Therapeutic Roles of Heparin Anticoagulants in Cancer and Related Disorders

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What is Heparin?

A mucopolysaccharide occurring especially in the liver and lungs that prolongs the clotting time of blood by preventing the formation of fibrin*.

Produced by basophiles and mast cells.

Two types: UFH and LMWH

*Fibrin is a white insoluble fibrous protein formed from fibrinogen by the action of thrombin, especially in the clotting of blood.
Basic Unit of the Chemical Structure of Heparin

Minimum sequence for AT binding

A = (CH2)₃

Regular region Irregular region Regular region Regular region
Main Sugars Occurring in Heparin

- $(\alpha)$-L-iduronic acid-2-sulfate
- 2-deoxy-2-sulfamino-$(\alpha)$-D-glucose-6-sulfate
- $(\beta)$-D-glucuronic acid
- 2-acetamido-2-deoxy-$(\alpha)$-D-glucose
- $(\alpha)$-L-iduronic acid

Other straight-chains may also be present, which makes UFH heterogeneous GAGs
Manufacturing Process for LMWHs and uLMWHs

UFH → Depolymerization → LMWHs → Depolymerization → Lower LMWHs → Depolymerization → Very-Low LMWHs
# Bovine vs. Porcine UFH

<table>
<thead>
<tr>
<th>Properties</th>
<th>Bovine UFH</th>
<th>Porcine UFH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Xa Activity</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Anti-IIa Activity</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>% LMW Fractions</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Bleeding Incidence</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>HIT / HITTS Incidence</td>
<td>Higher</td>
<td>Lower</td>
</tr>
<tr>
<td>Antithrombotic Efficacy</td>
<td>Less</td>
<td>More</td>
</tr>
<tr>
<td>Major Classes of Therapeutic Anticoagulant and Antithrombotic Drugs Available in the Market Place</td>
<td></td>
<td></td>
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<tr>
<td>-------------------------------------------------------------------------------------------------</td>
<td></td>
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<tr>
<td><strong>Thrombin (IIa) and Xa Inhibitors</strong></td>
<td><strong>Platelet Inhibitors</strong></td>
<td></td>
</tr>
<tr>
<td>Heparins (UFH, LMWH)</td>
<td>Cyclic peptides</td>
<td></td>
</tr>
<tr>
<td>Antithrombin agents (e.g., Hirudin, Hirulog)</td>
<td>Ticlopidine, Clopogrel</td>
<td></td>
</tr>
<tr>
<td>TFPI</td>
<td>ReoPro and YM337</td>
<td></td>
</tr>
<tr>
<td>Peptidomimetics (e.g., Argatroban, Pentasacharides)</td>
<td>Recombinant agents</td>
<td></td>
</tr>
<tr>
<td>Oligopeptides (e.g., Bivalirudin)</td>
<td>Peptidomimetics</td>
<td></td>
</tr>
</tbody>
</table>
Major Anticoagulant and Antithrombotic Therapies Currently Used to Manage TE Indications

Figure 3

Antithrombin Drugs

Cholesterol Lowering Drugs

Biotechnology-Derived Heparin-like Drugs

Anti-Xa Drugs

Approved Antithrombin Agent

Anti-TF Drugs

Heparinoids

Newer Developments in Antithrombotic Therapy

Plasma Activated Protein C

Oral Heparins and GAGS
Major Biochemical, Cellular, Molecular and Pharmacologic Effects of UFH and LMWH Therapy

- GAG Sparing Effect
- Endothelial Modulation
- Factor VII/VIIa
- Selectin Modulation
- TFPI, t-PA Release
- Anti-Xa/Anti-IIa
- Profibrinolytic Effects
- Drug Interactions
Potential Indications for Heparins

- Cancer
- Unstable Angina and Non-Q MI
- DIC/Sepsis
- DVT
- Prophylaxis/Treatment
- Surgical and Interventional Anticoagulants
- Hemodialysis
- IBD
- Atrial Fibrillation/Stroke

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Background (Cancer-Heparin)

