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**Graham et al (Stroke, bleeding, and mortality risks in elderly Medicare beneficiaries treated with dabigatran or rivaroxaban for nonvalvular atrial fibrillation.**

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No head-to-head trials have compared the efficacy of novel oral anticoagulants in preventing ischemic stroke or thromboembolism in nonvalvular atrial fibrillation. Graham et al conducted a retrospective new-user cohort study of 118 891 individuals with nonvalvular atrial fibrillation who were  $\geq 65$  years of age, anticoagulant-naive, and enrolled in fee-for-service Medicare and who initiated treatment with rivaroxaban or dabigatran between 2011 and 2014. Primary outcomes were thromboembolic stroke, intracranial hemorrhage, major extracranial bleeding, and mortality. To adjust for potential confounding because of baseline imbalances in study covariates, they used inverse probability of treatment weighting based on the propensity score.

A total of 52 240 dabigatran-treated and 66 651 rivaroxaban-treated individuals (47% women), contributing 15 524 and 20 199 person-years of follow-up were included. Rivaroxaban use was associated with a reduction in thromboembolic stroke (hazard ratio [HR], 0.81; 95% confidence interval [CI], 0.65–1.01); an increase in the risk of intracranial hemorrhage (HR, 1.65; 95% CI, 1.20–2.26) and major extracranial bleeding (HR, 1.48; 95% CI, 1.32–1.67), including major gastrointestinal bleeding (HR, 1.40; 95% CI, 1.23–1.59); and an increase in mortality (HR, 1.15; 95% CI, 1.00–1.32). In patients aged  $\geq 75$  years or with CHADS<sub>2</sub> (congestive heart failure, hypertension, age 75 years or above, diabetes, prior stroke or transient ischemic attack or thromboembolism) score  $\geq 2$ , rivaroxaban was associated with increased mortality compared with dabigatran. Cumulative incidence graphs showed early separation of event rates with continued divergence throughout follow-up for intracranial hemorrhage, major gastrointestinal bleeding, and mortality but convergence of event rates for thromboembolic stroke after day 240.

This study provides useful information on outcomes in patients receiving dabigatran versus rivaroxaban for atrial fibrillation. The study had several limitations: it was a retrospective and observational study; therefore, there may have been confounding by unmeasured factors. Patient selection was biased toward healthier individuals because

those on dialysis or residing in skilled nursing facilities were excluded, and it excluded individuals who had previously taken anticoagulants or were  $\leq 65$  years of age, limiting generalizability. The mean duration of on-treatment follow-up was  $< 4$  months, thereby reducing sample size at longer durations of use. Long-term, prospective, randomized controlled trials of novel oral anticoagulants are needed to determine efficacy for stroke prevention in individuals with atrial fibrillation.

**Wang et al (Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA.* 2016;316:70–78. doi:10.1001/jama.2016.8662.)**

Clopidogrel is a prodrug requiring transformation into an active metabolite by hepatic cytochrome p450 (CYP) to exert its antiplatelet effects. CYP2C19 polymorphisms are predictors of clopidogrel nonresponsiveness; however, little is known about their effect on clopidogrel efficacy in stroke. Wang et al conducted a prespecified post hoc analysis of the CHANCE trial (Clopidogrel in High-Risk Patients with Acute Non-disabling Cerebrovascular Events) to explore the association between CYP2C19 genetic variants (\*2, \*3, \*17) and clinical outcomes of patients with acute minor stroke or transient ischemic attack treated with the combination of clopidogrel and aspirin compared with aspirin alone. Noncarriers were defined as patients with no CYP2C19 loss-of-function allele. The primary efficacy outcome was new stroke at 90 days. The secondary efficacy outcome was a composite of new composite vascular events (ischemic stroke, hemorrhagic stroke, myocardial infarction, or vascular death), and the safety outcome was any bleeding.

Among 2933 individuals, 66.4% were men, the mean age was 62.4 years, and 58.8% were carriers of loss-of-function alleles (\*2, \*3). Clopidogrel in combination with aspirin reduced the rate of new stroke in noncarriers but not in carriers of loss-of-function alleles (noncarrier: 6.7% with clopidogrel–aspirin versus 12.4% with aspirin alone; HR, 0.51 [95% CI, 0.35–0.75]; carrier: 9.4% with clopidogrel–aspirin versus 10.8% with aspirin alone; HR, 0.93 [95% CI, 0.69–1.26];  $P=0.02$  for interaction). Similar results were observed for the secondary outcome (noncarriers: 6.7% with clopidogrel–aspirin versus 12.5% with aspirin alone; HR, 0.50 [95% CI, 0.34–0.74]; carriers: 9.4% with

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clopidogrel–aspirin versus 10.9% with aspirin alone; HR, 0.92 [95% CI, 0.68–1.24];  $P=0.02$  for interaction). There was no difference in bleeding between carriers and noncarriers (2.3% for carriers and 2.5% for noncarriers in the clopidogrel–aspirin group versus 1.4% for carriers and 1.7% for noncarriers in the aspirin-alone group;  $P=0.78$  for interaction).

This study suggests that genetic testing may be useful in personalizing antiplatelet therapy in populations where prevalence of *CYP2C19* loss-of-function alleles is high. The study's strengths include its large sample size, prespecified analyses, genetic information collected on all

subjects enrolled at 73 sites, and presence of a randomized control group. The study is limited by generalizability (predominantly Asian population). Routine genotyping for *CYP2C19* to select clopidogrel responders may not be ready for prime time because of limited prospective data from randomized clinical trials, inadequate cost-effectiveness analyses, and lack of well-studied alternative antiplatelet agents. Furthermore, the effectiveness of clopidogrel in stroke treatment may be influenced by patient noncompliance, drug–drug interactions, and comorbidities. Nevertheless, this study provides useful information for designing future prospective randomized controlled trials that include alternative medications and broader populations.

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