Yeni kuşak antikoagülan ve antitrombositer ilaçlar, literatür ne diyor?

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Giriş-Atrial Fibrilasyon (AF) ve Akut koroner sendrom (AKS) da sekonder korunma

- Varfarin (VKA) gerek AF'li ve gerek ise AKS'li hastalarda iskemik olayları önlemede etkinliğinin kanıtlanmış olmasına rağmen kullanım zorlukları nedeniyle külfetlidir, bu durum yeni tedavi arayışlarını zorunlu kılmıştır

- Böylece, yeni kuşak oral antikoagülan (YKOA) ilaçlar geliştirilmiştir.

Cabral KP, Ansell J, Hylek EM. Future directions of stroke prevention in atrial fibrillation: the potential impact of novel anticoagulants and stroke risk stratification. J Thromb Haemost 2011;9:441–9.
Van Es RF, et al. Aspirin and coumadin after acute coronary syndromes (the ASPECT-2 study): a randomised controlled trial. Lancet 2002:360:109–113.
Hurlen M, et al. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med 2002;347:969–974.

YKOA'ların Avantajları

- Varfarine nispetle intrakraniyal kanama açısından daha güvenlidir.
- Tromboembolik olayları önleme açısından en az varfarin kadar etkin, bazıları da varfarinden daha etkindir.
- Koagülasyon takibi gerektirmemektedir.
- Hızlı etki başlangıcı
- Gıdalarla ve ilaçlarla etkileşimleri son derece azdır

Kullanıma Giren Yeni Nesil Oral Antikoagülanlar…

Koagülasyon yolundaki farklı faktörlere etki eden yeni kuşak oral antikoagülanlar

- Dabigatran (RE-LY) Direkt Trombin inhibitörü
- Rivaroxaban (ROCKET-AF) Direkt Faktör Xa inhibitörü
- Apixaban (ARISTOTLE) Direkt Faktör Xa inhibitörü
- Edoxaban (ENGAGE AF-TIMI 48) Direkt Faktör Xa inhibitörü

1 hayat kurtarmak için, NNT (kaç hasta tedavi edilmeli)?

Tablo 1. CHA2DS2-VASc.

Risk faktörü	Puan
C – Konjestif kalp yetmezliği	1 puan
H – Hipertansiyon	1 puan
A – Yaş ≥75	2 puan
D – Diabetes mellitus	1 puan
S – İnme/Transient iskemik atak/Tromboembolizm	2 puan
V – Vasküler hastalık (geçirilmiş myokard enfarktüsü, periferik arter hastalığı, veya aortik plak)	1 puan
A – Yaş 65-74 arası	1 puan
Sc – Cinsiyet kategorisi (kadın cinsiyet)	1 puan

CHA2DS2-VASc skoru 2-9 iken

- varfarinle 109 hasta,
- dabigatranla 78 hasta,
- rivaroksaban ile 88 hasta,
- apiksaban ile 87 hasta tedavi edilmeli

Farklı CHADS2 ve CHA2DS2-VASc skorlarında YOAK için 'number needed to treat' (NNT) değerleri

	Tedavisiz	Varfarin	NNT	Dabigatran 150	NNT	Rivaroksaban	NNT	Apiksaban	NNT
$CHADS_2$ skoru									
0	0.20	0.10	**1000**	0.06	**732**	0.08	**812**	0.08	**805**
1	1.00	0.50	**200**	0.33	**149**	0.44	**167**	0.40	**165**
2-6	3.01	1.65	**74**	1.09	**52**	1.45	**60**	1.30	**59**
CHA_2DS_2-VASc skoru									
0	0.07	0.04	**3333**	0.03	**2315**	0.04	**2665**	0.03	**2637**
1	0.10	0.05	**2000**	0.03	**1464**	0.04	**1623**	0.04	**1611**
2-9	2.00	1.08	**109**	0.71	**78**	0.95	**88**	0.85	**87**
Tüm	1.00	0.53	**213**	0.35	**154**	0.47	**174**	0.42	**172**

AF ile ilişkili İnme ve Sistemik Tromboemboli Klinik Çalışmalar…

Risk of Bleeding With 2 Doses of Dabigatran Compared With Warfarin in Older and Younger Patients With Atrial Fibrillation

An Analysis of the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) Trial

John W. Eikelboom, MBBS; Lars Wallentin, MD; Stuart J. Connolly, MD; Mike Ezekowitz, MD; Jeff S. Healey, MD; Jonas Oldgren, MD; Sean Yang, BComSc; Marco Alings, MD; Scott Kaatz, DO; Stefan H. Hohnloser, MD; Hans-Christoph Diener, MD; Maria Grazia Franzosi, PhD; Kurt Huber, MD; Paul Reilly, MD; Jeanne Varrone, MD; Salim Yusuf, MD

Background—Dabigatran 150 and 110 mg twice a day and warfarin are effective for stroke prevention in atrial fibrillation. The purpose of this study was to compare their risks of bleeding in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial.

Methods and Results—The RE-LY trial randomized 18 113 patients to receive dabigatran 110 or 150 mg twice a day or warfarin dose adjusted to an international normalized ratio of 2.0 to 3.0 for a median follow-up of 2.0 years. Compared with warfarin, dabigatran 110 mg twice a day was associated with a lower risk of major bleeding (2.87% versus 3.57%; $P=0.002$), whereas dabigatran 150 mg twice a day was associated with a similar risk of major bleeding (3.31% versus 3.57%; $P=0.32$). There was a significant treatment-by-age interaction, such that dabigatran 110 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in patients aged <75 years (1.89% versus 3.04%; $P<0.001$) and a similar risk in those aged ≥75 years (4.43% versus 4.37%; $P=0.89$; P for interaction <0.001), whereas dabigatran 150 mg twice a day compared with warfarin was associated with a lower risk of major bleeding in those aged <75 years (2.12% versus 3.04%; $P<0.001$) and a trend toward higher risk of major bleeding in those aged ≥75 years (5.10% versus 4.37%; $P=0.07$; P for interaction <0.001). The interaction with age was evident for extracranial bleeding, but not for intracranial bleeding, with the risk of the latter being consistently reduced with dabigatran compared with warfarin irrespective of age.

Conclusions—In patients with atrial fibrillation at risk for stroke, both doses of dabigatran compared with warfarin have lower risks of both intracranial and extracranial bleeding in patients aged <75 years. In those aged ≥75 years, intracranial bleeding risk is lower but extracranial bleeding risk is similar or higher with both doses of dabigatran compared with warfarin.

