Rivaroxabanはエノキサパリンと比較し正味の臨床上の有益性は認められない

MAGELLAN：Rivaroxabanは急性疾患で入院した患者における静脈血栓塞栓予防の点でエノキサパリンに優る

MAGELLAN: Rivaroxaban compares favorably with enoxaparin in preventing venous thromboembolism in acutely ill hospitalized patients

Rivaroxabanに関して既に蓄積された臨床試験のデータに大量の臨床試験データを加えた MAGELLANトライアルにより、急性疾患で入院した患者における静脈血栓塞栓予防において、短期使用（10日間）についてはエノキサパリンに対する非劣性が、長期使用に関してはエノキサパリン使用後のプラセボ投与に対する優越性が示された。第60回American College of Cardiology学会で発表されたこの研究結果によると出血率はスタディを通して低かったが、rivaroxaban群においては高かった。52ヵ国の患者8,101人のうち4,050人をrivaroxabanで35日間治療する群に、4,051人をエノキサパリンで10日間治療する群に無作為に割り付けた（両群ともにプラセボの経口投与または皮下注投与が行われた）。一次有効性項目に関しては10日後までは両薬剤ともに同等の結果であり、このエンドポイントに合致したのは両群ともに2.7%であった（非劣性に関して p=0.0025）。35日間の有効性に関してはrivaroxabanの方がエノキサパリン後のプラセボ投与よりも有意に良好な結果であり、4.4%の患者が一次有効性エンドポイントに達したのに対しエノキサパリン群では5.7%であった（優越性に関してp=0.0211）。しかし、10日間および35日間ともにエノキサパリンの方がrivaroxabanよりも出血率は有意に低かった（両者ともp<0.0001）。

Full Text

Adding to the extensive clinical trial data already amassed for rivaroxaban, an international research team found that the MAGELLAN trial showed non-inferiority to enoxaparin in short-term use (10 days) and superiority to enoxaparin followed by placebo in long-term use (35 days), in the prevention of venous thromboembolism (VTE) in acutely ill hospitalized patients. Bleeding rates were generally low across the study but were higher in the rivaroxaban arm, according to research presented at the American College of Cardiology's 60th Annual Scientific Session.

The MAGELLAN study is a phase III clinical trial that compared the oral anticoagulant rivaroxaban with subcutaneous enoxaparin in patients admitted to the hospital for an acute medical condition (including acute heart failure, acute infectious disease, and acute respiratory insufficiency). The study was designed to determine which treatment would better prevent VTE - which comprises deep vein thrombosis (DVT) and pulmonary embolism (PE). It evaluated how the standard regimen of enoxaparin (10 days) performed in comparison to short-term (10 days) rivaroxaban. It also evaluated an extended treatment regimen of rivaroxaban (35 days) compared to enoxaparin (10 days) followed by placebo, as the optimal duration of VTE prophylaxis is unknown in this setting.

"Every year, venous blood clots kill more than 1 million people, including approximately 300,000 in the U.S. and more than 500,000 in Europe," said lead study author Alexander T. Cohen, honorary consultant vascular physician in the Department of Surgery and Vascular Medicine at King's College Hospital, London. "VTE is often associated with recent surgery or trauma, but 50 percent to 70 percent of symptomatic thromboembolic events and 70 percent to 80 percent of fatal pulmonary embolism (PE) occur in non-surgical patients. Thus, this study population of acutely ill medical patients is an important group in which to test the optimal therapy for preventing VTE."

Randomizing 8,101 patients from 52 countries, the researchers treated 4,050 patients with rivaroxaban for 35 days and 4,051 patients with enoxaparin for 10 days (both groups also received either an oral or subcutaneous placebo). The study's primary efficacy outcome was a composite of asymptomatic proximal DVT (detected by ultrasonography), symptomatic DVT, symptomatic non-fatal PE, and VTE-related death. The primary safety outcome was a composite of treatment-related major bleeding and clinically relevant non-major bleeding.

After a follow-up conducted at 10 days (to determine the non-inferiority of rivaroxaban), the researchers found that the two drugs performed to the same level with regard to the primary efficacy outcome, with 2.7 percent of patients in both drug cohorts experiencing this endpoint (relative risk ratio=0.968; p=0.0025 for non-inferiority, one-sided).

After a follow-up conducted at 35 days (to determine the superiority of rivaroxaban), the study team saw that rivaroxaban performed significantly better than enoxaparin followed by placebo, with 4.4 percent of patients experiencing the primary efficacy outcome compared to 5.7 percent, respectively (relative risk ratio 0.771, p=0.0211 for superiority, two-sided).

When the team examined the primary safety outcome, however, they found that the enoxaparin group demonstrated a significantly reduced rate of bleeding than the rivaroxaban group at both 10 and 35 days. Specifically, 1.2 percent of patients in the enoxaparin group experienced some kind of clinically relevant bleeding at the 10-day point, compared to 2.8 percent of patients in the rivaroxaban group (relative risk ratio=2.3; p< 0.0001). At 35 days, 1.7 percent of patients in the enoxaparin group experienced clinically relevant bleeding, compared to 4.1 percent of patients in the rivaroxaban group (relative risk=2.5; p<0.0001). Therefore, a consistent net clinical benefit with rivaroxaban could not be established in the heterogeneous population studied.

Cohen added that while rivaroxaban's significantly higher bleeding rate was a surprising finding, the rates of other adverse events - including cardiovascular problems, impacted liver function, and mortality - were similar in both groups.

"MAGELLAN investigated VTE prophylaxis in the largest and most diverse population of hospitalized, acutely ill patients to date, and managing the risk of blood clots in these patients is extremely complex due to their age, co-morbid conditions, and duration of immobilization," Cohen said. "As observed in previous studies in this area, we found an ongoing risk of VTE past the initial period of hospitalization. We did not see a consistently positive benefit-risk balance with rivaroxaban use, and thus further analysis is required to identify which groups of patients in MAGELLAN may derive benefit from thromboprophylaxis with rivaroxaban."

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