Factor Xa Inhibitors for Primary Prevention of Atherosclerotic Events

Atherosclerosis is a leading cause of morbidity and mortality, and additional treatments are needed.

Low Factor X Levels May Prevent Atherosclerotic Plaque
Factor X is a key step on the coagulation cascade leading to fibrin (blood clot) formation. A small segment of the population is deficient in Factor X. After two brothers with Factor X deficiency in their late 60's had coronary calcium scans, they had *zero* detectable plaque, despite decades of one brother having elevated lipids and a BMI over 30. A possible explanation was their *hereditary, mild Factor X deficiencies*.

There is evidence that low Factor X levels might prevent atherosclerotic plaque:

- Factor Xa inhibitors have been **shown to prevent plaque in mice and** play a significant role in **mediating cellular signaling effects associated with the initial development of atherosclerosis in humans** (Zhou, Moran and Spronk).

- The prevalence of plaque in patients and/or cardiovascular events from atherosclerosis are **directly correlated with lower or higher clotting factors**. (Shoenfeld, Spiel, Kamhuisan, Angelini, Mega and Dogliotti)

- Coronary artery calcification (CAC), a measure of atherosclerotic plaque, increases with age and has been shown to **be a reliable predictor of mortality and cardiovascular risk** (Budoff , Nakanishi and Carr).

- Studies have shown that Factor Xa inhibitors can **slow or even reverse the progression of coronary artery calcification**, and that this beneficial effect is greater than with warfarin (Cabral, Dogliotti, Mega, Ruff, Caluwé and Janssen).

These studies and others found fewer cardiovascular events in study participants who received a low dose of a Factor Xa inhibitor (sometimes with aspirin) rather than older anticoagulants or a placebo.

We propose that Factor Xa inhibitors may be a useful treatment to prevent and reduce atherosclerotic lesions.

This proposal is based on evidence that Factor X may trigger acute inflammatory responses that lead to leukocyte migration, and ultimately plaque formation. Thus, inhibition of Factor Xa is expected to reduce atherosclerosis.

The potential of Factor Xa inhibitors for primary prevention is clear. There is evidence that a clinically effective dose of a Factor Xa inhibitor will not result in a significant increase in bleeding (Agnelli).

Adams Pharmaceuticals has patent applications on the use of Factor Xa inhibitors for the treatment and prevention of atherosclerosis. Contact us for additional information.

Evidence that Factor X and/or Factor Xa level may be modifiable risk factors:

1. Zhou Q et al. "Evaluation of Plaque Stability of Advanced Atherosclerotic Lesions in Apo E-Deficient Mice after Treatment with the Oral Factor Xa Inhibitor Rivaroxaban," *Mediators of Inflammation*, (2011), Article ID 432080, 9 pages. DOI:10.1155/2011/432080. Also see: Moran C et al, "Parenteral administration of factor Xa/IIa inhibitors limits experimental aortic aneurysm and atherosclerosis," *Sci. Rep*. 7, 43079; doi: 10.1038/srep43079 (2017). Also see: Spronk H et al, "Pleiotropic effects of factor Xa and thrombin: what to expect from novel anticoagulants," *Cardiovascular Research*, (2014) 101, 344–351.
2. Hara T et al., "Rivaroxaban, a novel oral anticoagulant, attenuates atherosclerotic plaque progression and destabilization in ApoE-deficient mice," *Atherosclerosis* (2015); 242(2); 639-646. DOI:10.1016/j.atherosclerosis.2015.03.023
3. Shoenfeld Y et al., "Accelerated atherosclerosis in autoimmune rheumatic diseases," *Circulation*. 2005 Nov 22; 112(21):3337-47.
4. Spiel A et al., "von Willebrand factor in cardiovascular disease: focus on acute coronary syndromes." *Circulation.* 2008 Mar 18;117(11):1449-59. doi: 10.1161/CIRCULATIONAHA.107.722827.
5. Kamhuisan P et al, "Cardiovascular risk in patients with hemophilia," *Blood*, (2014) 123(9), 1297-1301. DOI: 10.1182/blood-201311-453159.
6. Angelini D et al, "Managing older patients with hemophilia", *Hematology*, December 5, 2015, 41-47, DOI: 10.1182/asheducation-2015.1.41
7. Mega J et al., "Rivaroxaban in Patients with a Recent Acute Coronary Syndrome." *N Engl J Med* 2012;366:9-19.
8. Dogliotti A et al., "Novel Oral Anticoagulants in Atrial Fibrillation: A Meta-analysis of Large, Randomized, Controlled Trials vs Warfarin" *Clin. Cardiol*. 36, 2, 61–67 (2013)
9. Cabral K, "The role of factor Xa inhibitors in venous thromboembolism treatment," *Vasc Health Risk Manag*. 2015; 11: 117–123.
10. Budoff M et al, "Expert review on coronary calcium," *Vasc Health Risk Manag*. 2008 Apr; 4(2): 315–324.
11. Ruff C et al., "Meta-analysis of large NOAC trials shows favourable risk/benefit ratio over warfarin - Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials," *The Lancet*, Online Publication, 4 December 2013
12. Nakanishi R et al., "All-cause mortality by Age and Gender based on Coronary Artery Calcium Scores," *International Journal of Cardiology* , Volume 185 , 275 - 281, April 15, 2015
13. Agnelli G et al., "Apixaban for Extended Treatment of Venous Thromboembolism," *N Engl J Med* 2013;368:699-708, December 8, 2012. Also see: Ohman EM et al, "Clinically significant bleeding with low-dose rivaroxaban versus aspirin, in addition to P2Y12 inhibition, in acute coronary syndromes (GEMINI-ACS-1): a double-blind, multicentre, randomised trial," *The Lancet*, March 17, 2017. pii: S0140-6736(17)30751-1. doi: 10.1016/S0140-6736(17)30751-1.
14. Six clinical trials are underway looking directly at whether Factor Xa inhibitors slow or reverse development of coronary artery calcification. These research projects are each described on ClinicalTrials.gov. Study NCT02090075 is lead by Dr. Matthew Budoff in the USA; study NCT02544932 lead by Dr. Weon Kim in South Korea; study NCT01776424 is lead by Hamilton Health Sciences in Canada; study NCT02161965 is lead by Dr. Georges Leftheriotis in France; study NCT02376010 is lead by Dr. Mathhew Budoff in the USA; and study NCT02610933 is lead by Dr. Rogier Caluwe in Belgium. Also see: Supplemental information from Dr. Rogier Caluwé about "Effect on Vascular Calcification of Replacing Warfarin by Rivaroxaban With or Without VitK2 in Hemodialysis Patients" -- at https://docs.google.com/presentation/d/14lCVyYCQ1lpYy93AB8KMV_u_jCB1JoNnpDqBEX5S9Ho/edit#slide=id.p4
15. Carr J et al., "Association of Coronary Artery Calcium in Adults Aged 32 to 46 Years With Incident Coronary Heart Disease and Death," *JAMA Cardiol*. Published online February 8, 2017. doi:10.1001/jamacardio.2016.5493
16. Preis M et al, "Factor XI deficiency is associated with decreased risk for cardiovascular and venous thromboembolism events," *Blood*, 2017, 129: 1210-1215.Published online December 30, 2016.
17. "Phase 3 COMPASS Study of XARELTO® (rivaroxaban) Stopping Early for Efficacy; Study Meets Primary Endpoint of Prevention of Major Adverse Cardiac Events in Patients with Coronary Artery Disease or Peripheral Artery Disease," *Janssen statement*, February 8, 2017, available online at http://www.janssen.com/phase-3-compass-studyxarelto-rivaroxaban-stopping-early-efficacy-study-meets-primary-endpoint-0.

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6/14/2017