Clinical Trial Registration—http://www.clinicaltrials.gov. Unique identifier: NCT00262600. (***Circulation***. **2011;123:2363-2372.**)

Dabigatran Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY)

- *AF hastalarında **inme ve sistemik emboli** açısından **dabigatran ve warfarinin** etkinlik ve güvenliliklerinin kıyaslandığı prospektif ve randomize bir çalışmadır*
- *Dabigatran günde **2 kez 110 mg** veya **150 mg** dozunda verilmiş, warfarin dozu ise INR 2-3 arası tutulacak şekilde ayarlanmıştır*

Eikelboom JW, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363–72.

Dabigatran Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY)

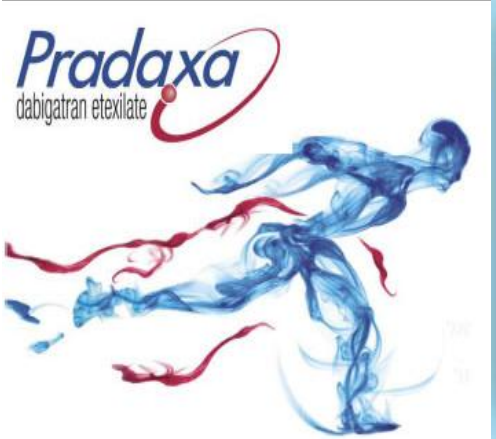
- *Çalışmaya **18,113 hasta** dahil edilerek 2 yıl boyunca takip edilmiştir*
- *Primer sonlanımlarda inme ve sistemik emboli açısından dabigatran **110 mg dozunun** (%1,54/yıl) warfarinden (%1,71/yıl) **non-inferior** olduğu, dabigatran **150 mg dozunun** (%1,11/yıl) ise warfarinden **daha üstün** olduğu bulunmuştur*

Eikelboom JW, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363–72.

Dabigatran Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY)

- ***Major ve ölümcül kanamalar açısından düşük doz dabigatran*** *warfarine göre* ***daha az riskli*** *iken* ***yüksek doz*** *dabigatran warfarinle* ***benzer riskli*** *saptanmıştır*
- ***İntrakraniyal kanamalar*** *ise* ***her iki dozda*** *da warfarinden* ***daha düşük*** *oranda gözlenmiştir*
- *Dabigatranda düşük dozda gözlenmeyen ancak* ***yüksek dozda*** *gözlenen bir yan etki ise warfarine kıyasla* ***artmış gastrointestinal kanamalardı***

Eikelboom JW, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011;123:2363–72.



- Dabigatran yüksek doz (2x150mg) FDA tarafından 2012'de AF hastalarında inme profilaksisinde onaylanmıştır, aynı zamanda kreatin klerensi 15-30mL/dk olan hastalarda 2x75mg kullanımı onaylanmıştır.

- ESC kılavuzlarında kanama riski düşük olan hastalarda (HAS-BLED skoru 0-2) 2x150mg/gün, kanama riski yüksek hastalarda (HAS-BLED skoru≥3) 2x110mg önerilmektedir

Recommendations	Class[a]	Level[b]	Ref[c]
Recommendations for prevention of thromboembolism in non-valvular AF—bleeding			
Assessment of the risk of bleeding is recommended when prescribing antithrombotic therapy (whether with VKA, NOAC, aspirin/clopidogrel, or aspirin).	I	A	25, 54, 59, 60
The HAS-BLED score should be considered as a calculation to assess bleeding risk, whereby a score ≥3 indicates 'high risk' and some caution and regular review is needed, following the initiation of antithrombotic therapy, whether with OAC or antiplatelet therapy (LoE = A). Correctable risk factors for bleeding [e.g. uncontrolled blood pressure, labile INRs if the patient was on a VKA, concomitant drugs (aspirin, NSAIDs, etc.), alcohol, etc.] should be addressed (LoE = B). Use of the HAS-BLED score should be used to identify modifiable bleeding risks that need to be addressed, but should not be used on its own to exclude patients from OAC therapy (LoE = B).	IIa	A B	25, 54, 60
The risk of major bleeding with antiplatelet therapy (with aspirin–clopidogrel combination therapy and – especially in the elderly – also with aspirin monotherapy) should be considered as being similar to OAC.	IIa	B	18, 21, 23, 24, 26, 35
Recommendations for prevention of thromboembolism in non-valvular AF—peri-cardioversion			
For patients with AF of ≥48 h duration, or when the duration of AF is unknown, OAC therapy (e.g. VKA with INR 2-3 or dabigatran) is recommended for ≥3 weeks prior to and for ≥4 weeks after cardioversion, regardless of the method (electrical or oral/i.v. pharmacological).	I	B	93
In patients with risk factors for stroke or AF recurrence, OAC therapy, whether with dose-adjusted VKA (INR 2-3) or a NOAC, should be continued lifelong irrespective of the apparent maintenance of sinus rhythm following cardioversion.	I	B	110

Thoracic S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology 2010;12(10):1360-420

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 8, 2011 VOL. 365 NO. 10

Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation

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ABSTRACT

BACKGROUND

The use of warfarin reduces the rate of ischemic stroke in patients with atrial fibrillation but requires frequent monitoring and dose adjustment. Rivaroxaban, an oral factor Xa inhibitor, may provide more consistent and predictable anticoagulation than warfarin.

METHODS

In a double-blind trial, we randomly assigned 14,264 patients with nonvalvular atrial fibrillation who were at increased risk for stroke to receive either rivaroxaban (at a daily dose of 20 mg) or dose-adjusted warfarin. The per-protocol, as-treated primary analysis was designed to determine whether rivaroxaban was noninferior to warfarin for the primary end point of stroke or systemic embolism.

RESULTS

In the primary analysis, the primary end point occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 in the warfarin group (2.2% per year) (hazard ratio in the rivaroxaban group, 0.79; 95% confidence interval [CI], 0.66 to 0.96; P<0.001 for noninferiority). In the intention-to-treat analysis, the primary end point occurred in 269 patients in the rivaroxaban group (2.1% per year) and in 306 patients in the warfarin group (2.4% per year) (hazard ratio, 0.88; 95% CI, 0.74 to 1.03; P<0.001 for noninferiority; P=0.12 for superiority). Major and nonmajor clinically relevant bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 in the warfarin group (14.5% per year) (hazard ratio, 1.03; 95% CI, 0.96 to 1.11; P=0.44), with significant reductions in intracranial hemorrhage (0.5% vs. 0.7%, P=0.02) and fatal bleeding (0.2% vs. 0.5%, P=0.003) in the rivaroxaban group.

CONCLUSIONS

In patients with atrial fibrillation, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism. There was no significant between-group difference in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. (Funded by Johnson & Johnson and Bayer; ROCKET AF ClinicalTrials.gov number, NCT00403767.)

