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# Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

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# Introduction

- Anticoagulation with direct oral anticoagulants (DOACs) reduces the risk of ischemic stroke and systemic embolism among persons with atrial fibrillation.Early initiation may increase the risk of intracranial hemorrhage, whereas later initiation may increase the risk of early stroke recurrence.


- Some recommendations (EHRA)suggest initiation of anticoagulation at 1, 3, 6, or 12 days after a transient ischemic attack or after a minor, moderate, or severe ischemic stroke(NIHSS Score), respectively (the “1-3-6-12–day rule”).This guidance, which has been based on the observation that the risk of hemorrhagic transformation is related to infarct size, is followed in many countries. A neuroimaging-based risk-stratification approach may help to minimize the risk of intracranial hemorrhage. although studies and small randomized trials suggest that early use of DOACs may be safe,


We conducted the Early versus Late Initiation of Direct Oral Anticoagulants in Post-ischemic Stroke Patients with Atrial Fibrillation (ELAN) randomized trial, which aimed to estimate the safety and efficacy of early initiation of DOACs as compared with later, guideline-based initiation, using imaging-based selection criteria in persons who have had a recent stroke and have atrial fibrillation.


## Methods

- The trial was conducted at 103 stroke centers 15 countries between November 6, 2017, and September 12, 2022
- Participants were eligible if they had had an ischemic stroke and if they had permanent, persistent, or paroxysmal nonvalvular atrial fibrillation or atrial fibrillation diagnosed during hospitalization for the stroke


- Ischemic stroke was defined as evidence of acute cerebral infarction on magnetic resonance imaging (MRI) or computed tomography (CT) or as a clinical diagnosis of ischemic stroke with symptoms lasting more than 24 hours
- An infarct of 1.5 cm or smaller was defined as minor; an infarct in the distribution of a cortical superficial branch of the middle, anterior, or posterior cerebral artery was defined as moderate; and larger infarcts in the distribution of these arteries or a brain-stem or cerebellar infarct larger than 1.5 cm were defined as major

- Petechial hemorrhage within infarcted brain tissue was not an exclusion criterion for enrollment, but confluent parenchymal hematoma within infarcted brain tissue or intracranial hemorrhage remote from infarcted tissues was not allowed.


- Participants were randomly assigned in a 1:1 ratio with the use of a centralized Web-based system to early initiation of DOAC or later initiation of DOAC
- Early treatment was defined as initiation of a DOAC within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke. Later treatment was defined as initiation of a DOAC in participants with a minor stroke on day 3 or 4 after stroke onset, in participants with a moderate stroke on day 6 or 7, and in participants with a major stroke on day 12, 13, or 14.

# Outcomes:

- The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death within 30 days.
- Secondary outcomes assessed at 30 and 90 days were the following: recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, vascular death, nonmajor bleeding, death from any cause,


# Statistical Analysis:

- The main aim of the trial was to estimate the effect of early initiation as compared with later initiation of anticoagulation and to estimate the degree of precision of these estimates. Therefore, no statistical hypotheses as to superiority, inferiority, or noninferiority were tested.
- The primary composite outcome and secondary binary outcomes was analyzed with the use of a penalized logistic-regression model

