



## **Maastricht Consensus Conference on Thrombosis MECC, Maastricht 11-13 februari 2015**



Thrombosis is the mechanism behind a variety of serious diseases and medical conditions, and a subject of growing research interest. The process plays a major role in cardiovascular disease and venous thromboembolism (VTE), which is increasingly considered as a class of diseases of so far underestimated importance. Recent research also identifies important roles for thrombosis and clotting mechanisms in oncology and infectious diseases.

The Maastricht Consensus Conference on Thrombosis is a new initiative aiming to assemble scientists of mixed disciplines with interest in the field, offering a platform for inspiration and discussion. The first meeting, held from February 11 until February 13, was focused on VTE. It introduced a new format of concise introductory lectures followed by workshops discussing wishes and ideas for a research agenda. The outcome of the discussions will be published as a consensus report; this Highlight report offers an overview of the subjects discussed focussing on the introductory talks.

In primitive organisms haemostasis, immunity and inflammation are all mediated by the same cell, the haemocyte. Higher animals have acquired differentiated blood cells with separate roles. However, there are many functional crosslinks between the cell lines that become



apparent in pathologic processes, according to **Yukio Ozaki**, university of Yamanashi.

### **Platelets & inflammation**

In atherosclerosis platelets may function as inflammatory mediators

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in narrow collaboration with macrophages and smooth muscle cells. Platelets, once activated, release various micro particles, ligands and cytokines that activate neutrophils and drive inflammatory processes that, for instance, can damage endothelium. There is no doubt that more complex functions of platelets play a role in VTE. Interesting substances for research are von Willebrand Factor (using an antibody against the glycoprotein reduced the odds of emboli formation in DVT) and platelet GP1 $\alpha$ . Neutrophil Extracellular Trap (NET) formation is another hot topic in research. Overwhelmed by massive invasion of bacteria or other pathogens, neutrophils have the ability to emit extracellular net-like fibres from their nuclei, mainly composed of DNA, trapping platelets, erythrocytes and pathogens, in order to prevent further dissemination of the infection.

NET-formation is also supposed to provide a 'scaffold' for thrombus formation and toll-like receptor 4 on platelets appears to have a key role in initiating this process. 'Platelets are stuffed with a variety of granules containing a wealth of biologically active substances', according to

Ozaki, 'and should be considered as a highly advanced drug delivery system'. In the workshop Ozaki chaired, antiplatelet therapy for VTE was considered premature, but studies into the functions of the C-type lectin like receptor 2 (CLEC2) and the contents of platelet vesicles were considered as a major topic of interest.



### Leukocytes & thrombosis

**Wolfram Ruf**, Johannes Gutenberg University

Mainz, elaborated on the increasingly recognised role of leukocytes in intravascular thrombosis, indeed with vascular injury or at least vessel wall dysfunction as a prerequisite. Coagulation is suppressed by the vessel wall via the thrombomodulin-protein C pathway; when this mechanism is hampered, pro-coagulant processes are favoured. Vascular injury not only induces TF-dependent coagulation activation, but also releases a variety of 'injury signals' such DNA, RNA and polyphosphates that, together with the contact activation pathway, lead to thrombin generation and ultimately thrombotic events. In models of vascular injury such as the

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FeCl<sub>3</sub> model, where the TF-pathway and the contact pathway separately can be blocked, thrombin generation consequently appears driven by both components. There is also growing evidence that innate defence pathways stimulate TF-activation by smooth muscle cells and leucocytes. Also complement-activation and neutrophil NET-formation can activate the TF-pathway. Furthermore, platelet-leukocytes interactions can lead to release of elastase that can degrade TFPI.

### Biochemical links

Specific injury signals have been directly linked to TF-activation. TF largely resides on the cell surface in an inactive, encrypted conformation. Activation (by decryption) takes place in the outer leaflet of cell membranes and appears to be dependent on protein disulfide isomerase (PDI), an enzyme with a key role in for instance neutrophil adhesion, and the thiol pathways known for regulatory functions in inflammatory states. An unmet need discussed in the workshops was the lack of adequate animal models. Research so far depends on healthy animals, whereas (recurrent) venous thrombosis is

characterized by extensive vascular damage and chronic inflammation.



