

Molecular and Structural Heterogeneity of Anticoagulant Drugs



TFPI

Fibrinolytic modulators

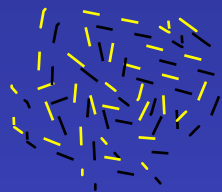
TAFI
PAI-1 inhibitor
Factor XIIIa inhibitor



HEPARIN



HIRUDIN



LMWH

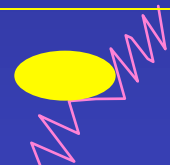
Peptidomimetics

Di-, tripeptides and
peptidomimetics

HIRULOG

Oligopeptides

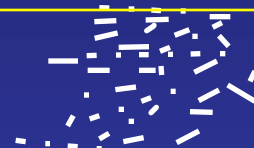
Recombinant drugs



Cyclic peptides



Heparin-derived oligosaccharides



Organomimetics



Peptidomimetics



r-Thrombomodulin
r-Antithrombin

TFPI = tissue factor pathway inhibitor; TAFI = thrombin-activatable fibrinolysis inhibitor-1; PAI-1 – plasminogen activator inhibitor-1

Safety Considerations with Anticoagulant Drugs

1. Bleeding
2. Allergic reactions
3. Thrombocytopenia
4. Skin necrosis
5. Liver toxicity
6. Vascular reactions
7. Rebound thrombosis
8. Anticoagulant resistance
9. Drug interactions
10. Population variations (gender, age and ethnicity)