- Cancer is a complex disease.
- A major cause of mortality.
- Heterogeneity causes difficulty in effective treatment design.
- Cancer patients have coagulation abnormalities (DIC).
- Inflammation and autoimmunity adds up to cancer.
- Western sedentary lifestyle also contributes to cancer and CVD leading to VTE / PE episodes.
- Haparin’s anionic property is responsible for inhibitory effects on malignant process, angiogenesis, tumor cell adhesion, and malignant cell transformation.
Top 5 Medical Co-morbidities Related to DVT

• Hypertension
• Immobility
• **Cancer**
• Obesity (BMI >30)
• Cigarette Smoking
Effects of Heparins in Cancer

• **Inhibits**
  – Angiogenesis
  – Activated coagulation proteases
  – Growth factors
  – Coagulation factors
  – Oncogene expression

• **Stimulates**
  – Immune system
  – Differentiation
  – Apoptosis
Comparison of Some of the Main LMWHs in the Marketplace - with Regards to its Biochemical Properties

<table>
<thead>
<tr>
<th>LMWH</th>
<th>Trade Name</th>
<th>Median MW (D)</th>
<th>Anti-Xa (IU/mg)</th>
<th>Anti-IIA (IU/mg)</th>
<th>Xa/IIa Ratio</th>
<th>Chemical Characteristics</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalteparin</td>
<td>Fragmin</td>
<td>5,000</td>
<td>122</td>
<td>60</td>
<td>2.0</td>
<td>Presence of 2,5-anhydro-D-mannose at reducing terminus</td>
<td>Pharmacia-Upjohn-Kissei</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Lovenox</td>
<td>4,800</td>
<td>104</td>
<td>32</td>
<td>3.3</td>
<td>Presence of 4,5-unsaturated uronic acid at non-reducing terminus</td>
<td>Rhone-Poulenc-Rorer</td>
</tr>
<tr>
<td>Nadroparin</td>
<td>Fraxiparin</td>
<td>4,500</td>
<td>94</td>
<td>31</td>
<td>3.0</td>
<td>Presence of 2,5-anhydro-D-mannose at reducing terminus</td>
<td>Sanofi-Winthrop</td>
</tr>
<tr>
<td>Raviparin</td>
<td>Clivarin</td>
<td>3,900</td>
<td>130</td>
<td>40</td>
<td>3.3</td>
<td>Presence of 2,5-anhydro-D-mannose at reducing terminus</td>
<td>Knoll-Abbott</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Innohep, Logiparin</td>
<td>4,500</td>
<td>90</td>
<td>50</td>
<td>1.8</td>
<td>Presence of 4,5 unsaturated uronic acid at non-reducing terminus</td>
<td>Braun Novo/Leo/DuPont</td>
</tr>
</tbody>
</table>

- **Most effective LMWH in preventing CAT. It benefits similar across sub-groups (such as age, gender, cancer type, obesity, and previous DVT).**
- **This is the only FDA-approved LMWH for treatment (as monotherapy) without any oral anticoagulant (e.g., Warfarin).**
- **Most commonly used LMWH for all clinical indications where UFH is avoided to prevent TE complications.**
# VTE Incidence in Various Tumors

<table>
<thead>
<tr>
<th>Oncology Setting</th>
<th>VTE Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer (Stage I &amp; II) without further treatment</td>
<td>0.2%</td>
</tr>
<tr>
<td>Breast Cancer (Stage I &amp; II) with Chemo</td>
<td>2%</td>
</tr>
<tr>
<td>Breast Cancer (Stage IV) with Chemo</td>
<td>8%</td>
</tr>
<tr>
<td>Non-Hodgkin’s Lymphomas with Chemo</td>
<td>3%</td>
</tr>
<tr>
<td>Hodgkin’s Disease with Chemo</td>
<td>6%</td>
</tr>
<tr>
<td>Advanced Cancer (1-year survival=12%)</td>
<td>9%</td>
</tr>
<tr>
<td>High-grade Glioma</td>
<td>26%</td>
</tr>
<tr>
<td>Multiple Myeloma (Thalidomide + Chemo)</td>
<td>28%</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td>43%</td>
</tr>
<tr>
<td>Solid Tumors (anti-VEGF + Chemo)</td>
<td>47%</td>
</tr>
<tr>
<td>Wilms Tumor (cavoatrial extension)</td>
<td>4%</td>
</tr>
</tbody>
</table>
Blood and Hemostasis