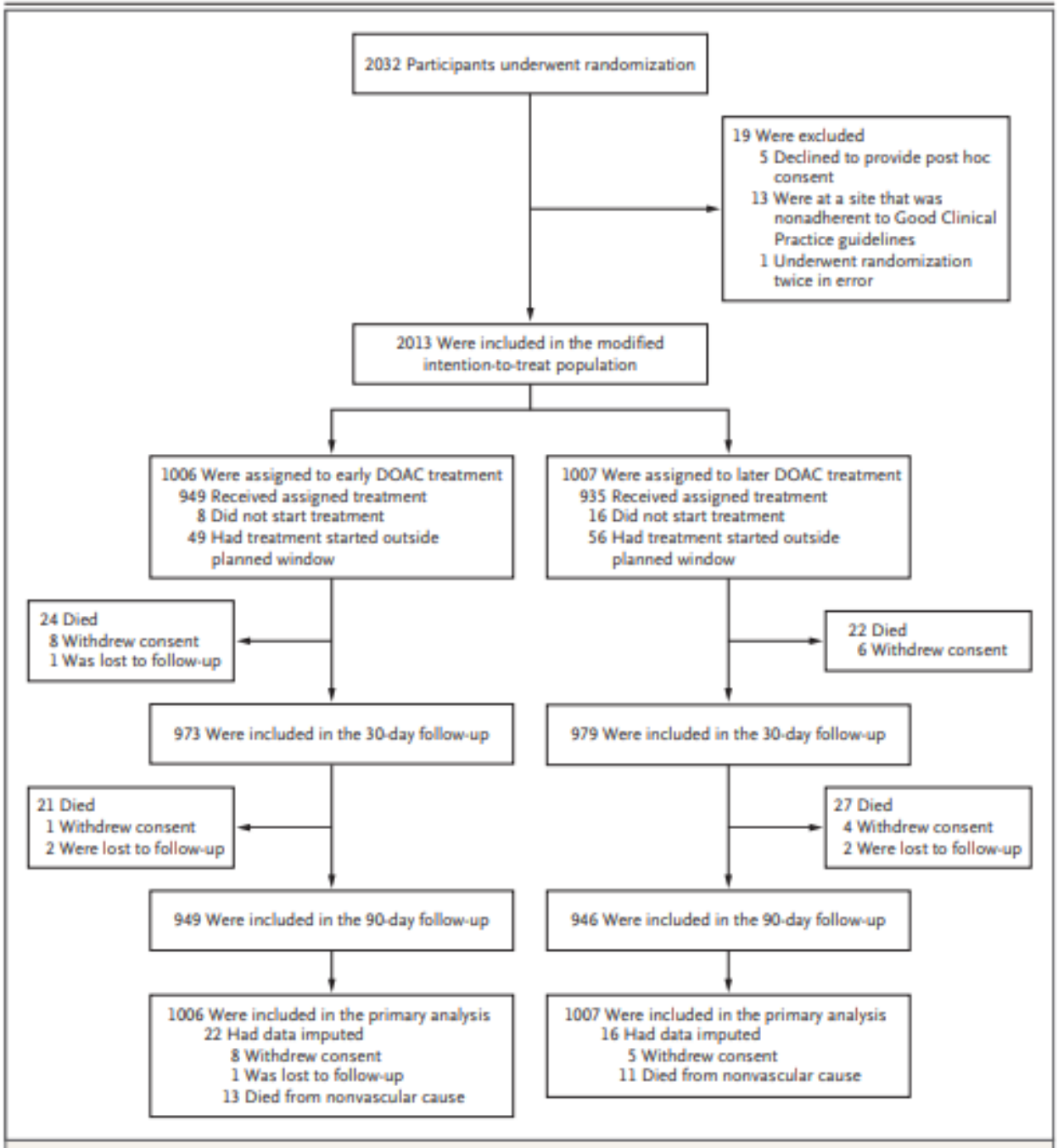
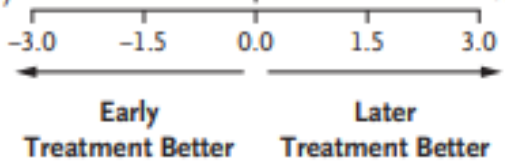

2032 Participants underwent randomization
19 Were excluded
5 Declined to provide post hoc consent
13 Were at a site that was nonadherent to Good Clinical Practice guidelines
1 Underwent randomization twice in error
2013 Were included in the modified intention-to-treat population
1006 Were assigned to early DOAC treatment
949 Received assigned treatment
8 Did not start treatment
49 Had treatment started outside planned window
1007 Were assigned to later DOAC treatment
935 Received assigned treatment
16 Did not start treatment
56 Had treatment started outside planned window
24 Died
8 Withdrew consent
1 Was lost to follow-up
22 Died
6 Withdrew consent
973 Were included in the 30-day follow-up
979 Were included in the 30-day follow-up
21 Died
1 Withdrew consent
2 Were lost to follow-up
27 Died
4 Withdrew consent
2 Were lost to follow-up
949 Were included in the 90-day follow-up
946 Were included in the 90-day follow-up
1006 Were included in the primary analysis
22 Had data imputed
8 Withdrew consent
1 Was lost to follow-up
13 Died from nonvascular cause
1007 Were included in the primary analysis
16 Had data imputed
5 Withdrew consent
11 Died from nonvascular cause

