The 22nd Annual Benjamin Oluwakayode Osuntokun Memorial Lecture

B.O. Osuntokun Trust

1996

Venous Thrombo–Embolism

– an often overlooked disorder

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Introduction

I feel honoured and delighted to deliver the 22nd memorial lecture of Late Professor Benjamin Oluwakayode Osuntokun. I have been fortunate to have attended virtually all the previous 21 memorial lectures except 3 of them. I have always admired the ease at which each erudite speaker had delivered his or her lecture, though I was left in no doubt that a lot of hard work had gone into preparing these lectures. Not in my widest dream did I think I would be asked to deliver this memorial lecturer at this stage of my life, judging by the caliber of the previous speakers.

For this special privilege given me, I must at this juncture thank profusely Prof. Bopo Osuntokun and members of the Board of trustees for considering me worthy to give this memorial lecture. Prof Bopo Osuntokun taught my husband and I in the medical school and left us in no doubt, along with Prof. Oyin Olurin that nothing but the best of care was good enough for their patients.

Perhaps the elegance and beauty of these 2 Ophthalmologists must have impressed my husband that when we wanted to apply for Residency training in UCH, Temitayo Shokunbi felt I should opt for Opthalmology as my choice of specialty, perhaps hoping that I could be moulded into a similar image of Prof. Oyin Olurin and Prof. BopoOsuntokun. I cleverly dodged into the haematology discipline, as Prof. G.J.A. Esan has always been my role model and mentor.

Four Haematologists have given this memorial lecture in the following order:

1. Prof. Etim M. Essien (of blessed memory). Title: A forest long ago and Yesterday: what about Tomorrow? Year 2000
2. Prof. Lucio Luzzatto. Title: The Role of Heredity and Environment in the Causation of Cancer. Year 2003
3. Prof. G.JA.. Esan. Title: Laboratory Services and the Quality of medical Care. Year 2008
4. Prof. Olufunmilayo Falusi Olopade. Title: Precision

Medicine for All: Building on the Osuntokun legacy of Excellence in Clinical Medicine. Year 2016

Did I know Prof. Benjamin Olukayode Osuntokun? Yes I did. He was the Dean of our medical school (1974 – 1978) when I was a student. He gave us some lectures in Neurology, my classmates were all in awe of him. His lecture gave me the notion that you had to be a genius to be a Neurologist, and I felt I had better look elsewhere. He would walk quietly along UCH corridors, always well dressed and not given to frivolous corridor discussions with his colleagues.

There was something majestic about him, which I could not figure out until I went through his CV and the list of publications that he prepared to mark his 60th Birthday anniversary. I always made it a point of duty to greet him, to which he would quietly nod his head, and in my mind I would say if only this man knew how much admiration his students had for him.

For the younger generation who desire to have a glimpse of who Prof. Osuntokun was, I would recommend you read the first memorial lecture by Prof. Lateef Salako NNOM titled "Then and Now: Unraveling the mysteries of ill Health through Research".

The publication on "An Ataxic Neuropathy in Nigeria" by professor B.O. Osuntokun was well spoken off in many specific discussions on Medicals science in Africa. The amount of scientific work that was conducted in this study sponsored, through a Rockfeller Research Fellowership was immense. The work was first presented at the First Neurological Symposium in 1966. The study involved 84 patients with ataxic neuropathy in the coastal towns sensory loss, ataxic gait, rombergism, bilateral optic atrophy, perceptive deafness and wasting and weakness in the legs. one third had mucocutaneous evidence of ariboflavinosis. Serum folic acid and B12 were normal or high in these patients. The paper concluded that the syndrome of Ataxic Neuropathy was due to chronic exposure to dietary cyanide. This is one of the best examples of unravelling the mystries of ill health through research.

My late brother Prof. Gabriel Oluremi Olaofe, a mathematician (also an old student of Christ's School and a classmate of Prof. G.J.A Esan) spoke highly of Prof. B.O Osuntokun, almost hinting me that you had better strive for nothing but excellence since you chose to study Medicine rather than Mathematics.

History of VTE

The earlier cases of DVT were seen between 1271–1700s, Unlike the situation for varicose veins, leg ulcers, or lower limb edema, to which there are extensive references in antique art and literature, the first description of a case truly compatible with a DVT first appeared during the Middle Ages. In the manuscript titled 'La vie et les miracles de Saint Louis', it was reported that, in 1271, Raoul, a 20-year-old Norman cobbler suffered unilateral pain and swelling of the right calf that subsequently extended up to the thigh (Fig. 1)

In antiquity, neither famous Greek physicians such as Hippocrates and Oribasius, nor Roman physicians such as Galen or Caelius Aurelianus, reported a case suggesting a diagnosis of DVT; this is also true of the art of ancient Egypt, Persia, and South America. Nevertheless, it is likely that this disease is as old as human kind, and it may have affected famous historical figures

Brenner opined on the basis of happenings in the New Testament, that Jesus Christ himself may have suffered from a PE, but this hypothesis is debated. The oriental scientist

Avicenna (980– 1037) warned against the risk of 'particle migration' in cases of vein surgery, consistent with embolization of a DVT, but provided no formal description. Thus, although venous thrombosis is a frequent disease, it appears that no cases clearly compatible with the diagnosis of DVT were reported before the description of the case of Raoul. After this first unquestionable description by Guillaume de Saint Pathus, the number of reported cases of DVT increased rapidly, and the first pathologic hypotheses arose, leading to the first treatment attempts.

During the Renaissance, physicians hypothesized that pregnancyrelated DVT, which was the leading, or even only, cause of reported DVT at that time, was the consequence of retention of 'evil humors'. It was also thought that postpartum DVT was caused by retention of unconsumed milk in the legs ('milk leg'). Thus, in the late 1700s, breast-feeding was encouraged to prevent DVT. Of course, the most frequent and popular method among physicians to discharge evil humors during the 17th century was blood letting, as immortalized in Moliere's theatre play 'The Imaginary Invalid (1673)'. This technique was used to treat DVT and many other diseases until the end of the 19th century.

From the 17th century, the humoral theory, which was previously used to explain DVT pathophysiology, was gradually abandoned. In 1676, Wiseman suggested that DVT was the consequence of an alteration of blood, and then, in 1793, Hunter hypothesized that it was an occlusion of the vein by blood clots. In 1784, well before Virchow

demonstrated the relationship between DVT and fatal PE (1856), Hunter had performed venous ligations above the thrombosus to prevent extension of clots. In the absence of any other truly effective treatment for preventing fatal PE, this technique became more widely used at the end of the 19th century. It was assumed to be of 'immense value in reducing the incidence of PE'. The ligation could be performed at the femoral, common femoral, iliac and inferior vena cava (IVC) levels in cases of proximal thrombosis, and more rarely in cases of distal thrombosis, although this latter therapeutic intervention remained controversial. However, during the 19th century, the most commonly accepted underlying mechanism for DVT was the inflammation of the vein wall provoked by and/or provoking an infectious phenomenon. This was consistent with the observation that DVT is, in many cases, associated with fever, and frequently occurred postpartum, after septic surgical procedures, or during bed rest for an infectious disease. Consequently, the treatments prescribed involved anti-inflammatory medication and the prevention and treatment of infection. These therapeutic attitudes, based on the theory of inflammation and infection, started to become obsolete in the early 1900s.

By the middle of the 19th century, the major pathologic mechanisms of venous thrombosis had been discovered. They were first summarized in the famous Virchow's triad (1856), theorized by Andral in 1831 and which Virchow probably never described. However, it was only towards the

1920s that a consensus appeared regarding the three factors contributing to thrombosis: stasis, vessel wall alteration, and hypercoagulability. During this period, a number of therapeutic breakthroughs, most of them discovered by accident, revolutionized DVT treatment.

Venous thromboembolism (VTE) is rapidly changing into a common disease. Deep vein thrombosis (DVT), a component of VTE was the first to be diagnosed, though its description was more recent in the history of medicine when compared to other diseases such as varicose veins. The first well-documented case of DVT was reported during the middle ages,evidenced by a unilateral edema in the ankle, which then extended to the leg. The number of reported DVT cases has steadily increased, particularly in pregnant and postpartum women.

Fig. 1. Raoul, the first case of deep vein thrombosis (1271)

Epidemiology Of Venous Thromboembolism

Venous thromboembolism is a common disease. It is believed to have an increasing incidence globally and has been categorized as a major public health problem. VTE has a propensity for recurrence, which considerably reduces the chances of survival in those affected. The cost of management is substantial in terms of the investigations required to establish a diagnosis, and the enormous cost depending on the type of anticoagulation employed.

VTE is a disease with multifactorial causes, involving an interaction between acquired or inherited predispositions to thrombosis (i.e thrombophilia) and environmental exposure (i.e clinical risk factors). The most commonly documented risk factors for VTE are increasing age, obesity, hospitalization for acute illness or surgery, active cancer, trauma or fracture, immobility or leg paresis, nursing- home confinement and in women of child bearing age, pregnancy and puerperium, oral contraception and hormone therapy to mention a few.Overall, about 25% to 50% of patients with first-time VTE (i.e. unprovoked VTE)has an idiopathic origin, without a readily identifiable risk factor.

The incidence of VTE is higher in African – American than in Caucasians but lower in Asians, Asian- and Native-Americans. The estimated annual incidence in persons of European ancestry ranges from 104 – 183, 29 – 78, and 45 – 117 per 100 000

person-years respectively for VTE, PE ± DVT, and for leg DVT alone.

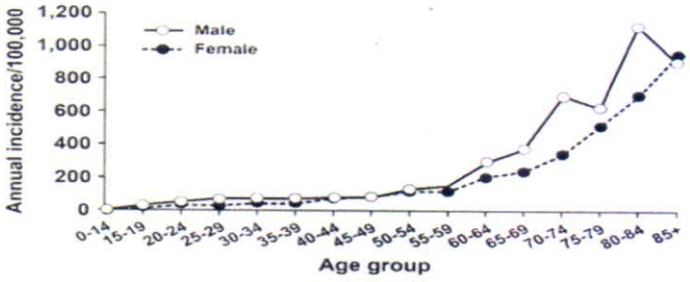
The overall first and recurrence VTE rate range from 142 to over 300 per 100,000 person-years; while the estimated rates for PE ± DVT and DVT alone range from 51 – 75 and 91 – 255 per 100,000 respectively. In this, current or recent hospitalization accounts for 330 compared with 8per 100 000 for persons residing in the community meaning that being hospitalized carries about 42 fold risk VTE. It has been estimated that an average of about 548,000 hospitalizations with VTE occurred each year among USA residents aged 18 years and above, of which 349,000 were DVT and 278,000 were PE. A crude estimate of an extrapolation to the Nigerian population of about 200 million suggests that about 330,120 Nigerians are likely to be hospitalized for VTE annually, about 64% of this are due to DVT(n=210,240) and 36%(n=1119,879) are PE.

In Africa, the prevalence of DVT in patients after surgery varies between 2.4% and 9.6%, and incidence in pregnant and postpartum women varies between 338 to 448 per 100 000 births per year. Tuberculosis was associated with a prevalence of DVT of 61.5% in a single study.

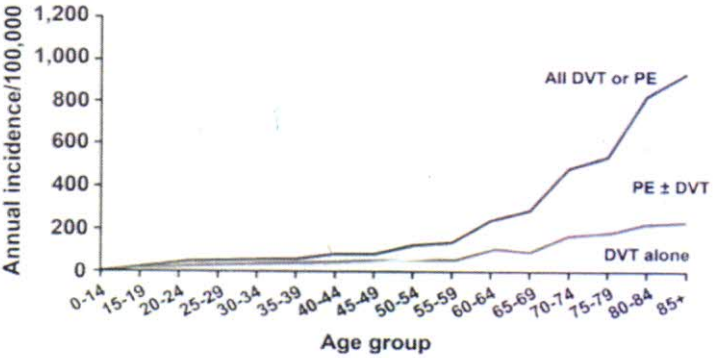
The prevalence of PE in patients with medical illness varied between 0.14% and 61.5% with a mortality rate of between 40% and 69.5%. The case-fatality rate after surgery was 60% in a single study. Overall, the prevalence of VTE in Africa appears to be lower than what has been found in most studies performed in the US population of African origin.

Kotila et al in Ibadan reported a prevalence of 35.6 patients per year over a five year period . Patients with distal deep vein thrombosis (DVT) were in the majority (76%) compared with

proximal DVT and PE which were 21% Vs 3%. About 4% of the patients had a recurrence of the VTE,the male patients having twice the likelihood of a re-thrombosis. Common comorbid states observed are cerebrovascular disease (14.5%), cancers (12.2%), retroviral disease (6.7%) and diabetes (6.2%). Prostatic cancer was more common than other cancers while patients with retroviral disease are more likely to have an extensive DVT.



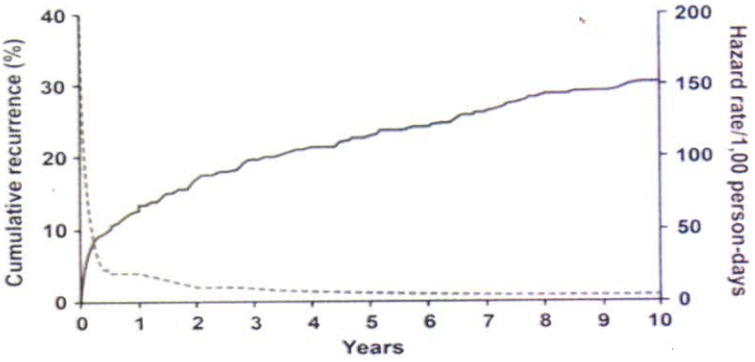
Annual incidence of venous thromboembolism by age and sex.
and Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrom J (2007) Incidence and mortality of venous thrombosis: a population-based study. J ThrombHaemost 5:692–699.



Annual incidence of all venous thromboembolism, deep vein thrombosis (DVT) alone, and pulmonary embolism with or without deep vein thrombosis (PE ± DVT) by age.
Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd (1998) Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population- based

Old age is a blessing from God however there are a few challenges. VTE incidence rises exponentially with increasing age, <5 cases per 100,000 persons <15 years old to ≈ 500 cases (0.5%) per 100,000 persons at age 80 years.The incidence rates increase markedly with age for both men and women and for both DVT and PE.As regards gender distribution, the overall age-adjusted incidence rate is higher for men (130 per 100,000) then women (110 per 100,000;) with a male: female ratio of 1.2:1. Incidence rates are somewhat higher in women during child bearing years, while incidence rates after age 45 years are generally higher in men. PE accounts for an increasing proportion of VTE with increasing age for both sexes. The percentage of incident VTE events that are idiopathic (i.e. unprovoked VTE) ranges from 25 to 40 %

One of the complications of VTE is the propensity for recurrence and risk after the first event, and this is highest within the first 6–12 months inspite of anticoagulant therapy, with a recurrence rate of about 7% at 6 months and this rate never falls to zero. The estimated recurrence rate in the first 10 years after initial diagnosis is 30%.The absolute rates of recurrence for VTE, PE ± DVT and DVT alone range from 19 – 39, 4 -13, and 15 – 29 per 100,000 person-years, respectively.