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*A complete listing of the steering committee members and trial investigators in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) is provided in the Supplementary Appendix, available at NEJM.org.

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N Engl J Med 2011;365:883-91.

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)

- *AF hastalarında warfarin ile **Rivaroxaban** etkinlik ve güvenliliklerinin kıyaslandığı çift kör, randomize çok merkezli bir çalışmadır*
- *Çalışmaya CHADS2 skor ortalamaları **3,5** olan **14.264** hasta dahil edilmiş olup hastalar ortalama **590** gün boyunca izlenmiştir*

Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883– 891.

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)

- *Rivaroxaban grubunda hastalara günde tek doz **20 mg** veya **15 mg** (kreatin klerensi 30-49mL/dak olan hastalara);*
- *Warfarin grubuna INR 2-3 arası tutulacak şekilde warfarin verilmiştir; her iki gruba da körlüğü korumak amacıyla bir plasebo tablet de verilmiştir*

Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883– 891.

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)

- *Primer sonlanımda inme ve sistemik emboli açısından **rivaroxabanın (%1,7/yıl) warfarinden (%2,2/yıl) non-inferior** olduğu gösterilmişir, ancak üstünlük saptanmamıştır*

Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883– 891.

Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF)

- ***Majör kanamalar*** *açısından rivaroxaban ve warfarin grupları arasında* ***belirgin fark gözlenmemiş*** *(sırasıyla %3,6 ve %3,4; p=0,58),*
- *Gastrointestinal sistem kanamaları rivaroxaban grubunda (%3,2) warfarin grubuna (%2,2) kıyasla* ***daha sık*** *gelişmiştir (p<0,001)*
- ***İntrakraniyal ve ölümcül kanamalar*** *ise rivaroxaban ile anlamlı şekilde* ***daha az*** *sıklıkta ortaya çıkmıştır*

Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883– 891.

Xarelto
rivaroxaban tablets

- Rivaroxaban 2011'de FDA tarafından AF hastalarında inme profilaksisinde onaylanmıştır

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 15, 2011 VOL. 365 NO. 11

Apixaban versus Warfarin in Patients with Atrial Fibrillation

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ABSTRACT

BACKGROUND

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation but have several limitations. Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.

METHODS

In this randomized, double-blind trial, we compared apixaban (at a dose of 5 mg twice daily) with warfarin (target international normalized ratio, 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for noninferiority, with key secondary objectives of testing for superiority with respect to the primary outcome and to the rates of major bleeding and death from any cause.

RESULTS

The median duration of follow-up was 1.8 years. The rate of the primary outcome was 1.27% per year in the apixaban group, as compared with 1.60% per year in the warfarin group (hazard ratio with apixaban, 0.79; 95% confidence interval [CI], 0.66 to 0.95; P<0.001 for noninferiority; P=0.01 for superiority). The rate of major bleeding was 2.13% per year in the apixaban group, as compared with 3.09% per year in the warfarin group (hazard ratio, 0.69; 95% CI, 0.60 to 0.80; P<0.001), and the rates of death from any cause were 3.52% and 3.94%, respectively (hazard ratio, 0.89; 95% CI, 0.80 to 0.99; P=0.047). The rate of hemorrhagic stroke was 0.24% per year in the apixaban group, as compared with 0.47% per year in the warfarin group (hazard ratio, 0.51; 95% CI, 0.35 to 0.75; P<0.001), and the rate of ischemic or uncertain type of stroke was 0.97% per year in the apixaban group and 1.05% per year in the warfarin group (hazard ratio, 0.92; 95% CI, 0.74 to 1.13; P=0.42).

CONCLUSIONS

In patients with atrial fibrillation, apixaban was superior to warfarin in preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality. (Funded by Bristol-Myers Squibb and Pfizer; ARISTOTLE ClinicalTrials.gov number, NCT00412984.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Granger at the Duke Clinical Research Institute, Duke University Medical Center, DUMC Box 3850, Durham, NC 27715, or at christopher.granger@duke.edu.

*The members of the steering committee, as well as other committee members and investigators in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study, are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1107039) was published on August 28, 2011, and updated on August 30, 2011, at NEJM.org.

N Engl J Med 2011;365:981-92.

Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)

- *Apixaban'nın AF hastalarında warfarin ile kıyaslandığı ARISTOTLE çalışması; **18.201** hastanın dahil edildiği, ortalama CHADS2 skorları **2,1** olan hastaların ortalama **1,8 yıl** boyunca takip edildiği randomize, çift-kör bir çalışmadır*

Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.

Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)

- *İki gruba ayrılan hastalara **apixaban 2x5mg** veya INR 2-3 arası tutulacak şekilde doz ayarlı warfarin tedavisi verilmiştir*
- ***İnme ve sistemik emboliyi** içeren primer sonlanımlarda apixabanın **(%1,27/yıl)** warfarinden **(%1,60)** üstün olduğu bulunmuştur*

Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.

Apixaban for Reduction In Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE)

- ***Majör kanama*** *warfarin grubunda (%3,09/yıl), apixaban grubuna (%2,13/yıl) kıyasla* ***daha sık gelişmiştir***
- *Ayrıca apixaban* ***daha az intrakraniyal kanamaya ve mortaliteye*** *neden olmuştur*

Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.

- Apixaban 2012'de FDA tarafından AF hastalarında inme profilaksisinde onaylanmıştır

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Edoxaban versus Warfarin in Patients with Atrial Fibrillation

Robert P. Giugliano, M.D., Christian T. Ruff, M.D., M.P.H., Eugene Braunwald, M.D., Sabina A. Murphy, M.P.H., Stephen D. Wiviott, M.D., Jonathan L. Halperin, M.D., Albert L. Waldo, M.D., Michael D. Ezekowitz, M.D., D.Phil., Jeffrey I. Weitz, M.D., Jindřich Špinar, M.D., Witold Ruzyllo, M.D., Mikhail Ruda, M.D., Yukihiro Koretsune, M.D., Joshua Betcher, Ph.D., Minggao Shi, Ph.D., Laura T. Grip, A.B., Shirali P. Patel, B.S., Indravadan Patel, M.D., James J. Hanyok, Pharm.D., Michele Mercuri, M.D., and Elliott M. Antman, M.D., for the ENGAGE AF-TIMI 48 Investigators*

ABSTRACT

BACKGROUND

Edoxaban is a direct oral factor Xa inhibitor with proven antithrombotic effects. The long-term efficacy and safety of edoxaban as compared with warfarin in patients with atrial fibrillation is not known.

METHODS

We conducted a randomized, double-blind, double-dummy trial comparing two once-daily regimens of edoxaban with warfarin in 21,105 patients with moderate-to-high-risk atrial fibrillation (median follow-up, 2.8 years). The primary efficacy end point was stroke or systemic embolism. Each edoxaban regimen was tested for noninferiority to warfarin during the treatment period. The principal safety end point was major bleeding.

