- Over a median follow-up of 2 years, NOAC was associated with a
  - 17% reduction in stroke or systemic embolism (SE)
  - 28% reduction in hemorrhagic stroke
  - 19% reduction in all-cause mortality

**Table 3. HR and associated 95% CI for efficacy outcomes in the matched cohorts after treatment initiation**

| Efficacy outcomes | **Warfarin** (n = 3,315) | **NOAC** (n = 3,315) | HR (95% CI) | p-value |
|---|---|---|---|---|
| | No. of patients with event (incidence per 100 person-years) | | | |
| ***Primary outcome:*** | | | | |
| Stroke or SE | 269 (3.86) | 232 (3.31) | **0.83 (0.70, 0.99)** | **0.043** |
| Ischemic or unspecified stroke | 171 (2.42) | 164 (2.32) | 0.93 (0.75, 1.16) | 0.526 |
| Hemorrhagic stroke | 87 (1.21) | 64 (0.89) | **0.72 (0.52, 0.99)** | **0.046** |
| TIA | 29 (0.40) | 26 (0.36) | 0.85 (0.50, 1.45) | 0.563 |
| SE | 19 (0.26) | 11 (0.15) | 0.56 (0.27, 1.18) | 0.129 |
| ***Secondary outcomes:*** | | | | |
| Myocardial infarction | 238 (3.39) | 225 (3.20) | 0.93 (0.77, 1.11) | 0.410 |
| All-cause mortality | 418 (5.79) | 343 (4.74) | **0.81 (0.70, 0.94)** | **0.004** |

# NOAC was safer than warfarin, with lower rates of ICH/GI bleed

- NOAC was associated with a
  - 23% reduction in any intracranial hemorrhage (ICH) or gastrointestinal (GI) bleed
  - 39% reduction in ICH

**Table 4. HR and associated 95% CI for safety outcomes in matched cohorts after treatment initiation**

| **Safety outcomes** | **Warfarin** (n = 3,315) | **NOAC** (n = 3,315) | **HR (95% CI)** | **p-value** |
|---|---|---|---|---|
| | No. of patients with event (incidence per 100 person-years) | | | |
| ***Primary outcome:*** | | | | |
| ICH or GI bleed | 340 (5.01) | 270 (3.96) | **0.77 (0.66, 0.91)** | **0.001** |
| ICH | 162 (2.27) | 102 (1.43) | **0.61 (0.48, 0.78)** | **<0.001** |
| GI bleed | 179 (2.75) | 169 (2.59) | 0.92 (0.75, 1.14) | 0.451 |

# Methodology - Impact on healthcare cost

| | |
|---|---|
| **Study type** | ▪ Simplified Markov model |
| **Data Sources** | ▪ NEHR prescribed drugs data (2017 – 2019)<br>▪ Hospitalization data on treatment cost (2015 – 2019)<br>▪ Drug utilisation data for drug cost (2015 – 2018) |
| **Analyses** | ▪ Model output:<br>  ▪ Number of cases of all-cause death, stroke/SE and ICH/GI bleed avoided & avoidance in the hospitalizations treatment cost from reduced stroke/SE and ICH/GI bleed<br>▪ Assumptions:<br>  ▪ Assumes same number of patients in both treatment groups<br>  ▪ Based on actual number of patients on NOAC in the 2017 – 2019 (NEHR), we projected number of patients in the subsequent years based on Singapore population growth and AF prevalence<br>  ▪ Assumes mean treatment cost remain unchanged (2015 - 2019) |

# Over 500 deaths avoided and $12 million saved over 5 years from reduction in stroke/SE and ICH/GI bleed hospitalizations

- Based on actual and projected number of AF patients on NOAC in the first 5 years after subsidy listing:

## Averted no. of cases over 5 years (2017 to 2021)

**564**

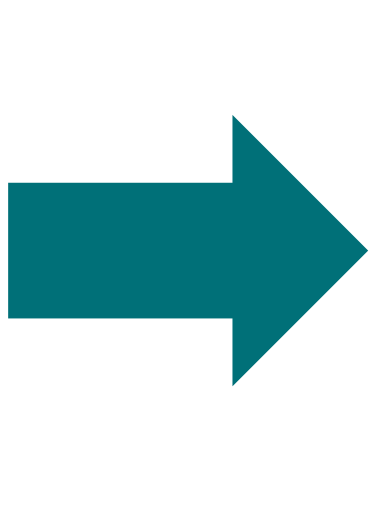
deaths

**287**

Stroke/SE hospitalisations

**572**

ICH/GI bleed hospitalisations



### Healthcare cost savings*

**SGD $12M**

**~USD $9M**

* Does not include difference in treatment costs

# Study limitations

- Due to the limitation of the data sources, the treatment quality of the warfarin group in terms of time in therapeutic range (TTR) was not evaluated. Asian population has been reported to have a lower TTR control[1] and it could be a possible confounding factor
- In addition, we did not consider the proportion of patients on standard dose vs. reduced dose of NOAC, when reduced dose is frequently prescribed in the local context especially for the elderly patients or patients with increased risk of bleeding

[1]Oh S, et al. Vitamin K antagonist control in patients with atrial fibrillation in Asia compared with other regions of the world: Real-world data from the GARFIELD-AF registry. *Int. J. Cardiol.* 2016;223:543-47.

# Conclusion

- Consistent with clinical trials and other real-world findings, this large cohort study confirmed that NOAC reduced risk of stroke or SE, ICH/GI bleed and avoid all-cause mortality in a multi-ethnic Asian population
- In addition, using NOAC over warfarin has potential to bring about cost savings to the healthcare system through reduction in hospitalization costs

# Thank you!

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