Cumulative incidence of first venous thromboembolism recurrence (continuous line), and the hazard of first recurrence per 1000 person-days (dotted line).
Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ 3rd (2000) Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med 160:761–768

It is important to bring to the fore Independent predictors of VTE recurrence and these include increasing patient age (per 10 years), body mass index (per 10 kg/m2), male sex, active cancer and neurologic disease with leg paresis . Additional predictors of recurrence include idiopathic VTE, a lupus anticoagulant or antiphospholipid antibody, antithrombin, protein C or protein S deficiency, hyperhomocysteinemia, a persistently increased plasma D-dimer among patients with idiopathic VTE, and possibly residual vein thrombosis. Among active cancer patients, VTE recurrence risk can be further stratified by cancer site (pancreatic, brain, lung and ovarian cancer, myeloproliferative or myelodysplastic disorders), stage IV cancer, cancer stage progression and leg paresis.

However, several risk factors present at the time of the incident VTE event are associated with either a reduced risk of recurrence or are not predictive of recurrence . For women,

pregnancy or the postpartum state, oral contraceptive use, hormone therapy, and gynecologic surgery are associated with a reduced risk of recurrence. Recent surgery and trauma/fracture either have no effect or predict a reduced risk of recurrence. Additional characteristics having no significant effect on recurrence risk include recent immobilization, tamoxifen therapy, and failed prophylaxis. For these patients, and for patients with isolated calf vein thrombosis, a shorter duration (i.e., 6 weeks) of acute therapy is likely to be adequate

Finally, patients with a recurrent event are significantly more likely to have the same type of VTE event as the initial VTE event.

COST OF TREATMENT

It has been estimated that the adjusted mean predicted costs were 2.5-fold higher for patients with VTE related to current or recent hospitalization for acute medical illness compared to hospitalized controls matched on active cancer status from the VTE event date (or index date for controls) to 5 years post index event.

Similarly, the adjusted mean predicted costs were 1.5-fold higher for patients with VTE related to current or recent hospitalization for major surgery compared to hospitalized controls matched to cases on type of surgery and active cancer status from the VTE event date (or index date for controls) to 5 years post index

Survival (%) after deep vein thrombosis vs. pulmonary embolism.

Time	Deep vein thrombosis alone	Pulmonary embolism
0 days	97.0	76.5
7 days	96.2	71.1
14 days	95.7	68.7
30 days	94.5	66.8
90 days	91.9	62.8
1 year	85.4	57.4
2 years	81.4	53.6
5 years	72.6	47.4
8 years	65.2	41.5

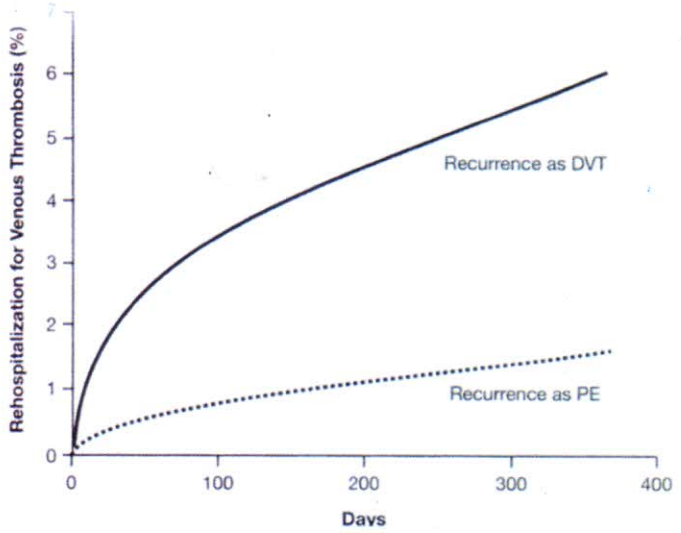
Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ 3rd (1999) Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. Arch Intern Med 159:445–453

Baseline characteristic	Odds ratio	95 % CI
Body mass index (kg/m^2)	1.08	1.05, 1.11
Major surgery	18.95	9.22, 38.97
Hospitalization for acute medical illness	5.07	3.12, 8.23
Nursing home confinement	4.63	2.77, 7.74
Trauma/fracture	4.56	2.46, 8.46
Active cancer	14.64	7.73, 27.73
Neurologic disease with leg paresis	6.10	1.97, 18.89
Pregnancy or postpartum	4.24	1.30, 13.84
Oral contraceptives	4.03	1.83, 8.89
Estrogen alone	1.81	1.06, 3.09
Non-contraceptive estrogen plus progestin	2.53	1.38, 4.63

Barsoum MK, Heit JA, Ashrani AA, Leibson CL, Petterson TM, Bailey KR (2010) Is progestin an independent risk factor for incident venous thromboembolism? A population-based case- control study. Thromb Res 126:373–378

The survival after VTE is worse than expected and as expected the survival after PE is much worse than after DVT alone. Early mortality after VTE is strongly associated with presentation as PE, advanced age, cancer, and underlying cardiovascular disease. The risk of early death among PE patients is 18-fold higher compared with patients with DVT alone. Death occurs in ≈ 6% of DVT cases and 12% of PE cases within 1 month of diagnosis. Pulmonary embolism is an independent predictor of reduced survival for up to 3 months after onset. For almost one-quarter of PE patients, the initial clinical presentation is sudden death. Independent predictors of reduced early survival after VTE include increasing age, male sex, lower body mass index, confinement to a hospital or nursing home at VTE onset, congestive heart failure, chronic lung disease, serious neurologic disease, and active cancer. Additional clinical predictors of poor early survival after PE include syncope and arterial hypotension. Evidence of right heart failure based on clinical examination, plasma markers (e.g. cardiac troponin T, brain natriuretic peptide) or echocardiography predicts poor survival among normotensive PE patients. Survival over time may be improving for those PE patients living sufficiently long to be diagnosed and treated.

Time course of rehospitalization for recurrent DVT or PE among patients initially hospitalized for DVT without prior hospitalization for VTE. (Modified from White et al. *Arch Int Med* 2000;160:2038.)



Time course of rehospitalization for recurrent DVT or PE among patients initially hospitalized for DVT without prior hospitalization for VTE. **(Modified from White et al. *Arch Int Med* 2000;160:2038.)**

Causes of Venous Thromboembolism

Central to the pathogenesis ofvenous thromboembolism(VTE) is the Virchow's triad of slowing down of blood flow (stasis), hypercoagulability of blood and vessel wall damage(endothelial dysfunction). Forvenous thrombosis to develop, increased systemic coagulability and stasis are most important, with vessel wall damage being more important in arterial thrombosis, except if there has been a previous injury to the veins from indwelling catheter and damage from previous thrombosis. Thus, the causes of VTE are actually risks factors that increase the chance of Virchow's triad being in place.

Risk factors include genetic,acquired,behavioural or acomplex interaction of these factors in producing thrombosis. VTE can also be viewed asprovoked or unprovoked on the basis of identifiable (or no identifiable) risks factors.This dichotomization is important because it bears relevance to the duration of therapy.

Genetic Risk Factors

An array of hereditary traits increases risk of venous thrombosis. Deficiencies in the natural anticoagulant – proteinC,S and antithrombin are the most prominent genetic risk factors for venous thrombosis.Individuals of non-O blood type have 2-4-fold increase in the risk of VTE, compared to those with blood group O. Biological mechanisms to explain this association include lower levels of von Willebrand factor and factor VIII in individuals with type O blood, as higher levels of both of these factors are related to increased risk of VTE. Prothrombin allele (20210A), Factor V Leiden in which there is resistance of inactivation of FVa by activated protein C, and mutation involving fibrinogen. Factor V Leiden and prothrombin 20210A are not seen in Africans and Asians but are relatively common in Western countries, where they are not regarded as rare mutations but as genetic polymorphism that is maintained in the population.

Among other hereditary traits related to VTE risk, the most common are the factor V Leiden and prothrombin G20210A mutations especially in individuals of European descent. Estimates of prevalence of such mutations in the general population are 4 to 6% for the factor V Leiden mutation and 1.7 to 3% for the prothrombin mutation. Prevalence of both mutations is markedly lower in non-white populations. Mutations for factor V are autosomal dominant, and

heterozygous individuals experience a 3 to 7-fold increase in the risk for VTE. Homozygosity for factor V mutations, while very infrequent, increases this risk further. Several studies have reported an increased risk of deep vein thrombosis, but not pulmonary embolism in patients with FV Leiden. However, a combination of selection and diagnostic biases may partially explain these findings. The prothrombin mutation is also associated with an approximately 3-fold increase in risk of VTE.

Even with these inheritable genetic risk factors venous thromboembolism frequently results from gene-environment interaction, so additional risk factors such as surgery, immobilization, lifestyle, cancer*et cetera* are often present in patients with heritable thrombophilia when they develop thrombosis.

Acquired Risk Factors

Patient admitted to hospital have high risks of thrombosis, irrespective of the reason for admission. Of all medical conditions,cancer is by far the strongest risk factor,increasing the risk of thrombosis over 50-fold in the first 6 months after diagnosis. Patients with cancer and thrombosis have reduced lifespan compared with cancer patients without thrombosis.

Surgical patients especially orthopaedic, neurosurgical or patients who underwent pelvic surgeries are at higher risks.

Traditionally, these risks have been attributed to immobilization, however in experimental settings, healthy people on bed rest do not appear to have increased incidence of VTE. Hence, inflammation associated with illnesses may be contributory to thrombosis in immobilization. Furthermore, physiological condition such as pregnancy is associated within creased risks of thrombosis because of a procoagulant state in pregnancy. Drugs such as oral contraceptives and hormone replacement in post menopausal women are associated with increased risk of thrombosis.

The first report of deep vein thrombosis (DVT) following flying appeared in 1954 by Homans, who described two cases of thrombosis occurring after flights from USA to Venezuela. The term economy class syndrome' was first used in an article in 1988 to describe three cases of thrombosis after long-haul air flights. DVT has also been described in individuals after long bus and car journeys. Thus, 'travellers' thrombosis' has been suggested as a more encompassing term. Prolonged immobilisation appears to be the central theme rather than the flight in itself. The relative hypoxia and low air pressure (in the cabin) may decrease fibrinolytic activity and have been shown to be associated with increased markers of activated coagulation. Additionally, dehydration occurs in pressurised cabins and this may be more marked in individuals who take alcohol or sedatives. Travelers thrombosis appears to occur in individuals with additional risk factors, therefore, the

aetiology of VTE in travellers is probably multifactorial and prolonged immobilisation associated with long journeys appears to be the most likely trigger of thrombosis. In terms of prevention, simple advice such as good hydration and taking a walk on board can be given with no requirement for additional intervention. Compression stockings should be considered for high-risk patients.

Obesity is a well-documented risk factor for VTE. Case-control and cohort studies estimated that obesity (body mass index (BMI) $\geq 30\ kg/m^2$) increased risk of VTE more than 2-fold when compared to a normal weight (BMI $<25\ kg/m^2$), with similar estimates for men and women. Furthermore, obesity is more strongly related to venous than arterial thrombosis as has been shown independently in women and men. In addition, both peripheral and central adiposity are strong correlates of VTE risk for both men and women. Mechanistically, it is possible that obesity impacts risk of VTE through increases in adipose mass. Adipose tissue is metabolically active, secreting substances which have been previously associated with VTE risk like plasminogen activator inhibitor-1 (which inhibits fibrinolysis) and some forms of estrogen.

VTE occurs at a rate 4 to 5 times higher during and immediately after pregnancy relative to the agespecific rate when women are not pregnant. The risk of VTE is highest immediately after delivery, during which thrombosis is 20

times more likely. Increased risk of VTE results in part from a pregnancy-induced hypercoagulable state that has likely arisen from evolutionary mechanisms to deal with haemorrhagic challenges present by child birth and miscarriage. It has been suggested that anatomical obstructions created by the expanding uterus or decreases in a woman's overall activity also act to increase VTE risk by lessening venous outflow. Increases in the levels of clotting factors VII, VIII, and X, von Willebrand factor, prothrombin fragments 1 + 2, and D-dimerduring pregnancy, as well as decreases in circulating free protein S, all combine to promote thromboemboli formation. The risk of thrombosis remains elevated from conception until these factors return to their normal levels (about 8 weeks post delivery).

Table 1: VTE Predisposing Factors By Category Of Risks

Low risk	Moderate risk	High risk	Very high risk
• Any age without known risks	Age >40yrs plus poor ambulation Oral contraceptive pills/ estrogen Chronic venous insufficiency Pregnancy and puerperium (6 weeks) Long haul flights (>8 hours) in the last month Trauma/abdominal surgery Acute inflammatory or infectious disease Rheumatological disease	Respiratory failure/ decompensated COPD/Pneumonia Cardiac failure/COPD Obesity Inflammatory bowel disease Myeloproliferative syndrome Active cancer or cancer therapy Nephrotic syndrome Extensive burns Myocardial infarction/acute coronary syndrome Critical care patients Sepsis Stroke Lower limb immobility	Major trauma Thrombophilia History of DVT/PE Respiratory failure on mechanical support

DIAGNOSIS OF VENOUS THROMBOEMBOLISM

The diagnosis of DVT and PE has evolved over the years both in Nigeria and outside the country. There are basic investigations required in the diagnosis of VTE,They are D-Dimer, Doppler Ultrasound scan,Venography, CT-Pulmonary Angiography,Ventilation perfusion scan

Based on the expertise and advancement in Technology, there are guidelines adapted for each group including the NSHBT guideline for VTE diagnosis in Nigeria. All the guidelines developed depends on strategy using an algorithm.This has become a practicable, safe and cost-effective means of investigating patients with suspected VTE. The algorithm involves the use of the following main components in a step-wise approach:

1. Clinical prediction rules (Wells score)
2. D-dimer testing
3. Imaging techniques

In patients with suspected VTE, detailed clinical history, examination and supportive work up investigations e.g. full blood count, serum electrolyte, urea and creatinine, liver function tests (LFTs), electrocardiogram (ECG), chest x-ray (CXR), clotting profile, etc. should be carried out as appropriate and relevant to the individual patient.

1. Clinical Prediction Rules (Wells Score)

The first step in the diagnosis of VTE is to use the clinical prediction rules. Well's prediction score is the most widely used and validated score in the diagnosis of VTE. This is shown below in the tables 3 & 4.

Table 3: CLINICAL PREDICTION RULES FOR DVT WELLS SCORE

VARIABLES	POINTS
Active Cancer (ongoing treatment or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of lower extremities	1
Recently bedridden for ≥ 3 days or major surgery within 4 week	1
Localized tenderness along distribution of deep venous system	1
Swelling of entire leg	1
Calf swelling ⩾ 3cm compared to asymptomatic contralateral one (measured 10 cm below tibial tuberosity)	1
Pitting oedema confined to symptomatic leg	1
Collateralsuperficialveins (non - varicose)	1
Past history of DVT	1
Alternative diagnosis at least as likely as DVT	-2

Wells P.S, Anderson D.R, Bormanis J, Guy F, Mitchell M, Gray L, et al.Value of assessment of pretest probability of deep-vein thrombosis in clinical management.The Lancet. 1997 Dec 20; 350(9094): 1795–8.