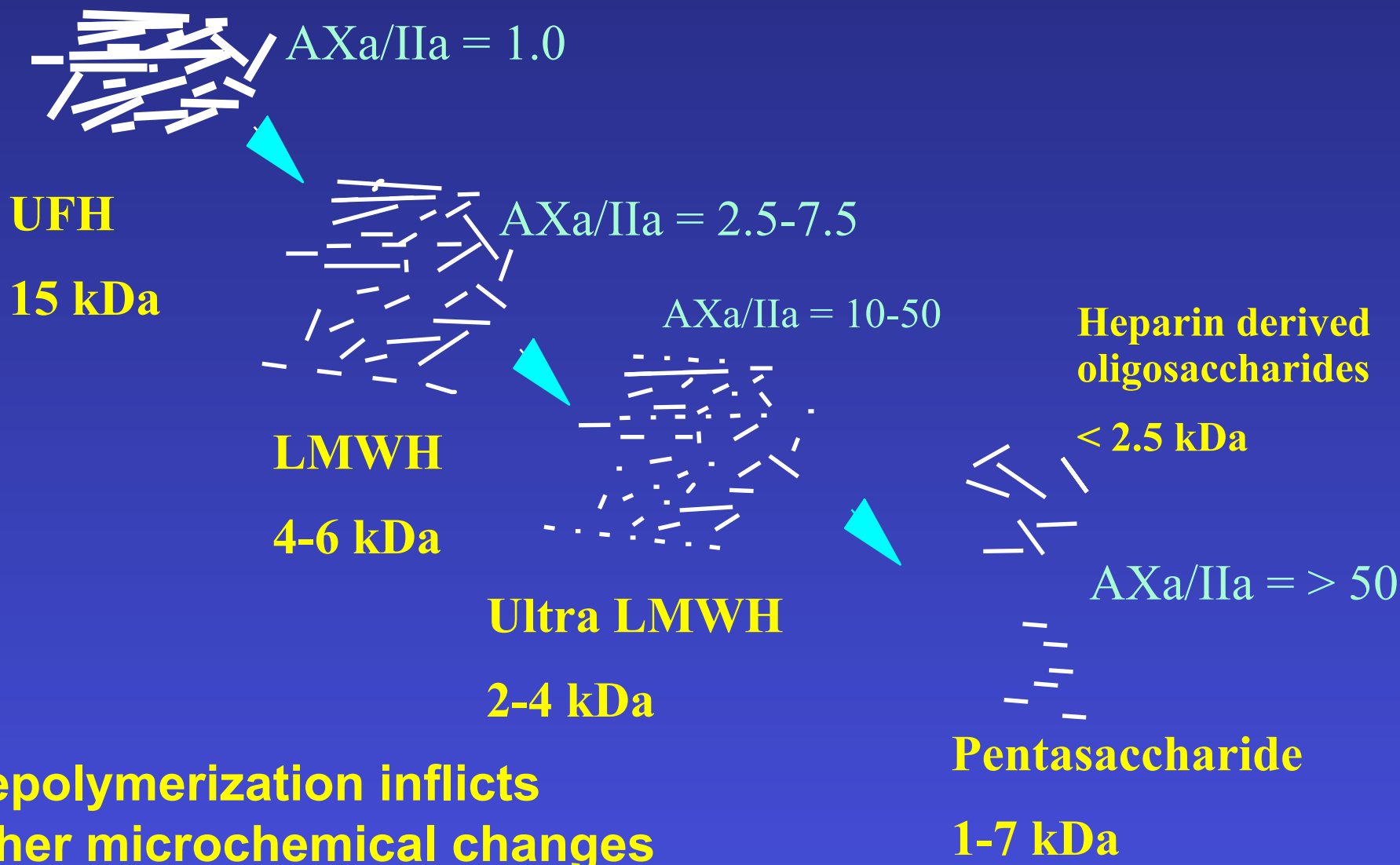
Molecular Heterogeneity of Heparin



- High Molecular Weight
- Medium Molecular Weight
- Small Molecular Weight

Both functional and molecular heterogeneity is observed. Different brands of heparin exhibit different safety, efficacy profile

Manufacturing Process for Low Molecular Weight Heparin and Lower Low Molecular Weight Heparins



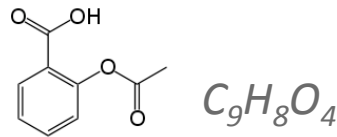
Comparison of Molecular Structure of Therapeutic Agents

Therapeutic Agent

Molecular Structure

Molecular Weight

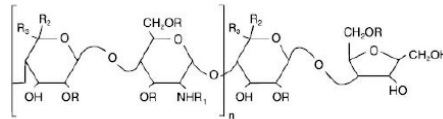
Acetylsalicylic Acid (*Aspirin*)



180 Daltons

Low Molecular Weight Heparins

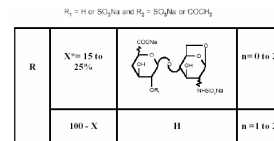
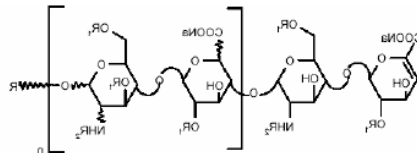
Fragmin



R = H or SO₃Na
 R₁ = COCH₃ or SO₃Na
 R₂ = H R₃ = COONa
 or
 R₂ = COONa R₃ = H
 n = 3-20

< 3000 Daltons 3-15%
 3000-8000 Daltons 65-78%
 >8000 Daltons 14-26%

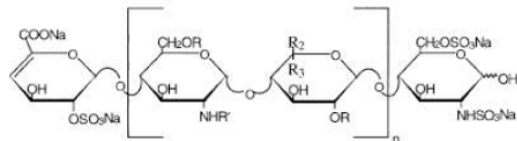
Lovenox



*X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end.