### Erythrocytes & thrombosis

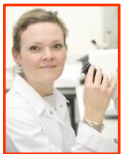
Qualifying the erythrocyte as ‘the forgotten cell’ **Bas de Laat**, university Maastricht and Synapse, pointed out that they too have an influence on hemostasis and thrombosis. Forming the main stream in laminar shearing, erythrocytes push the platelets to the wall in a process called ‘skinning’. With an increase in hematocrit and higher erythrocyte count, the combined effect of more skinning of platelets, higher viscosity of the blood and decreasing flow velocity, the risk of thrombosis will increase. This may for instance be the case in erythrocytosis or dehydration.

Furthermore, rouleaux formation, which is mostly due to low flow but may also result from a change in the composition of plasma or changes in cell deformability as in sickle cell disease, may attribute to the risk. Erythrocytes do support cleavage of prothrombin to thrombin; a small part of the erythrocytes is phosphatidylserine (PS)-positive.

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Erythrocytes can bind to platelets due to an Intercellular Adhesion Molecule-4 (ICAM4) integrin interaction, which makes platelets 'engulf' erythrocytes into a thrombus. In flow experiments by De Laat, platelet activating substances such as thrombin, CRP, AA and ADP enhanced this interaction. Blocking the GPIIb/IIIa-receptor with the tripeptide blocker RGD hampered the interaction, proving that the integrin is involved. Adding ICAM-4 peptide also inhibited the interaction. Targeting the ICAM-4 -GPIIb/IIIa interaction might provide a therapeutic strategy according to De Laat. Also in his workshop the lack of adequate models, especially considering flow rates was mentioned; ICAM 4 was considered a promising tool for prediction of blood loss during surgery.



### On coagulation and fibrinolysis

Arterial thrombi have a completely different structure than their venous counterparts. Arterial thrombi are dense structures built out of fibrin, while venous thrombi are gelatinous and contain much more blood cells. So the underlying

biochemistry and the mechanisms involved are different as well and the approach in thrombolysis should be different, said **Nicola Mutch**, university of Aberdeen in her introduction on coagulation and fibrinolysis.

The contact pathway is activated when there is reciprocal activation of factor XII and prekallikrein on a negatively charged surface. Ultimately FXIIa activates FXI, which enters the coagulation cascade. There has been a lot of discussion about the involvement of the contact pathway because individuals deficient in FXII do not exhibit any bleeding tendencies, while those lacking FXI have mild bleeding tendencies. This is probably because there is back activation of the contact pathway via FXI by thrombin, according to Mutch. However in 2005 several groups have shown that FXII deficient mice show defective thrombus formation and have better survival in induced VTE. This advantage is lost with infusion of factor XII. So FXII seems not to contribute to physiological fibrin formation in vessel injury, but does function in pathological situations to sustain fibrin formation during thrombus growth, which makes it an

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attractive target for development of anticoagulants. However inhibition of FXI has also been shown to modulate thrombosis with minimal bleeding risk. Very recently, a FXI antisense oligonucleotide has been shown to improve the outcome of thrombosis prevention in orthopaedic surgery compared to enoxaparin.

### FXII

Anyhow, there is a role for the intrinsic pathway in driving VTE. In the body it can be activated for instance by RNA, misfolded protein, collagen, polyphosphate and NETS. Platelets induce NET-formation which activates FXII. Modulation of the structure of FXIIa appears to regulate the structure of the fibrin clot, independently of thrombin generation, through a direct interaction with fibrin.

### FXIII

FXIII is a trans glutamate enzyme that circulates as a heterodimer. It is activated by thrombin and calcium. It can crosslink the  $\alpha$  and  $\gamma$ -chains of fibrin and can also crosslink inhibitors of fibrinolysis such as thrombin activated fibrinolysis inhibitor (TAFI) and plasminogen activator inhibitor (PAI)-2. These actions ultimately

result in the formation of a more stable clot with better resistance to fibrinolysis. A recent study showed that mice lacking FXIII showed diminished thrombi weight, attributable to diminished retention of erythrocytes in the thrombus. Inhibition of FXIIIa results in shorter thrombi. A pool of FXIII is present in platelets and is exposed on activation. It is not released in granules but more or less translocated from the cytoplasm to the membrane and from there to the surrounding fibrin.

