- I'm Jeffrey Weitz, professor of medicine and biochemistry and biomedical sciences at McMaster university, an executive director of the thrombosis and atherosclerosis research institute. We'll be presenting the results of the axiomatic total knee replacement study. This study is a phase two dose ranging study, comparing oral milvexian with enoxaparin for postoperative thromboprophylaxis in patients undergoing elective, knee arthroplasty.

Rationale of this Study

This study was undertaken to test the hypothesis that milvexian reduces the risk of venous thromboembolism after elective knee arthroplasty. Milvexian is a small molecule inhibitor of factor XI-A. It is orally available and is rapidly absorbed after oral administration with a time to maximum concentration of about two to four hours. It has a half-life of about 12 hours. It is metabolised in the liver, and about 20% is excreted through the kidneys. The purpose of this study was to determine whether Milvexian has antithrombotic activity in patients undergoing elective knee arthroplasty.

Study Design and Patient Population

This study was a phase two, prospective, parallel group, adaptive design trial comparing seven different dose regiments of Milvexian with enoxaparin for post-operative thromboprophylaxis in patients undergoing knee replacement surgery. So patients were randomised to receive Milvexian in once or twice daily dosage regimens, ranging from 25 milligrammes to 200 milligrammes or to receive subcutaneous enoxaparin. The treatments were given for between 10 and 14 days, at which point all patients underwent mandatory venography of their operated leg and the primary efficacy outcome was any venous thromboembolism which was defined as asymptomatic deep vein thrombosis. That was detected on the mandatory venogram, confirmed symptomatic deep vein thrombosis or nonfatal pulmonary embolism or death from any cause. The principle safety outcome was any bleeding, the composite of major clinically relevant non-major or minor bleeding. We also looked at clinically irrelevant bleeding, which was defined as the composite of major or clinically relevant non-major bleeding.

Key Findings

A priori, proof of efficacy was defined as showing either, that Milvexian reduced the rate of post-operative venous thromboembolism to less than 30%. The 30% was chosen as a benchmark because it's a conservative estimate of the rate of venous thromboembolism without thromboprophylaxis who patients undergoing elective knee arthroplasty, and the second criteria was to demonstrate a dose response relationship in terms of the rate of postoperative venous thromboembolism with twice daily in milvexian regimens. And the study met both efficacy criteria, the rate of venous thromboembolism with the combined twice daily milvexian regimens was 12%, which was significantly lower than the 30% benchmark. And there was a significant dose relationship with both twice daily milvexian and once daily, milvexian. And the study evaluated milvexian regimens ranging from 25 milligrammes to 200 milligrammes, given either twice daily or once daily. With daily doses of milvexian of a hundred milligrammes or more, the rate of venous thromboembolism with milvexian was significantly lower than that with enoxaparin. And most importantly, over a 16 fold range of milvexian doses from total daily doses ranging from 25 milligrammes to 400 milligrammes. The rates of any bleeding were 4% with milvexian and 4% with enoxaparin. Rates of clinically relevant bleeding, which was defined as the composite of major or clinically relevant non-major bleeding were 1% with milvexian and 2% with enoxaparin. There were no major bleeds with milvexian. There was one major bleed with enoxaparin. So over this very wide range of milvexian concentrations, there was no dose response in terms of bleeding, but there was a definite dose response in terms of efficacy with significant reductions in the rate of venous thromboembolism with milvexian compared with enoxaparin and enoxaparin is the standard of care in many centres and in many countries for postoperative thromboprophylaxis in patients undergoing knee replacement surgery.

Take Home Messages

The take home message of this study is that milvexian is an effective antithrombotic agent that reduces the risk of post-operative venous thromboembolism after elective, knee replacement surgery and is associated with a low risk of bleeding.

Next Steps

The next steps with milvexian are to assess its safety, not only in this population but also, its safety as an add on to single or dual anti-platelet therapy. And to evaluate this second phase two study, evaluated milvexian compared with placebo on top of anti-platelet therapy in patients with non-cardio embolic stroke, is underway. The axiomatic secondary stroke prevention study, and we'll report out sometime next year.