**Table 1. Characteristics of the Participants at Baseline.***

| Characteristic | Early-Treatment Group (N=1006) | Later-Treatment Group (N=1007) |
|---|---|---|
| Median age (IQR) — yr | 77 (70–84) | 78 (71–84) |
| Female sex — no. (%) | 459 (45.6) | 456 (45.3) |
| Region — no. (%) | | |
| Central Europe | 615 (61.1) | 618 (61.4) |
| United Kingdom and Ireland | 249 (24.8) | 250 (24.8) |
| Israel | 17 (1.7) | 17 (1.7) |
| India | 26 (2.6) | 29 (2.9) |
| Japan | 99 (9.8) | 93 (9.2) |
| Medical history — no. (%) | | |
| Ischemic stroke | 128 (12.7) | 140 (13.9) |
| Transient ischemic attack | 45 (4.5) | 51 (5.1) |
| Systemic embolism | 19 (1.9) | 31 (3.1) |
| Hypertension | 690 (68.6) | 673 (66.8) |
| Myocardial infarction | 80 (8.0) | 87 (8.6) |
| Diabetes | 185 (18.4) | 161 (16.0) |
| Median $CHA_2DS_2$-VASc score (IQR)† | 5 (4–6) | 5 (4–6) |
| Prestroke score on the modified Rankin scale — no./total no. (%)‡§ | | |
| 0–2 | 889/1005 (88.5) | 898/1006 (89.3) |
| 3–5 | 116/1006 (11.5) | 108/1007 (10.7) |
| Stroke severity according to infarct size — no. (%) | | |
| Minor | 378 (37.6) | 374 (37.1) |
| Moderate | 399 (39.7) | 397 (39.4) |
| Major | 229 (22.8) | 236 (23.4) |
| NIHSS score — median (IQR)§ | | |
| At admission¶ | 5 (2–12) | 5 (2–11) |
| At time of randomization | 3 (1–6) | 3 (1–6) |
| Initial treatment for stroke — no./total no. (%)¶ | | |
| Thrombolysis | 391/986 (39.7) | 377/987 (38.2) |
| Thrombectomy | 207/986 (21.0) | 232/987 (23.5) |

**A**

| Outcome within 30 Days | Early-Treatment Group (N=984) | Later-Treatment Group (N=991) | Adjusted Risk Difference (95% CI) |
|---|---|---|---|
| | *no. of events (%)* | | *percentage points* |
| Primary-outcome event | 29 (2.9) | 41 (4.1) | −1.18 (−2.84 to 0.47) |
| Major extracranial bleeding | 3 (0.3) | 5 (0.5) | −0.25 (−0.90 to 0.41) |
| Symptomatic intracranial hemorrhage | 2 (0.2) | 2 (0.2) | 0.01 (−0.52 to 0.53) |
| Recurrent ischemic stroke | 14 (1.4) | 25 (2.5) | −1.14 (−2.41 to 0.13) |
| Systemic embolism | 4 (0.4) | 9 (0.9) | −0.55 (−1.34 to 0.23) |
| Death from vascular cause | 11 (1.1) | 10 (1.0) | 0.13 (−0.84 to 1.09) |