RESULTS

The annualized rate of the primary end point during treatment was 1.50% with warfarin (median time in the therapeutic range, 68.4%), as compared with 1.18% with high-dose edoxaban (hazard ratio, 0.79; 97.5% confidence interval [CI], 0.63 to 0.99; P<0.001 for noninferiority) and 1.61% with low-dose edoxaban (hazard ratio, 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiority). In the intention-to-treat analysis, there was a trend favoring high-dose edoxaban versus warfarin (hazard ratio, 0.87; 97.5% CI, 0.73 to 1.04; P=0.08) and an unfavorable trend with low-dose edoxaban versus warfarin (hazard ratio, 1.13; 97.5% CI, 0.96 to 1.34; P=0.10). The annualized rate of major bleeding was 3.43% with warfarin versus 2.75% with high-dose edoxaban (hazard ratio, 0.80; 95% CI, 0.71 to 0.91; P<0.001) and 1.61% with low-dose edoxaban (hazard ratio, 0.47; 95% CI, 0.41 to 0.55; P<0.001). The corresponding annualized rates of death from cardiovascular causes were 3.17% versus 2.74% (hazard ratio, 0.86; 95% CI, 0.77 to 0.97; P=0.01), and 2.71% (hazard ratio, 0.85; 95% CI, 0.76 to 0.96; P=0.008), and the corresponding rates of the key secondary end point (a composite of stroke, systemic embolism, or death from cardiovascular causes) were 4.43% versus 3.85% (hazard ratio, 0.87; 95% CI, 0.78 to 0.96; P=0.005), and 4.23% (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; P=0.32).

CONCLUSIONS

Both once-daily regimens of edoxaban were noninferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding and death from cardiovascular causes. (Funded by Daiichi Sankyo Pharma Development; ENGAGE AF-TIMI 48 ClinicalTrials.gov number, NCT00781391.)

From Brigha and Harvard (R.P.G., C.T.R., E.M.A.); Mo New York (J. Case Medical Thomas Jeffe delphia (M.D Hamilton, ON Hospital, Jihl (J.S.); Institu Poland (W.R.); Cardiology Research Center, Moscow (M.R.); National Hospital Organization, Osaka National Hospital, Osaka, Japan (Y.K.); Quintiles, Durham, NC (J.B., S.P.P.); and Daiichi Sankyo Pharma Development, Edison, NJ (M.S., I.P., J.J.H., M.M.). Address reprint requests to Dr. Giugliano at the Division of Cardiovascular Medicine, Brigham and Women's Hospital, TIMI Study Group, 350 Longwood Ave., 1st Flr., Boston, MA 02115, or at rgiugliano@partners.org.

Drs. Giugliano and Ruff contributed equally to this article.

*Members of the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) team are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on November 10, 2013, at NEJM.org.

N Engl J Med 2013;369:2093-104.
DOI: 10.1056/NEJMoa1310907

ENGAGE AF-TIMI 48 klinik çalışması 46 ülke 1.393 merkez ve 21.105 hasta ile bugüne kadar bu endikasyon alanında gerçekleştirilmiş en büyük klinik çalışma olarak kabul edilmektedir

Edoxaban once daily to prevent stroke or systemic embolism (ENGAGE AF-TIMI 48)

- *AF hastalarında warfarin ile Edoxaban etkinlik ve güvenliliklerinin kıyaslandığı çift kör, randomize çok merkezli bir çalışmadır*
- *Çalışmaya CHADS2 skor ortalamalarına göre **orta-yüksek riskli** olan **21,105** hasta dahil edilmiş olup hastalar ortalama **2,8 yıl** boyunca izlenmiştir*

Giugliano RP, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093–104.

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Giugliano RP, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093–104.

Edoxaban once daily to prevent stroke or systemic embolism (ENGAGE AF-TIMI 48)

- *Edoxaban grubunda hastalara **günde tek doz 30 mg (düşük doz) veya 60 mg (yüksek doz);** warfarin grubuna INR 2-3 arası tutulacak şekilde warfarin verilmiştir*
- *Primer sonlanımda **inme ve sistemik emboli** açısından her iki dozda Edoxabanın (%1,18/yıl, %1,61/yıl) warfarinden (%1,50/yıl, %1,61/yıl) **non-inferior** olduğu gösterilmiştir*

Giugliano RP, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093–104.

Edoxaban once daily to prevent stroke or systemic embolism (ENGAGE AF-TIMI 48)

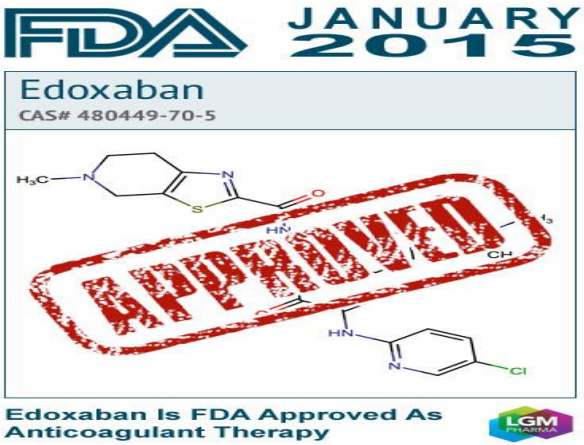
- ***Majör kanamalar*** *açısından* ***her iki doz*** *Edoxaban ve warfarin grupları arasında* ***belirgin fark gözlenmiş*** *(sırasıyla %2,75, %1,61 ve %3,43; her ikisi için p<0.001),*
- *Yıllık* ***kardiyovasküler nedenlerden ölüm oranları*** *açısından Edoxaban ve warfarin grupları arasında* ***belirgin fark gözlenmiş*** *(sırasıyla %2,74 ve %3,17; p=0,01),*

Giugliano RP, et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369:2093–104.