< 0 points = low probability (prevalence of DVT 3%)

0-2 points = intermediate probability (prevalence of DVT 17%)

> 2 points = high probability (prevalence of DVT 75%)

Dichotomized scores:

< 2 point = DVT Unlikely

≥ 2 points = DVT Likely

Wells CLINICAL PROBABILITY SCORES FOR PULMONARY EMBOLISM

Well's Clinical Probability for Pulmonary Embolis

Risk factors, symptoms or signs	*Points*
Signs or symptoms of DVT	3
Alternative diagnosis is less likely than PE	3
Heart rate > 100 bpm	1.5
Immobilization/surgery in the previous 4 weeks	1.5
Prior history of DVT or PE	1.5
Haemoptysis	1
Active Cancer	1

Wells P.S, Anderson D.R, Bormanis J, Guy F, Mitchell M, Gray L, et al.Value of assessment of pretest probability of deep-vein thrombosis in clinical management.The Lancet. 1997 Dec 20; 350(9094): 1795–8.

Three category (three level) scheme:

Low probability <2.0 point

Intermediate probability 2.0-6.0 points

High probability ≥ 6.0 points

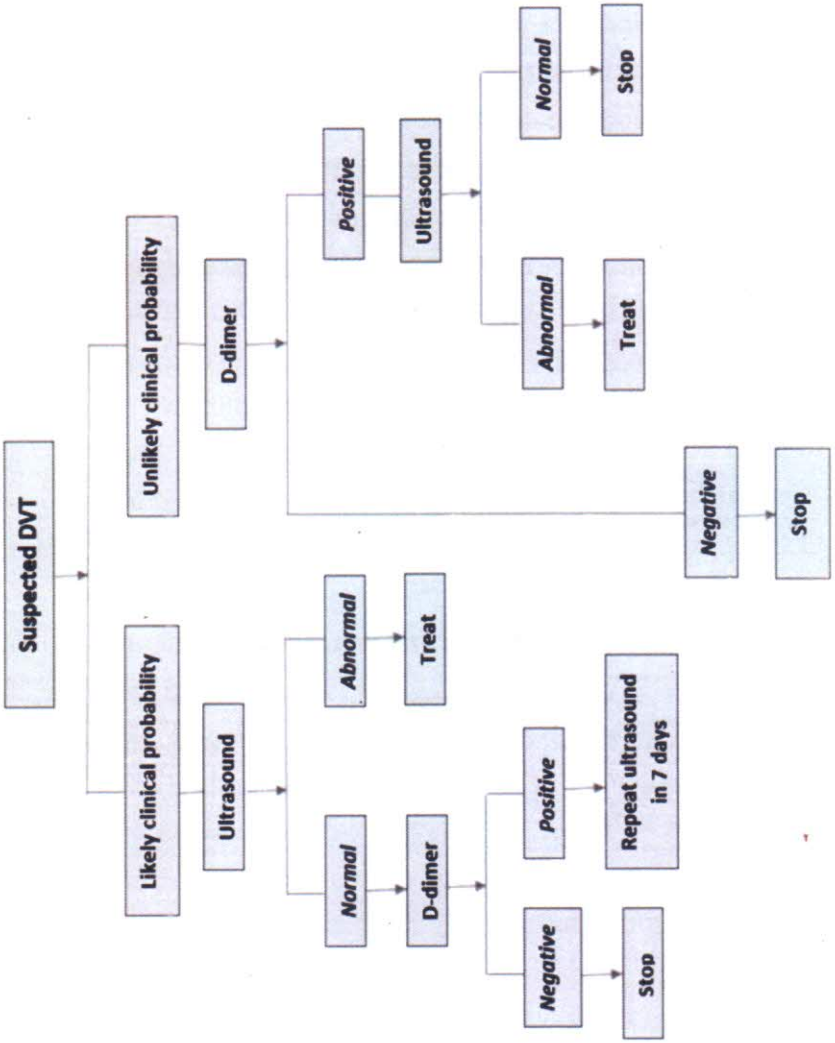
Two category (two level) scheme:

PE unlikely: 0-4 points

PE likely: > 4 points

Proportion of patients PE/DVT	Number of points	Prevalence of
• High probability* 60%	≥6.5	10%
• Moderate probability* 25%	4.5-6.0	30%
• Low probability† 5%	≤4.0	60%
• High probability* 60%	≥3	10%
• Moderate probability* 25%	1 or 2	30%
• Low probability† 5%	≤0	60%

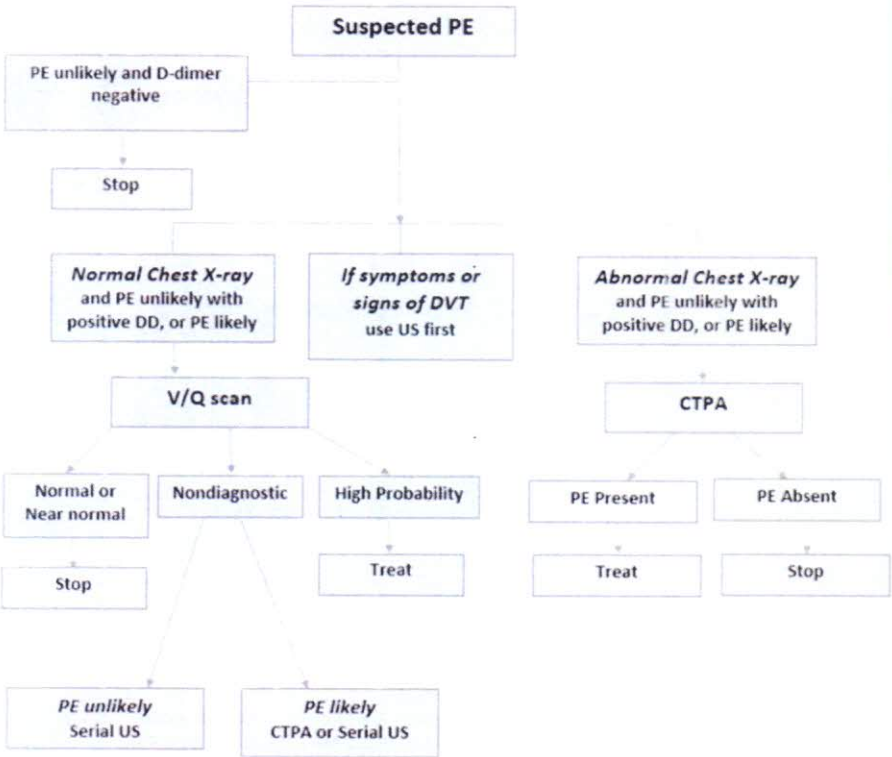
DVT DIAGNOSTIC ALGORITHM



American Academy of Family Physicians/American College of Physicians.Panel on Deep Venous Thrombosis/Pulmonary Embolism. Current Diagnosis of Venous Thromboembolism in Primary Care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians. Ann Intern Med. 2007; 146: 454–458.

I. The first step is to use a validated clinical rule (Well's Score) to determine pretest probability
II. For UNLIKELY pretest probability a negative age-adjusted D-dimer test excludes DVT and negates the need for further diagnostic imaging.
III. All other patients may require imaging
IV. A negative D-dimer result should not be used to exclude VTE in patients with LIKELY clinical probability because of the higher false negative rate in this subgroup.

PE DIAGNOSTIC ALGORITHM



a. Clinical assessment and D-dimer testing have the advantage of PE diagnosis in settings where radiographic imaging is not readily available
b. Thoracic US is positive in 20% of patients with clinical features of PE and in 50% of those with likely pretest probability and symptoms of DVT
c. The use of CTPA in combination with clinical pretest has a high negative and positive predictive value
d. Positive CTPA results can be considered diagnostic if the clinical pretest probability is high/likely or if the PE is located in a segmental or a larger vessel. If at the level of sub-segmental arteries, the result should be discussed with the radiologist to rule out false positive CTPA results.

Diagnosis of lower extremity DVT

Low PTP/prevalence

- The guideline recommends using a strategy starting with D-dimer for excluding DVT in a population with low prevalence/ PTP (10%),
- This is followed by proximal lower extremity ultrasound or whole-leg ultrasound for patients requiring additional testing.
- If D-dimer is not readily available, alternate acceptable strategies include performing proximal lower extremity or whole-leg ultrasound alone.

Intermediate prevalence/PTP

- The guideline suggests a strategy using whole-leg ultrasound, or starting with proximal lower extremity ultrasound for evaluating patients suspected of having DVT in this population
- No further testing is required if the whole-leg ultrasound is negative,
- But if no alternative diagnosis is identified, a negative initial proximal ultrasound should be followed by serial proximal ultrasound.
- In an intermediate PTP population where the prevalence is lower, other potentially acceptable strategies include proximal lower extremity ultrasound alone with no additional follow-up testing for negative results, or a strategy starting with D-dimer for excluding DVT followed by proximal lower extremity ultrasound or whole-leg ultrasound for patients requiring additional testing.

High PTP/prevalence

- The guideline suggests a strategy starting with proximal lower extremity or whole-leg ultrasound for assessing patients suspected of having DVT in a population with high prevalence/PTP.
- This should be followed by serial ultrasound if the initial ultrasound is negative and no alternative diagnosis is identified.

Diagnosis of Pulmonary Embolism

Low PTP/prevalence

- The guideline recommends using a strategy starting with D-dimer for excluding PE in a population with low prevalence/PTP
- This is followed by ventilation-perfusion (VQ) scan or computed tomography pulmonary angiography (CTPA) for patients requiring additional testing.

If D-dimer is not readily available, alternate acceptable strategies include performing VQ scan or CTPA alone

Intermediate prevalence/PTP

- The panel suggests a strategy starting with D-dimer for excluding PE in a population with intermediate prevalence/PTP (20%),
- This is followed by VQ scan or CTPA for patients requiring additional testing.
- If D-dimer is not readily available, alternate acceptable strategies include performing VQ scan or CTPA alone.

Patients who are likely to have a non-diagnostic VQ scan should undergo CTPA

High PTP/prevalence

The panel suggests a strategy starting with CTPA for assessing patients suspected of having PE in a population with high prevalence/PTP.

Anticoagulants Used in the Treatment Of Deep Vein Thrombosis

Introduction

Anticoagulants are the primary strategy for the prevention and treatment of Venous Thromboembolism (VTE) and are commonly used in both the inpatients and outpatient's basis. The economic burden of managing patients with VTE is enormous, some of which are due to the cost of the anticoagulants and the management of the complications. Though there are inter- and intra-classes variation in the complications of anticoagulants, including but not limited to bleeding, the complications may be associated with high morbidity and mortality rates if not properly managed.

The management of VTE is divided into three phases, viz: acute (5-10 days), long term (for up to three months) and extended phase (beyond three months). In addition to the phases of the VTE, benefits and potential risks, adequate knowledge and understanding of the Clinical Pharmacology of anticoagulants are desirable before usage.

Anticoagulants therapy started in the early 20th century with the discovery of Unfractionated heparin (UFH), and later the vitamin K antagonists such as Dicoumarol. Thereafter, Low Molecular Weight Heparin (LMWH), synthetic heparin (fondaparinux) and Non-vitamin K antagonists' oral anticoagulants (NOACs) like Ximelagatran were discovered. Table 1 shows the timeline for the development of anticoagulants.

Classification of Anticoagulants

Anticoagulants are classified into the following: Parenteral and oral anticoagulants. The parenteral anticoagulants include indirect thrombin inhibitors like heparin, LMWH and fondaparinux, and direct thrombin inhibitors like lepirudin. The oral anticoagulants include coumarin derivatives (warfarin), direct Xa inhibitors (rivaroxaban) and oral direct thrombin inhibitors (dabigatran). Figure 1 shows the classification of anticoagulants with examples.

Parenteral anticoagulants

Unfractionated Heparin

UFHs are naturally occurring highly Sulfated mucopolysaccharide found in the secretory granules of the mast cells and is synthesized from UDP-sugar precursors as a polymer of alternating D-glucuronic acid and N-acetyl-D-glucosamine residues. Heparin is usually extracted from the porcine or bovine lung mucosal tissues. UFH has an average molecular weight of 15,000 Daltons (range 3000 to 30000 Da) and approximately 45 saccharide units. Only one-third of the heparin molecules contain the unique pentasaccharide sequence which can bind the antithrombin and is responsible for the majority of the anticoagulant activities of the heparin. They are indirect thrombin inhibitors because they require the presence and binding to antithrombin III to exert their action.

Mechanism of Action

UFHs exert their effect by binding to the antithrombin III (AT) to form a heparin-antithrombin III complex and accelerate the rate at which it irreversibly inhibits and inactivates thrombin and other

activated clotting factors, such as factors IX, X, XI, and XII. This prevents the polymerization of fibrinogen to fibrin and the subsequent formation of clots. The activated coagulation factors that are primarily inhibited by antithrombin are thrombin and factor Xa, by acting as a suicide substrate. The rate of inhibition of activated factors Xa and thrombin (IIa) by heparin, expressed as anti-factor Xa to factor IIa ratio is 1:1. To inhibit thrombin, heparin must bind to both the coagulation enzyme and AT, whereas binding of heparin to the enzyme is not necessary for the inhibition of factor Xa. To be able to bridge the antithrombin and thrombin together, the heparin molecules must contain at least 18 or more saccharides units which equates to a heparin with a molecular weight of 54,000 daltons. This explains why LMWHs and fondaparinux possess little or no inhibition of thrombin. Figure 2 shows the mechanism of action of heparin.

Pharmacokinetics

The preferred route of administration for UFH are intravenous infusion (IV) and subcutaneous injection. The intravenous route is rapid with immediate onset of action, achieve therapeutic plasma concentration faster, and therefore, a preferred and appropriate route of administration when rapid anticoagulation is desired. However, there is a delayed onset of action of 1-2hours of anticoagulation when UFH is administered through a Subcutaneous injection. Following a SC injection of UFH, it binds to plasma protein on entering the blood stream achieving a bioavailability of 30-70% depending on the dose given. Generally, the higher the dose of UFH, the higher the bioavailability. The dose-dependent half-life of UFH ranges between 30-90 minutes

and maybe longer with higher doses of UFH. Also, the elimination of the UFH from the systemic circulation is equally dose-dependent, and comprises of two phases, each following a different order of kinetics. The initial phase is rapid, saturable, enzymatic degradation and follows saturable zero-order kinetics. The second phase on the order hand, is slower, non-saturable and renal-mediated first order process. A lower and higher dose of UFH are eliminated by the enzymatic and renal-mediated first-order processes respectively.

Due to the inter-individual variability in the dose-response and potential changes in the response to UFH over time, there is a need to monitor and adjust the dose of UFH. The anticoagulant responses to UFH are monitored with activated Partial Thromboplastin Time (aPTT) and, alternatively, with Anti-factor Xa level monitoring (or the heparin assay). The desired therapeutic range of aPTT is 1.5 to 2.5 times the control aPTT or institution-specific therapeutic aPTT range. The institution-specific therapeutic aPTT should correlate with plasma heparin concentration of 0.2-0.4 units/mL or 0.3-0.7units/mL by protamine titration or amidolytic anti-factor Xa assay respectively. The aPTT is commonly used worldwide to monitor response to UFH but in patients with heparin resistance and those with baseline elevated aPTT due to antiphospholipid antibodies, anti-factor Xa assay becomes a more accurate and better method of monitoring responses to UFH. Table 2 compares the pharmacology of unfractionated Heparin, L MWH and fondaparinux.