• Oxygen in the air is central to *blood* circulation.
• *Hemostasis* maintains circulating blood fluidity.
• *Hemostatic System* is fundamentally governed by:
  – Vascular endothelium
  – Platelets
  – Coagulation cascade
  – Fibrinolytic system
  – Other cellular cross-talks
• *Hemostasis* is a process of cessation of blood loss from a damaged vessel and consists of coordinated network of proteins, pro-coagulants, platelets, etc.
Inter-dependence of Blood (Hemostatic System) and Genetic Factors with Environment Resulting in the Increased Risks for Cancer-Associated TE Complications
Thrombosis and TE

• Thrombosis is an initiating reaction to vascular injury where TF released from blood cells play crucial roles.

• In pathological thrombosis, several inter-dependent systems/mechanisms become activated, such as:
  – primary hemostasis (platelet-vessel wall interactions)
  – secondary hemostasis (fibrin formation)
  – fibrinolysis

  Resulting in clot formation and inappropriate hemostasis.

• Clotting factors (biological amplifiers) - serine proteases.

• Genetic and acquired/hereditary risk factors also interact dynamically with environment in this process.
Genetic Risk Factors and TE

- Hereditary disorders have increased prothrombotic risk.
- Hereditary defects are: mutations in Protein S, Protein C, Antithrombin, Factor V Leiden, increased levels of Factors VIII, IX, XI.
- These mutations may selectively interact with other environmental factors leading to TE complications.
- Air travel, malignancy, higher BMI coupled with Factor V Leiden mutation /environmental factors results in TE.
- Molecular clock influences thrombotic events through regulation of time-dependent gene expression.

- Association of TE with genetic risk factors also results in cancer incidence.
Schematic Representation of Some of the Major Interactions of Platelets, Tumor Cells, and Vascular Endothelial Components Resulting in Prothombotic Environment
Regulation of VEGF Production and Angiogenesis by the Cytoplasmic Tail of TF

- TF regulates VEGF expression in human cancer cell-lines.
- Cells with increased TF are more angiogenic – therefore, more metastatic.
- Cytoplasmic tail of TF (containing 3 Ser residues) mediate signal transduction.
- Signaling pathways activated by TF/VIIa engagement of PAR-2 &/or thrombin pathways are directly involved in regulating tumor growth, angiogenesis & metastasis.
TF in Cancer: Lack of Standardized Assays

- IHC of tumor specimens
- TF ELISA
- TF MP procoagulant activity assay
- Impedance-based flow cytometry
Role of TFPI

- Natural (endogenous) inhibitor of TF
- Synthesized in vascular endothelium
- Serves as endothelial biomarker (AT-independent)
- Contains 276 AA residues with 18 Cysteine residues and 3 N-linked glycosilation sites, after removal of a 28-residue signal peptide.
- 3 polymorphisms have been identified in TFPI gene
- Plasma levels of **total** and **free** TFPI do not always correlate with experimental studies or clinical indications (b/c of the differential regulatory effects of anticoagulants/antithrombotics in vivo.)
Platelet Physiology and Functions

- **Platelets** (thrombocytes), anucleated blood cells.
- Arise from large megakaryocytes (bone marrow), and derived from hematopoietic stem cells.
- Interacts with soluble physiological agonists:
  - Epinephrine
  - ADP
  - Thromboxane
  - PAF
  - Cell matrix components (collagen, fibronectin, laminin)
  - Pathogenic microorganisms
- Activated platelets release angiogenic growth factors, thereby contribute to tumor angiogenesis
Impact of Various Heparin MW Fractions on Angiogenesis

- Pro-angiogenic bFGF and some isoforms of VEGF bind heparins and modulate their bioavailability

- Only 3,000–6,000 D fractions attenuate bFGF-induced angiogenesis (dose-dependently)

- Thus, LMWH preparations seem to be ideal fractions to exert anti-tumor effects in experimental models (and some clinical trials)
Environment and Platelet Physiology