Daiichi-Sankyo

Savaysa
Edoxaban 30mg , 60mg
Film Coated Tablet

- Edoxaban FDA tarafından AF hastalarında inme profilaksisinde kullanılmak üzere onay almıştır



Thrombosis Research 135 (2015) 1117–1123

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Safety of the direct-acting anticoagulants in patients with atrial fibrillation: a meta-analysis

Fen Rong [a,*], Bin Jia [b], Pinxian Huang [a], Henry S. Lynn [b], Wei Zhang [b]

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Thrombosis Research

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Regular Article

Safety of the direct-acting anticoagulants in patients with atrial fibrillation: a meta-analysis

Fen Rong [a,*], Bin Jia [b], Pinxian Huang [a], Henry S. Lynn [b], Wei [et al]

Yeni oral antikoagülanların hepsi vitamin K antagonistlerine kıyasla non-inferiorite göstermiştir

Tüm yeni nesil oral antikoagülanlar hemorajik inme ve intrakraniyel kanama riskinde anlamlı bir azalmaya yol açmış, majör kanama riskinde varfarine kıyasla belirgin artışa yol açmamışlardır

Article history:
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Available online 11 April 2015

Keywords:
DOACs
Warfarin
Safety
Meta analysis

Introduction: Atrial fibrillation (AF) is known as one of the independent risk factors for stroke and might significantly increase its risk. Nowadays, direct-acting oral anticoagulants (DOACs) have been developed and demonstrated a more promising option to warfarin, the conclusion for safety is heterogeneous in different studies. It indicates the importance of comprehensive comparison of safety between DOACs and warfarin.
Material and Methods: Four studies including ARISTOTLE, ENGAGE AF-TIMI 48, RE-LY and ROCKET-AF were included in the meta-analysis to perform separate meta-analyses for high-dose regimen, low-dose regimen and their combination. The events included major bleeding, intracranial haemorrhage, gastrointestinal bleeding, non-major clinically relevant and minor bleeding.
Results: Regardless of high dose or low dose regimen, DOACs were associated with lower risk of intracranial haemorrhage but due to no significant association for gastrointestinal bleeding, the overall effect measured by the major bleeding was also insignificant (High dose: RR = 0.86, 95% CI 0.73 to 1.01; Low dose: RR = 0.63, 95% CI 0.38 to 1.04). However, the combined result of high-dose and low-dose regimens showed DOACs were associated with lower risk of major bleeding events (RR = 0.77, 95% CI 0.63 to 0.95).
Conclusions: Meta-analyses have showed the comparative safety of the direct-acting oral anticoagulants than warfarin in most endpoints and even better in intracranial haemorrhage. Therefore, without the need of INR monitoring, DOACs demonstrated promising alternatives to warfarin in prevention of stroke in patients with AF.

YKOA'ların Klinik Kullanım Alanları

- AF ile ilişkili İnmeden korunmda
- DVT ile ilişkili VTE önlenmesi
- PE tedavisi
- AKS de sekonder korunma

Hangi Hastaya, Ne Zaman?

Varfarin kullanan bir non-valvüler AF hastasında

- İstenen antikoagülasyon seviyesini (INR 2-3) elde etmek mümkün olamıyorsa (TTR < %60 ise), labil INR yada INR kontrolü kötü
- INR takibi çeşitli nedenlerden dolayı düzenli yapılamıyorsa,
- Varfarine bağlı yan etkiler meydana gelmişse,
- Varfarin kullanmakta iken tromboembolik bir olay yaşanmışsa

YOAK lar düşünülmelidir

Akılda Tutulması Gerekenler…

- **Böbrek fonksiyon testi bozukluğu** yine warfarin tedavisini ön plana çıkarmak için bir neden (**Kreatin klirensi≤15 ml/dk** olan hastalarda bu ajanlar kullanılmamalı)
- Atriyal fibrilasyon dışında bir antikoagülasyon nedeni varlığında (örneğin protez kapak, hiperkoagülabilite, vs.) yeni nesil antikoagülan kullanımı şu aşamada kontrendikedir

YOAK'ların kullanımı sırasında kanama yönetimi

- Antidot ilaç bulunmamaktadır!!! **(uygun doz seçimi)**
- ***TDP etkisiz*** (ortamda faktör eksikliği olmaması, trombin veya faktör Xa inhibitörü varlığı)
- Dabigatran kanamalarında kryopresipitat, apiksaban ve rivaroksaban kanamalarında ise protrombin konsantreleri???
- **Aktif kömür kullanımı** ve takiben **hemodiyaliz (Dabigatran için)**

CTran H, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J. 2014;44:525-36.

YOAK'ların kullanımı sırasında kanama yönetimi

ESC önerileri:

İlk olarak hemodinamik durumu kontrol et, böbrek fonksiyon testleleri ile bazal koagülasyon testlerini iste	
Minör kanama	Bir sonraki dozu atla ya da tedaviye ara ver
Orta – ciddi kanama	Destekleyici/semptomatik tedavi başla, mekanik kompresyon uygula, sıvı replasmanı ve kan transfüzyonu sağla, eğer dabigatran dozu yeni alınmış ise aktif kömür kullanımı açısından değerlendir.
Çok ciddi kanama	Aktive rekombinan FVII veya protrombin konsantresi başla. Dabigatran kullanan hastalarda aktif kömür ve hemodiyaliz uygula.

CTran H, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. Intern Med J. 2014;44:525-36.

Reversal of Other Blood Thinners

NOAC	Direct Thrombin Inhibitor	Factor Xa inhibitor		
	Dabigatran (Pradaxa®)	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Edoxaban (Lixiana®)
Dialysis Removable	✓	✗	✗	✗
Specific Antidote	Idarucizumab	Andexanet alpha		

- Idarucizumab & andexanet alpha have been granted breakthrough therapy designation by US FDA.

Praxbind® (idarucizumab) ile kanama yönetimi

- For emergency surgery/urgent procedures
- In life-threatening or uncontrolled bleeding
- Dabigatran treatment can be initiated 24 hours after administration of PRAXBIND
- The recommended dose of PRAXBIND is 5 g, provided as two separate vials each containing 2.5 g/50 mL vial idarucizumab

Oral Antiplatelet (Antiagregan, Antitrombositer) İlaçlar

- Klopidogrel

- Prasugrel (TRITON-TIMI 38)

- Tikagrelor (PLATO)

Akut koroner sendrom tedavisinde oral antitrombosit tedavi

Akut koroner sendromların tedavisinde (AKS) Aspirin ve Klopidogrelden oluşan dual antiplatelet tedavi **(optimal platelet inhibisyonu!)** yıllardır kabul görmüş bir tedavi modalitesidir.

Akut koroner sendrom tedavisinde oral antitrombosit tedavi

- Prasugrel ve Tikagrelor **EMA** (Avrupa) ve **FDA**'dan (Amerika) kısa sürede ilaç ruhsatlarına onay almış ve nispeten hızlı bir şekilde **ESC** ve **AHA** kılavuzlarına AKS tedavisinde **Sınıf I** endikasyonla girmiştir

Akut koroner Sendromda Yeni Oral Antiplateletler Klinik Karşılaştırmalı Çalışmalar…

TRITON-TIMI 38
Faz III Çalışma Tasarımı

AKS (UA/NSTEMI veya STEMI) ve planlanmış PKG
N=13,608

↓

Randomize
Çift kör

↙ ↘

Prasugrel	Klopidogrel
60-mg LD/10-mg MD	300-mg LD/75-mg MD
+ ASA	+ ASA

Ortalama takip süresi= 14.5 ay

- Primer etkinlik sonlanım noktası:
  - –KV ölüm, ölümcül olmayan MI veya inme
- Güvenlilik sonlanım noktaları:
  - –TIMI major veya minor kanama

Wiviott et al. *N Engl J Med*. 2007;357:2001-2015.