Fondaparinux.

Fondaparinux is a synthetic analogue of AT-binding pentasaccharide present in heparin and LMWHs. It was discovered based on the knowledge that the minimum heparin segments required for high-affinity binding to AT contained pentasaccharide. The modification of the structure in the pentasaccharide units of the fondaparinux increases its affinity for AT and hence increased specific activity and prolongation of its half-life. The molecular weight of fondaparinux is 1,728 Dalton. It has a better pharmacokinetic/pharmacodynamic profile than LMWHs and UFH (Table 2).

Mechanism of Action

Similar to the UFH and LMWHs, fondaparinux bind to AT to exert its effect(Figure 2C). However, because of its small size, it specifically inhibits only the factor Xa without any inhibitory action on thrombin.

Pharmacokinetics

Following subcutaneous administration, the absorption of fondaparinux is complete, rapid and achieve a 100% bioavailability. It has a volume of distribution of 7-11 litres limited to blood volume, and highly bound to plasma protein (>97%). Peak plasma levels are achieved about 2 hours after administration. There is no evidence of metabolism of fondaparinux and is eliminated as unchanged drug in the kidney with an elimination half-life of about 17 hours in healthy subjects with normal renal function. There is a prolongation of the half-life and AUC of fondaparinux in the elderly and subjects with a clearance of less

than 30 mL/min. Like with LMWHs, routine coagulation monitoring is not advocated. However, in case there is a need for monitoring, Chromogenic-based anti-factor Xa assay that has been calculated with fondaparinux is recommended. Also, the anticoagulant response of fondaparinux can be assessed with prothrombin-induced clotting time.

Toxicities/Adverse Effects of Heparin

1. Bleeding: Bleeding is the major complication of UFH. The incidence of major bleeding is 1-5% following Intravenous injection of UFH for venous thromboembolism. The risk factors for bleeding include recent surgery, trauma, peptic ulcer disease, and platelet dysfunction (including concomitant aspirin or other antiplatelet drugs use). Anticoagulation effects of heparin wane within an hour of discontinuation of the drug. Therefore, for mild bleeding, drug discontinuation may be the only measure required for the management of excessive blessing in addition to supportive care, without an antidote. However, for life-threatening haemorrhage, protamine sulfate is recommended. Protamine sulfate binds tightly to heparin and neutralizes its anticoagulant effect. Protamine binds only heparin with long molecule hence will only partially reverse the anticoagulant effect of LMWHs but does not affect that of fondaparinux.
2. Heparin-Induced Thrombocytopaenia (HIT): There is a reduction in the platelet count to less than 150,000/mL or a 50% reduction from the baseline or pretreatment level. It

usually occurs in about 0.5% of medical patients 5-10 days after commencement of therapy with UFH. Some complications of HIT include venous thromboembolism, arterial thrombosis, limb ischaemia, myocardial infarction, stroke, bilateral adrenal haemorrhage, skin lesion at the site of subcutaneous injection and other variety of systemic reactions. Treatment includes discontinuation of heparin or LMWHs, alternative anticoagulants like bivalirudin or argatroban or fondaparinux should be given.

LMWHs should be avoided because of cross-reaction, and warfarin use should be delayed until platelet count return to normal to avoid precipitation of venous limb gangrene or skin necrosis.

3. Other toxicities include osteoporosis, abnormalities of liver function tests (only heparin or LMWHS), inhibition of synthesis of aldosterone by the adrenal glands and occasional hyperkalemia). Other rare adverse effects include hypersensitivity reactions and alopecia.

Parenteral Direct thrombin Inhibitors

Direct thrombin inhibitors did not require plasma cofactors like antithrombin III to exert their inhibitory action on thrombin. They possess the intrinsic activity and bind thrombin directly and block their enzymatic activity (Figure 3). The effect includes the blockade of the thrombin-catalyzed or -induced reactions, including fibrin formation, activation of coagulant factors V, VIII, XIII, protein C, and platelet aggregation. The development of

direct thrombin inhibitors was to avert some challenges associated with indirect thrombin inhibitors. In contrast to heparins, their anticoagulants response are more predictable because they do not bind to plasma proteins and are not neutralized by PF4 and high molecular-weight multimers of von Willebrand factor generated at sites of vascular injury, and lack of immune-mediated thrombocytopaenia.Also, they inhibit both the fibrin-bound and fluid-phase thrombin, due to the intrinsic activity of directly binding thrombin without a need to bind antithrombin III, unlike heparins.

Oral Anticoagulants

The oral anticoagulants (Figure 1) include the coumarin derivatives or vitamin K antagonists (acenocoumarol, phenprocoumon, and warfarin), direct factor Xa inhibitors (rivaroxaban) and oral direct thrombin inhibitors (dabigatran etexilate).

Dicoumarol, the first vitamin K antagonist was discovered more than 75 years ago as the aetiology of an outbreak of an unfamiliar disease characterized by fatal bleeding in cattle that ate spoiled sweet-clover hay (Melilotus alba and M. officinalis). The coumarins (warfarin) was initially used as a rodenticide in 1948 and 1952 was first used in human in a suicide attempt. Thereafter, the use of coumarins became popular. Since introduced, some of the advantages of coumarins include clinical familiarity with use, well-studied clinical pharmacology, cost, readily available biomarker, and availability of antidotes. However, inherent disadvantages in the coumarins include the following properties: narrow therapeutic index, they require frequent monitoring, significant inter individual dose requirement and response variations, common drug-drug interactions, drug-food interactions, drug-alcohol interactions and potential adverse effects. For examples, severe bleeding from warfarin use remains

one of the commonest adverse drug reactions requiring hospital admissions. The increasing demands for oral anticoagulation necessitated the need for the development of newer oral anticoagulants targeting thrombin and factor Xa, and with improvement over the coumarins in terms of efficacy and safety profile.

Warfarin

Warfarin is derived from WARF (Wisconsin Alumni Research Foundation) and -arin from coumarin. Warfarin is an example of vitamin K antagonist and is commonly used oral anticoagulants worldwide. Warfarin is a synthetic anticoagulant with a molecular weight of 308.3 g/mol. It is a racemic mixture of R and S enantiomers, and this affects their pharmacokinetic and pharmacodynamic properties. It impairs the synthesis of the vitamin K dependent coagulation factors II, VII, IX, and X, and anticoagulant protein C, S, and Z in the liver.

Mechanism of Action

After the synthesis in the liver, the vitamin k dependent coagulation factors II, VII, IX, and X, and anticoagulant proteins C, S, and Z will remain biologically inactive until activation by gamma-carboxylation of their 9-13 amino-terminal glutamic acid residues. This reaction requires CO2, O2, reduced vitamin K (KH2) and is catalyzed by gamma-glutamyl carboxylase enzyme, To sustain this decarboxylation reaction, there is a need for continuous regeneration of the reduced vitamin K from its epoxide; KO (oxidized) form. Vitamin K Epoxide Reductase (VKOR) converts the vitamin KO to vitamin K while vitamin K1 reductase transforms the vitamin K to vitamin KH2 by vitamin K1 reductase. Warfarin competitively inhibits both the VKOR and vitamin K1 reductase leading to the accumulation of the biologically inactive vitamin KO, which eventually inhibit the synthesis of vitamin K dependent coagulation factors II, VII, IX, and X, and anticoagulant

protein C, S, and Z in the liver (Figure 4). S-warfarin is about 3-5 times more potent than R-warfarin, reflecting the significant differences in their receptor affinity to Vitamin K reductase enzymes.

At therapeutic doses, the functional amount of each vitamin K dependent coagulation factor synthesized in the liver is decreased by 30-70% by warfarin. However, warfarin has no effect on the activity of the fully decarboxylated coagulation factors present in the circulation. Therefore, before the anticoagulant effect of warfarin commences, the decarboxylated coagulation factors must be cleared from the circulation. This clearance depends on the half-lives of the different coagulation factors II, VII, IX, and X, and anticoagulant protein C, S, and Z (Table 4). As a result, it takes about 4 to 5 days to achieve the full anticoagulation effect of warfarin. Over this period, there is a need for the overlapping of the warfarin anticoagulation with rapidly acting parenteral anticoagulants like heparin, LMWH or fondaparinux.

Pharmacokinetics

Warfarin is rapidly and extensively absorbed from the gastrointestinal tract, and the bioavailability is nearly complete following oral and rectal administration. Although there exists a significant inter-individual variation in the absorption. Factors including generic and food affect absorption from the GIT. For example, the presence of food in the GIT reduces the rate but not the extent of warfarin absorption in the GIT. The peak plasma concentration of warfarin is achieved within 2-8 hours after administration.

Warfarin crosses the placenta and an equal maternal plasma warfarin concentration may be achieved by the fetus. It is therefore not recommended during pregnancy. During lactation, on the other hand, the available limited data suggest warfarin may not be distributed into the breast milk of humans.

Pharmacogenomics is playing an important role in the dose selection of warfarin, especially where there is a facility for such. Genotype-based regimens have been considered a reliable and accurate method to determine warfarin dosing. Other factors that

may influence response to warfarin include advanced age, alcohol use, chewing tobacco, cigarette smoking, clinical congestive heart failure, diarrhoea, dietary vitamin K intake, fever, following heart valve replacement, haemodialysis, hepatic diseases, hypoalbuminaemia, nutritional status, pregnancy/lactation, renal diseases and thyroid diseases.

Monitoring and compliance

Due to the narrow therapeutic index of warfarin and various factors that may influence response to warfarin including drug interactions (Table 5), individuals on warfarin therapy require close monitoring and may require frequent dose adjustment. Prothrombin Time (PT) expressed as International Normalized Ratio (INR) is used to routinely monitor responses to warfarin therapy. For most indications, the accepted therapeutic INR range is 2-3. A higher INR may be required for patients with mechanical heart valves in the mitral position or mechanical heart valves in other position with a coexisting heart failure or individuals with a history of stroke.

Adverse Effects

1. Bleeding is the most common adverse effect of warfarin. The incidence of bleeding at a therapeutic INR range of 2-3 is 3% per annum. The risk of bleeding increases with increased INR. Some other factors that increase the risk of bleeding include intensity and duration of treatment, use of other medications that affect haemostasis and presence of an anatomical source of bleeding.
2. Birth defects
3. Skin necrosis
4. Purple toe syndrome
5. Other infrequent reactions include alopecia, urticaria, dermatitis, fever, nausea, diarrhoea, abdominal cramps and anorexia.

Direct-acting Oral Anticoagulants (DOACs)

Since they were discovered, DOACs appear to be safer, relatively easier to manage and better as options to the traditional vitamin K

antagonists. They do not require Antithrombin III or any other co-factors to bind a single coagulation factor (IIa or Xa) in the common coagulation pathway (Figure 5). In addition, because of their small molecules, they have good penetration ability and bind both clot-bound and free-floating thrombin. Unlike the vitamin K antagonists, they require no monitoring because of predictable pharmacokinetics and pharmacodynamics profile, more rapid onset of action, less long-lasting duration of action, have a wide therapeutic index and less drug-drug and food-drug interactions. Besides, the majority of the DOACs-associated bleeding can be managed by drugs withdrawal because of their short half-lives. However, some challenges with the use of the DOACs especially in the developing countries include the cost, availability and limited clinical experience of the health care professionals about their usage in the real world. Examples of DOACs are direct oral thrombin inhibitors (dabigatran) and Xa inhibitors (rivaroxaban, apixaban, edoxaban). Table 6 compare the pharmacological properties of Direct-acting Oral Anticoagulants (DOACs).

Direct Oral Thrombin Inhibitor

Dabigatran

Dabigatran is the only direct oral thrombin inhibitor that is currently available for clinical use. It is a highly polarized and hydrophobic molecule that is not absorbed following oral administration. Dabigatran etexilate is a synthetic lipophilic prodrug with a molecular weight of 628 Da, and this formulation promotes absorption in the gastrointestinal tract before it is rapidly converted to active dabigatran by plasma esterases.

Mechanism of action

Dabigatran is a potent direct oral thrombin inhibitor that competitively and reversibly blocks the active site of free and clot-bound thrombin. It also inhibits thrombin-induced platelet aggregation. Hence, the thrombin-mediated conversion of fibrinogen to fibrin, feedback activation of coagulation and platelet activation are all prevented by the dabigatran.

Pharmacokinetics

After oral ingestion, the PH-dependent absolute bioavailability of dabigatran is about 6%. An acidic environment is required for enhanced and maximal dissolution and absorption. The dabigatran etexilate is formulated as a capsule, and crushing, chewing, or breaking of the capsule should be avoided before ingestion. Intake of the dabigatran etexilate without capsule shell increases the oral bioavailability by about 75% and may lead to excessive exposure to the drug. The bioavailability is independent of the dose and dietary intake. The peak onset of action of dabigatran is about 2 hours, and a steady-state is achieved in 3 days after multiple administration. It has a volume of distribution of 50-70 litres and plasma protein binding of 35%. It has an elimination half-life of 12-14 hours.

Monitoring

Routine anticoagulant monitoring is not required when given in fixed doses because it produces a predictable anticoagulant response and few drug-drug interactions. Routine monitoring is reserved and may be required for patients undergoing invasive interventions and emergency cases. In such cases and when the estimation of plasma concentration is required, diluted thrombin time (dTT) or ecarin-based assays must be used.

Adverse effects

The major adverse effect of dabigatran is bleeding and the annual incidence (3%) at 150 mg twice daily is similar to warfarin. However, the risk of intracranial bleeding is reduced by about 70% in patients on dabigatran in contrast to warfarin. The risk of bleeding in patients with dabigatran is increased in those greater than 75 years, renal impairment and concurrent use of antiplatelet or nonsteroidal anti-inflammatory drugs (NSAIDs). Most bleeding to dabigatran will be managed by the withdrawal of the drug, but in life-threatening bleeding, idarucizumab (dabigatran antidote) can be given.

Other less common but important adverse effects that have been reported by patients taking dabigatran are dabigatran-induced oesophagitis or oesophageal injury, dyspepsia, impairment of the function of the liver and kidney, myocardial infarction or acute coronary syndrome and hypersensitivity reactions (urticaria, rash, pruritus, and anaphylactic shock).

Direct Oral Factor Xa Inhibitors

Rivaroxaban, Apixaban and Edoxaban

The three direct oral factor Xa inhibitors share the same mechanism of action (Figure 5). They are active drugs and require no activation to elicit their action. Competitively and selectively, each reversibly binds the active sites and inhibits free (free-floating) and clot-associated factor Xa (within prothrombinase complex), which lead to decreased thrombin generation. Also, they suppress the aggregation of platelet and fibrin formation.

Pharmacokinetics

Rivaroxaban

It is rapidly absorbed after oral ingestion and achieves a maximal plasma concentration within 3 hours in a dose-dependent manner. The maximum absorption occurs in the stomach and meal enhanced absorption. It has an absolute bioavailability of about 80%. About 95% of rivaroxaban binds to the plasma protein, and it has an elimination half-life of about 6-12 hours. About two-thirds of rivaroxaban are metabolized by CYP3A4 to inactive metabolites that are excreted in the urine and faeces, while about one-third are excreted unchanged in the urine. Rivaroxaban is also a substrate of P-glycoprotein (P-gp) efflux system, and therefore, the plasma concentration may be reduced or increased by P-gp and CYP3A4 inducers or inhibitors respectively.