- Environmental toxicants (e.g., pesticides, herbicides, fungal toxins) affect platelet functions.
- Industrial pollutants (e.g., CO, CS$_2$, Pb, Cd) greatly influence platelet physiology.
- Automobile exhaust affects platelet functions leading to bronchial asthma.
- Environmental pollutants enhance plasma phospholipase activity leading to inflammation.
- Free radicals, lipid peroxides inhibit prostacyclin synthase and NOS, deplete platelet glutathione.
- Up-regulation of cell signaling pathways lead to TE, downregulation of such signal transduction may lead to bleeding, wound-healing, and autoimmune responses.
Diet and Ageing

- Macro- and micro-nutrients (with bioactive food components) alter pre-disposition to thrombosis.
- Dietary carbohydrates influence thromboxane $A_2$ production, platelet aggregation, bleeding time, etc.
- Changes in the nutritional environment with ageing influence the risk of thrombophilia.
- Hypercaloric diets (with glycemic loads) increases the risks of obesity and other CVD.
- Diet with one or more regular soft drinks daily is associated with increased risk of metabolic syndrome.
- Circulating levels of inflammatory markers are linked with ageing.
- Sarcopenia results in lowered metabolic rate.
- Changes in plasma/blood osmolarity trigger problems.
Natural Compounds and Products

- Herbal and other natural compounds are widely used to treat cancer and TE disorders.
- Risks of immune-mediated and CV disorders are reduced with high consumption of vegetables/fruits.
- Potent therapeutic phytocompounds help increase bile acid production, elimination of excess cholesterol, and elevation of hepatic antioxidant status.
- Phytochemicals have great potential in preventing cancer and TE with virtually no cytotoxicity, low cost, and excellent oral bioavailability.
Air Pollution and Weather

- Indiscriminate use of chemicals as pesticides has introduced persistent toxins in the environment.
- Air pollution and cigarette smoking has long been associated with increased CVD morbidity/mortality.
- Seasonal variations influence thrombosis and PE.
- Environmental particles and fossil fuel pollutants contribute to PE and thrombosis.
- Inhaled particles and polluted vapor droplets absorbed by lungs affect systematic inflammation / coagulation.
- Long air travels “Economy-Class Syndrome” with pre-existing co-morbid conditions has greater risk of TE.
Inconclusive evidence to date

Experimental data supportive of anti-tumor effects but exact mechanisms not established

Clinical trials provide supportive data for LMWH but are heterogeneous in design and methodology

- Tumor types
- Stage or course of disease
- Treatment history or concurrent cancer therapies
- LMWH agents
- Doses and regimens of LMWHs

Lee A, ICTHIC, 2010
Cancer and Thrombosis
State-of-the-Science

1. Does activation of blood coagulation affect the biology of cancer positively or negatively?
   • Epidemiologic evidence is suggestive that VTE is a bad prognostic sign in cancer.

2. Can we treat tumors more effectively using coagulation protein targets?
   • Experimental evidence is supportive of the use of anti-thrombotic strategies for both prevention of thrombosis and inhibition of tumor growth.

3. Can anticoagulation alter the biology of cancer?
   • Results of recent, randomized, clinical trials of LMWHs in cancer patients indicate superiority to oral agents in preventing recurrent VTE; increasing survival (not due to prevention of VTE) not clear.
LMWH in Cancer

**Survival Studies**

- **INPACT** (NSCLC, Prostate, Pancreatic)
  - Nadroparin+Chemo vs. Chemo

- **ABEL** (limited SCLC)
  - Bemiparin+Chemo vs. Chemo

- **TILT** (NSCLC)
  - Tinzaparin+Chemo vs. Chemo

- **FRAGMATIC** (Newly Diagnosed LC)
  - Dalteparin+Chemo vs. Chemo
Semuloparin for Thromboprophylaxis in Patients Receiving Chemotherapy for Cancer

Giancarlo Agnelli, M.D., Daniel J. George, M.D., Ajay K. Kakkar, M.B., B.S., Ph.D., William Fisher, M.D., Michael R. Lassen, M.D., Patrick Mismetti, M.D., Patrick Mouret, M.D., Umesh Chaudhari, M.D., Francesca Lawson, M.D., and Alexander G.G. Turpie, M.D., for the SAVE-ONCO Investigators*

CONCLUSIONS
Semuloparin reduces the incidence of thromboembolic events in patients receiving chemotherapy for cancer, with no apparent increase in major bleeding. (Funded by Sanofi; ClinicalTrials.gov number, NCT00694382.)
Semuloparin (AVE5026), uLMWH

Proposed Indication: Prophylaxis of VTE in patients receiving chemo for locally advanced or metastatic solid tumors.

