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Acil Tıp Uzmanları Derneği

Akut Koroner Sendrom'da Yeni Nesil Antikoagülanlar

Dr. Özgür SÖĞÜT

Haseki Eğitim ve Araştırma Hastanesi,
Acil Tıp Kliniği, İSTANBUL

Sunu Planı

- *AKS de sekonder korunma*
- *Yeni Nesil Antikoagulanlar*
- *7 adet Ana CÇalısma*
- *2 Derleme ve 2 Meta-Analiz*

Giriş-AKS de sekonder korunma

- Geçen 20 yıl akut koroner sendrom (AKS) sonrası hastalar için kısa ve uzun dönem klinik sonuçları önemli ilerlemeler göstermiştir.
- Tedavi ve klavuzlara bağlı gelişmeler, 1994 yılında % 10,4 olan hastane mortalitesinde 2006 yılında % 6.3, bir azalmaya neden olmuştur.

Rogers WJ, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008;156:1026–34.

Giriş-AKS de sekonder korunma

- Buna rağmen, AKS olayı sonrası hayatta kalan hastaların% 17'si, ikincil profilaksi olmaksızın tekrarlayan olaylar yaşayacak ve hatta yeni antitrombotikler ile 12 ay boyunca % 10 gibi nüks riski devam etmektedir.
- Bu yüksek nüks oranları daha etkin ikincil korunma strateji ihtiyacını vurgulamaktadır.

Rogers WJ, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008;156:1026–34.

Giriş-AKS de sekonder korunma

- Yeni nesil antiplatelet tedavilerin yanı sıra, yeni nesil antikoagülanlar da geliştirilmiştir.
- İlk olarak atriyal fibrilasyonlu hastalarda test edilmiş ve inmenin önlenmesinde etkili olduğu gösterilmiştir.

Rogers WJ, et al. Trends in presenting characteristics and hospital mortality among patients with ST elevation and non-ST elevation myocardial infarction in the National Registry of Myocardial Infarction from 1990 to 2006. Am Heart J 2008;156:1026–34.

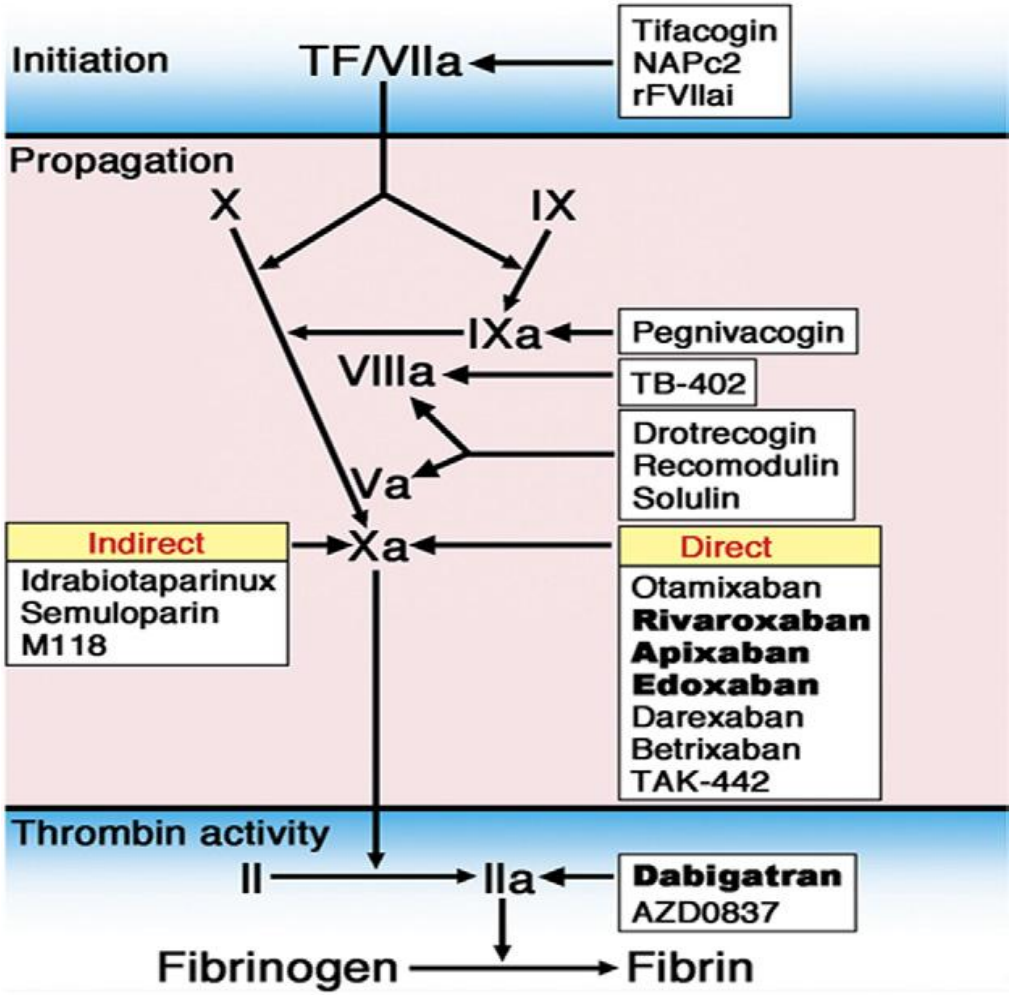
Giriş-AKS de sekonder korunma

- Varfarin (VKA) AKS'li hastalarda iskemik olayları önlemede etkinliğinin kanıtlanmış olmasına rağmen ***kullanım zorlukları*** nedeniyle külfetlidir, bu durum yeni tedavi arayışlarını zorunlu kılmıştır
- Yeni nesil oral antikoagülanlar kullanımı VKA'lardan daha uygundur ve bu nedenle bu durumda avantaj sağlayabilir.

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.

Kullanıma Giren Yeni Nesil Oral Antikoagülanlar…

Koagülasyon yolundaki farklı faktörlere etki eden yeni nesil oral antikoagülanlar



Yeni Nesil Oral Antikoagulanların AVANTAJLARI

- 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

Koagülasyon yolundaki farklı faktörlere etki eden yeni nesil oral antikoagülanlar-AKS

- Dabigatran(RE-DEEM)
- Ximelagatran (ESTEEM)
- Rivaroxaban (ATLAS ACS-TIMI 46, ATLAS ACS 2–TIMI 51
- Apixaban (APPRAISE-1, APPRAISE-2)
- Darexaban (RUBY-1)
- Edoxaban

Akut koroner Sendromda Yeni Nesil Antikoagulanların Kullanımı ile ilgili yapılan Klinik Çalışmalar…

European Heart Journal (2011) 32, 2781–2789
doi:10.1093/eurheartj/ehr113

CLINICAL RESEARCH
Acute coronary syndromes

Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial

Jonas Oldgren[1]*, Andrzej Budaj[2], Christopher B. Granger[3], Yasser Khder[4], Juliet Roberts[5], Agneta Siegbahn[1,6], Jan G.P. Tijssen[7], Frans Van de Werf[8], and Lars Wallentin[1], for the RE-DEEM Investigators

[1]Uppsala Clinical Research Center and Department of Medical Sciences, Uppsala University, S-751 85 Uppsala, Sweden; [2]Postgraduate Medical School, Department of Cardiology, Grochowski Hospital, Warsaw, Poland; [3]Duke Clinical Research Institute, Durham, NC, USA; [4]Boehringer Ingelheim, Paris, France; [5]Boehringer Ingelheim, Bracknell, UK; [6]Department of Medical Sciences, Clinical Chemistry, Uppsala University, Uppsala, Sweden; [7]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; and [8]University Hospitals Leuven, Leuven, Belgium

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See page 2734 for the editorial comment on this article (doi:10.1093/eurheartj/ehr051)

Aim After an acute coronary syndrome, patients are at risk of recurrent ischaemic events, despite contemporary treatment, including aspirin and clopidogrel. We evaluated the safety and indicators of efficacy of the novel oral direct thrombin inhibitor dabigatran.

