静脈血栓塞栓症の治療においてエドキサバンはワルファリンよりも安全である

Hokusai-VTE：再発性深部静脈血栓症および肺塞栓症の予防において1日1回のエドキサバンの効果はワルファリンと同等である

Hokusai-VTE: Once daily edoxaban comparable to warfarin for averting recurrent deep-vein thrombosis and pulmonary embolism

静脈血栓塞栓症（VTE）の治療において、経口抗凝固薬エドキサバンは標準治療のワルファリンと比較し、両剤とも低分子ヘパリン（LMWH）初回治療に加えた場合、有効性は同等であり安全性は優れているとのトライアル結果が2013年European Society of Cardiology学会で発表され、同時に*New England Journal of Medicine*に掲載された。Hokusai-VTEトライアルは近年の他の経口抗凝固薬トライアルの対象患者に比べより広範囲のVTE患者を対象とし、肺動脈塞栓症（PE）および右室機能低下を有する患者（30%）、腎機能障害および低体重のために出血リスクの高いサブグループ（20%）も含まれた。合計で、深部静脈血栓患者4,921人およびPE患者3,319人が皮下LMWHによる初期治療を受けその後1日60mgのエドキサバン（出血リスクの高い患者では30mg）、またはワルファリン（標準治療）を3～12か月投与される群に無作為に割り付けられた。一次エンドポイントである再発性有症状VTEはエドキサバンおよびワルファリンでそれぞれ3.2% 対3.5%に発現し（非劣性に関してP <0.001）、エドキサバンのワルファリンに対する非劣性が認められた。しかし、PEおよび右室機能障害の認められる患者群において、有効性はエドキサバンの方が優れていた（3.3%対6.2%、ハザード比 0.52）。

Full Text

In the treatment of venous thromboembolism (VTE), the oral anticoagulant edoxaban resulted in equal efficacy and better safety compared to standard warfarin when either drug was used with initial low molecular weight heparin (LMWH), according to the results of the Hokusai-VTE trial.

In the landscape of new trials with oral anticoagulants, the Hokusai-VTE findings offer fresh insight into a previously under-represented subgroup of patients with pulmonary embolism (PE), suggesting that treatment for this group might need to be different than for other VTE patients, said lead investigator Harry R. Büller, M.D., who presented the findings at the 2013 European Society of Cardiology Congress.

"I think our findings are going to shake things up a little bit," said Dr. Büller, from the Department of Vascular Medicine at Academic Medical Center in Amsterdam.

"What makes this study unique is new insight that there are subgroups in which we might need to revisit what we currently think about the treatment of VTE.

The Hokusai-VTE trial included a broader spectrum of VTE patients compared to those included in other recent oral anticoagulant trials, including a large subgroup (30%) of patients with PE and right ventricular dysfunction, and another subgroup (20%) at high risk for bleeding due to renal impairment and low body weight.

In total, 4,921 patients with deep-vein thrombosis and 3,319 with pulmonary embolism received initial subcutaneous LMWH therapy and were then randomized to receive either 60 mg of edoxaban daily (30 mg for those at higher risk for bleeding, i.e., creatinine clearance 30-50 mL/min or body weight below 60 kg), or warfarin (per standard of care) for 3 to 12 months.

For the primary efficacy endpoint of recurrent symptomatic venous thromboembolism, the study found that edoxaban was non-inferior to warfarin, with the primary endpoint of recurrent symptomatic VTE occurring in 3.2% vs. 3.5% respectively (P <0.001 for noninferiority). However, in the subgroup of patients with pulmonary embolism and evidence of right ventricular dysfunction, efficacy was superior with edoxaban (3.3% vs. 6.2%, hazard ratio [HR] 0.52).

For the principal safety outcome of clinically relevant bleeding, edoxaban was superior with a rate of 8.5% compared to 10.3% in the warfarin group, (P =0.004 for superiority).

And among the sub-group of patients at high risk for bleeding, "by halving the daily dose of edoxaban to 30 mg, efficacy was maintained with significantly less bleeding than observed in the warfarin group," he said. In this high-risk subgroup clinically relevant bleeding occurred in 7.9% of those treated with edoxaban, compared to 12.8% of those treated with warfarin, while superior efficacy was maintained in the edoxaban arm (3.0% vs. 4.2%). Previous trials of oral anticoagulants have not identified these specific sub-groups, noted Dr. Büller.

"It was a nice and surprising finding that the combination of LMWH and edoxaban in the PE group resulted in a highly significant and clinically relevant reduction of about 50% in recurrent disease."

"Our findings are likely to be generalizable. In a global setting," he added. "We included patients with both provoked and unprovoked venous thromboembolism and treatment durations varied from 3 to 12 months at the discretion of the treating physician.

The success of edoxaban compared to warfarin is good news in the quest for simplified treatment of VTE, said Dr. Büller. "The problem with warfarin is that food and alcohol and many, many medications interfere with the level and so therefore you're obliged to do careful laboratory testing every 3 to 4 weeks or even more frequently to measure the INR and adjust the dose," he said. "The great advantage of the new oral anticoagulants is they have very predictable kinetics and dynamics and therefore can be given in a fixed dose and do not need monitoring."

But, along with enthusiasm for oral anticoagulants, there is also growing hope in the field that injectable heparin might also be safely eliminated, thus switching 2 inconvenient therapies for one pill said Dr. Büller.

"Two previous oral anticoagulant studies have omitted LMWH altogether (EINSTEIN PE and AMPLIFY) and were applauded because of the simplicity of just giving pills, " said Dr. Büller, who was the lead author of one of those studies (*N Engl J* Med 2012; 366: 1287–97).

But, both EINSTEIN PE and AMPLIFY were criticized for under-representing the severely ill sub-groups that make up a large part of the Hokusai-VTE population, he said.

"The whole field was rushing to the conclusion that we could get rid of both heparin, and warfarin, but I think the findings of the Hokusai-VTE study show that in these subgroups it looks like it would be pretty unwise to omit heparin. Our study adjusts that thinking just a little bit, and may start us reconsidering."

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Harry R. Buller chaired the Hokusai VTE study steering Committee and received compensation for his consultancy and advisory board membership from Daiichi Sankyo.

Conference News