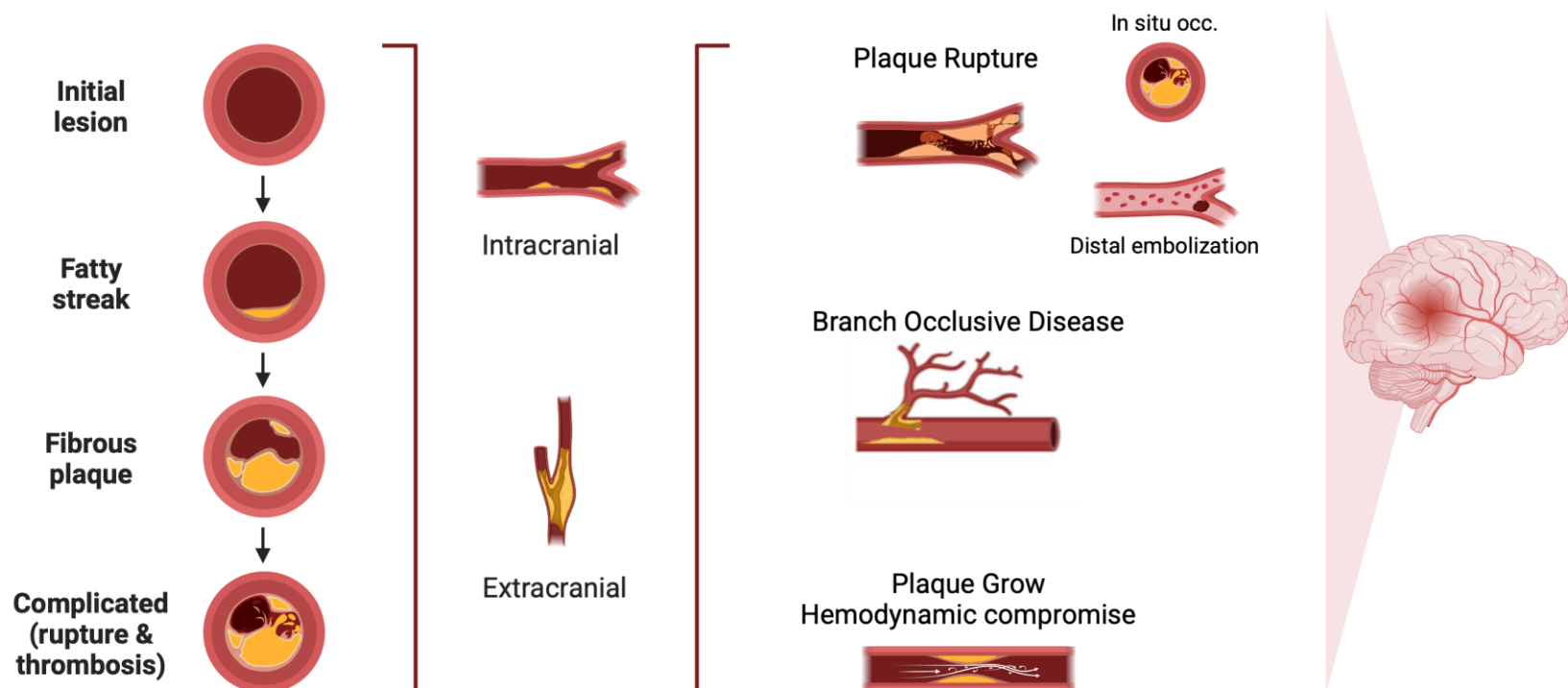


Atherosclerosis and Atherosclerotic Stroke

- Atherosclerosis is a systemic disease with a huge global burden
- Classical & novel vascular risk factors play a key role in development of plaques
- Atherosclerotic plaque vulnerability: main determinant of clinical disease
- Atherosclerotic stroke: A non cardio-embolic ischemic strokes associated with atherosclerosis
- Varies among races and populations ~ 1:4 strokes
- Atherosclerotic stroke is a major worldwide health care problem
- Remains an unmet need despite standard antiplatelet therapy with high risk of recurrence

Atherosclerosis progression

Atherosclerotic Stroke



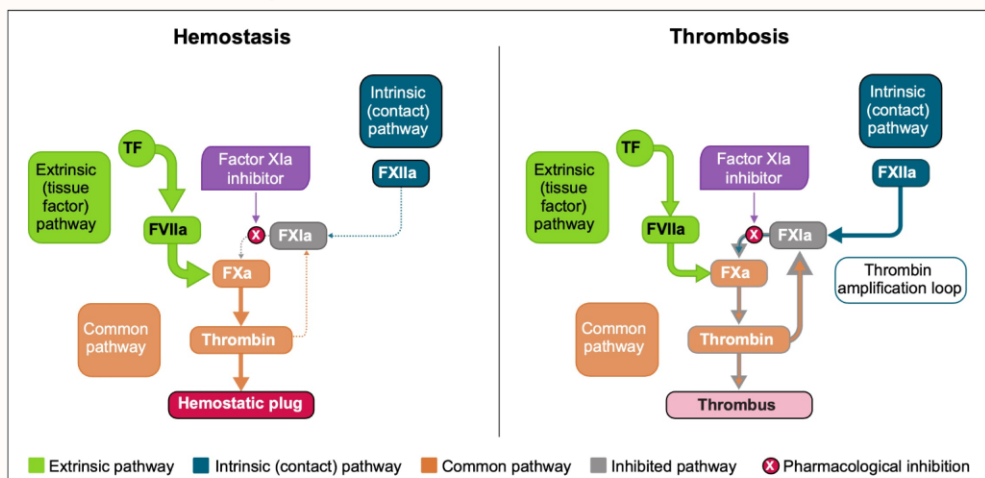
Treatment principles



- Antithrombotics are the mainstay for secondary prevention
- Early initiation of SAPT or DAPT is recommended for acute prevention, followed by SAPT for most patients
- Strategies aim to balance the reduction of ischemic events with hemorrhagic complications
- Aspirin is foundational (CAPRIE, ISTCC)
- Short-term DAPT ($\leq 21-90$ days; CHANCE, POINT, THALES) reduces recurrence
- Long-term DAPT increases bleeding risk — avoid
- Dual pathway inhibition with low-dose anticoagulant plus aspirin decreases risk of ischemic stroke but increases risk of major bleeding (COMPASS)
- Personalized approaches remain limited (e.g., CYP2C19 LOF carriers)

Emerging Approaches: Factor XI/XIa Inhibition in Combination with Antiplatelet Therapy

Uncouple pathologic thrombus formation from hemostasis



- Pathological thrombus growth occurs through the activation of FXI to FXIa via thrombin and a positive feedback loop.
- FXIa role for hemostasis and formation of a hemostatic plug is minor due to being part of the intrinsic pathway.

- Factor XIa inhibitors: uncouple hemostasis from thrombosis by preventing pathological thrombus formation without significant increase in major bleeding.
- This mechanism applies irrespective of underlying atherosclerosis.
- Phase 2 RTCs: reduction in ischemic stroke recurrence, particularly in atherosclerotic disease
- Phase 3 RTCs:
 - OCEANIC-STROKE (Asundexian): complete and met primary efficacy and safety endpoints; included participants *with or without* atherosclerotic disease
 - LIBREXIA-STROKE (Milvexian)
 - FXIa inhibition in combination with antiplatelet therapy for dual pathway inhibition concept