Methods and results In this double-blind, placebo-controlled, dose-escalation trial, 1861 patients (89.2% on dual antiplatelet treatment) in 161 centres were enrolled at mean 7.5 days (SD 3.8) after an ST-elevation (60%) or non-ST-elevation (40%) myocardial infarction and randomized to twice daily treatment with dabigatran 50 mg ($n = 369$), 75 mg ($n = 368$), 110 mg ($n = 406$), 150 mg ($n = 347$), or placebo ($n = 371$). Primary outcome was the composite of major or clinically relevant minor bleeding during the 6-month treatment period. There were 96 primary outcome events and, compared with placebo, a dose-dependent increase with dabigatran, hazard ratio (HR) 1.77 (95% confidence intervals 0.70, 4.50) for 50 mg; HR 2.17 (0.88, 5.31) for 75 mg; HR 3.92 (1.72, 8.95) for 110 mg; and HR 4.27 (1.86, 9.81) for 150 mg. Compared with placebo, D-dimer concentrations were reduced in all dabigatran dose groups by an average of 37 and 45% at weeks 1 and 4, respectively ($P < 0.001$). Fourteen (3.8%) patients died, had a myocardial infarction or stroke in the placebo group compared with 17 (4.6%) in 50 mg, 18 (4.9%) in 75 mg, 12 (3.0%) in 110 mg, and 12 (3.5%) in the 150 mg dabigatran groups.

Conclusions Dabigatran, in addition to dual antiplatelet therapy, was associated with a dose-dependent increase in bleeding events and significantly reduced coagulation activity in patients with a recent myocardial infarction.

Keywords Acute coronary syndromes • Anticoagulants • Direct thrombin inhibitor • Myocardial infarction

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Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome *(RE-DEEM)*

- *İkili Antiplatelet tedavi alan Akut koroner sendromlu (AKS) hastalarında, Dabigatran'ın çoklu dozlarda eklenmiş*
- *Etkinlik ve güvenliliklerinin kıyaslandığı çift kör, randomize çok merkezli bir çalışmadır*
- *Çalışmaya*, 161 merkezden ST yükselmeli MI (60%) ya da non-ST yükselmeli MI (40%) **1861** *hasta dahil edilmiş olup hastalar ortalama **6 ay** boyunca izlenmiştir*

Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32:2781–9.

Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome *(RE-DEEM)*

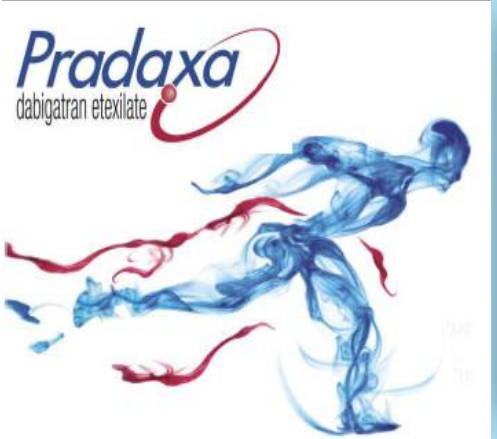
- *Dabigatran günde 2 kez 50 mg, 75 mg, 110 mg veya 150 mg dozunda ve plasebo olarak verilmiş*
- *Doza bağımlı olarak major ve minör kanamalarda kilinik olarak önemli bir artış saptandı (plaseboyla karşılaştırılmış).*
- *Kanama açısından en yüksek oranlar Dabigatran günde 2 kez 110 mg ve 150 mg alan grupta gözlenmiş (*%3.56 ve %3.88, sırasıyla)

Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32:2781–9.

Dose Finding Study for Dabigatran Etexilate in Patients With Acute Coronary Syndrome *(RE-DEEM)*

- *Gastrointestinal kanama ve epistaksis en sık gözlenen kanamalar.*
- **Akut koroner sendrom sonrası gelişebilecek kardiyovaskuler ölüm, myokard infarktüsü ve inme oranlarında** *Dabigatran günde* ***2 kez 110 mg*** *veya* ***150 mg*** *dozlar ile plasebo karşılaştırıldığında anlamlı olmayan bir azalma saptanmış* (%3 ve %3.5, sırasıyla)

Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32:2781–9.



- Dabigatran çalışma dozlarında akut koroner sendrom sonrası gelişebilecek kardiyovasküler ölüm, myokard infarktüsü ve inmeden korunmada **etkin değildir**
- Doza bağımlı artmış kanama oranlarından dolayı **güvenilir değildir**

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Lancet. 2003 Sep 6;362(9386):789-97.

Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial.

Wallentin L[1], Wilcox RG, Weaver WD, Emanuelsson H, Goodvin A, Nyström P, Bylock A; ESTEEM Investigators.

Author information

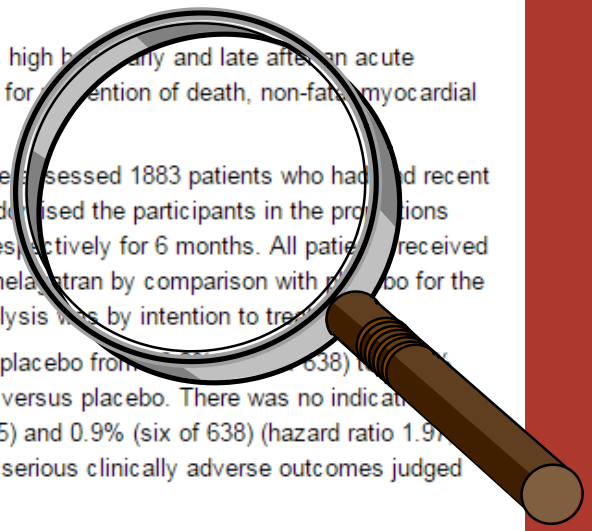
Abstract

BACKGROUND: Despite important advances in treatment, the risk of recurrent ischaemic events is high b[illegible]ly and late after an acute coronary syndrome. We aimed to assess the effectiveness of ximelagatran and acetylsalicylic acid for [illegible]ention of death, non-fat[illegible] myocardial infarction, and severe recurrent ischaemia after a recent myocardial infarction.