Exposure to rivaroxaban is increased in patients with renal impairment and severe hepatic diseases. Dose reduction is recommended for patients with CrCl of 15-50mL/min, from 20 mg to 15 mg daily.

Apixaban

Following oral administration, the bioavailability of apixaban is 50% and a peak plasma concentration is achieved between 1 to 3 hours. Food does not affect the rate and extent of absorption. The plasma protein binding is about 87%, and it has a volume of distribution of about 21 litres. It has an elimination half-life of about 12 hours. About 27% of the drug are excreted unchanged in the urine. The rest is mainly metabolized by CYP3A4 with minor contributions from CYP1A2, CYP2C8, CYP2C9, CYP2C19 and CYP2J2. The metabolites are excreted in the bile, faeces and urine. Dose reduction is recommended in patients having any two of the following; age > 80years, bodyweight of 60kg or less and serum creatinine concentration of 1.5 mg/dL or higher.

Monitoring

Direct Oral Factor Xa Inhibitors are given in fixed doses and due to predictable pharmacokinetic and pharmacodynamic profile, do not require routine anticoagulant monitoring. However, in case there is a need to measure the drug level, anti-factor Xa assays using specific drug calibrators can be used. Also, at least a yearly assessment of renal function is required for patients with normal baseline renal function, and more frequent assessment of renal function as required, in those with renal dysfunction.

Contraindications: Direct Oral Factor Xa Inhibitors are contraindicated in stroke prevention in patients with mechanical heart valves.

Adverse Effects

Bleeding is the major adverse effect similar to other anticoagulants, however, the rate of intracranial bleeding in patients with rivaroxaban, apixaban, and edoxaban are at least 50% lower when compared with those on warfarin. Also, the rate of life-threatening bleeding is equally lower in Direct Oral Factor Xa Inhibitors than that with warfarin. Other adverse effects include back pain, nausea, abnormal hepatic function and skin rash.

Drug Interactions

All Direct Oral Factor Xa Inhibitors are substrates of P-glycoprotein, hence inhibitors or inducers of P-gp may affect the plasma concentration of the drugs and the anticoagulant response. Also, rivaroxaban and apixaban are metabolized by CYP3A4 while edoxaban is only minimally metabolized by the CYP3A4. Therefore, inhibitors and inducers of CYP3A4 can affect their metabolism, plasma concentrations and anticoagulation response.

Table 1: Timeline for the development of anticoagulants

Anticoagulants	Year of development
Heparin	1939
Dicoumarol	1941
Warfarin	1954
LMWH	1985
Bivalirudin	2000
Fondaparinux	2001
Dabigatran, Rivaroxaban	2008
Apixaban	2011
Edoxaban	2015

Table 2: Comparison of the pharmacology of subcutaneous Heparin, LMWH, andfondaparinux

Features	Heparin	LMWH	Fondaparinux
Sources	Biological	Biological	Synthetic
Molecular Weight (Da)	15000	5000	1500
Target	XIIa, IXa, XIa, Xa and IIa; Xa: IIa	Xa > IIa	Xa
Subcut. Bioavailability (%)	30(at low dose)	90	100
$t_{1/2}$(hr)	1	4	17
Monitoring Test	aPTT, Anti-Factor-Xa	Anti-Factor-Xa	Anti-Factor-Xa
Renal Excretion	No	Yes	Yes
Antidote (protamine reversal)	Complete	Partial	None
Platelet factor 4	High affinity	Lower affinity	Lower affinity
Bleeding	1-5%	<3%	<1%
Heparin Induced Thrombocytopaenia	<5%	<1%	<0.1%

Table 4: Approximate Half-lives of the vitamin dependent coagulation factors II, VII, IX, and X, and anticoagulant proteins C, S, and Z

Factors	Approximate $t_{1/2}$ (hours)
VII	6
IX	24
X	36
II	50
Protein C	8
Protein S	24
Protein Z	42

Figure 4: The pharmacology and mechanism of action of warfarin

Table 5: Examples of important warfarin drug and food interactions

Mechanism	Effect	Examples
Reduced absorption	Reduced warfarin efficacy	Cholestyramine in the GIT
Induction of hepatic enzymes (CYP2C9)	Reduced warfarin efficacy	Barbiturates, carbamazepine, rifampicin
Decreased volume of distribution and a short $t_{1/2}$	Reduced warfarin efficacy	Hypovolaemia e.g. nephrotic syndrome
Relative warfarin resistance	Reduced warfarin efficacy	Vitamin-K rich foods or supplements ingestion (large quantity) Increased level of coagulation factors (e.g. Pregnancy)
Inhibition of hepatic enzymes (CYP2C9)	Enhance warfarin efficacy	Amiodarone, azole antifungals, cimetidine, clopidogrel, cotrimoxazole, disulfiram, fluoxetine, isoniazid, metronidazole, sulfinpyrazone, tolcapone, zafirlukast
Relative deficiency of vitamin K	Enhance warfarin efficacy	Inadequate diet (postoperative parenteral diet) Elimination of intestinal flora by antimicrobial agents
Low concentration of coagulation factors	Enhance warfarin efficacy	Impaired function, congestive heart failure, hypermetabolic states (e.g. hyperthyroidism)

Table 6: Pharmacological properties of Direct oral anticoagulants (factor IIa and Xa inhibitors) *12 16 53 72

Pharmacologic properties	Dabigatran etexilate	Rivaroxaban	Apixaban	Edoxaban
Source	Synthetic	Synthetic	Synthetic	Synthetic
MWT(Da)	628	436	460	548
Target	IIa	Xa	Xa	Xa
Prodrug	Yes	No	No	No
Dosing	Twice daily	Once-daily	Twice daily	Once-daily
Monitoring	ECT	dTT Anti-Xa	Anti-Xa activity	Anti-Xa activity
Bioavailability (%)	6	80	50	62
Peak onset (hr)	2	3	1-3	1-2
Half-life(hr)	12-14	6-12	12	10-14
Food effects	—	Delay Tmax 2–4h	Delays Tmax 2–4 h	Not reported
Plasma protein binding (%)	35	95	87	55
Metabolism	Esterases	CYP3A4/5>CYP2J2	CYP3A4	Hydrolysis > CYP3A4
Renal excretion	80	36	27	50
Dosing reduction	Yes (CrCl 15 - 30mL/ml)	Yes (CrCl 15 - 50mL/ml)	Yes (Age>80 years, — — —	Yes (CrCl 15 - 50mL/ml, CrCl 15-30mL/ml, potent enzymes inhibitors
Antidote	Idarucizumab	Andexanet alfa	Andexanet alfa	Andexanet alfa
Drug interactions	P-gp inhibitors	Potent inhibitors of P -gp CYP2J2, and CYP3A4	Potent inhibitors of P-gp and CYP3A4	Potent inhibitors of P - gp and CYP3A4
Allowed in pregnancy	No	No	No	No
Induces HIT	No	No	No	No
Contraindication	Mechanical heart valves	Lower CrCl 15mL/ml	Lower CrCl 15mL/ml	Lower CrCl < 15mL/ml and >90 mL/ml

P-gp: P-glycoprotein, CYP3A4-Cytochrome P450 3A4, HIT- heparin induced thrombocytopenia ECT- ecarin clotting time, dTT- plasma diluted thrombin time

Low Molecular Weight Heparins (LMWHs)

LMWHs are synthetic heparins obtained through the enzymatic or chemical depolymerization of UFH with subsequent isolation and extraction of the low molecular weight fragments. The mean molecular weight of LMWHs is 5000 da, which corresponds to about 17 saccharide units. Examples of LMWHs are dalteparin, enoxaparin, bemiparin, nadroparin, tinzaparin and pamaparin. Like UFH, they are used in the prophylaxis of venous thromboembolic disease (VTE) on acute or elective admission to the hospital, and they are used in the definitive treatment of patients with VTE.

In contrast to UFH, LMWHs have much more improved pharmacodynamics and pharmacokinetic properties, a more favourable side effect profile, reduced incidence and intensity of adverse effects(lower incidences of osteoporosis and heparin-induced thrombocytopenia) and a more predictable anticoagulant response. As a result, routine anticoagulant response monitoring and dose adjustment are not necessary for most patients on LMWHs.

Mechanism of Action of LMWHs

Similar to UFH, LMWHs bind the antithrombin III (AT) which accelerate and irreversibly inactivates Factor IIa and Xa (Figure 2). However, unlike UFH, the 17 saccharide units are too short to provide enough bridging necessary for the activity antithrombin to inhibit thrombin, therefore, providing partial or no inhibition of thrombin. LMWHs have greater anti-Factor Xa activity than anti-Factor IIa activity, with a ratio of anti-Factor Xa to anti-Factor IIa activity ranges from 3:1 to 2:1 depending on their

preparation.Besides, LMWHs have a lower affinity for platelet factor 4, unlike UFH with high affinity. Platelet factor 4 usually bind heparin and prevent it from interacting with antithrombin. The activity of UFH is thus limited in the vicinity of platelet-rich thrombin.

Pharmacokinetics

When compared with UFH, LMWHs have a better pharmacokinetics profile (Table 2). There is more uniform absorption after subcutaneous injection with about 90% bioavailability. Their anticoagulant effects are more predictable than UFH. The elimination half-life of LMWHs is 4-6 hours following subcutaneous injection and is dose dependent. LMWHs are metabolized in the liver and or depolymerization to majorly inactive or metabolite with reduced activity. They are exclusively cleared by the kidney and their biologic half-life may be prolonged in patients with renal impairment. Hence, LMWHs may accumulate and leads to bleeding in patients with renal impairment. They are contraindicated in patients with Creatinine Clearance < 30mL/min.

Routine monitoring is not required for patients on LMWHs. However, patients that may require monitoring include renal impairment, severe obesity, pregnant women and children. The recommended test for LMWHs is anti-Xa level.The serum concentration of LMWHs is not measurable because they are a mixture of longer and shorter glycosaminoglycan fragments.

Sickle Cell Disease (SCD) and venous thromboembolism

The incidence of VTE in Sickle Cell Disease is unknown.

Vasculopathy and hypercoagulability are now considered to play a major role in the complications of Sickle Cell Disease, such as childhood stroke, acute chest syndrome and pulmonary hypertension.

The risk of VTE among adults with Sickle Cell Disease has not been fully established; however there seems to be a higher risk of PE compared to DVT in adult SCD patients. A similar paradoxical phenomenon in PE versus DVT risk has also been observed in individuals with sickle cell trait (HbA + S) in a case control study by Austin et al.

In a study by Rakhi et al involving 1,523 American SCD patients, the incidence rate for VTE was 5.2 events/1000 person years with a cumulative incidence of 11.3% by age 40years. Among patients with SCD, those who are SS or Sβ°Thal had the highest incidence rate of VTE with 7.6 events/1000person years but the incidence of PE exceed that of DVT.

In the same study, with a mean follow-up of 5.9years, first VTE events were observed in 46 patients, 35 of whom had SS/Sβ°Thal, 8 patients had SS - - thallassaemia, implying that amongst SCD patients, VTE was commonest in those with SS or Sβ° Thallassaemia. The mortality rate for SCD patients with a history of VTE was 6.4% /year compared to 1.9% /year for SCD patients without VTE. In other words, SCD patients with VTE are at a higher risk of death than those without VTE.

In a 4½yr retrospective review of 371 adult patients with VTE in

UCH, cancer associated thrombosis was the most common identifiable risk factor, while Haemoglobinopathy was the least common risk factor.

Pathogenesis of Haemostatic disorders in the sickle cell disease patient is multifactorial and complex. The adult SCD patient tends to have progressive multi-organ damage. It appears that the haemostatic balance as the SCD ages tends to shift towards a haemorrhagic state, which is the 3rd leading cause of death in the SCD patients. There tends to be a progressive increase in INR and APTT in the sickle cell disease patient, which can be ascribed to the progressive well known sickle cell hepatopathy.

Several studies on haemostasis in the Sickle cell Disease patients observed decreased levels of natural anticoagulants such as low Antithrombin, Protein C and Protein S on one hand, but increased levels of FVIII, vWF and Fibrinogen on the other.The sum total of these findings would tilt the haemostatic balance to a state of hyper coagulability, yet VTE is not as common as expected in the SCD patients compared to haemorrhagic events.

There is increased D-Dimer level in the SCD patients both in the steady state and more so when they are in crisis, as well as activation of platelets and the fibrolytic system. These findings will imply chronic on-going fibrin generation and degradation. The net effect may ultimately depend on the state of the end organ in patients with SCD.

Hariharan et al has shown that in a retrospective review of 6,423 SCD patients in USA covering the period 1991 – 2014, the cumulative index of bleeding in the patients is 15.5% by age 40years and 33.6% at age 60years. Gastrointestinal bleeding was seen in 65.6%, intracranial haemorrhage in 14.2%, haemophthalmos occurred in 7.1%, gross haematuria in 4.3% and other types of bleeding 8.8%.

Of particular interest was that, there was a strong association between VTE and ischaemic stroke, with risk of intracranial haemorrhage, implying an association between haemorrhagic stroke and a prior history of VTE (usually within 3 months of the thrombotic event.), and may in part be due to anticoagulation.

Cancer Associated Thrombosis

The first report of what seemed to be Cancer Associated Thrombosis (CAT) was in 1823 by Jean Baptiste, a French physician.Armand Trousseau in 1865 reported an association between Gastric Cancer and Venous thrombo – embolism.

VTE is now regarded as a common complication of in patients with malignant diseases. VTE is a major cause of morbidity and mortality in cancer patients. The absolute risk of VTE depends on the tumour type, the stage of the cancer and the type of antineoplastic drugs employed for the treatment of that cancer.

The VTE could be in the deep veins (DVT), or in the pulmonary arteries as pulmonary embolism (PE), or could occur as visceral or splanchnic vein thrombi. Several risk factors for VTE tend to coexist in cancer patients such as immobility, prolonged hospital admissions, surgery, use of indwelling central catheter, chemotherapy and the use of new molecular targeted therapies.

In addition, non-bacterial endocarditis, and hepatic veno-occlusive disease, superficial thrombo phlebitis may also occur in cancer patients. It is a well-known fact that tumor cells induce a hypercoagulable state.

Biomarkers suggestive of a hypercoagulable state have been found in cancer patients such as elevated platelet

counts, elevated leucocyte count, low haemoglobin, raised D-dimer level and tissue factor.

The occurrence of VTE in cancer patients worsens the prognosis, and it (VTE) is the second leading cause of death .

VENOUS THROMBOEMBOLISM IN PREGNANCY

The estimated risk of developing VTE while pregnant is 5-10 fold higher than when not pregnant and this risk is even higher up to 35-fold in the post partum period, particularly in the first three weeks. Pulmonary embolism, which may occur alone or together with DVT, carries a higher potential of death, and is the leading cause of maternal death in the developed world.

Deep venous thrombosis and PE in terms of morbidity and complications may present as post thrombotic syndrome, pulmonary hypertension, venous insufficiency and an uncommon severe form of DVT resulting from extensive venous occlusion called phlegmasia cerulean dolens, which may result into amputation of the limb.

