リバーロキサバンは心血管系および下肢のイベントを減少させる(LBT Session, Abstract 1154, 1157)

COMPASS & COMPASS PAD：リバーロキサバンは安定冠動脈疾患および末梢動脈疾患のアウトカムを改善する

COMPASS & COMPASS PAD: Rivaroxaban improves outcomes in stable coronary and peripheral artery disease

安定冠動脈疾患または末梢動脈疾患患者において、リバーロキサバンとアスピリンの併用は脳卒中および心筋梗塞（MI）を減少させ、下肢切断リスクを低下させる、とのトライアルの結果が2017 ESC Congressで発表され、*NEJM*に掲載された。主なトライアルであるCOMPASSにおいて、アスピリンにリバーロキサバンを併用することで、アスピリン単独に比べ、心血管死、脳卒中、またはMIを24%減少させ、生存率を18%改善した。付随試験であるCOMPASS PADトライアルにおいて、リバーロキサバンとアスピリンの併用は、末梢動脈疾患患者において下肢切断を含む下肢を脅かす虚血を46%減少させた。

Full Text

Rivaroxaban plus aspirin improves survival and reduces stroke and heart attack in patients with stable coronary or peripheral artery disease, according to late-breaking results from the COMPASS and COMPAS PAD trials presented in a Hot Line-LBCT Session at the 2017 ESC Congress and published in the *NEJM*.

One-third of the 55 million deaths in the world each year are from cardiovascular causes. Patients with known coronary or peripheral artery disease are at risk of death, stroke and heart attack. Aspirin is the single most widely used treatment to prevent strokes and heart attacks but is only modestly effective.

The COMPASS trial tested two possible ways to improve on aspirin, by using the combination of rivaroxaban and aspirin, or by using rivaroxaban alone, to protect against heart attack and stroke in patients with stable coronary or peripheral artery disease.

The trial randomized 27,395 patients from 33 countries in North America, South America, Asia, Western Europe, Eastern Europe, South Africa and Australia. The treatments tested were rivaroxaban 2.5mg twice daily plus aspirin 100mg once daily and rivaroxaban 5mg twice daily, each of which were compared to standard therapy with aspirin 100mg once daily. The primary endpoint was a composite of cardiovascular death, stroke or myocardial infarction.

On 6 February 2017 the Data Safety Monitoring Board recommended that the rivaroxaban and aspirin arms be stopped because of a clear superiority of the combination of rivaroxaban and aspirin over aspirin alone.

The results indicate that the addition of rivaroxaban to aspirin, compared with aspirin alone, reduced cardiovascular death, stroke, or heart attack by 24%, and improved survival by 18%. Rivaroxaban 5mg twice daily was not superior to aspirin alone. The addition of rivaroxaban to aspirin increased bleeding, and the most common site of bleeding was in the stomach or lower bowel. There was no significant increase in fatal or brain bleeding.

Dr. John Eikelboom, co-principal investigator and associate professor, McMaster University, Hamilton, Canada, said: "The substantial benefits seen with rivaroxaban and aspirin support the approach of using low doses of the two treatments in combination. Recent trials in other disease areas have demonstrated substantial benefits from using low doses of a combination of drugs and this concept is now further supported by the results of COMPASS."

Prof Stuart Connolly, co-principal investigator and professor of medicine at McMaster University, suggested that the increase in bleeding should be considered in the context of the overall findings. He said: "Many of these bleeds were not serious and despite the increase in bleeding the results clearly show a net benefit for patients, as highlighted by the 18% reduction in mortality."

The data indicates that for every 1 000 patients treated for an average of 23 months, rivaroxaban plus aspirin prevents 13 heart attacks, strokes, or cardiovascular deaths, and seven deaths from any cause, at a cost of 12 major bleeds, most of which were readily treatable. The benefits of the drug combination were achieved in patients in whom lipid-lowering and blood pressure-lowering drugs, and angiotensin converting enzyme (ACE) inhibitors were widely used.

"It is noteworthy that the benefits of the combination of rivaroxaban and aspirin are on top of proven therapies," said Prof. Salim Yusuf, chair of the COMPASS Steering Committee and director of the Population Health Research Institute at McMaster University. "If rivaroxaban plus aspirin is widely adopted, the potential benefits are enormous. Use of the combination in 10% of the approximately 300 million persons around the world with known cardiovascular disease would prevent as many as 100 000 deaths and twice as many premature vascular events each year."

In the companion COMPASS PAD trial, rivaroxaban plus aspirin reduced limb-threatening ischemia, including amputation, by 46% in patients with peripheral artery disease.

Peripheral artery disease (PAD) affects an estimated 200 million people worldwide and is strongly associated with concomitant coronary, cerebral, and peripheral atherosclerosis. Patients are at increased risk of heart attack, stroke and death from cardiovascular causes, as well as limb-threatening ischemia and amputation. Aspirin is the standard antithrombotic therapy but is only modestly effective.

Patients with PAD were recruited to the COMPASS trial from 558 centers in 33 counties in North and South America, Asia, Western and Eastern Europe, South Africa and Australia. One-third of COMPASS PAD patients were current smokers and 44% had diabetes - the two strongest risk factors for PAD.

The treatments tested were rivaroxaban 2.5mg twice daily plus aspirin 100mg once daily and rivaroxaban 5mg twice daily, each of which were compared to standard therapy with aspirin 100mg once daily. The primary endpoint was a composite of myocardial infarction, stroke, or cardiovascular death.

Consistent with the overall results of COMPASS, in patients with PAD the addition of low dose rivaroxaban to aspirin, compared with aspirin alone, reduced cardiovascular death, stroke or myocardial infarction by 28%, and limb-threatening ischemia, including amputation, by 46%. Considering both outcomes together, rivaroxaban and aspirin lowered major adverse cardiovascular or limb events by 31%.

Rivaroxaban alone versus aspirin did not reduce major adverse cardiovascular events, but did reduce major adverse limb events. However, taking cardiovascular and limb events together, rivaroxaban alone was not superior to aspirin.

The combination of rivaroxaban and aspirin increased the risk of major bleeding, but did not increase the risk of fatal or critical organ bleeding, and most major bleedings were reversible.

Prof. Sonia Anand, Professor of Medicine at McMaster University, Hamilton, Canada, who led the PAD component of the COMPASS trial, said: "This is an important advance for patients with peripheral artery disease. Until now we have only had aspirin which is modestly effective. To now have a therapy that reduces major adverse cardiovascular events and major adverse limb events by one-third is going to be a great benefit for these high-risk patients."

The results indicate that for every 1 000 PAD patients treated for an average of 21 months, rivaroxaban 2.5mg twice daily plus aspirin 100mg once daily prevents 27 patients from having a serious cardiovascular event at a cost of 12 major bleeds, most of which were readily treatable. The benefits were attained on top of proven secondary prevention therapies, including lipid-lowering and blood pressure-lowering drugs, and angiotensin converting enzyme inhibitors.

The potential impact of the combination of rivaroxaban and aspirin in PAD patients is significant. Prof Salim Yusuf, Chair of the COMPASS Steering Committee and director of the Population Health Research Institute at McMaster University, said: "PAD patients have a threefold risk of heart attack and stroke, and there is no antithrombotic therapy which reduces both cardiovascular and limb events. Use of low dose rivaroxaban and aspirin appears to be the right combination at the right dose to lower rates of cardiovascular and limb events in this high-risk population."

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