METHODS: In this placebo-controlled, double-blind, multicentre, multinational dose-guiding study we [illegible]sessed 1883 patients who had [illegible]d recent ST-elevation or non-ST-elevation myocardial infarction. Within 14 days after the index event we rand[illegible]ised the participants in the pro[illegible]ions 1/1/1/1/2 to oral ximelagatran at doses of 24 mg, 36 mg, 48 mg, or 60 mg twice daily, or placebo, res[illegible]ctively for 6 months. All patie[illegible] received acetylsalicylic acid 160 mg once daily. The primary efficacy outcome was the dose response of ximela[illegible]tran by comparison with p[illegible]bo for the occurrence of all-cause death, non-fatal myocardial infarction, and severe recurrent ischaemia. Analysis w[illegible]s by intention to tre[illegible]

FINDINGS: Oral ximelagatran significantly reduced the risk for the primary endpoint compared with placebo fro[illegible]638) t[illegible]% (154 of 1245) (hazard ratio 0.76, 95% CI 0.59-0.98, p=0.036) for the combined ximelagatran groups versus placebo. There was no indicat[illegible] dose response between the ximelagatran groups. Major bleeding events were rare, 1.8% (23 of 1245) and 0.9% (six of 638) (hazard ratio 1.9[illegible] 95% CI 0.80-4.84) in the combined ximelagatran and placebo groups, respectively. We recorded no serious clinically adverse outcomes judged related to the investigational drug.

INTERPRETATION: Oral direct thrombin inhibition with ximelagatran and acetylsalicylic acid is more effective than acetylsalicylic acid alone in preventing major cardiovascular events during 6 months of treatment in patients who have had a recent myocardial infarction.



Comment in

Improving antithrombotic treatment in patients after myocardial infarction. [Lancet. 2003]

PMID: 13678873 [PubMed - indexed for MEDLINE]

Improving antithrombotic treatment in patients after myocardial infarction *(ESTEEM)*

- *Aspirin tedavisi alan yeni Akut koroner sendromlu (AKS) hastalarında,* **Ximelagatran** *çoklu dozlarda eklenmiş*
- *Etkinlik ve güvenliliklerinin plasebo ile kıyaslandığı çift kör, randomize bir çalışmadır*
- *Çalışmaya*, ST yükselmeli MI ya da non-ST yükselmeli MI toplam **1883** *hasta dahil edilmiş olup hastalar ortalama* ***6 ay*** *boyunca izlenmiştir*

Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet 2003;362:789–797

Improving antithrombotic treatment in patients after myocardial infarction *(ESTEEM)*

- **Ximelagatran** *günde 2 kez 24 mg, 36 mg, 48 mg veya 60 mg dozunda ve plasebo olarak verilmiş*
- *Primer sonlanım noktası;* ***tüm nedenlere bağlı*** **ölüm, ölümcül olmayan myokard infarktüsü ve ciddi tekrarlayan iskemi**
- Primer sonlanım noktası oranları **Ximelagatran** ile kombine hastalarda *plasebo ile karşılaştırıldığında anlamlı bir azalma saptanmış (*%12.7 vs %16.3, sırasıyla; p=0.036).

Wa
infarction: the ESTEEM randomised controlled trial. Lancet 2003;362:789–797

Improving antithrombotic treatment in patients after myocardial infarction *(ESTEEM)*

- Major kanama olayları plasebo ile karşılaştırıldığında **Ximelagatran grubunda** 2 kat artmış olarak saptanmış (%0.9 vs %1.8).

- Aspirin ile birlikte **oral trombin inhibitörü olan Ximelagatran,** tek başına Aspirine oranla yeni AKS geçirmiş hastalarda 6 ay süreyle verilmesi kardiyovasküler olayları önlemede daha etkilidir.

Wallentin L, Wilcox RG, Weaver WD, et al. Oral ximelagatran for secondary prophylaxis after myocardial infarction: the ESTEEM randomised controlled trial. Lancet 2003;362:789–797

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Abstract

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Lancet. 2009 Jul 4;374(9683):29-38. doi: 10.1016/S0140-6736(09)60738-8. Epub 2009 Jun 17.

Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial.

Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, Hricak V, Barnathan ES, Bordes P, Witkowski A, Markov V, Oppenheimer L, Gibson CM; ATLAS ACS-TIMI 46 study group.

Collaborators (376)

Abstract

BACKGROUND: Rivaroxaban is an oral direct factor Xa inhibitor that has been effective in prevention of venous thromboembolism in patients undergoing elective orthopaedic surgery. However, its use after acute coronary syndromes has not been investigated. In this setting, we assessed the safety and efficacy of rivaroxaban and aimed to select the most favourable dose and dosing regimen.

METHODS: In this double-blind, dose-escalation, phase II study, undertaken at 297 sites in 27 countries, 3491 patients stabilised after an acute coronary syndrome were stratified on the basis of investigator decision to use aspirin only (stratum 1, n=761) or aspirin plus a thienopyridine (stratum 2, n=2730). Participants were randomised within each strata and dose tier with a block randomisation method at 1:1:1 to receive either placebo or rivaroxaban (at doses 5-20 mg) given once daily or the same total daily dose given twice daily. The primary safety endpoint was clinically significant bleeding (TIMI major, TIMI minor, or requiring medical attention); the primary efficacy endpoint was death, myocardial infarction, stroke, or severe recurrent ischaemia requiring revascularisation during 6 months. Safety analyses included all participants who received at least one dose of study drug; efficacy analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00402597.

FINDINGS: Three patients in stratum 1 and 26 in stratum 2 never received the study drug. The risk of clinically significant bleeding with rivaroxaban versus placebo increased in a dose-dependent manner (hazard ratios [HRs] 2.21 [95% CI 1.25-3.91] for 5 mg, 3.35 [2.31-4.87] for 10 mg, 3.60 [2.32-5.58] for 15 mg, and 5.06 [3.45-7.42] for 20 mg doses; p<0.0001). Rates of the primary efficacy endpoint were 5.6% (126/2331) for rivaroxaban versus 7.0% (79/1160) for placebo (HR 0.79 [0.60-1.05], p=0.10). Rivaroxaban reduced the main secondary efficacy endpoint of death, myocardial infarction, or stroke compared with placebo (87/2331 [3.9%] vs 62/1160 [5.5%]; HR 0.69, [95% CI 0.50-0.96], p=0.0270). The most common adverse event in both groups was chest pain (248/2309 [10.7%] vs 118/1153 [10.2%]).

INTERPRETATION: The use of an oral factor Xa inhibitor in patients stabilised after an acute coronary syndrome increases bleeding in a dose-dependent manner and might reduce major ischaemic outcomes. On the basis of these observations, a phase III study of low-dose rivaroxaban as adjunctive therapy in these patients is underway.

FUNDING: Johnson & Johnson Pharmaceutical Research & Development and Bayer Healthcare AG.

Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46)

- *Yalnız Aspirin alan grup yada İkili Antiplatelet inhibisyonu yapılan (Aspirin+thienopyridine) grubundaki Akut koroner sendromlu (AKS) hastalarda, Rivaroksaban çoklu dozlarda eklenmiş*
- *Etkinlik ve güvenliliklerinin kıyaslandığı çift kör, randomize çok merkezli faz 2 çalışmadır*
- *Çalışmaya*, 27 Ülkeden, 297 merkezden **3491** AKS *hasta dahil edilmiş olup hastalar ortalama **6 ay** boyunca izlenmiştir*

Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACSTIMI 46): a randomised, double-blind, phase II trial. Lancet 2009; 374:29 –38.

Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46)

- *Rivaroksaban günde 2 kez 5 mg, 10 mg, 15 mg veya 20 mg dozunda ve plasebo olarak her iki hasta grubuna verilmiş*
- *Doza bağımlı olarak major ve minör kanamalarda (primer sonlanım) anlamlı olarak bir artış her iki grupta saptandı (plaseboyla karşılaştırılmış).*
- Akut koroner sendrom sonrası gelişebilecek kardiyovaskuler ölüm, myokard infarktüsü ve inme toplamı (sekonder sonlanım) oranlarında Rivaroksaban verilen hastalarda *plasebo ile karşılaştırıldığında anlamlı bir azalma saptanmış (*3.9% vs 5.5%; p=0.0270).

Mega JL, Braunwald E, Mohanavelu S, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACSTIMI 46): a randomised, double-blind, phase II trial. Lancet 2009; 374:29 –38.

Xarelto
rivaroxaban tablets

Dusuk doz Rivaroxaban akut koroner sendrom sonrası gelişebilecek kardiyovaskuler ölüm, myokard infarktüsü ve inmeden korunmak için standart antitrombotik tedaviya ek olarak kullanılabileceği konusunda Faz 3 calısması planlanmıstır.

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ESTABLISHED IN 1812 JANUARY 5, 2012 VOL. 366 NO. 1

Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., and C. Michael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*

ABSTRACT

BACKGROUND

Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.

METHODS

In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

RESULTS

Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P=0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P=0.03). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.002) and from any cause (2.9% vs. 4.5%, P=0.002), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P=0.04).

CONCLUSIONS

In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer HealthCare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Mega at the Cardiovascular Division, Department of Medicine, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at jmega@partners.org.

*Investigators in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) are listed in the Supplementary Appendix, available at NEJM.org.

This article (10.1056/NEJMoa1112277) was published on November 13, 2011, at NEJM.org.

N Engl J Med 2012;366:9-19.

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Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 *(ATLAS ACS 2–TIMI 51)*

- *İkili Antiplatelet inhibisyonu yapılan (Aspirin+thienopyridine) Akut koroner sendromlu (AKS) hastalarda ilk 7 gün içinde, Rivaroksaban ikili dozlarda ve plasebo eklenmiş*
- *Etkinlik ve güvenliliklerinin kıyaslandığı çift kör, randomize çok merkezli faz 3 çalışmadır*
- *Çalışmaya,* **15,526** AKS *hastası dahil edilmiş olup hastalar ortalama* ***13,3 ay*** *boyunca izlenmiştir*

Mega JL, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 *(ATLAS ACS 2–TIMI 51)*

- 55 yaş üstü, diabet, önceki MI, gastrointestinal kanama, intrakranial kanama, stroke ya da GIA olan hastalar çalışmaya dahil edilmemiş.
- Primer sonlanım noktası (**kardiyovaskuler ölüm, myokard infarktüsü ve inme)** oranları Rivaroksaban verilen hastalarda *plasebo ile karşılaştırıldığında anlamlı bir azalma saptanmış (*8.9% vs 10.7%, sırasıyla; p= 0.008).
- **Rivaroksaban 5 mg bid** verilen hastalarda *plasebo ile karşılaştırıldığında* primer sonlanım noktası oranları *(*8.8% vs 10.7%, sırasıyla; p= 0.03) saptanmış.
- ***Rivaroksaban 2.5 mg bid verilen*** hastalarda *plasebo ile karşılaştırıldığında azalmış* primer sonlanım noktası oranları *saptanmış (*9.1% vs 10.7%, sırasıyla; p= 0.03).

Mega JL, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 *(ATLAS ACS 2–TIMI 51)*

- Rivaroksaban ***verilen*** hastalarda *plasebo ile karşılaştırıldığında major kanamalar* (sırasıyla, %2.1 vs. %0.6, sırasıyla; p<0.001) *ve intrakranial kanama oranları daha yüksek gözlemlenmiş* (0.6% vs. 0.2%, sırasıyla; p= 0.009).
- Fatal kanama açısından *rivaroxaban ve plasebo arasında* ***belirgin fark gözlenmemiş*** (0.3% vs. 0.2%, sırasıyal; p =0.66)
- Dahası Rivaroksaban ***2.5 mg bid verilen ve 5 mg bid verilen hastalar karşılaştırıldığında fatal kanama oranları 2.5 mg dozlarda anlamlı olarak 4 kat daha düşük*** (0.1% vs. 0.4%, sırasıyla P =0.04) saptanmış.

Mega JL, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 *(ATLAS ACS 2–TIMI 51)*

Yeni oral antikoagülanlardan **rivaroksaban (Xarelto)günde 2 kez 2.5 ve 5 mg dozlarda akut koroner sendrom sonrası gelişebilecek kardiyovaskuler ölüm, myokard infarktüsü ve inmeden korunmada etkilidir.**

Rivaroksaban major kanama ve intrakranial kanamaları artırmakla birlikte ölümcül kanamalarda artısa neden olmaz (öz. 2.5 mg günde 2 kez) neden olmaz.

Mega JL, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366(1):9-19.

Xarelto
rivaroxaban tablets

Rivaroksaban (Xarelto) akut koroner sendrom sonrası gelişebilecek kardiyovaskuler ölüm, myokard infarktüsü ve inmeden korunmak için kullanılabileceği konusunda Avrupa'da onaylandı.

Apixaban, an Oral, Direct, Selective Factor Xa Inhibitor, in Combination With Antiplatelet Therapy After Acute Coronary Syndrome

Results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) Trial

APPRAISE Steering Committee and Investigators

Background—After an acute coronary syndrome, patients remain at risk of recurrent events. Apixaban, an oral direct factor Xa inhibitor, is a novel anticoagulant that may reduce these events but also poses a risk of bleeding.

Methods and Results—Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) was a phase 2, double-blind, placebo-controlled, dose-ranging study. Patients (n=1715) with recent ST-elevation or non–ST-elevation acute coronary syndrome were randomized to 6 months of placebo (n=611) or 1 of 4 doses of apixaban: 2.5 mg twice daily (n=317), 10 mg once daily (n=318), 10 mg twice daily (n=248), or 20 mg once daily (n=221). Nearly all patients received aspirin; 76% received clopidogrel. The primary outcome was International Society of Thrombosis and Hemostasis major or clinically relevant nonmajor bleeding. A secondary outcome was cardiovascular death, myocardial infarction, severe recurrent ischemia, or ischemic stroke. At the recommendation of the Data Monitoring Committee, the 2 higher-dose apixaban arms were discontinued because of excess total bleeding. Compared with placebo, apixaban 2.5 mg twice daily (hazard ratio, 1.78; 95% confidence interval, 0.91 to 3.48; $P=0.09$) and 10 mg once daily (hazard ratio, 2.45; 95% confidence interval, 1.31 to 4.61; $P=0.005$) resulted in a dose-dependent increase in major or clinically relevant nonmajor bleeding. Apixaban 2.5 mg twice daily (hazard ratio, 0.73; 95% confidence interval, 0.44 to 1.19; $P=0.21$) and 10 mg once daily (hazard ratio, 0.61; 95% confidence interval, 0.35 to 1.04; $P=0.07$) resulted in lower rates of ischemic events compared with placebo. The increase in bleeding was more pronounced and the reduction in ischemic events was less evident in patients taking aspirin plus clopidogrel than in those taking aspirin alone.