In her own thrombolysis studies Nicola Mutch saw that haematocrit also has impact on the resistance to lysis with tPA. The higher the haematocrit, the less resistant thrombi were to lysis, so she supposed that with higher blood cell contents the clots contain less fibrin and become more vulnerable to lysis. With increasing haematocrit thrombi are also significantly shorter.

### Fibrinolysis

Fibrinolysis is, like coagulation, a cascade dependent on a series of reactions. There is difference in uPA vs. tPA mediated lysis. tPA requires fibrin for its activation, uPA does not

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but its activation is dramatically increased by the cellular receptor uPAR. Furthermore uPA dependent clot lysis is strongly enhanced in PAI-2 deficient mice. However, it is clear that uPA and not tPA is involved in venous thrombolysis.



### Haemodynamics

Also **Scott Diamond**, university of Pennsylvania, elaborated on the differences between arterial and

venous thrombosis. Arterial thrombosis is an event driven by plaque rupture, where venous thrombosis has totally different mechanics. Flow is an effective way to deliver reactive molecules but it is also the way to remove them, so a different flow pattern makes a different clot. Another aspect is the much higher density of platelets in the setting where high shear stress drives lots of platelets to the wall, producing very high concentrations of platelets and the factors they release. Under high flow and shear stress the endothelium reacts with a very typical, and generally beneficial, type of gene expression. Very little is known about what makes low flow pathogenic to the endothelium. In

low flow conditions the transport of platelets to the wall completely stops. Diamond's group developed microfluidic devices mimicking all kinds of flow conditions and succeeded in creating the typical arterial or venous type flow clots. Under pathogenic very low flow conditions red blood cells transiently begin to interact with platelets bound to collagen. Neutrophils can also interact with platelets, and enhance fibrin formation on fibrinogen adherent platelets. These processes seem dependent on the contact pathway and it is clear to Diamond that neutrophils can generate FXIIa. Furthermore there is an important role of cathepsin G, these processes are blocked by corn trypsin inhibitor (CTI, an inhibitor of FXIIa) but not by anti-TF. In the workshop discussions it was emphasised that there are few diagnostics for the endothelium and the influence of factors such as local anatomy, loss of elasticity and aging are totally enigmatic. Many suggestions were done; among them to recover endothelium from patients for transcriptional analysis.

Extracellular vesicles may play an important role in haemostasis and thrombosis, but the state of the art

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around the theme was discussed



**Rienk Nieuwland**, AMC Amsterdam as 'work in progress'. Although vesicles vary widely in sizes they remain extremely small, the bigger ones measuring 200 nm. Very body fluid is 'stuffed with vesicles, according to Nieuwland , but also ocean water contains them, often from bacteria who use them as a tool for communication or exchange of genetic materials. In the human body they can be found to contain genetic information, cytokines, growth factors, second messengers an even 'waste'. Saliva contains vesicles

providing a coagulant surface and TF; mixing plasma with saliva halves the clotting time of plasma, making wound licking a rational activity. These vesicles have also been linked to intravascular coagulation in cancer and meningococcal sepsis.

Furthermore there are reports of genetic information exchange between cells, for instance in cancer cells, rendering their neighbouring cells more tumour prone. Standardisation of measurements however is a primary requirement for further research into the role of vesicles in pathophysiologic processes.





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### SESSIONS ON EPIDEMIOLOGY, BIOMARKERS AND IMAGING

Venous thrombosis is a major contributor to the global burden of disease. DVT has an incidence of 2 per 1000 per year, it results in 35% PE, of which up to 6% acute fatalities and 20% after one year. Apart from that, there is chance of post thrombotic syndrome of 25% on the long term and a recurrence rate of 3-5% per year. Anticoagulant therapy on the other hand has a risk of major bleeding of 1-3% per year. Prevention is the key to reduction of morbidity and mortality, so epidemiologic studies and formulation of prediction models are essential for adequate medical management.