TRITON-TIMI 38: Hasta alım şeması

Koroner anatomi görülmeden yükleme yapılmıştır

UA/NSTEMI semptom başlangıcı sonrası

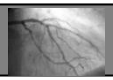
≤72 saat ve TRS ≥3

STEMI semptom başlangıcından 12 saat - 14 gün sonra (Post-STEMI)

STEMI semptom başlangıcı sonrası ≤12saat

(Primer PKG)

Diyagnostik Kateterizasyon



PKG planı

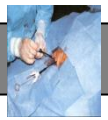
Medikal tedavi veya CABG planı

Randomize etme

Randomizasyon

Çalışma İlacı Yükleme Dozu

PKG*



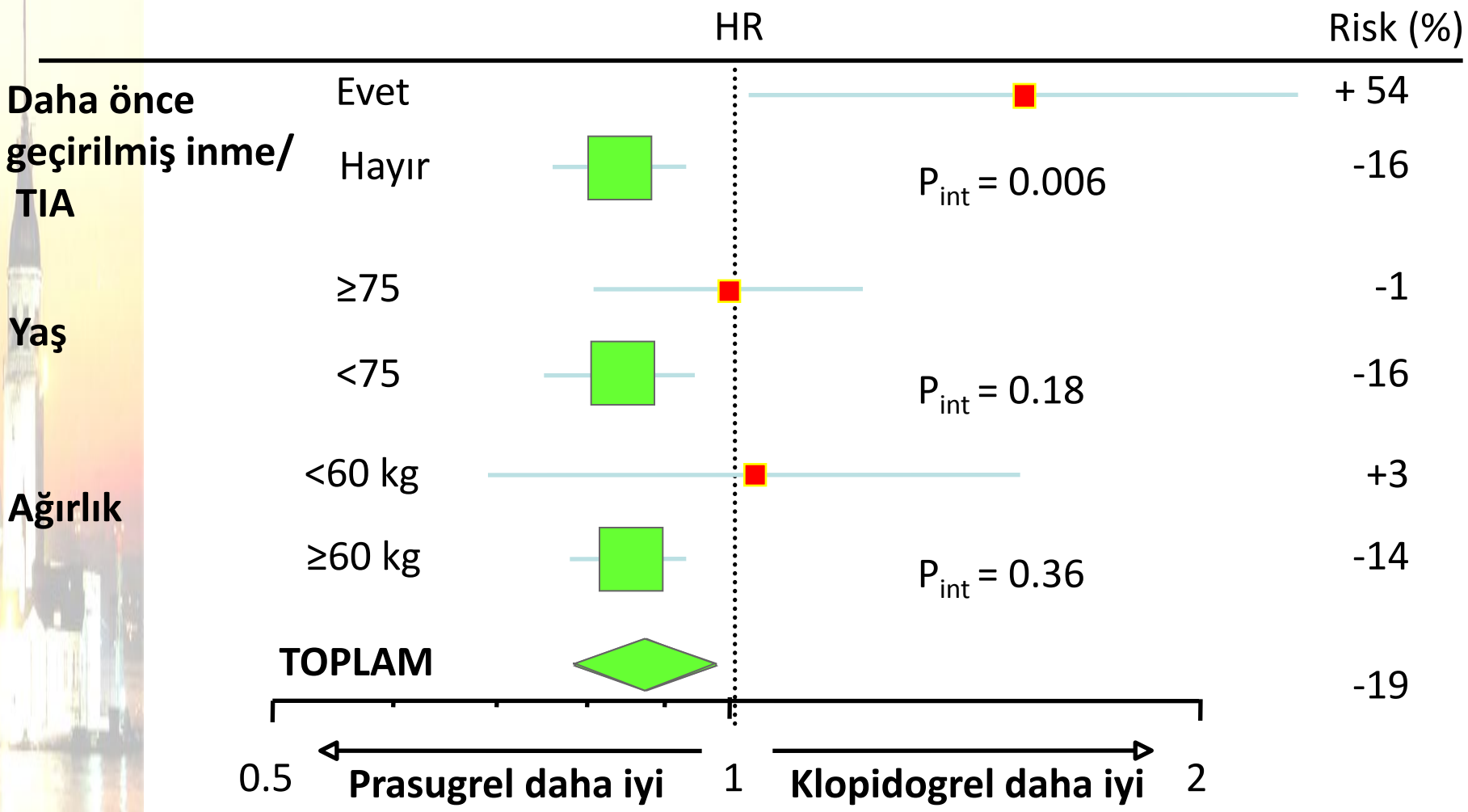
* Eşlik eden tedavi ve cihaz seçimi hekim insiyatifinde