**B**

| Outcome within 90 Days | Early-Treatment Group (N=968) | Later-Treatment Group (N=965) | Adjusted Risk Difference (95% CI) |
|---|---|---|---|
| | *no. of events (%)* | | *percentage points* |
| Primary-outcome event | 36 (3.7) | 54 (5.6) | −1.92 (−3.82 to −0.02) |
| Major extracranial bleeding | 3 (0.3) | 8 (0.8) | −0.61 (−1.37 to 0.14) |
| Symptomatic intracranial hemorrhage | 2 (0.2) | 2 (0.2) | 0.00 (−0.54 to 0.53) |
| Recurrent ischemic stroke | 18 (1.9) | 30 (3.1) | −1.29 (−2.72 to 0.13) |
| Systemic embolism | 4 (0.4) | 10 (1.0) | −0.70 (−1.53 to 0.13) |
| Death from vascular cause | 17 (1.8) | 16 (1.7) | 0.07 (−1.13 to 1.27) |

**Table 2. Primary and Secondary Efficacy Outcomes.**

| Outcome | Early-Treatment Group (N=1006) | Later-Treatment Group (N=1007) | Adjusted Odds Ratio (95% CI)* |
|---|---|---|---|
| | *no./total no. (%)* | | |
| **Primary outcome: composite outcome at 30 days** | 29/1006 (2.9)† | 41/1007 (4.1)† | 0.70 (0.44 to 1.14)‡ |
| **Secondary outcomes at 30 days** | | | |
| Major extracranial bleeding | 3/984 (0.3) | 5/991 (0.5) | 0.63 (0.15 to 2.38) |
| Symptomatic intracranial hemorrhage | 2/984 (0.2) | 2/991 (0.2) | 1.02 (0.16 to 6.59) |
| Recurrent ischemic stroke | 14/984 (1.4) | 25/991 (2.5) | 0.57 (0.29 to 1.07) |
| Systemic embolism | 4/984 (0.4) | 9/991 (0.9) | 0.48 (0.14 to 1.42) |
| Vascular death | 11/984 (1.1) | 10/991 (1.0) | 1.12 (0.47 to 2.65) |
| Nonmajor bleeding | 30/984 (3.0) | 27/991 (2.7) | 1.13 (0.67 to 1.93) |
| Modified Rankin scale score ≤2§ | 624/997 (62.6) | 626/1000 (62.6) | 0.93 (0.79 to 1.09) |
| **Secondary outcomes at 90 days** | | | |
| Major extracranial bleeding | 3/968 (0.3) | 8/965 (0.8) | 0.40 (0.10 to 1.31) |
| Symptomatic intracranial hemorrhage | 2/968 (0.2) | 2/965 (0.2) | 1.00 (0.15 to 6.45) |
| Recurrent ischemic stroke | 18/968 (1.9) | 30/965 (3.1) | 0.60 (0.33 to 1.06) |
| Systemic embolism | 4/968 (0.4) | 10/965 (1.0) | 0.42 (0.12 to 1.21) |
| Vascular death | 17/968 (1.8) | 16/965 (1.7) | 1.04 (0.52 to 2.08) |
| Death from any cause¶ | 45/994 (4.5) | 48/995 (4.8) | 0.93 (0.61 to 1.43) |
| Nonmajor bleeding | 39/968 (4.0) | 41/965 (4.2) | 0.94 (0.59 to 1.47) |
| Modified Rankin scale score ≤2§ | 659/989 (66.6) | 654/994 (65.8) | 0.93 (0.79 to 1.09) |
| Any serious adverse event‖ | 132/947 (13.9) | 157/993 (15.8) | |

# DISCUSSION:

- Current clinical practice is to delay the initiation of anticoagulation after ischemic stroke, as recommended in several guidelines that are based on expert consensus. For example, European guidelines suggest assessment of stroke severity with the use of the NIHSS score and delay of anticoagulation for 3 days after minor stroke, 6 days after moderate stroke, and 12 days after severe stroke on the basis of this score.


- American Heart Association–American Stroke Association guidelines recommend delaying anticoagulation beyond 14 days if there is a high risk of hemorrhagic transformation of an ischemic brain infarct and beginning anticoagulation between day 2 and day 14 if the risk of this complication is low. We studied initiation of DOACs within 48 hours after stroke onset in participants with minor or moderate stroke and on day 6 or 7 in those with major stroke.