Epidemiologic studies are focussed on aetiology on the one hand, and clinical prediction on the other hand. VTE is a highly multifactorial disease and **Susanne Cannegieter**, Leiden university, showed a seemingly endless list of established risk factors. She paid special attention to the risk factor 'male sex' for the intriguing fact that the risk of a first event of the sexes is equal, but in women the risk of recurrence is

nearly halved when reproductive risk factors are excluded. Another issue further epidemiologic studies should address is the fact that one third of events is still defined as 'unprovoked'. Furthermore there is over- as well as underuse of anticoagulant prophylaxis.

Emphasising that individual patients widely differ in almost every aspect, Cannegieter pleaded for more unravelling of the pathogenesis on the level of individual patients. In the following discussions there was of lot emphasis on further validation and refining of prediction models. Participants spoke out a preference for more comprehensive models over 'simple but quick to apply' models, and attention was requested for the group medical or pregnant patients with medium risk: a large group for whom there is little guidance.



#### Genetic studies

So how about the contribution of genetics? Underlying heritability of VTE is estimated to be 50% but known genetic risk factors account for only 30% of idiopathic cases, suggesting



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that many genetic risk factors still have to be discovered. The most applied strategy is the candidate gene approach, but since the discovery of FII G20210A, no other risk factor has been found this way, as was pointed out by **Pierre Morange**, University Aix et Marseille. Genome wide association studies (GWAS) are the new trend. In general such studies have discovered some 9000 SNPs with a p-value  $< 5 \times 10^{-8}$ , however the associated OR for disease of such an individual SNP seldom exceeds 2. Six GWAS studies in VTE confirmed the role for known risk factors, such as mutations in FV, FII and FGG and showed new risk associations with low ORs.

Quantitative approaches, in which genome wide SNP scans were associated with plasma levels of clotting factors, yielded new genetic associations outside so far known biological pathways, such as Syntaxin-Binding Protein 5 (STXBP5), a protein involved in development and exocytosis of storage granules in platelets and endothelium. However, many coagulation traits studied by GWAS revealed associations with genetic variants, but no relationship with VTE was shown. So far 31 SNP's have been associated with VT. Five of

those have been combined into a risk score by the group of Roosendaal, which significantly improves the predictive power of other prognostic models after a first event. Whatever genetic risk scores may contribute to estimating the risk of recurrence; the GWAS approach is not suitable for the search of rare mutations causing clearly heritable diseases. In these cases whole exome sequencing is the approach of choice.

### Thrombin generation test



**Tilman Hackeng**, university Maastricht, dropped the question whether the thrombin generation test should be applied in clinical practice. In use for 60 years now, there's no doubt the test has proven value in coagulation research labs, and it offers a broad range of refinements to assess diverse aspects of the coagulation pathway. However a 'normal' thrombin generation hardly exists as Hackeng illustrated by testing the blood of 29 employees in his department with no known clotting disorder. Induction with 1 pM tissue factor yielded thrombin peaks varying from 13 to 271 nM. Furthermore the test still lacks

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standardisation of a number of pre-analytical variables. So in its current form, the test is useless for predicting an individual's risk of bleeding or thrombosis. On the other hand it is very useful for monitoring individual patient's risks or treatment. Apart from that, the test has very useful subtests for the functions of TFPI, Protein S or APC. In the following discussions the potential values of the test were highly appreciated; many suggestions were done for standardisation, among them the pricey one that CTI or a better inhibitor of the contact activation pathway should be used routinely. It was stated that multiple protocols should be developed for multiple tailored tests. The test was considered suitable for guiding treatment in haemophilia, but not yet for monitoring NOACs because evidence is lacking and, for instance, apixaban and rivaroxaban have different effects on thrombin generation. Some voices however suggested the test could have a role in dose determination.