Günlük İdame Tedavisi & Uzun Dönem Takip

Wiviott SD et al. *Am Heart J* 2006;152:627-635

TRITON-TIMI 38

Net klinik yarar alt grup analizi

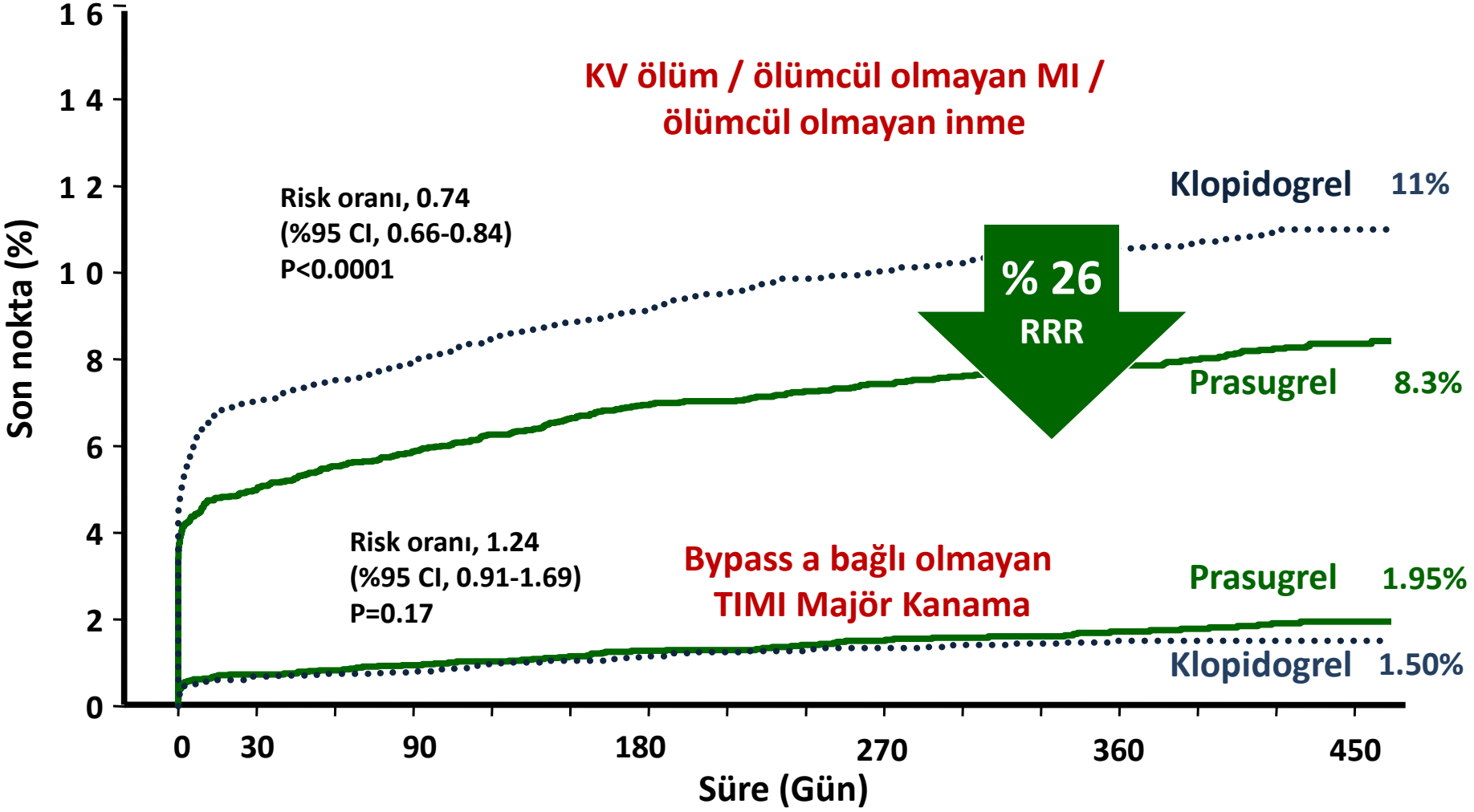


Wiviott SD et al. Am J Cardiol 2011;108(7):905-11

TRITON-TIMI 38

<75 Yaş, ≥60 kg ve inme/GİA öyküsü olmayan hastalarda

Primer sonlanım noktasında %26 azalma



Wiviott SD et al. Am J Cardiol 2011;108(7):905-11

CMRO

Current Medical Research & Opinion 2014, 1–13

0300-7995

doi:10.1185/03007995.2014.944638

Article ST-0131.R1/944638

Original article

An analysis of TRITON-TIMI 38, based on the 12 month recommended length of therapy in the European label for prasugrel

TIRITON-TIMI 38 calısmasının Avrupa kullanım onay onerılerıne gore analızı

- **Prasugrel kullanım süresi için öneri 12 aydır**

  Prasugrel'den fayda görmeyen 3 subgrup

- **1.** Transiyent iskemik atak (TİA) ve inme geçirme öyküsü olanlarda net klinik zarar oldugu görülmüş
- **2.** 75 yaş ve üstü hastalarda net klınık yararsızlık(Avrupada kullanım onayı incelendığinde 1&5 mg)
-
- **3.** 60 kg altında da net klinik yararsızlık (Avrupada kullanım onayı incelendiğinde 1&5 mg)

CRUSH Çalışması: Prasugrel ezilerek kullanıldığında daha hızlı antitrombosit etki sağlar

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http://dx.doi.org/10.1016/j.jacc.2016.02.045

Crushed Prasugrel Tablets in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention

The CRUSH Study

Fabiana Rollini, MD, Francesco Franchi, MD, Jenny Hu, MD, Megha Kureti, MD, Niti Aggarwal, MD, Ashwin Durairaj, MD, Yongwhi Park, MD, Michael Seawell, MD, Pedro Cox-Alomar, MD, Martin M. Zenni, MD, Luis A. Guzman, MD, Siva Suryadevara, MD, Patrick Antoun, MD, Theodore A. Bass, MD, Dominick J. Angiolillo, MD, PhD

RESULTS Compared with whole tablets, crushed prasugrel led to reduced $P2Y_{12}$ reaction units by 30 min post-LD, which persisted at 1, 2 (164 vs. 95; least square mean difference = 68; 95% confidence interval: 10 to 126; primary endpoint), and 4 h post-LD. Significant differences were no longer present at 6 h post-LD. Parallel findings were shown with platelet reactivity index. Accordingly, high on-treatment platelet reactivity rates were reduced with crushed prasugrel. PK analyses showed a >3-fold faster absorption with crushed compared with whole prasugrel.

CONCLUSIONS In STEMI patients undergoing PPCI, crushed prasugrel leads to faster drug absorption, and consequently, more prompt and potent antiplatelet effects compared with whole tablet ingestion. (Pharmacological Effects of Crushing Prasugrel in STEMI Patients; NCT02212028) (J Am Coll Cardiol 2016;■:■–■) © 2016 by the American College of Cardiology Foundation.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 10, 2009 VOL. 361 NO. 11

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators*

ABSTRACT

BACKGROUND

Ticagrelor is an oral, reversible, direct-acting inhibitor of the adenosine diphosphate receptor P2Y12 that has a more rapid onset and more pronounced platelet inhibition than clopidogrel.

METHODS

In this multicenter, double-blind, randomized trial, we compared ticagrelor (180-mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300-to-600-mg loading dose, 75 mg daily thereafter) for the prevention of cardiovascular events in 18,624 patients admitted to the hospital with an acute coronary syndrome, with or without ST-segment elevation.

RESULTS

At 12 months, the primary end point — a composite of death from vascular causes, myocardial infarction, or stroke — had occurred in 9.8% of patients receiving ticagrelor as compared with 11.7% of those receiving clopidogrel (hazard ratio, 0.84; 95% confidence interval [CI], 0.77 to 0.92; P<0.001). Predefined hierarchical testing of secondary end points showed significant differences in the rates of other composite end points, as well as myocardial infarction alone (5.8% in the ticagrelor group vs. 6.9% in the clopidogrel group, P=0.005) and death from vascular causes (4.0% vs. 5.1%, P=0.001) but not stroke alone (1.5% vs. 1.3%, P=0.22). The rate of death from any cause was also reduced with ticagrelor (4.5% vs. 5.9% with clopidogrel; P<0.001). No significant difference in the rates of major bleeding was found between the ticagrelor and clopidogrel groups (11.6% and 11.2%, respectively; P=0.43), but ticagrelor was associated with a higher rate of major bleeding not related to coronary-artery bypass grafting (4.5% vs. 3.8%, P=0.03), including more instances of fatal intracranial bleeding and fewer of fatal bleeding of other types.