- we chose to use an imaging-based definition of stroke severity .
- Our data suggest that the incidence of symptomatic intracranial hemorrhage is low with early anticoagulation if imaging-based classification is used.


- The limitations of our trial are the exclusion of persons who were already receiving therapeutic anticoagulation at baseline . The trial also has limited statistical power to explore subgroups, and therefore no conclusions can be drawn from these results. We do not have data on the ethnic group and race of the participants.


- The trial population was predominantly from European centers, which have a high proportion of White participants. Extrapolation of the results to other populations may not be possible. Finally, persons with parenchymal hemorrhage type 1 or 2 in the Heidelberg classification (hemorrhagic transformation within or within and beyond the region of the infarct) at the time of randomization were not included in this trial, so we cannot comment on the safety of early anticoagulation in this group.

# Early versus Later Anticoagulation for Stroke with Atrial Fibrillation

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## CLINICAL PROBLEM

In persons with atrial fibrillation who have had an acute ischemic stroke, the effect of early as compared with later initiation of direct oral anticoagulants (DOACs) is unclear. Early initiation may increase the risk of intracranial hemorrhage, whereas the risk of early stroke recurrence is a concern with later initiation.

## CLINICAL TRIAL

**Design:** An international, open-label, randomized trial examined the safety and efficacy of early initiation of DOACs as compared with later, guideline-based initiation in participants with atrial fibrillation and a recent stroke. The trial was designed to estimate outcomes with both approaches but not to test their relative superiority or inferiority. The assessors were unaware of the trial-group assignments.

**Intervention:** 2013 participants with atrial fibrillation and ischemic stroke confirmed by imaging were randomly assigned to early initiation of any approved DOAC (≤48 hours after stroke onset in participants with minor or moderate stroke or on day 6 or 7 in those with major stroke) or later initiation (on day 3 or 4 in participants with minor stroke, day 6 or 7 in those with moderate stroke, or day 12, 13, or 14 in those with major stroke). The primary outcome was a composite of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death ≤30 days after randomization.

## RESULTS

**Efficacy:** The incidence of a primary-outcome event was estimated to range from slightly lower to slightly higher (based on the 95% confidence interval) with early use of DOACs than with later use.

**Safety:** The incidence of adverse events was similar in the two groups.

## LIMITATIONS AND REMAINING QUESTIONS

- The trial excluded persons who were already receiving therapeutic anticoagulation at baseline.
- Classification of stroke severity was not centrally adjudicated.

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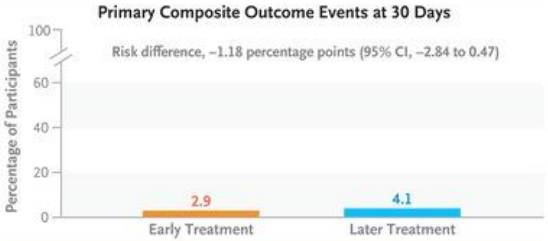
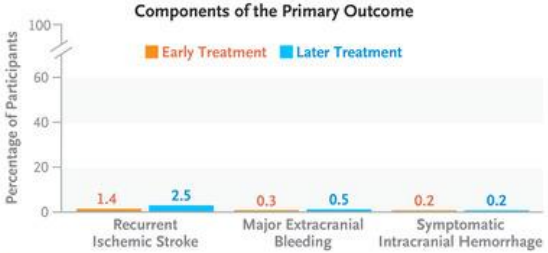
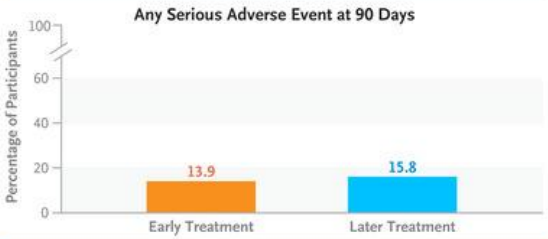



## CONCLUSIONS

In this trial, the incidence of recurrent ischemic stroke, systemic embolism, major extracranial bleeding, symptomatic intracranial hemorrhage, or vascular death at 30 days was estimated to range from 2.8 percentage points lower to 0.5 percentage points higher with early than with later use of DOACs.