The risk of thrombosis during pregnancy and puerperium is attributed to homeostatic changes that occur during this period and involves an interplay among the 3 components of Virchow's triad of hypercoagulable state, stasis and vascular damage.The components of this triad occur in pregnancy and in the puerperium. During normal pregnancy, the concentrations of the clotting factors fibrinogen, VII, VIII, von Willebrand factor, IX, X, and XII are all increased, resulting in a hypercoagulable state, which exposes pregnant women to an increased risk of thrombosis. The mechanical

obstruction by the growing uterus compromises venous outflow and subsequently increases the susceptibility of pregnant and postpartum women towards developing thromboembolism.

The challenges of VTE in the pregnant woman as a leading cause of death range from inadequate risk assessment to insufficient treatment and delayed diagnosis arising from contraindication to x-ray exposure and the clinical utility of d-dimer which is still a matter of debate.

The estimated incidence of VTE in pregnancy depends on the population studied with a range of 0.5 to 2.2 per 1000 deliveries. Of this figure, DVT constitute 75-80% and the rest are PE in the US and Norway maternal mortality resulting from VTE is around 1.5 and that of PE is 0.48 per 100 000 deliveries. VTE is responsible for 10% and PE causes 12.9% of maternal deaths in the US and UK respectively.Furthermore, VTE is the second most common cause of maternal death after cardiovascular disease in the US and it is the fifth common overall cause of death in the UK.

Pregnancy increases the risk of thromboembolic disorders by 20 times.

The prevalence of VTE 1.2 – 2/1000 deliveries and is responsible for 1.1 maternal deaths per 100,000.

Eighty percent (80%) of VTE in pregnancy is due to DVT and PE constitute 20%

Patients with intrauterine death have a six fold increase in the incidence of VTE compared to normal delivery.

There are very few studies of D-dimer in normal

pregnancy, and it has become apparent that D-dimer may not be an easy tool to exclude or predict the presence of VTE in pregnancy.

The Lyn risk score uses the following indices to assess the risk of thrombosis in pregnancy such as personal history of DVT, recurrent VTE, presence of thrombophilia, immobilization, twin pregnancy, age > 35yrs.

The risk of VTE significantly drops after six weeks post partum.

Covid-19 and Venous Thromboembolism

SARS-COV 2 belongs to a large family of virus called Coronavirus, the present nCOV has not been previously identified in humans.

Coronavirus causes a wide range of illnesses in humans mostly respiratory or gastrointestinal,the first case of this present pandemic was reported in Wuhan city, Hubei Province, China in December 2019

Four cases of "pneumonia of unknown etiology" was reported, it was later named by WHO as 2019 novel Coronavirus (2019-nCoV) on January 7, 2020

It was renamed as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) after genomic sequencing was done. The disease this new virus causes was named Coronavirus Disease 2019 (COVID-19)

Pathogenesis of Hypercoagulability in Covid-19

Individuals with COVID-19 have been reported to be hypercoagulable.This prothrombotic stateis termed thromboinflammation or COVID-19-associated coagulopathy (CAC). Individuals with COVID-19 also have pulmonary intravascular coagulopathy(PIC)

The pathogenesis of hypercoagulability in COVID-19 is however not fully understood but this is thought to be exemplified by the Virchow's triad.

All the three major components of Virchow's triad are

involved in severe COVID-19 infection

1. **Endothelial injury**: SARS-CoV-2 virus itself, intravascular catheters and cytokines bring about an endothelial injury.
2. **Stasis**: Immobilization can cause stasis of blood flow in all hospitalized and critically ill patients, regardless of whether they have COVID-19.
3. **Hypercoagulable state** – Elevated factor VIII, elevated fibrinogen, circulating prothrombotic microparticles, neutrophil extracellular traps (NETs) and hyperviscosity.

The hypercoagulable state associated with COVID-19 has been referred to by some as a DIC-like state, this is because many affected individuals are acutely ill and meet criteria for probable DIC in a scoring system published by the ISTH in 2009.

The major clinical finding in COVID-19 is thrombosis, whereas the major finding in acute decompensated DIC is bleeding.

COVID-19 has some similar laboratory findings to DIC, including a marked increase in D-dimer and in some cases, mild thrombocytopenia. However, other coagulation parameters in COVID-19 are distinct from DIC

In contrast, acute decompensated DIC is associated with low fibrinogen. In one of the largest series that reported on thromboembolic events in COVID-19 patients, none of the patients developed overt DIC.

Typically, bleeding predominates in acute decompensated DIC and thrombosis predominates in chronic compensated DIC although there is significant overlap. The hypercoagulable state in patients with COVID-19 bears more similarity to compensated DIC than to acute DIC.

VTE has also been reported in COVID-19 patients, incidence is however not well established.

Previous reports showed incidence ofVTE ranging between **1.1% in non-ICU hospital wards to 69% in ICU** patients screened with lower extremity Doppler ultrasound. It is also reported to be seen in up to one-third of patients in the intensive care unit (ICU), in spite of prophylactic anticoagulation

Several autopsy reports have also emphasized the contributions of hypercoagulability and associated inflammation in patients who die from COVID-19. Post-mortem examination of 21 individuals with COVID-19 found prominent PE in four and microthrombi in alveolar capillaries in five. Three had evidence of thrombotic microangiopathy with fibrin thrombi in glomerular capillaries.

Another post-mortem examination of 12 individuals with COVID-19 (8 male; 10 hospitalized) revealed DVT in 7 of 12 (58 percent). All cases of DVT had bilateral leg involvement, and none were suspected before death.Five had evidence of thrombosis in the lungs and PE was the cause of death in four.

Appropriate investigations of the Covid-19 patients

Since the pathogenesis of the disease has revealed features related to both chronic decompensated DIC and VTE, the role of Haematologists is to ensure proper evaluation of the patients towards prevention of DIC and VTE

Evaluation of these patients for coagulation abnormalities could be challenging but it is worthwhile.Decisions should be jointly made by the infectious disease experts and Haematologist based on the evaluation of the patient.

International Society on Thrombosis and Haemostasis (ISTH), the American Society of Hematology (ASH), and the American College of Cardiology (ACC) guidelines should be followed.

Complete blood count (CBC) including platelet count, blood film review, Prothrombin time [PT]/INR and activated partial thromboplastin time, [aPTT]), Fibrinogen, D-dimer are some of the investigations needed to be done. Others include Computed tomography with pulmonary angiography (CTPA) to confirm or exclude the diagnosis of PIC

A ventilation/perfusion (V/Q) scan is an alternative if CTPA cannot be performed or is inconclusive, although V/Q scan may be unhelpful in individuals with significant pulmonary involvement from COVID-19.

In–patient VTE prophylaxis

Venous thromboembolism (VTE) prophylaxis is appropriate in all hospitalized patients with COVID-19, unless there is a contraindication to anticoagulation.

All hospitalized medical patients should be treated with prophylactic-dose LMW heparin or unfractionated heparin if LMW heparin is unavailable for thromboprophylaxis

Perioperative VTE prophylaxis is especially important for patients with COVID-19 who are hospitalized for a surgical procedure.

VTE prophylaxis is also recommended in obstetric patients with COVID-19 who are in the hospital prior to or following delivery

In patients for whom no confirmatory testing is possible, it may be reasonable to treat empirically with full-dose anticoagulation based on one or more of the following:

1. Sudden deterioration in respiratory status in an intubated patient consistent with PE.
2. Unexplained respiratory failure especially if the fibrinogen and/or D-dimer is very high.
3. Physical findings consistent with thrombosis.

In conclusion, Covid 19 is currently a pandemic with community transmission in Nigeria

The roles of Haematlogists cannot be over- emphasized both in monitoring and treatment of patients as most of the patients are hypercoagulable.

Case Series Of VTE In UCH, Ibadan

Case 1: Rate of Decline of D-Dimer in a 68yr Old Patient with Deep Venous Thrombosis and Pulmonary Embolism: A Case Report

History

A 68 year old widow, a farmer, referred to the University College hospital Ibadan from the University health centre on account of a week history of fever and a two day history of sudden onset of easy fatigability.She developed high grade fever with chills, weakness and progressive effort intolerance for one month, worsening about two days prior to presentation, and dyspnea at rest. She had led a fairly sedentary lifestyle in the preceding 10 years.There was a history of exposure to smoke from processing garri by roasting on firewood. She is a known hypertensive for 15 years on tabs amiloride/hydrochlorothiazide 15mg/150mg daily.There was no leg swelling, abdominal pain or swelling, palpitations, cough, chest pain, paroxysmal nocturnal dyspnea or orthopnea.There was no acute blood loss, no passage of melaena stools or haematochezia. She initially presented at the source of referral where she was commenced on oral antimalarial (athemeter- lumefantrine) and Co-amoxiclav and subsequently referred to the UCH.

Examination findings:

Examination revealed an obese, elderly woman in moderate respiratory distress, afebrile, not pale, anicteric and mildly dehydrated. She was conscious and alert with normal findings on cardiovascular system examination. Her respiratory rate was 36 cycles/min however, breath sounds were reduced at the upper lung zones with coarse crepitations at the lung bases bilaterally. An initial assessment of chest infection to rule out acute coronary syndrome, pulmonary embolism and heart failure was made. She was commenced on intranasal oxygen but did not respond to the oxygen therapy.She received antimalarial (tabs arthemeter/ lumefantrine) and empirical antibiotics (IV ciprofloxacin and metronidazole).

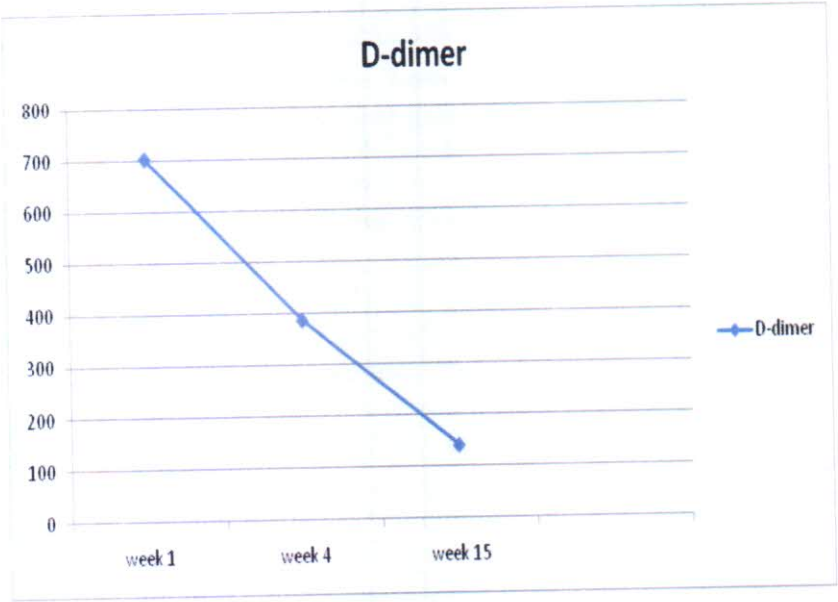
Investigations:

Full blood count revealed mild leukocytosis.INR was 1.2 at baseline and remained stable following anticoagulation with subcutaneous enoxaparin.D-dimer at baseline was 701.5ng/ml and declined to 385.8ng/ml and 139.8ng/ml after four and 14 weeks on anticoagulation respectively. Doppler ultrasound scan of the lower limbs was difficult on account of obesity but revealed a right lower limb deep venous thrombosis. Chest CT angiography showed filling defect in the branches of the right pulmonary artery. Echocardiography revealed dilated right atrium and ventricle, dilated inferior vena cava, grade I left ventricular dysfunction, ejection fraction of 90% and no significant pericardial effusion. ECG revealed multiple inverted T waves in the inferior leads with right atrial enlargement. Chest xray showed widespread patchy opacities in both lung fields.

Full Blood Count @ 24/5/16

PCV (%)	36
WBC (/mm3)	11,880
PLT (/mm3)	192,000
Neutrophil (%)	47
Lymphocyte (%)	36
Monocyte (%)	15
Eosinophil (%)	0.3
Basophil (%)	1.0

Pattern of D-dimer decline with anticoagulation



Anticoagulant Therapy

She was commenced on SC clexane on the second day of admission at 80 mg 12 hourly for two weeks. She developed ecchymotic patches at the sites of clexane injections. Clexane was discontinued on day 14 and she was commenced on tabs Dabigatran 150 mg b.d. She was discharged after 27 days on admission. She is being followed up by the Haematologists, Chest physicians and the Dieticians.She remains well and is compliant with the Dabigatran therapy.

Case 2: Response to New Oral Anticoagulants in Nigerian Patients with Venous Thromboembolism

Introduction: In recent years, new drugs for anticoagulation targeting individual components of the coagulation cascade have been developed. These include the direct FXa inhibitors and the direct thrombin inhibitors.

Aims: This study was aimed at determining the response to NOACs in Nigeria patients with VTE.

Method: We retrospectively analysed twenty eight (28) patients who have had these novel oral anticoagulants (NOACS), within the last two years at the University College Hospital Ibadan, Nigeria.

Result: Eighteen (64.3%) of them were females while 10 (35.7%) were males. The age range was 23-87 years and 21 (75%) of them were above 50 years of age. Most of them were in the middle/upper social class consisting of Retired Professors, CEOs, Doctors and senior government officials. Laboratory diagnosis was with the aid of pulmonary CT-angiogram, Doppler ultrasound of the limbs, D-dimer, electrocardiography and echocardiography findings suggestive of a VTE.They all had sub cut. clexane for 10-14 days at the commencement of therapy before switching to NOACs. Seventeen patients used Dabigatran, nine used Rivaroxaban while two had Apixaban. Most of them were

anticoagulated for at least 6 months with complete resolution of the symptoms.

The commonest indications for anticoagulation were lower limb DVT -18(65%), pulmonary embolism-6(21%) and combined DVT and PE-4(15%). All the patients had immobility as a risk factor. Other risk factors include obesity - 6, intracranial lesion - 3, stroke - 3, malignancies - 3, and uterine fibroids – 2

Conclusion: Our patients showed satisfactory response to NOACs. The costs of these drugs are quite high (Dabigatran - 65USD, Rivaroxaban - 195USD/month, Apixaban is not available locally) and are not readily affordable for the general population in our setting. These drugs should be subsidized by the government by making them available on the health insurance scheme.