CONCLUSIONS

In patients who have an acute coronary syndrome with or without ST-segment elevation, treatment with ticagrelor as compared with clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke without an increase in the rate of overall major bleeding but with an increase in the rate of non-procedure-related bleeding. (ClinicalTrials.gov number, NCT00391872.)

From the Uppsala Clinical Research Center, Uppsala, Sweden (L.W., C.H., S.J.); Duke Clinical Research Institute, Durham, NC (R.C.B., K.W.M., R.A.H.); Grochowski Hospital, Warsaw, Poland (A.B.); Thrombolysis in Myocardial Infarction Study Group, Brigham and Women's Hospital, Boston (C.P.C., B.M.S.); AstraZeneca Research and Development, Mölndal, Sweden (H.E.), and Wilmington, DE (J.H.); Århus University Hospital, Århus, Denmark (S.H.); Universitätsklinikum Heidelberg, Heidelberg, Germany (H.K.); Bristol-Myers Squibb Clinical Trials U.K., Nottingham, United Kingdom (A.S.); INSERM Unité 698, Assistance Publique–Hôpitaux de Paris and Université Paris 7, Paris (P.G.S.); and the University of Sheffield, Sheffield, United Kingdom (R.F.S.). Address reprint requests to Dr. Wallentin at Uppsala Clinical Research Center, University Hospital, 75185 Uppsala, Sweden, or at lars.wallentin@ucr.uu.se.

*The Study of Platelet Inhibition and Patient Outcomes (PLATO) investigators are listed in the Appendix and the Supplementary Appendix, available with the full text of this article at NEJM.org.

This article (10.1056/NEJMoa0904327) was published on August 30, 2009, at NEJM.org.

N Engl J Med 2009;361:1045-57.

PLATO'dur (Platelet Inhibition and Patient Outcomes)

- Bu çalışmada ST segmenti yükselmesi olan veya ST segmenti yükselmesi olmadan AKS ile hastaneye başvuran **18.624** hastada kardiyovasküler olayların önlenmesinde **Tikagrelor** (*180-mg yükleme dozu, ondan sonra günde iki defa 90 mg) ile;*
- ***Klopidogrel*** *(300 - 600 mg yükleme dozu, bundan sonra günde bir kere 75 mg) karşılaştırılmış*

PLATO'dur (Platelet Inhibition and Patient Outcomes)

- 12. ayda, primer sonlanım noktaları; Kardiyovasküler ölüm, miyokardiyal enfarktüs veya inme
- **Tikagrelor** alan hastaların %9,8'inde görülürken klopidogrel alan hastaların %11,7'sinde görülmüştür (P<0,001).
- **Tikagrelor ve Klopidogrel** grupları arasında majör kanama oranları arasında anlamlı fark saptanmadı (sırasıyla %11,6 - %11,2)

STEMİ'de Oral antiplatelet tedavi önerileri (Klavuzlar)

AHA 2013 STEMİ Klavuzu

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association.

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction : A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

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Mümkün olduğunca erken veya PKG sırasında

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg load before procedure	I	B
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A
• 81 mg daily is the preferred maintenance dose*	IIa	B
$P2Y_{12}$ inhibitors		
Loading doses		
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B
Maintenance doses and duration of therapy		
DES placed: Continue therapy for 1 y with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
BMS† placed: Continue therapy for 1 y with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
DES placed:		
• Clopidogrel, prasugrel, or ticagrelor* continued beyond 1 y	IIb	C
• Patients with STEMI with prior stroke or TIA: prasugrel	III: Harm	B

AHA/ACC STEMi Kılavuzu, 2013

ESC 2014 Miyokardiyal Revaskülarizasyon Kılavuzu

European Heart Journal Advance Access published August 29, 2014

European Heart Journal
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ESC/EACTS GUIDELINES

2014 ESC/EACTS Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

ESC 2014 STEMİ Kılavuzu

Recommendations for antithrombotic treatment in patients with STEMI undergoing primary PCI

Recommendations	Class[a]	Level[b]
Antiplatelet therapy		
ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:	I	A
• Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication	I	B
• Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication	I	B
• Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
It is recommended to give $P2Y_{12}$ inhibitors at the time of first medical contact.	I	B

P2Y12 inhibitörleri ilk tıbbi temasta önerilir

Kararsız AP/NSTEMİ de Oral antiplatelet tedavi önerileri (Klavuzlar)

2016 ACC/AHA Amerikan Kılavuzu

2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

Developed in Collaboration with American Association for Thoracic Surgery, American Society of Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons

Endorsed by Preventive Cardiovascular Nurses Association and Society for Vascular Surgery

2016 Amerikan Kılavuzunda: 12 ay süre ile Klopidogrelden öncelikli olarak Tikagerelor ya da Prasugrel önerilir

PKG ile tedavi edilen AKS Hastalarında , P2Y12 tedavisi (Clopidogrel, Prasugrel, ya da Ticagrelor) en az 12 ay verilmelidir

COR		
I	B-R	or DES implantation, $P2Y_{12}$ inhibitor therapy (clopidogrel, prasugrel, or ticagrelor) should be given for at least 12 months.
I	B-NR	In patients treated with DAPT, the recommended daily dose of aspirin is 81 mg (range, 75 mg to 100 mg).
IIa		AKS hastalarında (NSTE-AKS veya STEMI) koroner stent implantasyonu yapıldıktan sonra DAPT ile tedavi edien hastalarda ve NSTE-AKS hastalarında sadece MEDİKAL tedavi ile (revasc. Yok) tedavi edilen hastalarda, P2Y12 inhibitörü tedavisi olarak klopidogrel yerine TİKAGRELOR tercih edilmesi makuldür.
IIa		AKS hastalarında (NSTE-AKS veya STEMI) koroner stent implantasyonu yapıldıktan sonra DAPT ile tedavi edilen hastalarda, yüksek kanama riski yoksa ve İnme/TIA öyküsü yoksa, P2Y12 inhibitörü tedavisi olarak klopidogrel yerine PRASUGREL tercih edilmesi makuldür.

B-R: Bir veya daha fazla randomize çalışma; B-NR: Bir veya daha fazla non-randomize çalışma

TEŞEKKÜRLER..