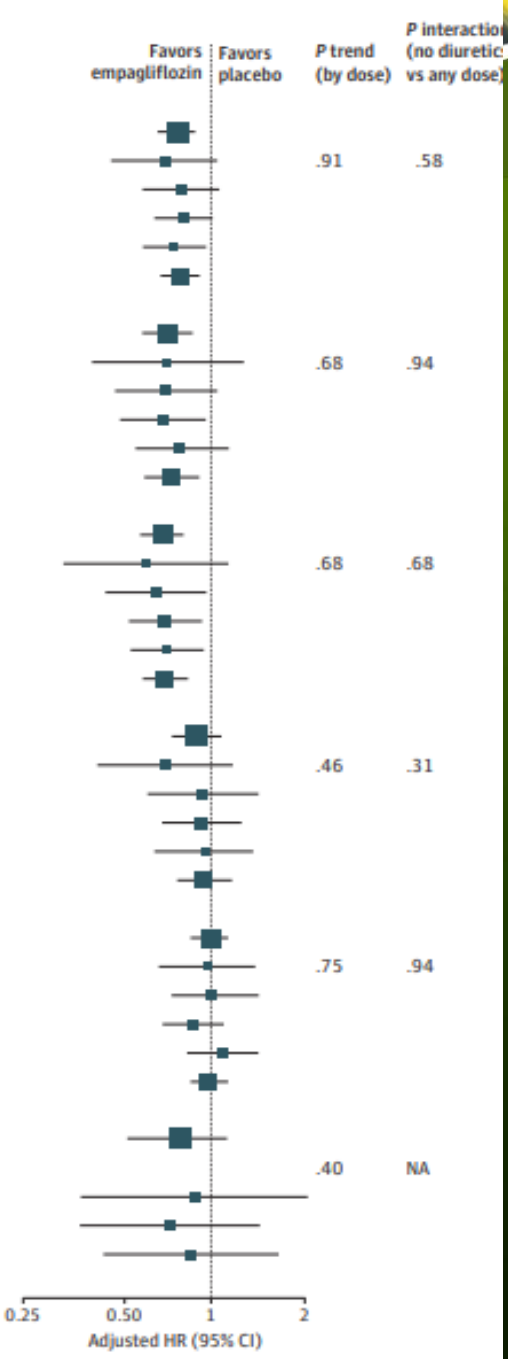

نتیجه گیری:

شروع زودرس آنتی کواگولان در این بیماران(AF+STROKE) خطر خونریزی را افزایش نمیدهد و یک درمان SAFE هست.

در طرف مقابل شروع زودرس آنتی کواگولان خطر استروک ایسکمیک مجدد را کاهش می دهد.

Figure 1. Comparison of Empagliflozin vs Placebo on Clinical Outcomes by Baseline Diuretic Use