### Visible proof

Anticoagulation drugs can be harmful, so physicians want proof of

VTE before starting treatment. **Menno Huisman**, Leiden university, discussed the needs and wishes in thrombosis imaging, starting off listing difficult locations such as the arm vein, the splanchnic vein, the sagittal vein, and thrombosis in tumours, where tumour and thrombus are sometimes hard to distinguish. There are also methods of imaging that are not particularly pleasant for the patient, such as trans oesophageal echocardiography, and for many techniques the reliability is not clearly established. In arterial thrombosis there is a lot of interest in the vessel wall and it seems hard to understand why in venous thrombosis the vessel wall gets so little attention.

However, the real challenge for the physician is to select the 20-30% with objective VTE (in the US this percentage is much lower) and this task will be easier with adequate preselection based on evidence based algorithms. So far the D-dimer test is highly selective but dramatically lacks specificity, according to Huisman, nevertheless in combination with clinical decision rules it is feasible. Pulmonary angiography is so far considered the

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gold standard in the diagnosis of PE; according to the PIOPED-study fatal PE occurred in 0.8% within one month after a negative result. The protocol of the Christopher study, based on a clinical decision rule, the D-dimer test and computed tomography pulmonary angiography (CTPA), yielded 0.5% after three months. A meta-analysis from Leiden showed that after a normal CTPA, a compression ultrasound is not necessary: a conclusion that has, to Huismans' irritation, so far not been incorporated in the European guidelines.

### Standardised reporting

CT venography is by far not as easy to interpret as CTPA, although it might be an option in splanchnic vein thrombosis. First results with MRA in detection of PE were highly promising, but later studies have shown a less impressive sensitivity and drawn attention to the risks of nephrogenic systemic fibrosis caused by the contrast medium. In the PIOPED-3 study only 57% of the patients with established PE were detected with the technique.

A very promising technique for recurrent DVT in the same leg

appears to be magnetic resonance direct thrombus imaging (MRDTI), showing 95% sensitivity and 100% specificity in a Leiden study. Hopes for the PET-scan appeared less justified: Scanning with 18FDG, based on the assumption that thrombosis is 'partly an inflammatory process', showed a sensitivity of 3% ('you'd better flip a coin', commented Huisman) and a specificity of 99% ('the thing just never lights up').

The discussions following his introduction inspired Huisman for a study into the results of standardised ultrasonography reporting for every first VTE, in order to provide a better basis for judgement in case of suspected recurrence. Furthermore there were suggestions to do MRA of the entire venous system, and compare this to MRDTI.



### Biomarkers

An attractive option for prediction of VTE is the use of biomarkers, but so far only the D-dimer test has proven reliability in otherwise healthy people according to **Nigel Mackman**, university of North Carolina, who emphasized that the test quickly loses its predictive value with rising age of the patient, even if

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the age adjusted cut-off value is applied. Since there are different mechanisms that lead to DVT, it is likely that combinations of biomarkers are needed. Cancer patients have a 4-7 fold increased risk of VTE and 20-30 percent of idiopathic VTE patients appear to have cancer, so most research in the field is done in cancer patients.

Many candidate biomarkers have been studied. Thrombocytosis is an established risk factor but there's discussion about the possible biomarkers for platelet activation. Leucocytosis predicts a risk ratio up to 2.4. Leukocytes are involved in VTE via NET formation and the most promising predictor for NET-formation could be citrullinated histon 3, according to Mackman, who also issued a warning against too much enthusiasm. Neutrophilia per se has never been revealed as an

independent risk factor for VTE in cancer patients and there is no clinical evidence at all that addressing NET-formation is a safe and effective way to prevent VTE.

Most of the established biomarkers have already been incorporated in de Khorana score, but after studying results of the CATS study, first investigator Ingrid Pabinger suggested to add only sP-selectin and the D-dimer test to the score. In the PHACS -study, comparing LMWH with no prophylaxis in patients starting chemotherapy, microvascular TF was predictive of VTE in pancreatic cancer but not in patients with other types of cancer. High risk patients showed activation of the coagulation system with the highest levels in pancreatic cancer patients, but only D-dimer decreased with the use LMWH, which also significantly decreased the rate of VTE.