Conclusions—We observed a dose-related increase in bleeding and a trend toward a reduction in ischemic events with the addition of apixaban to antiplatelet therapy in patients with recent acute coronary syndrome. The safety and efficacy of apixaban may vary depending on background antiplatelet therapy. Further testing of apixaban in patients at risk of recurrent ischemic events is warranted. (***Circulation***. **2009;119:2877-2885.**)

Key Words: anticoagulants ■ acute coronary syndromes ■ clinical trial ■ factor Xa inhibitor

Apixaban for Prevention of Acute Ischemic and Safety Events *(APPRAISE)*

- *Apixabanın Akut koroner sendromlu (STEMI ve non-STEMI hastalarında çoklu dozlarda plasebo ile kıyaslandığı APPRAISE çalışması;* ***1715*** *hastanın dahil edildiği, hastaların ortalama 6ay boyunca takip edildiği randomize, çift-kör faz-2 çalışmadır*
- *Hastaların büyük bir çoğunluğu ikili antiplatelet olarak Aspirin ve klopidogrel almaktaydı.*

Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119:2877– 85.

Apixaban for Prevention of Acute Ischemic and Safety Events *(APPRAISE)*

- *Apixaban günde 2 kez 2,5 mg* (n=317), 10 mg günde bir kez (n=318), 10 mg günde 2 kez (n=248), ya da 20 mg günde bir kez (n=221) *dozunda ve plasebo olarak verilmiş*
- *Primer sonlanım noktası;* **kardiyovaskuler ölüm, myokard infarktüsü ve inme**
- *Sekonder sonlanım noktası; minör ve major kanama*
- *Yüksek kanama oranlarından dolayı yüksek doz Apixaban verilen iki hasta kolunda çalışma sonlandırılmış*

Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119:2877– 85.

Apixaban for Prevention of Acute Ischemic and Safety Events *(APPRAISE)*

- *Doza bağımlı olarak major ve minör kanamalarda kilinik olarak önemli bir artış saptandı (plaseboyla karşılaştırılmış).*
- *Plasebo ile karşılaştırıldığında günde 2 kez 2,5 mg* Apixaban alan hasta kolunda 1.78 kat ve 10 mg günde bir kez 2,45 kat daha fazla artmış kanama oranları ile ilşkili saptandı.
- *En sık gözlenen kanamalar subkutan kanama, gingival kanama, epistaksis, hematuri ve gastrointestinal kanamalar idi.*

Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119:2877– 85.

Apixaban for Prevention of Acute Ischemic and Safety Events *(APPRAISE)*

- Akut koroner sendrom sonrası gelişen iskemik olay (MI ne iskemik inme) oranlarında plasebo ile karşılaştırıldığında *Apixaban günde 2 kez 2,5 mg ve* 10 mg günde bir kez alan hasta kolunda *anlamlı olmayan bir azalma saptanmış (sırasıyla,* %0.73 ve %0.61, sırasıyla)

Alexander JH, Becker RC, Bhatt DL, et al. Apixaban, an oral, direct, selective factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome: results of the Apixaban for Prevention of Acute Ischemic and Safety Events (APPRAISE) trial. Circulation 2009;119:2877– 85.

ORIGINAL ARTICLE

Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome

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ABSTRACT

BACKGROUND

Apixaban, an oral, direct factor Xa inhibitor, may reduce the risk of recurrent ischemic events when added to antiplatelet therapy after an acute coronary syndrome.

METHODS

We conducted a randomized, double-blind, placebo-controlled clinical trial comparing apixaban, at a dose of 5 mg twice daily, with placebo, in addition to standard antiplatelet therapy, in patients with a recent acute coronary syndrome and at least two additional risk factors for recurrent ischemic events.

RESULTS

The trial was terminated prematurely after recruitment of 7392 patients because of an increase in major bleeding events with apixaban in the absence of a counterbalancing reduction in recurrent ischemic events. With a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred in 279 of the 3705 patients (7.5%) assigned to apixaban (13.2 events per 100 patient-years) and in 293 of the 3687 patients (7.9%) assigned to placebo (14.0 events per 100 patient-years) (hazard ratio with apixaban, 0.95; 95% confidence interval [CI], 0.80 to 1.11; P=0.51). The primary safety outcome of major bleeding according to the Thrombolysis in Myocardial Infarction (TIMI) definition occurred in 46 of the 3673 patients (1.3%) who received at least one dose of apixaban (2.4 events per 100 patient-years) and in 18 of the 3642 patients (0.5%) who received at least one dose of placebo (0.9 events per 100 patient-years) (hazard ratio with apixaban, 2.59; 95% CI, 1.50 to 4.46; P=0.001). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo.

CONCLUSIONS

The addition of apixaban, at a dose of 5 mg twice daily, to antiplatelet therapy in high-risk patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in recurrent ischemic events. (Funded by Bristol-Myers Squibb and Pfizer; APPRAISE-2 ClinicalTrials.gov number, NCT00851441.)

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

*The investigators in the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) trial are listed in the Supplementary Appendix, available at NEJM.org.

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Apixaban for Prevention of Acute Ischemic Events 2 *(APPRAISE-2)*

- *Apixabanın standart antiplatelet tedavi (aspirin ve klopidogrel)* ***yüksek riskli*** *Akut koroner sendromlu (STEMI ve non-STEMI hastalarında} günde 2 kez 2,5 mg dozda plasebo ile kıyaslandığı APPRAISE çalışması;* 10,800 *hastanın dahil edilmesinin planlandığı, hastaların ortalama 241 gün boyunca takip edildiği randomize, çift-kör faz-3 çalışmadır*
- *Ancak major kanama komplikasyonu geliştiğinden çalışmaya* 7392 hasta dahil edilebilmiştir.

Alexander JH, Lopes RD, James S, et al., for the APPRAISE 2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365:699 –708.

Apixaban for Prevention of Acute Ischemic Events 2 *(APPRAISE-2)*

- *Primer sonlanım noktası;* **kardiyovaskuler ölüm, myokard infarktüsü ve iskemik inme**
- **Primer sonlanım noktası açısından** *günde 2 kez 2,5 mg dozda Apixaban plasebo ile kıyaslandığında anlamlı fark saptanmadı* (sırasıyla, % 7.5 vs. %7.9%; p = 0.51),
- Apixaban ***verilen*** hastalarda *plasebo ile karşılaştırıldığında major kanamalar* (sırasıyla, %1.3 vs. %0.5, sırasıyla; p=0.001) *ve*
- *İntrakranial kanama ve fatal kanama oranları Apixaban alan hastalarda daha yüksek gözlemlenmiş*.

Alexa … by after acute coronary syndrome. N Engl J Med 2011;365:699–708.

Apixaban for Prevention of Acute Ischemic Events 2 *(APPRAISE-2)*

Yeni oral antikoagülanlardan Apiksaban yüksek riskli akut koroner sendromlu hastalarda major kanama sıklığını artırır. AKS sonrası gelişebilecek iskemik olayların azaltılmasında etkili değildir.

Alexander JH, Lopes RD, James S, et al., for the APPRAISE 2 Investigators. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med 2011;365:699 –708.