Structure: Sodium salt of a LMWH that is obtained by phosphazene promoted depolymerization of heparin from porcine intestinal mucosa; the majority of components have a 4-deoxy-2-O-sulfo-α-L-threo-hex-4-enopyanosuronic acid structure at the non-reducing end and a 2-deoxy-6-O-sulfo-2-(sulfoamino)-D-glucopyranose structure at the reducing end of the chain.”


Activity: High anti-FXa (~160 U/mg), only residual anti-FIIa activity (~2 U/mg).

Blocking FXa, blocks the enzyme essential significant to the coagulation cascade, which is responsible for forming blood clots in the body.

Shorter Heparin Chain allows higher bioavailability & slower clearance (renal)

Enriched in AT binding sequences and LMW = less anti-FIIa activity.

Phase 1 Trail: Half-life was found to be 16-20 h (Enoxaparin = 4-5 h).

Preparation: highly selective depolymerization reaction using a phosphazene base, allowing lower molecular weights than typical LMWH.
SAVE-ONCO Trial (Semuloparın)

- Chemotherapy is recognized as increasing the risk factor for VTE in patients with cancer.

Inclusion Criteria:
- Cancer patient with locally advanced metastatic solid tumors of the lung, pancreas, colon-rectum, bladder, or ovary.

Exclusion Criteria:
- Patients requiring systematic venous thromboprophylaxis or curative treatment with anticoagulant or thrombolytic agent
- Patient at high-risk of bleeding
- Severe renal impairment (estimated creatinine clearance <30 mL/min)
- ECOG performance status 3&4
- Known hypersensitivity to UFH or LMWH

- Randomized, double-blind, multicenter trial, 3,212 patients in trial, 395 centers in 47 countries.
- Drug vs. Placebo group chosen by minimization algorithm taking into account primary cancer, cancer stage, and geographic region.
Results (SAVE-ONCO Trial)

• Primary Efficacy outcome was the composite of any symptomatic DVT in lower or upper limbs, any non-fatal PE or death related to VTE occurring between randomization and 3-days after last injection of study.

• Primary efficacy outcomes occurred in 20/1608 (1.2%) in Semuloparin group and 55/1604 (3.4%) in the Placebo group.

• Semuloparin was associated with reduction in the risk of both DVT and fatal & non-fatal PE.
Conclusions (SAVE-ONCO Trial)

• This double-blind study had sufficiently large sample size to assess the benefits and risks of Semuloparin in the target population.

• Semuloparin, compared with Placebo, reduces the incidence of VTE in patients with metastatic or locally advanced cancers.

• Semuloprin had no significant effect on major bleeding or mortality.
Importance of DVT Prophylaxis in Patients with Cancer: ASCO Guidelines

- VTE is a leading cause of death, occurring in 4-20% of CA patients
- Hospitalized CA pts and those on chemo tx have greatest VTE risk
  - Cancer increased the risk of VTE 4.1-fold
  - Chemotherapy increased the risk 6.5-fold
- **Major risk factors:** older age, co-morbid conditions, recent surgery or hospitalization, active chemo or hormonal therapy
- All hospitalized CA patients should be considered for prophylaxis
- CA patients undergoing surgery be considered for prophylaxis
- LMWH is the preferred drug
Panel recommends VTE thromboprophylaxis for all hospitalized patients with cancer who do not have contraindications to such therapy.

Panel also emphasized that an increased level of clinical suspicion of VTE should be maintained for cancer patients.

Following hospital discharge, it is recommended that patients at high-risk of VTE (e.g., cancer surgery patients) continue to receive VTE prophylaxis for up to 4-weeks post-op.

Generic Version of Brand LMWHs:

Are the Current Regulatory Guidelines Adequate?