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### SESSIONS ON MANAGEMENT OF VTE AND PTS

NOACs are widely accepted as the latest pharmacological improvement in the treatment and prevention of VTE. The major advantage of these drugs is a 40% reduction in major bleeding compared to VKA; and the clinical presentation of occurring bleedings is more benign. However, regarding efficacy, the advantage of these new drugs is limited.

After treatment of a first VTE, during anticoagulation, the risk of recurrence is about 2% in 6 months, the risk of major bleeding is around 1% and the risk of clinical relevant but not major bleedings is some 6% per six months. The extension trials show that stopping preventive medication in patients with an idiopathic VTE results in about 1% recurrence per month. So the preventive effect is about 8% per year against 2% major bleeding and 12% non-major bleeding.



Better anticoagulants with less bleeding risk would make the choice whether or not to continue anticoagulation

easier, said **Harry Büller**, university of Amsterdam. However, biological systems outside the coagulation system also affect the risk of VTE. In the Jupiter trial a 43% risk reduction of a first VTE was observed with rosuvastatin. ‘Consider it a bonus’ said Büller: the incidence of a first VTE was extremely low, but it proves that a statin reduces the risk. In the Pharmo PE study, held among patients taking VKA for recurrent PE, the use of statin, gave nearly 60% reduction making an NNT of 26. Other studies are not that positive, but in the Danish registry, comprising 44.000 VTE patients, 10% taking a statin ‘on top’ of anticoagulants still reported a 26% reduction. Looking at the pleiotropic effects of statins there is ‘biological evidence everywhere’ according to Büller: these drugs lower platelet activation, FV, FVII PAI-1, TF, and MMPs, they raise tPA and NO and reduce vascular inflammation.

#### NOACs in VTE

US patients with a VTE are treated with LMWH, followed by VKA, and after three months a decision is made



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whether to stop or continue anticoagulation. Especially in patients with unprovoked VTE a longer treatment is considered. This approach has some drawbacks: LMWH injection is sometimes difficult to teach and warfarin requires monitoring, said **Jeffrey Weitz**, McMaster University Hamilton. In Canada NOACs are licensed for VTE treatment which makes things a lot easier. Treatment with apixaban or rivaroxaban can be started orally. Dabigatran and edoxaban were 'brigged' by LMWH in the acute VTE trials: a consequence of the fact that in the phase II trials these drugs were tested in AF instead of VTE. For all four drugs it's important to notice that they can accumulate when the kidney function is compromised, especially dabigatran has 80% renal excretion.

### Safety of NOACs

NOACS are definitely safer than VKA, according to Weitz. Even the somewhat higher risk of gastrointestinal bleeding is not that apparent in VTE-patients; probably because they are younger than AF patients so the risk of mucosal lesions in the GI tract is smaller. A total of

962 patients in the studies had active cancer, and the results regarding prevention of recurrent VTE in this group were encouraging although it must be noticed that the active comparator was warfarin and not LMWH. Extension trials have been performed with all four NOACs. Rivaroxaban 20 mg showed a nearly 70% reduction in the risk of recurrent VTE and a very low rate of bleeding (0.7%). Dabigatran was compared to warfarin in the REMEDY trial and to placebo in the RESONATE trial. It proved less efficacious (1.8 vs. 1.3% recurrent VTE) but safer (0.9 vs. 1.8 major bleeding) than warfarin, and more effective (0.4 vs. 5.6% recurrent VTE) and hardly less safe (0.3 vs. 0% major bleeds) than placebo. The AMPLIFY extension study compared two doses of apixaban (2,5 mg and 5 mg) to placebo showing a equal reduction in VTE risk (from 8,8 % to 1.7% in in both groups) with a trend for less non-major bleeding (3.0%, 4.2% and 2.3% for apixaban 2,5 mg; 5 mg and placebo respectively) The Einstein Choice study is now comparing rivaroxaban 20 or 10 mg to aspirin.