European Heart Journal (2011) 32, 2541–2554
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FASTTRACK
ESC HOT LINE

RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome

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See page 2486 for the commentary on this article (doi:10.1093/eurheartj/ehr314)

Aims To establish the safety, tolerability and most promising regimen of darexaban (YM150), a novel, oral, direct factor Xa inhibitor, for prevention of ischaemic events in acute coronary syndrome (ACS).

Methods In a 26-week, multi-centre, double-blind, randomized, parallel-group study, 1279 patients with recent high-risk non-ST-segment or ST-segment elevation ACS received one of six darexaban regimens: 5 mg b.i.d., 10 mg o.d., 15 mg b.i.d., 30 mg o.d., 30 mg b.i.d., or 60 mg o.d. or placebo, on top of dual antiplatelet treatment. Primary outcome was incidence of major or clinically relevant non-major bleeding events. The main efficacy outcome was a composite of death, stroke, myocardial infarction, systemic thromboembolism, and severe recurrent ischaemia.

Results Bleeding rates were numerically higher in all darexaban arms vs. placebo (pooled HR: 2.275; 95% CI: 1.13–4.60, $P = 0.022$). Using placebo as reference (bleeding rate 3.1%), there was a dose–response relationship ($P = 0.009$) for increased bleeding with increasing darexaban dose (6.2, 6.5, and 9.3% for 10, 30, and 60 mg daily, respectively), which was statistically significant for 30 mg b.i.d. ($P = 0.002$). There was no decrease (indeed a numerical increase in the 30 and 60 mg dose arms) in efficacy event rates with darexaban, but the study was underpowered for efficacy. Darexaban showed good tolerability without signs of liver toxicity.

Conclusions Darexaban when added to dual antiplatelet therapy after ACS produces an expected dose-related two- to four-fold increase in bleeding, with no other safety concerns but no signal of efficacy. Establishing the potential of low-dose darexaban in preventing major cardiac events after ACS requires a large phase III trial.
ClinicalTrials.gov Identifier: NCT00994292

Keywords Anticoagulant • Acute coronary syndrome • Secondary prevention • Darexaban

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Study Evaluating Safety, Tolerability and Efficacy of Novel Oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome (RUBY-1)

- *Darexaban'nın standart antiplatelet tedavi (aspirin ve klopidogrel) yüksek riskli Akut koroner sendromlu (STEMI ve non-STEMI hastalarında 6 farklı dozlarda plasebo ile kıyaslandığı RUBY-1 çalışması;* 1279 *hastanın dahil edildiği, hastaların 26 hafta ortalama boyunca takip edildiği randomize, çift-kör faz-2 çalışmadır*

Steg PG, Mehta SR, Jukema JW, et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Eur Heart J 2011;32:2541–54.

Study Evaluating Safety, Tolerability and Efficacy of Novel Oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome (RUBY-1)

- *Primer sonlanım noktası; klinik önemi olan minör ve major kanamalar* olarak belirlenmiş.
- Ana etkinlik sonlanım noktası olarak; ölüm, inme, MI, sistemik tromboembolizm
- AKS li hastalar ikili antiplatelet tedaviye ek olarak günde iki kez 5 mg, günde tek doz 10 mg, günde iki kez 15 mg, günde bir kez 30 mg , günde iki kez 30 mg ve günde 60 mg tek doz Darexaban almış
- Plasebo grubunda kanama oranı %3.1 iken doza bağımlı olarak Darexaban grubunda kanama oranları anlamlı olarak 2 ila 4 kat daha yüksek bulunmuş.
- Ana etkinlik sonlanım noktası açısından plasebo ile karşılaştırıldığında anlamlı fark saptanmadı.

Steg PG, Mehta SR, Jukema JW, et al. RUBY-1: a randomized, double-blind, placebo-controlled trial of the safety and tolerability of the novel oral factor Xa inhibitor darexaban (YM150) following acute coronary syndrome. Eur Heart J 2011;32:2541–54.

Akut koroner Sendromda Yeni Nesil Antikoagulanlar Derleme ve Meta-Analiz…

European Heart Journal
Acute Cardiovascular Care
EUROPEAN SOCIETY OF CARDIOLOGY®

Review

New oral anticoagulant agents after ACS

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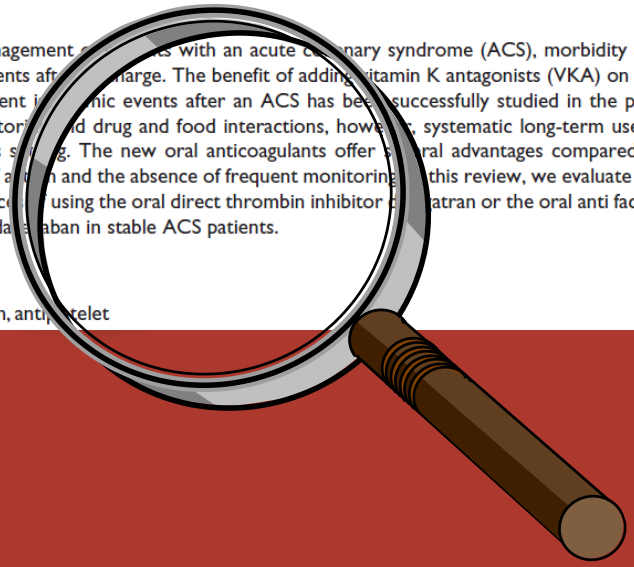
Peter R Sinnaeve[1], Tom Adriaenssens[1], Thomas Höchtl[2] and Kurt Huber[2]

Abstract

Despite tremendous progress in the management of patients with an acute coronary syndrome (ACS), morbidity and mortality remains high even in stable patients after discharge. The benefit of adding vitamin K antagonists (VKA) on top of antiplatelet therapy to prevent recurrent ischemic events after an ACS has been successfully studied in the past. Because of their need for frequent monitoring and drug and food interactions, however, systematic long-term use of VKA has not been recommended in this setting. The new oral anticoagulants offer several advantages compared to VKA, including a faster onset and offset of action and the absence of frequent monitoring. In this review, we evaluate the current evidence and practical consequences of using the oral direct thrombin inhibitor dabigatran or the oral anti factor Xa inhibitors apixaban, rivaroxaban, and darexaban in stable ACS patients.

Keywords

Acute coronary syndrome, anticoagulation, antiplatelet



Düşük doz Rivarokasaban ve Apixaban ikili antiplatelet tedaviye eklenmesi AKS sonrası klinik sonuçları iyileştirir. Ancak, artmış kanama riski bir bedel olarak düşünülmedir

Dabigatran ve Darexaban ikili antiplatelet tedaviye eklenmesi AKS sonrası klinik sonuçları iyileştirdiğine dair kanıtlar yetersizdir. Ayrıca her iki antikogulanda , artmış kanama komplikasyonu ile ilişkilidir.

Apiksaban ve rivaroksaban ikili antiplatelet tedavisi alan akut koroner sendromlu hastalarda tekrarlayan iskemilerin önlenmesi için faz III çalışmalarda değerlendirilmiştir. Artmış büyük kanama için tutarlı sonuçlar elde edilmiş, etkinliği konusunda çelişkili sonuçlar elde edilmiştir.