No, not Specific Enough!

Because of the complex nature of these agents requiring both the biologic and chemical expertise, there are no specific guidelines at this time.
Biomarkers that can be Useful While Assessing Cancer-Associated TE Events

- Blood counts
  - Platelet count
  - Leukocyte count
  - Hemoglobin
- D-dimer
- Selectins (e.g., sP-selection)
- Tissue factor
- C-reactive protein
- Factor VIII
- Heparin-PF4 antibodies
Disadvantages of Heparin(s)

- Bleeding
- Thrombocytopenia
- Poor Bioavailability
- Drug Interactions
- Anticoagulant Response Variations

Despite these disadvantages, heparin has remained the drugs of choice for the management of cardiovascular and thrombotic disorders.
Thrombosis in HIT

A catastrophic syndrome related to heparin therapy
Generation of Heterogeneous Antibodies with Heparin and PF4
Role of Heparin-PF4 Antibodies in the Pathogenesis of HIT

- Functional Antibodies
- Non-Functional Antibodies
- Selectins
- Leukocytes
- Platelets
- TF
- Heparan Sulfate
- PF4
- UFH
- Super-Active Antibodies
- Thrombogenesis
- Microparticles

Terminology:
- PF4: Proteinase-activated receptor-4
- UFH: Unfractionated Heparin
HIT / HITTS

- HIT is a devastating complication of UFH therapy - occurs in ~1-5% of patients.
- Formation of heterogeneous group of HPF4 antibodies and platelet / EC activation through FcγRIIa is crucial.
- It is not clear why only a sub-group of patients that form HPF4 antibodies also develop clinical HIT (HITTS).
- Ability (functionality) of HPF4 antibodies to activate platelets / EC depend on the source, type, duration, and administration route.
Microparticles

- Originate directly from membrane surface of activated or apoptotic cells
- Express surface antigens derived from parent cell
- Anucleate
- $< 1$ micrometer in diameter
- Procoagulant activity mediated by TF / PS
Generation of PMP in HIT

PF4

Heparin

Heparin/PF4/
Antibody

Heparan
Sulfate

Heparin
Q. What do the experimental studies tell us?

A. They suggest two things:

1. Tumor cell-derived, TF-rich MPs may be important as a predictive test for VTE.

2. All patients with oncogene-driven cancer may need prophylactic anticoagulation.
PMP Detection by Flow Cytometry

Citrated WB

3,000 rpm
15 min, RT

Plasma

Number of PMP/mL

Flow Cytometric Analysis

Anti-CD41 (FITC) or Mouse IgG (FITC)

1 x 10^5 (1.9 µm) Microspheres + Saline

30 min, RT
Antibody Labeling of PMP

- Labeling CD41 (GPIIb/IIIa) results in higher PMP counts than GPIlb
Conclusions

- Evidence is supportive of heparin anticoagulants for both prevention and inhibition of tumor growth.
- Cancer and VTE are closely linked. Cancer increases VTE risk (and may be occult when VTE is diagnosed).
- DVT 3-fold higher recurrence and bleeding, when treating cancer patients
  - LMWH monotherapy (e.g., Dalteparin) halves recurrence vs. Warfarin (CLOT Trial)
- Rate of PE diagnosis is increasing ~2-fold
- ACCP, ASCO, NCCN Guidelines endorse VTE / PE prevention with LMWH - and VTE treatment of cancer patients with LMWH monotherapy.
- Hospital costs are skyrocketing in surgical patients.
- As cancer therapies improve, Q-o-L will be extended
Future Perspectives

• TE disorder is the 3rd commonest cause of death.

• LMWHs are preferred treatment with Warfarin failure (especially in patients with high-risk of bleeding).

• Studies related to cancer biology and oncology outcomes coupled with autoimmune responses would be crucial for the well-being of the society.

• Clinically, the ability to metabolize heparins and the immunocompetence of the patient is likely to contribute towards the immunotoxic side-effects of therapy.

• Individual lifestyle, environmental factors, immunologic and genetic circumstances contribute to the paradigm.

• Better designed clinical trials need to be conducted to ensure that heparins have substantial therapeutic benefits.
Thank You!