| End point | Placebo No./total No. | Placebo Events/100 py | Empagliflozin No./total No. | Empagliflozin Events/100 py | Adjusted HR (95% CI) | *P* trend (by dose) | *P* interaction (no diuretic vs any dose) |
|---|---|---|---|---|---|---|---|
| CV death or first HHF | | | | | | | |
| All patients | 551/2991 | 8.7 | 415/2997 | 6.9 | 0.79 (0.69-0.90) | | |
| No diuretics | 60/589 | 5.0 | 42/590 | 3.5 | 0.72 (0.48-1.06) | .91 | .58 |
| <40 mg | 104/865 | 5.8 | 87/860 | 4.9 | 0.81 (0.61-1.08) | | |
| 40 mg | 179/889 | 10.5 | 152/883 | 8.6 | 0.82 (0.66-1.02) | | |
| >40 mg | 151/563 | 14.7 | 127/576 | 11.8 | 0.77 (0.61-0.98) | | |
| Any dose | 434/2317 | 9.6 | 366/2319 | 7.9 | 0.81 (0.70-0.93) | | |
| Total (first and recurrent) HHF | | | | | | | |
| All patients | 541 | NA | 407 | NA | 0.73 (0.61-0.88) | | |
| No diuretics | 41 | NA | 28 | NA | 0.73 (0.42-1.29) | .68 | .94 |
| <40 mg | 106 | NA | 76 | NA | 0.72 (0.50-1.05) | | |
| 40 mg | 189 | NA | 136 | NA | 0.71 (0.52-0.98) | | |
| >40 mg | 184 | NA | 163 | NA | 0.81 (0.58-1.15) | | |
| Any dose | 479 | NA | 375 | NA | 0.75 (0.62-0.92) | | |
| First HHF | | | | | | | |
| All patients | 352/2991 | 6.0 | 259/2997 | 4.3 | 0.71 (0.60-0.83) | | |
| No diuretics | 28/589 | 2.3 | 17/590 | 1.4 | 0.63 (0.34-1.15) | .68 | .68 |
| <40 mg | 70/865 | 3.9 | 50/860 | 2.8 | 0.68 (0.47-0.98) | | |
| 40 mg | 122/889 | 7.2 | 90/883 | 5.1 | 0.72 (0.55-0.94) | | |
| >40 mg | 122/563 | 11.9 | 98/576 | 9.1 | 0.73 (0.56-0.95) | | |
| Any dose | 314/2317 | 7.0 | 238/2319 | 5.1 | 0.72 (0.61-0.85) | | |
| CV death | | | | | | | |
| All patients | 244/2991 | 3.8 | 219/2997 | 3.4 | 0.91 (0.76-1.09) | | |
| No diuretics | 38/589 | 3.1 | 27/590 | 2.2 | 0.73 (0.44-1.19) | .46 | .31 |
| <40 mg | 49/865 | 2.6 | 45/860 | 2.4 | 0.95 (0.63-1.42) | | |
| 40 mg | 93/889 | 5.0 | 88/883 | 4.7 | 0.95 (0.71-1.27) | | |
| >40 mg | 57/563 | 4.8 | 56/576 | 4.7 | 0.96 (0.66-1.39) | | |
| Any dose | 199/2317 | 4.0 | 189/2319 | 3.8 | 0.95 (0.78-1.17) | | |
| All-cause mortality | | | | | | | |
| All patients | 427/2991 | 6.7 | 422/2997 | 6.6 | 1.00 (0.87-1.15) | | |
| No diuretics | 61/589 | 4.9 | 58/590 | 4.6 | 0.98 (0.69-1.41) | .75 | .94 |
| <40 mg | 92/865 | 4.8 | 92/860 | 4.9 | 1.03 (0.77-1.38) | | |
| 40 mg | 157/889 | 8.4 | 140/883 | 7.4 | 0.90 (0.71-1.12) | | |
| >40 mg | 109/563 | 9.2 | 123/576 | 10.3 | 1.10 (0.85-1.42) | | |
| Any dose | 358/2317 | 7.2 | 355/2319 | 7.2 | 1.00 (0.86-1.16) | | |
| Composite kidney end point | | | | | | | |
| All patients | 62/2991 | 1.2 | 50/2997 | 1.0 | 0.78 (0.54-1.13) | | |
| No diuretics | 9/589 | 0.9 | 3/590 | 0.3 | NA | .40 | NA |
| <40 mg | 11/865 | 0.7 | 11/860 | 0.7 | 0.90 (0.39-2.08) | | |
| 40 mg | 21/889 | 1.4 | 15/883 | 1.0 | 0.74 (0.38-1.45) | | |
| >40 mg | 19/563 | 2.0 | 19/576 | 2.0 | 0.87 (0.46-1.65) | | |
| Any dose | 51/2317 | 1.3 | 45/2319 | 1.1 | NA | | |




# Slide Title

**Product A**

- Feature 1
- Feature 2
- Feature 3

**Product B**

- Feature 1
- Feature 2
- Feature 3