心房細動においてapixabanはワルファリンよりも優れている

ARISTOTLE：心房細動患者の脳卒中予防、出血軽減、および救命に関してapixabanはワルファリンよりも優れている

ARISTOTLE: Apixaban superior to Warfarin in patients with atrial fibrillation for preventing stroke, reducing bleeding, and saving lives

2011年European Society of Cardiology学会で発表されNew England Journal of Medicineオンライン版に掲載された大規模トライアルARISTOTLEの結果、心房細動患者の脳卒中および全身性塞栓予防において新たな抗凝固薬 apixabanは標準薬ワルファリンよりも優れていることが示された。ARISTOTLEトライアルでは39ヵ国1,034施設の患者18,201人を apixaban（5mgを1日2回）またはワルファリン（平均1.8年間）を投与する群に無作為に割り付けた。Apixaban投与により脳卒中（p=0.011）および全身性塞栓症がさらに相対的に21%減少した。また、重大な出血は31%減少し（p<0.001）、総死亡率は11%減少した（p=0.047）。脳出血は約50%減少した。Apixabanによる有益性は、“治療域の時間”で計測した施設ごとのワルファリンの使用法に関係なく一律に認められた。Apixabanはワルファリンと比較し重要な臨床上の利点をもち合わせている：モニターの必要がないこと、および他の薬剤や食物との相互作用が少ないこと、と筆者らは特筆している。Apixabanは第Xa因子を直接阻害する経口薬で、投与患者はアスピリンを内服した患者よりも脳卒中や血栓を有する確率が54%少なかったとの昨年のトライアル結果から有望であることが示された。

Full Text

The large-scale ARISTOTLE trial presented at the 2011 European Society of Cardiology Congress and published online in the New England Journal of Medicine finds that apixaban, a new anticoagulant drug, is superior to the standard drug warfarin for preventing stroke and systemic embolism in patients with atrial fibrillation. Moreover, apixaban results in substantially less bleeding, and also results in lower mortality. The benefits of apixaban are consistent irrespective of how well warfarin is used at different centers, as measure by "time in therapeutic range."

The randomized, double-blind clinical trial known as ARISTOTLE randomized 18,201 patients at 1034 clinical sites in 39 countries to Apixaban (5mg twice daily) or to warfarin for an average of 1.8 years.

"These are important findings because they show when compared to warfarin, itself a very effective treatment to prevent stroke, apixaban resulted in an additional 21 percent relative reduction in stroke and systemic embolism. It also resulted in a 31 percent relative reduction in major bleeding, as well as an 11 percent relative reduction in overall mortality," says Granger. The better prevention of stroke was statistically significant with P=0.011, the lower rate of major bleeding at P<0.001, and the lower mortality at p=0.047. Hemorrhagic stroke was reduced by about 50%.

Wallentin notes that these benefits are with a drug that has major practical advantages over warfarin: it does not require monitoring and has few interactions with other medications or food. Apixaban was better tolerated than warfarin, with fewer discontinuations. And he stated "the benefits of reducing stroke and lower rates of bleeding were consistent across all major subgroups and despite the heterogeneity that exists in the quality of warfarin use across the world."

The number of events prevented per 1000 people, which indicate absolute risk reduction, were also impressive, says John Alexander, M.D., a study co-author and Duke cardiologist. "Apixaban prevented 6 patients from having a stroke, 15 patients from having major bleeding, and 8 patients from dying. The predominant effect on stroke prevention was on hemorrhagic stroke. Apixaban prevented 4 patients from having hemorrhagic stroke and 2 patients from having an ischemic or uncertain type of stroke."

"There is an enormous unmet need in terms of treatment of patients at risk for stroke associated with atrial fibrillation," says Granger. "Only about half of patients who should be treated are being treated. The disparity exists because warfarin treatment has several limitations."

The results were presented by the co-chairs of the ARISTOTLE trial in two late breaking clinical trial sessions at the European Society of Cardiology in Paris, France, and the main trial results were published simultaneously online in the New England Journal of Medicine. The time in therapeutic range analysis was presented by Lars Wallentin, professor of cardiology and director of the Uppsala Clinical Research Center in Sweden. The main trial results were presented by Christopher B. Granger, professor of medicine at Duke University in Durham, North Carolina, USA.

Warfarin is a vitamin K antagonist that is well documented for its ability to prevent blood clots. Previous studies indicate long-term use of warfarin in patients with atrial fibrillation and other stroke risk factors can reduce stroke by up to 70 percent. However, only about half of patients who could benefit from warfarin actually do. Patients on warfarin must have regular blood tests to monitor and adjust the dose and avoid certain foods and medications that interfere with warfarin's effect. Warfarin also increases bleeding risk including intracranial hemorrhage.

Because of these limitations, doctors and patients have been eagerly awaiting alternative therapies, one of which is currently available, and several others are currently under investigation in large clinical trials.

Apixaban is an oral direct factor Xa inhibitor that showed promise last year when trial findings presented at the European Society of Cardiology showed apixaban patients were 54 percent less likely to have a stroke or blood clot than those who took aspirin. Apixaban and aspirin showed similar risks of major bleeding.

"Our study indicates treatment with apixaban is more effective than warfarin in preventing stroke without the need for anticoagulation monitoring," says Wallentin.

The study also shows apixaban is safer than warfarin, according to Wallentin. "Our findings show a single dose of apixaban accomplishes the same stroke prevention goal as adjusted-dose warfarin with a substantially lower risk of all types of bleeding across different ages, and with lower rates of discontinuation."

Conference News