Case 3: Risk Factors for Venous Thromboembolism at the University College Hospital, Ibadan

Background:

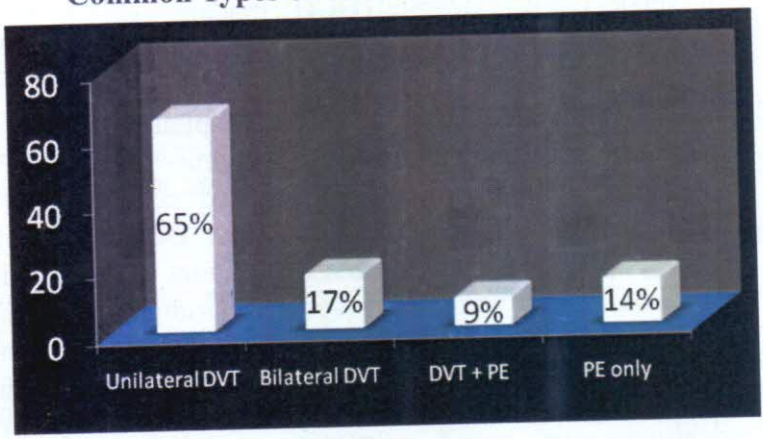
Venous thromboembolism (VTE) is a disease entity that consists of two related conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). VTE poses significant public health challenges as it is responsible for a high morbidity and mortality worldwide. Current opinion holds that background genetic abnormalities exist in almost all patients with thrombo-embolic disorder. However, risk factors (modifiable and non-modifiable) can be identified and play a major role in its pathogenesis. Considering the cost of managing VTE in poor resource settings such as found in Nigeria, VTE risk factor identification and thromboprophylaxis will reduce the burden of disease and its treatment cost.

Aims:
The study aimed to review the pattern of presentation, and to identify risk factors, in patients diagnosed with VTE at the University College Hospital (UCH), Ibadan

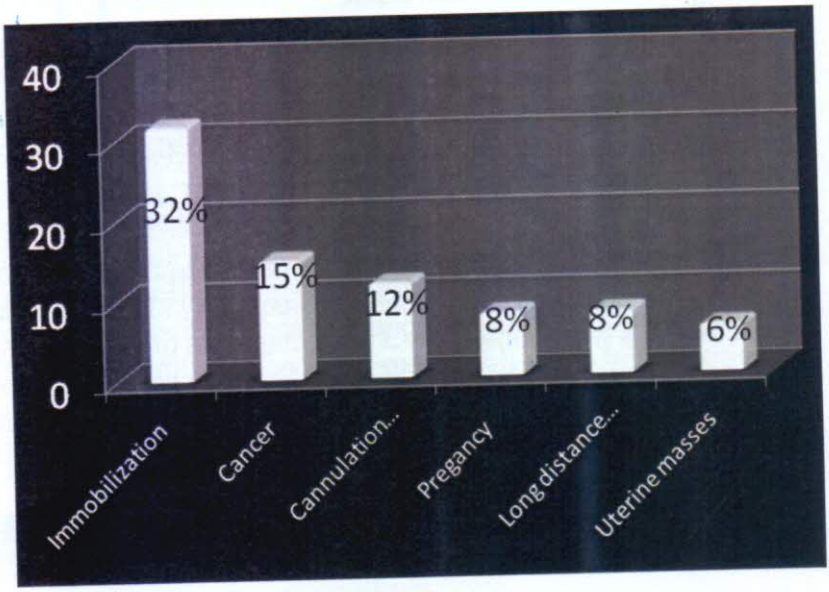
Method:
This is a retrospective study of the hospital records of 65 confirmed VTE patients (doppler ultrasound scan for DVT and CT-angiography for PE) diagnosed and managed at UCH, Ibadan between July 2016 and December 2017. Demographic data and possible risk factors documented in the case note were retrieved. In indigent patients, electrocardiography and echocardiography findings suggestive of a possible PE were considered diagnostic aids. The patients were treated for 3 to 6 months based on the type of VTE. Microsoft excel version 2013 was employed for carrying out the statistical analysis. Frequency, mean, and standard deviation were determined for variables.

Result:
65 patients were studied of which 27 were males and 38 females (M: F=1:1.4). Their age ranged between 15 and 87 years with a mean age of 51±17 years. Only 6 patients (9.4%) were <30 years; 44.6% were between 30-50 years, and 46% were >50 years. 53 patients (81.5%) had DVT of which 65% were unilateral and 16.9% bilateral DVT. No cases of distal DVT was seen in the period studied. Immobilization, found in 32.3% of the patients, was the most frequently identified risk factor. This was followed by a prior diagnosis of malignancy (15.4%) and the use of femoral cannulation for haemodialysis (12.3%). Common causes of immobilization were admission for neurotrauma, fractures (especially femoral), and post-surgeries (caesarean section and myomectomy). Finally, the presence of an underlying malignancy was the commonest identifiable risk in patients with bilateral DVT.

Common Types of Venous Thromboembolism



Risk Factors for Venous Thromboembolism



Conclusion:

All cases of DVT (bilateral for example) should be thoroughly screened to exclude malignancy. Prolonged immobilization should be avoided and prevented using physiotherapy and prophylactic anticoagulation. A high index of suspicion for DVT is required in cases of neurotrauma, pelvic surgery and fractures.

VTE Recurrence in M.A. 72yrs Female

72-year-old woman a trader a known patient with hypertensive heart disease who was first diagnosed with VTE in May,2016. She was on anticoagulation with tab Dabigatran 150mg bd for 6 months. However, 18 months afterwards, she presented with cough of 4 days and breathlessness of 12 hours duration. She had resonant percussion notes bilaterally, widespread rhonchi and fine crepitations. D-dimer was elevated at 2.5µg/nl (<0.5), ECG shows sinus rhythm, chest X-ray showed patchy opacity in the right lower lung zone and Doppler ultrasound revealed acute on chronic DVT in the left popliteal vein. Chest CT pulmonary angiography was not done due to financial constraint. She was managed for recurrent VTE and *Klebsiellapneumoniae*pneumonia. She had SC Clexane 80mg bd for 2 weeks, IV Cefuroxime, IV Lasix. Anticoagulation was then changed to tab Dabigatran 150mg bd. Currently, this is the 16th month after recommencement of Dabigatran.

Post Mortem Reports Of VTE In UCH 2015 – 2020

Serial No	Clinical history	Autopsy Findings	Risk Factors	Cause of Death
1. Age: 47 Sex: M Occ.: IT Engineer	Past medical history – Impaired plasma glucose. Slumped at home, Brought in Dead	Saddle embolus in both pulmonary arteries, extending into Pulmonary trunk. Another clot of 12cm long was found in the right femoral vein PROVISIONAL ANATOMICAL SUMMARY: - Saddle embolus of the pulmonary arteries - Right proximal deep venous thrombosis - Pulmonary petechial haemorrhage	Not clearly identified in the history and examination	Pulmonary Embolism: Right Proximal Deep Vein Thrombosis
2. Age: 80 Sex: F Occ.: Business woman	Past Medical history – Depression. Sudden Death while on admission at a private hospital	PROVISIONAL ANATOMICAL SUMMARY: - Thrombo-emboli within the pulmonary arteries - Pulmonary petechial haemorrhage	- Possibly Sedentary lifestyle - Obesity	Pulmonary Embolism Source: - Not found at autopsy, - No evidence of lower limb DVT
3. Age: 58 Sex: F Occ.: ?	Known Schizophrenia patient who presented with Catatonia of 4 days duration Patient collapsed while on admission.	PROVISIONAL ANATOMICAL SUMMARY: - Pulmonary embolism - Serous cystadenoma of the pancreas - Cardiomegaly with left ventricular hypertrophy - Mottled appearance of the liver - Acute tubular necrosis with left cortical cyst - Uterine leiomyoma with dermoid cyst of the left ovary	- Catatonia	Pulmonary Embolism Source - Lower limb Deep vein thrombosis
4. Age: 53 Sex: F Occ.: ?	Known patient with symptomatic uterine fibroids and menorrhagia - History of contraceptive use (injectables) - Presented with sudden onset of breathlessness and died within 3hrs of admission	Provisional Anatomical Summary: - Bilateral pulmonary artery thromboemboli - Uterine Leiomyoma.	- Uterine mass - Contraceptive use	Pulmonary Embolism Source - No evidence of lower limb DVT

5 Age: 37 Sex: F Occ.: Civil Servant	G2P1 +2 ,presented with severe eclampsia. Had emergency CS and died during surgery.	PROVISIONAL ANATOMICAL SUMMARY: - Pleural effusion - Multiple petechiae hemorrhages on the heart, pleural, liver and kidneys - Pulmonary thromboemboli - Multiple septic ulcers	- Eclampsia with DIC	Pulmonary Embolism with Multi organ failure. Source - Pulmonary microemboli from DIC in a patient with eclampsia and multi-organ dysfunction
6 Age: 83 Sex: M Occ.: ?	Past Medical History – Orthopaedic surgery on the right femur Known hypertensive who presented on account of sudden onset of breathlessness and loss of consciousness.	PROVISIONAL ANATOMICAL SUMMARY - Limb-length deformity - Embolus in right pulmonary trunk - Complicated atherosclerosis of the coronary arteries - Cardiomegaly with biventricular hypertrophy	- Reduced mobility	Pulmonary Embolism Source - Not found (Limited autopsy)
7 Age: 49 Sex: M Occ.: Publisher	Admitted on account of inability to use the right leg. Died suddenly while on admission.	Imaging findings of degenerative disease of lumbosacral spine with multilevel disc herniations. PROVISIONAL SUMMARY: - Saddle embolus - Right lower limb DVT	- Immobilization (disc herniation)	Pulmonary Embolism Source - Right proximal DVT.

International Society On Thrombosis And Haemostasis (ISTH)

The International Society on Thrombosis and Haemostasis is a leading thrombosis and haemostasis related professional organisation in the world with membership in about 100 countries.

The society is dedicated to transformative scientific discoveries and clinical practices, the development of young professional and the education of physicians, scientists and allied health professionals wherever they may live.

In order to achieve her cardinal objectives, the society has committee which includes:

i. Scientific and Standardization Committee (SSC) which in turn has about 16 subcommittees including - Biorheology, paediatric and neonatal thrombosis and haemostasis, other issues in thrombosis and haemostasis, haemostasis and malignancy, contact factors, disseminated intravascular coagulation etc.

ii. Education committee facilitates educational programs like reach the world programs which is basically an educational program/workshop on thrombosis and haemostasis for developing countries and other countries. Two Nigerian Haematologists have benefitted from the fellowship training program for reach the world countries.

iii. Similarly, the ISTH has partnered with Nigerian Society for Blood Transfusion to sponsor two educational courses/workshops in Nigeria. A pleasant fall out from this are the development of guideline for management of venous thromboembolism in Nigeria and the emergence of a vibrant Thrombosis and Haemostasis group within the NSHBT. The education committee through the ISTH academy also organizes webinar series on thrombosis and haemostasis disorders.

The ISTH is also involved in the development of guidelines for management of thrombosis and haemostatic disorders. Through the World Thrombosis day activity, the organisation also raises awareness for the prevention of venous

thromboembolism.

The ISTH, World Thrombosis Day and Time2Move sponsored an event to break a Guinness World Records title for the highest number of people participating in a chair-based exercise, at the 2017 ISTH Conference in Berlin. These 3 bodies organized a group-chair physical exercise on Wednesday, July 12 July among the conference attendees. I was one of the volunteer participants. We had trainers on the stage demonstrating which type of exercises can be performed on a chair, as a means of preventing venous thrombo-embolism. The team of organisershad planned to award our group a Guinness record if the participants for this group-chair exercise numbered up to 1,500 but we were about half the number required to win the Guinness record. All the same, each of us was given a medal for participating. I guess the joy is in participating and not necessarily in winning.

At the following ISTH meeting in Dublin in 2018, I was also an attendee. We had the opportunity of visiting the Guinness company where Guinness stout was being produced. At each of these conferences, several hours were devoted to causes of thrombo-embolic disorders, their treatment and prevention.

At the ISTH congress in Melbourne in Australia in 2019, I presented our experience in UCH, Ibadan on the use of NOACs anticoagulants. It should be noted that because of our poor economy, most of our patients cannot afford NOACs, and such patients are therefore given warfarin, which is far cheaper than NOACs.

The cost of NOAC for one month for the treatment of VTE in a patient is about N28,000 = 00 (Twenty eight thousand Naira) but for warfarin therapy for VTE per month, it is less than N1,000 = 00 (One thousand Naira). However for the use of NOACs, coagulation tests monitoring is not required whereas there has to be regular monitoring for warfarin therapy and dose adjustment accordingly. For these reasons, NOACs are becoming more acceptable to our patients.

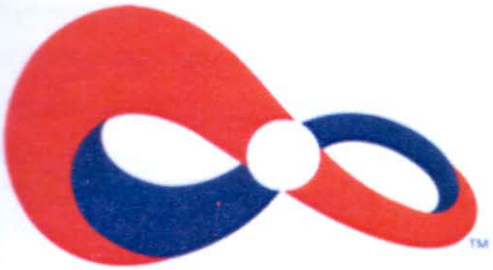
World Thrombosis Day

On October 13th 2014, the world thrombosis day (WTD) was founded by the International Society of Thrombosis and Haemostasis (ISTH). That day was chosen to commemorate the birthday (13th October) of Rudolf Virchow, a German Pathologist, Biologist and Anthropologist, who was the pioneer of Virchow's triad, highlighting the 3 important phenomenon in the pathophysiology of thrombosis i.e. stasis, endothelial injury and hypercoagulable state.

The purpose of WTD is to encourage a focused global awareness on thrombosis. Over 175 organizations worldwide participated on the first day in 2014 and new organizations around the world continue to join through educational forums, widespread media coverage and social media. The University College Hosiptal in the last 3 years have had activities on 13th October to celebrate WTD, with Seminars geered towards raising public awareness on thrombosis

Thrombotic disorders include myocardial infraction, cerebral infarction (ischaemic stroke) and venous thromboembolism. The eventual outcome of these thrombotic disorders are often serious but their onset could be prevented by life-style modifications and the use of appropriate anticoagulant prophylaxis.

The logo of WTD is as shown below



WORLD THROMBOSIS DAY
13 OCTOBER

This logo was designed by EkawatSuwantararoj from Thailand a patient with haemophilia (an inherited bleeding disorder). Ekawat has a Master's degree in Art and Design. The red part of the logo represents the artery and the blue colour represents the vein while the white crcle represents the clot (thrombus).

The mission of ISTH in founding the WTD is to increase global awareness on thrombosis, including its causes, risk factors, signs and symptoms, and evidence-based prevention and treatment; with the ultimate aim of reducing disability and death due to thrombosis.

The objectives of WTD are:

1. Highlight the burden of disease (thrombosis in general) and highlight the need for action, specifically underscoring the unrecognized threat and serious consequences (morbidity and mortality) related to venous thromboembolism (VTE) and atrial fibrillation (Afib)

2. Increase public awareness of the significance, risks, signs and symptoms of thrombosis, specifically VTE and AFib as an important cause of thromboembolic stroke.

3. Empower individuals to talk with their healthcare providers about their risks for thrombosis and appropriate prevention. Empower individuals to seek immediate medical attention if they have signs and symptoms.

4. Galvanize organizations in countries across the globe to conduct appropriate and aligned campaigns in their countries and regions.

5. Advocate for "system of care" to properly prevent, diagnose and treat VTE and Afib.

Guideline for management of Venous Thromboembolism in Nigeria

The burden of thrombotic disorders in Nigeria is not well known, and no clear national policy on what has now been regarded worldwide as a common disorder. In our medical practice in this country, it has been observed that a number of cases of sudden deaths, post-surgery deaths, and cancer related deaths were shown at post-mortem to be due to complications of thrombotic disorders.