İkli Antiplatelet tedavide klopidogrel yerine daha etkin ve kanama komplikasyonu açısından da daha güvenilir olan yeni antiplatelet ajanların (prasugrel veya tikagrelor) herhangi birinin kullanılması AKS hastalarında Üçlü tedavide önemli bir sorun olan kanama komplikasyonunu önleyebilir ve etkinliği artırabilir.

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STATE-OF-THE-ART PAPER

New Oral Anticoagulants in Atrial Fibrillation and Acute Coronary Syndromes

ESC Working Group on Thrombosis—Task Force on Anticoagulants in Heart Disease Position Paper

Coordinating Committee: Raffaele De Caterina, MD, PHD,* Steen Husted, MD, DSC,† Lars Wallentin, MD, PHD,‡
Task Force Members: Raffaele De Caterina, MD, PHD,* Steen Husted, MD, DSC,† Lars Wallentin, MD, PHD,‡ Felicita Andreotti, MD, PHD,§ Harald Arnesen, MD,‖ Fedor Bachmann, MD,¶ Colin Baigent, MD,# Kurt Huber, MD,** Jørgen Jespersen, MD, DSC,†† Steen Dalby Kristensen, MD,† Gregory Y. H. Lip, MD,‡‡ João Morais, MD,§§ Lars Hvilsted Rasmussen, MD, PHD,‖‖ Agneta Siegbahn, MD, PHD,‡ Freek W. A. Verheugt, MD,¶¶ Jeffrey I. Weitz, MD##

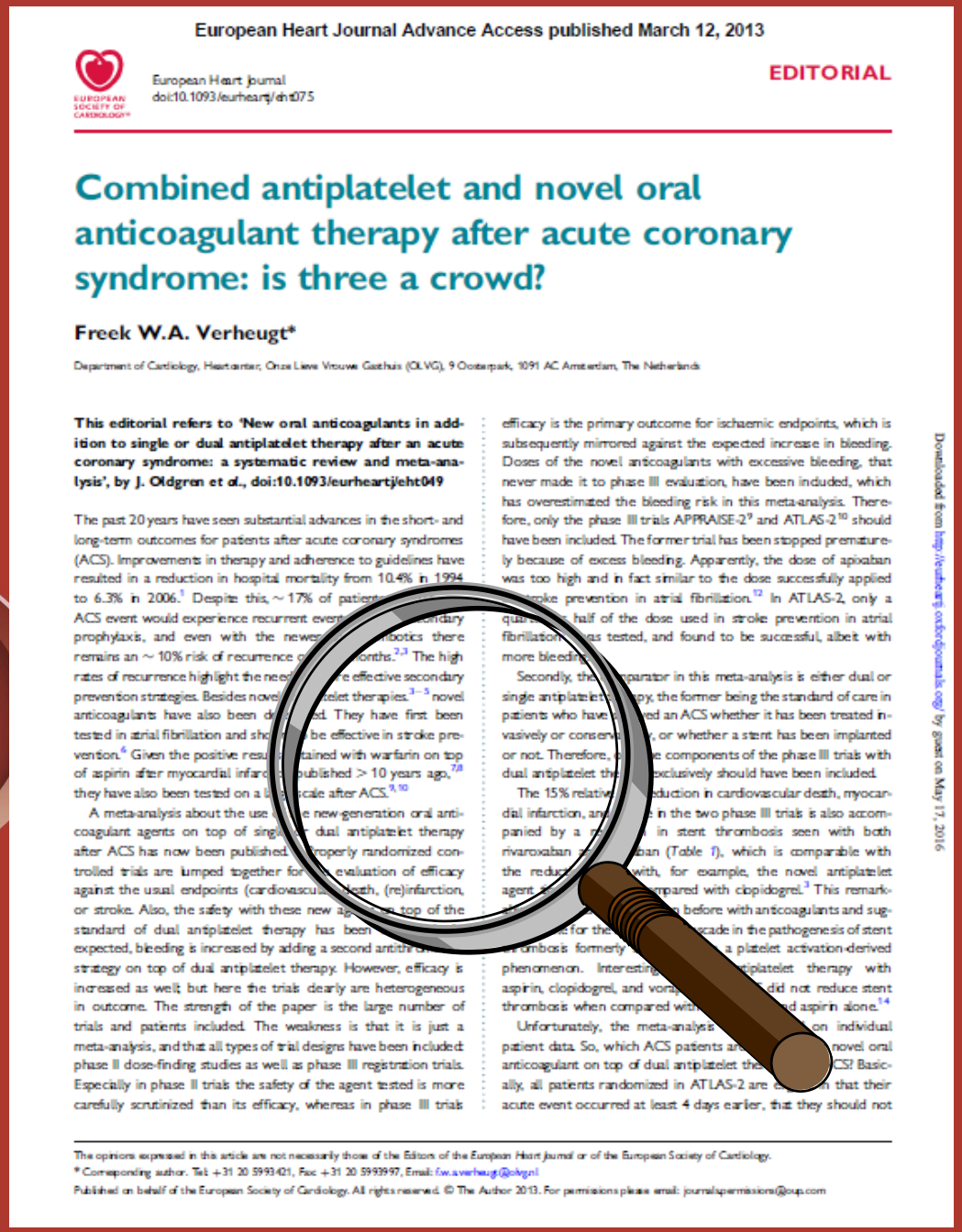
Chieti, Pisa, and Rome, Italy; Aarhus, Esbjerg, and Aalborg, Denmark; Uppsala, Sweden; Oslo, Norway; Lausanne, Switzerland; Oxford and Bir[illegible]ingdom; Amsterdam, the Netherlands; Hamilton, Ontario, Canada; Vien[illegible]ria; and Leiria, Portugal

Until recently, vitamin K a[illegible]sts were the only available oral anticoagul[illegible] but with numerous limitations that prompted the introd[illegible] of new oral anticoagulants targeting the sing[illegible]agulation enzymes thrombin (dabigatran) or factor Xa [illegible]aban, rivaroxaban, and edoxaban) and given in [illegible] doses without coagulation monitoring. Here we rev[illegible]e pharmacology and the results of clinical trials [illegible]these new agents in stroke prevention in atrial fibri[illegible]n and secondary prevention after acute coronary [illegible]mes, providing perspectives on their future incorpora[illegible] into clinical practice. In phase III trials in atrial fi[illegible]on, compared with warfarin, dabigatran etexilate 150 [illegible] B.I.D. reduced the rates of stroke/systemic em[illegible] without any difference in major bleeding; dabigatran e[illegible]late 110 mg B.I.D. had similar efficacy with de[illegible]d bleeding; apixaban 5 mg B.I.D. reduced stroke, syste[illegible] embolism, and mortality as well as major[illegible]g; and rivaroxaban 20 mg Q.D. was noninferior to warfarin fo[illegible]troke and systemic embolism without [illegible]ce in major bleeding. All these agents reduced intracranial hem[illegible]nge. Edoxaban is currently be[illegible] further large phase III trial. Apixaban and rivaroxaban were eval[illegible]d in phase III trials fo[illegible]ischemia in patients with acute coronary syndromes who were most[illegible]herapy, [illegible] results on efficacy but consistent results for increased major bleeding. Overall, the new oral anticoagulants [illegible]eplace vitamin K antagonists for many patients with atrial fibrillation and may have a role after acute cor[illegible]es. Although convenient to administer and manage, they present challenges that need to be addressed. [illegible]rdiol 2012; 59:1413–25) © 2012 by the American College of Cardiology Foundation

AKS'de ikili antiplatelet tedavi altında, sekonder korunmada, yeni oral antikoagülan tedavi eklenmesi % 15 oranında tekrarlayan iskemik olayları azaltır, fakat klinik olarak anlamlı kanama riskini üç kat artırır

Rivaroksaban'nın ana çalışmasında düşük dozda yapilan antikoagulasyon anlamlı derecede mortalitede azalma sağlamıştır.