Based on the existing evidence, the majority of newly diagnosed VTE

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patients can be treated with NOACS. Exceptions are patients with severe PE or extensive DVT, severe renal or hepatic problems, and patients with a high risk of bleeding (for instance after surgery). Warfarin treated patients less suitable for switching are those that are stable on warfarin, or those that frequently miss doses (lack of adherence). Furthermore there is not much information on patients with an antiphospholipid syndrome or other high-risk thrombophilias.

There are several molecules being studied with the potential to be used as an antidote against NOACs, but currently none are registered. One of these is Idarucizumab: a Fab fragment of a humanized mouse antibody against dabigatran and Andexanet alfa, a recombinant factor Xa with small modifications rendering it inactive in coagulation and showing high affinity for FXa inhibitors. Phase 3 studies with the antidotes are now ongoing.



### Direct coagulation inhibitors

Aiming to prevent thrombosis without raising the bleeding risk, it might be

an option to cut the connexion between the intrinsic and the extrinsic pathway of coagulation, as was pointed out by **David Gailani**, Vanderbilt University, Nashville Tennessee. Deficiency of FIX is associated with a severe bleeding disorder, deficiency of FXI results in a very mild disorder and people lacking FXII are asymptomatic. From an evolutionary perspective there is the thrombin generating system, based on vitamin K dependent proteases, and there is the contact system, based on FXII and prekallikrein, using high molecular weight kininogen as a cofactor.

### Bidirectional interface

In most animals there is no connexion between these systems because they lack FXI, which is exclusively present in mammals. Historically a component of the contact activation pathway, it has acquired new activities allowing it to interact with the thrombin system. One can consider FXI as a bidirectional interface between two more ancient systems, one required for haemostasis, the other one not, according to Gailani. FXII as well as FXI knockout mice show resistance



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against thrombosis without a bleeding tendency. In humans both FIX and FXI deficiency protect against thrombosis. Humans with high plasma levels have a doubled risk of thrombosis, a lack of FXII does not protect against VTE. In a primate model antibodies against FXI inhibited thrombus formation without affecting bleeding time.

### Proof of concept



At this moment a number of inhibitors of FXI are under study. In 2011 the antisense oligonucleotide (ASO) against FXI ISIS-416858 was tested in healthy volunteers. In some of them the level of FXI was reduced to 2% of normal, without causing any bleeding problems. Very recently **Harry Büller** reported of a phase 2 study with the same drug tested in two doses of 200 or 300 mg against enoxaparin 40 mg in the prevention of thrombosis in patients undergoing knee replacement surgery. The 200 mg dose reduced FXI by 68% and the 300 mg dose reduced it by 83%. Venography detected asymptomatic DVT in 27% of patients in the 200 mg dose, 4% in the 300 mg group dose

and 30% for enoxaparin. This study principally seems a proof of concept, because the clinical applicability is rather complex. The ASO-treatment had to be initiated 36 days before surgery, afterwards it took about a 100 days for FXI-levels to normalise, and there were quite some adverse events at the injection site.

### FIX, FXII, kallikrein and polyphosphate inhibitors



Less successful was the introduction of an FIXa inhibitor as was told by **Helen Philippou**, university of Leeds. The Revolixys kit was developed as a two component system consisting of peginvacogin, an aptamer targeting FIXa, and its complementary oligonucleotide active control agent, anivamersen. The highly promising drug studied in patients undergoing PCI was associated with allergic reactions of such frequency and severity that the DSMB decided to stop the study. In the meantime a fairly broad range of FXII and FXIIa inhibitors is in development. Humans lacking FXII do not experience any bleeding problems, mice with the condition

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have protection against thrombosis which is reversed by addition of FXII. Other contact pathway inhibitors address prekallikrein or kallikrein and polyphosphate inhibitors. Both classes of experimental drugs show anti-coagulant activity with minimal effects on bleeding in animal models, but side effects are still under study.