< 2000 Daltons ≤ 10%
 2000-8000 Daltons > 68%
 >8000 Daltons ≤ 18%

Tinzaparin



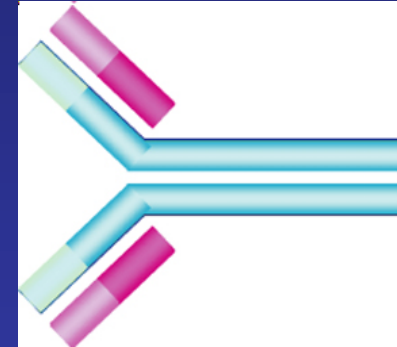
n = 1 to 25, R = H or SO₃Na, R' = H or SO₃Na or COCH₃
 R₂ = H and R₃ = COONa or R₂ = COONa and R₃ = H

< 2000 Daltons 10%
 2000-8000 Daltons 60-72%
 > 8000 Daltons 22-36%

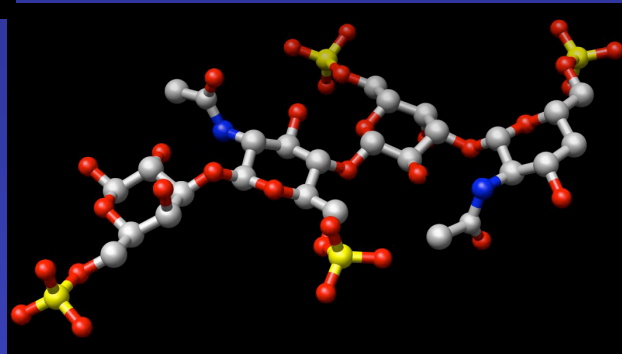
Biosimilar Drugs



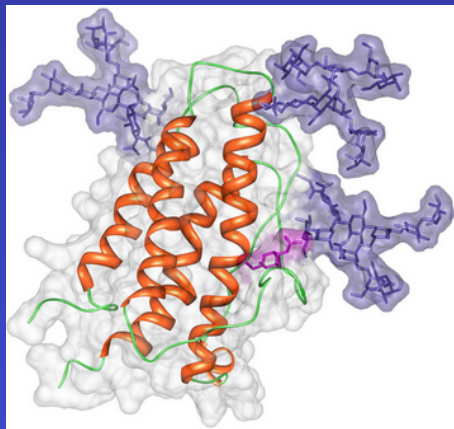
Proteins



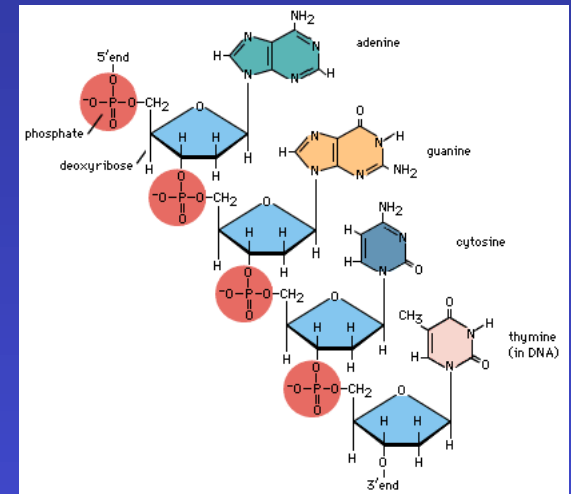
Antibodies



Polysaccharides



Glycosylated Proteins



Polynucleotides

Safety of Biosimilar Anticoagulants

- Unfractionated heparin

Anticoagulant efficacy and bleeding issues

- LMWHs

Pharmacodynamics and immunogenic issues

- Recombinant AT, TFPI, Hirudin, Activated Protein C, TM and others

Pharmacodynamic and immunogenic issues

Biosimilar anticoagulants can not be grouped together. Each class should be treated separately

Genericization of Biosimilar Drugs

1. **Biosimilar is a broad term which includes a variety of biopharmacologic agents including proteins, recombinant proteins, biopolymers, nucleic acid derivatives, lipids and other biologic agents.**
2. **Not all of the biosimilar drugs are the same.**
3. **Post-translational modification in recombinant proteins differentiates these from the natural proteins.**
4. **Pharmacodynamic behavior of a biosimilar drug may be very different.**
5. **A biosimilar can be manufactured by different processes.**
6. **Heparin and heparinoids should not be included in biosimilar drugs. These are very different from proteins.**
7. **Biosimilar should be differentiated from biogenerics which covers proteins and other biologics.**