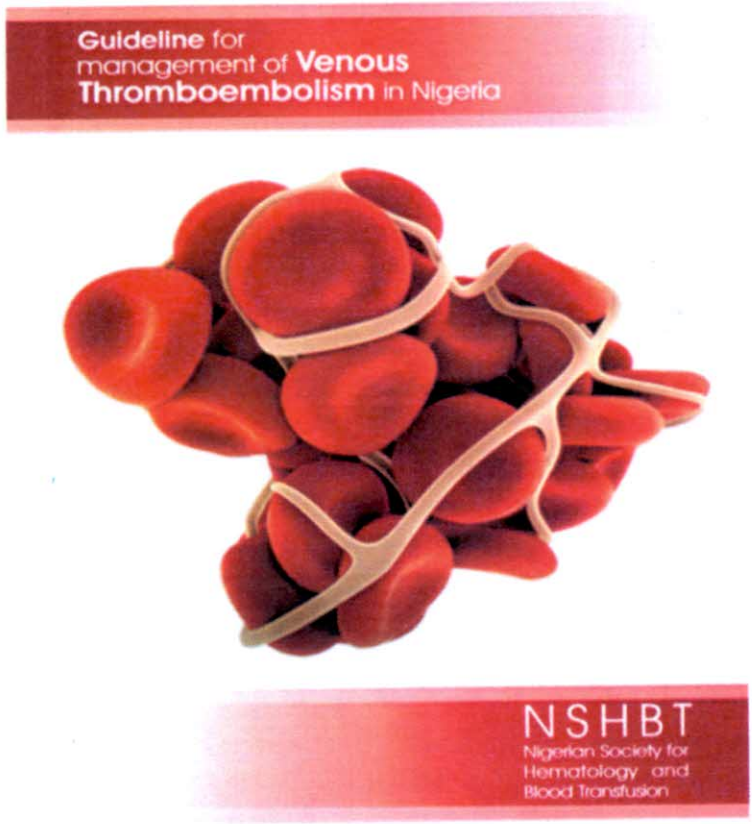
The Nigerian Society of Haematology and blood transfusion, in order to encourage knowledge in thrombo-embolic disorders, their prevention, diagnosis and treatment, developed a guideline on the management of these disorders. At the 42nd annual conference held in Lagos in October 2016, with national and international speakers from ISTH (International Society of Thrombosis and Haemostasis), the consensus was reached that NSHBT should promote the following;

1. Research on thrombosis and bleeding disorders
2. Increase the level of awareness, exposure and training of its members in thrombotic and bleeding disorders
3. The production of treatment guidelines for use by practitioners in Nigeria for thromboembolic disorders.

This guideline was produced over several months with physical meetings and online review throughout 2017 by a team of 8 haematologists (of which I am a member) in

Nigeria. The chairman of the committee was Prof. OmoladeAwodu, the current representative on ISTH council for the developing countries.

The guideline was reviewed and approved by experts in Thrombosis and bleeding disorders of the educational sub-committee of the ISTH, before it was mass produced for use by medical practitioners in Nigeria.



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CONCLUSION

VTE is a common cause of morbidity and mortality, particularly in hospitalized patients. The prevalence of VTE in Africa, including Nigeria is high especially following surgery, in pregnancy, postpartum, in patients with cancer and diabetes. Too often, VTE can go unrecognized and undiagnosed, and as such up to 25% of patients (by conservative estimate) at risk of developing a VTE in this country are not receiving prophylactic anticoagulation. The burden of thrombotic disorders in Nigeria is not fully known, but some causes of sudden deaths and post surgery deaths have been found to be due to VTE at postmortem. At the beginning of the COVID pandemic, the role of VTE in the morbidity and mortality in COVID patients was not immediately recognized.

The cause of VTE is multifactorial, resulting from complex interaction between genetic predispositions and acquired risk factors. Studies have shown that the incidence of VTE may be higher in the African populations than in other regions of the world.

In Nigeria, VTE remains under-diagnosed to a low index of suspicion, inadequate diagnostic facilities for VTE and poor financial support for comprehensive health care. We need to increase public awareness on the prevention of VTE. For improved management of VTE by clinicians, the Guideline for Management of VTE in Nigeria by NSHBT will be most useful.

ACKNOWLEDGEMENT

My sincere gratitude to Prof. Olabopo Osuntokun, the Osuntokun family (both nuclear and extended), and all members of the Board of trustees of the Benjamin Oluwakayode Osuntokun Trust for considering me worthy to give this memorial lecture.

My gratitude to all my teachers, including the late Prof. B.O. Osuntokun, who imbibed so much knowledge, discipline and empathy for patients that characterize the medical education of this great College of Medicine, University of Ibadan. I thank God I am one of those students.

I am highly indebted to Prof. G.J.A. Esan for editing this discourse and for his constant encouragement. I am grateful to my husband, who has always been my partner in progress, and who ensured that the tempo of the writing did not wane.

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I thank you all.

Definition of terms

Thrombosis is the formation of a solid mass from blood constituents within the vascular channels in – vivo (in a living being). In other words thrombosis is blood coagulation within the circulation in – vivo. The thrombus tends to be adherent to the internal wall of a blood vessel in a given location.

Thrombosis may occur in veins (venous thrombosis) or in arteries (arterial thrombosis). Venous thrombosis leads to congestion of the affected part of the body, while arterial thrombosis (and rarely severe venous thrombosis) affects the blood supply and leads to damage of the tissue supplied by that artery (ischemia and necrosis).

Embolus refers to any intravascular mass, air, fat or thrombus that travels along the vascular channel and capable of clogging small caliber blood vessels.

Deep Vein thrombosis (DVT)occurs when blood clots form in the deep veins of the legs (most often), pelvis or arms. DVT often starts around the valve pockets of the veins and extends proximally.

Pulmonary Embolism refers to the obstruction or occlusion of the pulmonary artery or its branches by thrombus, tumour, air or fat that has originated in the venous system or form the right side of heart.

Venous thromboembolism encompasses both DVT and PE. It refers to the formation of a thrombus in the deep veins and subsequent migration of the blood clot

within the venous circulation, through the right side of the heart into the pulmonary artery and lodging in the lungs. The spectrum of VTE ranges from clinically silent (unsuspected) to sub–clinical to massive embolism and subsequent death.

Provoked DVT or PEoccurs in a patient with an antecedent (within 3 months) and transient major clinical risk factor for venous thromboembolism (VTE), for example surgery, trauma, significant immobility (bedbound, unable to walk unaided or likely to spend a substantial proportion of the day in bed or in a chair), pregnancy or puerperiumor in a patient who is having hormonal therapy (oral contraceptive or hormone replacement therapy)

Unprovoked DVT or PE occurs in a patient with no antecedent major clinical risk factor for VTE who is not having hormonal therapy (oral contraceptive or hormone replacement therapy) or active cancer, thrombophilia or a family history of VTE, because these are underlying risks that remain constant in the patient

Post thrombotic (postphlebitic) syndrome refers to symptoms and signs of chronic venous insufficiency that develop following deep vein thrombosis (DVT) and is a common, burdensome, and costly complication.

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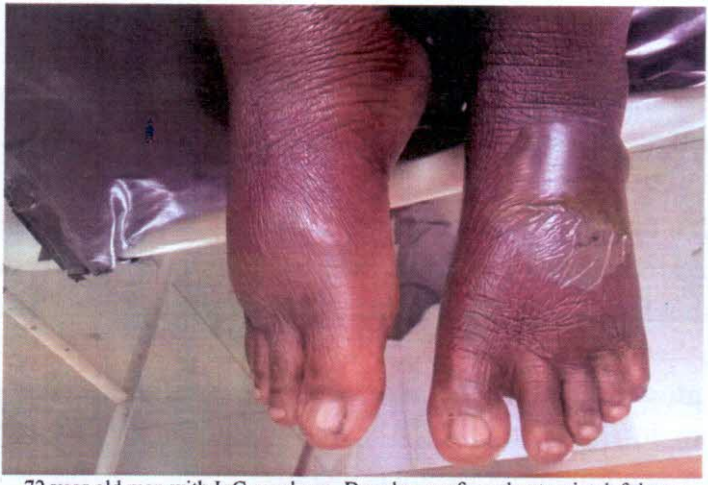
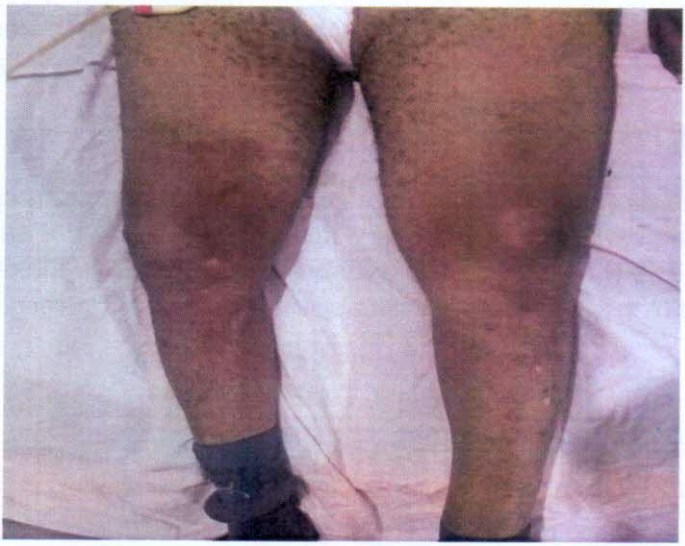


72 year old man with IgG myeloma, Doppler–confirmed extensive left lower limb proximal DVT. He developed large bullae on the dorsum of the left foot following the development of the DVT. (Acute DVT in the common femoral, superficial femoral and popliteal veins)



59 year old man with Right Ischaemic hemispheric cerebrovascular disease. Doppler ultrasound confirmed extensive left acute on chronic DVT. (Popliteal vein).

UNIVERSITY COLLEGE HOSPITAL, IBADAN

Venous Thromboembolism (VTE) Risk Assessment Tool No. 006651

To be Administered by Nurses, Doctors, Physiotherapists & Pharmacists. THIS FORM MUST BE FILLED IN TRIPLICATES

Patient's Name (Surname First) _____

Sex: M☐ F☐ Age _____ Weight (Kg) _____ Height (m) _____ BMI (Kg/m^2) _____ Hospital No. _____

Provisional Diagnosis _____

A	Each risk factor represents 1 point
☐	Age 14-60 Years
☐	Minor surgery planned[1]
☐	History of prior minor surgery[1]
☐	Varicose veins
☐	History of inflammatory bowel disease. including case note
☐	Swollen legs (current)
☐	Obesity (BMI 30 - 39)
☐	Acute myocardial infarction
☐	congestive heart failure
☐	Sepsis
☐	Abnormal pulmonary function test
☐	Breathlessness at rest
☐	Medical patient currently on bed rest
☐	Leg plaster cast or brace
☐	Other risk factors such as occupation[1] , social habits[3] alcohol . 1 bottle per day[3]

B	Each risk factor represents 5 points
☐	Elective major lower extremity arthroplasty
☐	Hip, pelvic or leg fracture(≤1 month)
☐	Stroke (≤1 month)
☐	Multiple Trauma (≤1 month)
☐	Acute spinal cord injury (paralysis) (≤1 month)
☐	Major surgery lasting over three hours[1]

C	For women only (each represents 1 point
☐	Combined contraceptives or hormone replacement therapy
☐	Pregnancy or postpartum (≤ 6weeks/42 days)
☐	History of unexplained stillbirth
☐	Pregnancy related complications

A	Each risk factor represents 2 points
☐	Age 60 - 74 years
☐	Major surgery ≥ 60 minutes
☐	Previous malignancy
☐	Central venous access (current)
☐	Morbid obesity (BMI ≥ 40)

E	Each risk factor represents 3 points
☐	Age over75 years
☐	Major surgery lasting 2-3 hours
☐	BMI ≥ 50 (Venous stasis syndrome)
☐	History of pulmonary embolism, superficial vein thrombosis, deep vein thrombosis
☐	Family history of DVT /PE
☐	Present cancer/or on chemotherapy
☐	Positive factor V Leiden
☐	Positive prothrombin (20210A) mutation
☐	Elevated serum homocysteine
☐	Positive lupus anticoagulant
☐	Elevated anticardiolipin antibodies
☐	Heparin induced thrombocytopenia (HIT)
☐	Other thrombophilia types

Total Risk Factor Score ☐

VTE Risk and Suggested Prophylaxis

Total risk Factor	Incidence of DVT	Risk Level	Prophylaxis regimen
0-4	≤ 40%	Low risk	Early ambulation; Adequate hydration; Elastic Stockings (ES) and Intermittent Pneumatic Compression (IPC)
5 or more	41 -80%	High Risk	Pharmacological LDUH; LMWH (≥3400 U), Warfarin or FXa I alone or in combination with ES or IPC

Legend

ES: Elastic Stockings
IPC: Intermittent Pneumatic Compression
LDUH: Low Dose Unfractionated Heparin
LMWH: Low Molecular Weight Heparin
Fxa I: Factor Xa inhibitor

Anticoagulants: Factors associated with increased bleeding		
Is patient experiencing any active bleeding?	Yes ☐	No ☐
Does patient have, or has had a history of HIT?	Yes ☐	No ☐
Is patient's platelet count ≤ 100,000/mm^3?	Yes ☐	No ☐
Is patient taking oral anticoagulants, platelet inhibitors (eg: NSAIDS, Clopidogrel, Salicylates)?	Yes ☐	No ☐
Is patient's creatinine clearance >2mg /dl?	Yes ☐	No ☐
If any of the above boxes is checked "YES," the patient may not be a candidate for anticoagulant therapy and you should consider alternative prophylactic measures (elastic stockings and/or IPC)		

Intermittent Pneumatic Compression (IPC)		
Does the patient have severe peripheral arterial disease?	Yes ☐	No ☐
Does the patient have congestive heart failure?	Yes ☐	No ☐
Does the patient have acute superficial/deep vein thrombosis?	Yes ☐	No ☐
If any of the above boxes is checked "YES," the patient may notbe a candidate for Intermittent Pneumatic Compression. You should consider alternative prophylactic measures		

Footnotes

1. Any surgical procedure lasting more than two hours and/or involving use of general anesthesia should be classified as major surgery.
2. Any occupation that requires long sitting for more than six hours or requires carrying heavy loads on the thighs is a risk factor for venous thromboembolism
3. Social habits= smoking, alcohol>1 bottle per day (250ml of beer/60ml of spirit)

NOTE that the clinical judgement of the managing consultant should ultimately guide decision to anticoagulate

Assessed by: Name: _____ Cadre: _____ Signature _____ Date _____

Adapted from **A. Caprini, MD, MS, FACS, RVT**Louis W. Ringler Professor of Surgery, NorthShore University Healthsystem, clinical Professor, of Surgery, University of Chicago Pritzker School of Medicine, chicago, IL 6

Supported By SANOFI

UCH Venous Thromboembolism (VTE) Risk Assessment Tool Form

Prof. Wuraola Shokunbi, with the immediate past President of the International Society on Thrombosis and Haemostasis (ISTH), Prof. Claire McLintock, M.D. (New Zealand), at the 2nd ISTH – NSHBT Educational Course on Haemostatic disorders, Abuja, 2019.

Participants at the 2nd ISTH – NSHBT Educational Course on Haemostatic Disorders Abuja, 2019

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