Bu ajanlar için etkin ve güvenilir olan doz aralığı (en etkili nokta-doz) saptamak için daha fazla çalışmalara ihtiyaç vardır.



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EDITORIAL

Combined antiplatelet and novel oral anticoagulant therapy after acute coronary syndrome: is three a crowd?

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This editorial refers to 'New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis', by J. Oldgren et al., doi:10.1093/eurheartj/eht049

The past 20 years have seen substantial advances in the short- and long-term outcomes for patients after acute coronary syndromes (ACS). Improvements in therapy and adherence to guidelines have resulted in a reduction in hospital mortality from 10.4% in 1994 to 6.3% in 2006.[1] Despite this, ~17% of patients ... ACS event would experience recurrent event... ...ndary prophylaxis, and even with the newe... ...botics there remains an ~10% risk of recurrence ... ...nths.[2,3] The high rates of recurrence highlight the need ... ...e effective secondary prevention strategies. Besides novel ... ...elet therapies.[3–5] novel anticoagulants have also been d... ...ed. They have first been tested in atrial fibrillation and sho... ...be effective in stroke prevention.[6] Given the positive resu... ...tained with warfarin on top of aspirin after myocardial infarc... ...published > 10 years ago,[7,8] they have also been tested on a l... ...cale after ACS.[9,10]

A meta-analysis about the use ... ...e new-generation oral anticoagulant agents on top of sing... ...dual antiplatelet therapy after ACS has now been published. ... ...properly randomized controlled trials are lumped together for ... ...evaluation of efficacy against the usual endpoints (cardiovascu... ...death, (re)infarction, or stroke. Also, the safety with these new ag... ...on top of the standard of dual antiplatelet therapy has been ... expected, bleeding is increased by adding a second antithr... strategy on top of dual antiplatelet therapy. However, efficacy is increased as well, but here the trials clearly are heterogeneous in outcome. The strength of the paper is the large number of trials and patients included. The weakness is that it is just a meta-analysis, and that all types of trial designs have been included: phase II dose-finding studies as well as phase III registration trials. Especially in phase II trials the safety of the agent tested is more carefully scrutinized than its efficacy, whereas in phase III trials efficacy is the primary outcome for ischaemic endpoints, which is subsequently mirrored against the expected increase in bleeding. Doses of the novel anticoagulants with excessive bleeding, that never made it to phase III evaluation, have been included, which has overestimated the bleeding risk in this meta-analysis. Therefore, only the phase III trials APPRAISE-2[9] and ATLAS-2[10] should have been included. The former trial has been stopped prematurely because of excess bleeding. Apparently, the dose of apixaban was too high and in fact similar to the dose successfully applied ...troke prevention in atrial fibrillation.[12] In ATLAS-2, only a qua... half of the dose used in stroke prevention in atrial fibrillation ...as tested, and found to be successful, albeit with more bleedi...

Secondly, the ...parator in this meta-analysis is either dual or single antiplatelet ...py, the former being the standard of care in patients who have ...ed an ACS whether it has been treated invasively or conserv... or whether a stent has been implanted or not. Therefore, ...e components of the phase III trials with dual antiplatelet th... ...exclusively should have been included.

The 15% relative ...eduction in cardiovascular death, myocardial infarction, an... ...in the two phase III trials is also accompanied by a ... in stent thrombosis seen with both rivaroxaban ...an (*Table 1*), which is comparable with the reduc... ...with, for example, the novel antiplatelet agent ... ...mpared with clopidogrel.[3] This remark... ...before with anticoagulants and sug... ...for the ...cade in the pathogenesis of stent ...rombosis formerly ... a platelet activation-derived phenomenon. Interestin... ...tiplatelet therapy with aspirin, clopidogrel, and vora... did not reduce stent thrombosis when compared with ... ...d aspirin alone.[14]

Unfortunately, the meta-analysis ... ...on individual patient data. So, which ACS patients ar... ...novel oral anticoagulant on top of dual antiplatelet th... ...CS? Basically, all patients randomized in ATLAS-2 are ... ...n that their acute event occurred at least 4 days earlier, that they should not

The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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Toplam 7 adet plasebo-kontrollü faz 2 ve 3 çalışması ikili antiplatelet tedavi alan 30,866 AKS (7-14 gün içinde) hastası analiz edildi.

Yeni AKS li hastalarda yeni nesil oral antikoagulanların antiplatelet tedaviye eklenmesi kardiyovasküler olay sıklığını azaltır ancak artmış kanama komplikasyonuyla ilişkilidir

Bu çalışmalarda yeni nesil oral antikoagulanlar aspirin ve klopidogrel gibi ikili antiplatelet tedavi alan hastalara eklenmiş. Klopidogrel yerine daha etkili olan yeni nesil oral antiplateletlerden (P2Y12 inhibitörleri) ticagrelor ya da prasugrel değerlendirildiği çalışma mevcut değildir.

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CLINICAL RESEARCH
Acute coronary syndromes

New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis

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Background Oral anticoagulation in … antiplatelet treatment … acute coronary syndrome might reduce ischaemic events but increase … risk. We performed a meta-analysis to evaluate the efficacy and safety of adding direct thrombin or facto… inhibition by any of the novel oral anticoag…ts (apixaban, dabigatran, darexaban, rivaroxaban, and ximela… to single (aspirin) or dual (aspirin and clopi…grel) antiplatelet therapy in this setting.

Methods and results All seven publ… randomized, placebo-controlled phase II and III …ies of novel oral anticoagulants in acute coronary synd…s were included. The database consisted of 3… patients, 4135 (13.4%) on single, and 26 731 (86.6%) … dual antiplatelet therapy, with a non-ST- or ST-e… on acute coronary syndrome within the last 7–14 days. … defined major adverse cardiovascular events (M…) as the composite of all-cause mortality, myocardial infa…n, or stroke; and clinically significant bleeding as … composite of major and non-major bleeding requiring medica… attention according to the study definitions. Whe… pared with aspirin alone the combination of an oral anticoagul… and aspirin reduced the incidence of MA… rd ratio (HR) and 95% confidence interval 0.70; 0.59–0.84], bu… increased clinically significant bleeding (… 1.54–2.09). Compared with dual antiplatelet therapy with aspirin and …idogrel, adding an oral antic… the incidence of MACE modestly (HR: 0.87; 0.80–0.95), but more … doubled the ble… Heterogeneity between studies was low, and results were similar wi… to phase II…

Conclusion In patients with a recent acute coronary syndrome, the addition of a new … lant to antiplatelet therapy results in a modest reduction in cardiovascular events but a substantial increase… most pronounced when new oral anticoagulants are combined with dual antiplatelet therapy.

Keywords Oral anticoagulants • Antiplatelet therapy • Acute coronary syndrome • Myocardial… Meta-analysis

TEŞEKKÜRLER..