### Aspirin



Aspirin is a drug that's undergone quite some paradigm shifts, said **Karina Meijer**, Groningen university. The children's

dose has been abandoned as well as the use of aspirin for low risk atrial fibrillation. On the other hand one is no longer sure that aspirin is not effective as VTE-prophylaxis in orthopaedic surgery. In 2008 the ACCP advised against aspirin and in favour of anticoagulants on the basis of DVT as outcome but the American Academy of Orthopaedic Surgeons endorsed aspirin because it had stronger evidence for prevention of fatal PE. Still, on the same evidence available, in 2012 the ACCP approved all pharmacologic means but suggested that LMWH is the best. However, in a recently published

study comparing 10 days of LMWH followed by four weeks of LMWH or aspirin, aspirin did actually a little bit better than LMWH on VTE-prevention as well as bleeding, although not statistically significant.

In multiple myeloma, the type of cancer with the highest risk of VTE, aspirin is traditionally the drug of choice. A Cochrane review reported LMWH to be not statically significant better, however real life data from Groningen recently revealed an unacceptable 15% VTE in patients, most of them on aspirin. The French MELISSE study showed 3% VTE with LMWH vs 7% with aspirin.

### Unambitious drug

Aspirin for secondary prophylaxis of VTE has been compared to placebo in the ASPIRE and WARFASA studies. Analysed together, the outcome was 7.5 vs 5.1% VTE favouring aspirin with hardly any more major bleeding. There are no direct comparisons between aspirin and anticoagulants. A network meta-analysis making indirect comparisons confirmed what Meijer already stated at the beginning of her talk: 'it is not an ambitious drug'. It helps a little bit

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and it harms a very little bit, but there are much better drugs, providing better protection without the drawback of a large increase in bleeding risk'. In the following discussions the possible role for aspirin in standard secondary prevention was rejected; if you need secondary prevention, anticoagulation is the preferred strategy. In orthopaedic surgery, it was decided there is no unmet clinical need. The group was highly interested in the role of aspirin in malignancy as an inhibitor of possibly hyperactive platelets but also for prevention of metastasis. The question whether aspirin is extra effective in situations in which the vessel wall is damaged could be addressed in studies focussing on preventing ipsilateral thrombosis and the data are probably available from studies already done. Furthermore it was reckoned that there is little data on the effect of other platelet inhibitors in VTE .



### PTS

Post Thrombotic Syndrome (PTS), discussed by **Arina ten Cate**, university Maastricht, is the most

prevalent complication of DVT affecting up to 50% of the patients, reducing quality of life and generating high costs, caused by venous ulceration. Oedema, skin changes and lipodermatosclerosis causing induration of the skin are the main manifestations, subjective symptoms are feelings of heaviness, pain, itching cramps and paraesthesia, worsening with activity and improving while the leg is elevated. PTS is a risk factor for recurrence of DVT. There are several scoring systems defining the condition and in 2008 the ISTH decided to choose for the Villalta score as the preferred one.

Pathophysiology is centred around lack of resolution of the thrombus. Incomplete thrombus resolution is associated with inflammation, causing collateral damage to the vessel wall, resulting in fibrosis and stiffness and valvular reflux. Valvular reflux as well as non-resolution and obstruction will lead to venous hypertension, which is transferred to the microcirculation where low shear stress will activate leucocyte adhesion and inflammatory reactions causing capillary leakage, oedema and so on. Therapeutic options are

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limited. Veno-active drugs available now are an  $\alpha$ -adrenergic agonist hydroxy ethylrutoside (Venoruton) and the flavonoid Daflon which causes venoconstriction by blocking the inactivation of noradrenalin. Drugs that may have some hope but have not been studied for the indication are statins, LMWH and several classes of anti-inflammatory drugs.

### Compression stockings: believe it nor not

The use of elastic compression stockings (ECS) delivering a pressure of 22 mmHg, has been studied by two European groups, showing a relative risk reduction of 50% and an absolute risk reduction of 25% yielding an NNT of 4. MRI studies show a significant reduction in venous diameter with a reduction in oedema and an increased flow. In animal models ECS even improve thrombus resolution.

So Arina ten Cate was surprised by the results of the SOX trial, published in the Lancet, showing no effect of ECS at all against 'placebo socks'. However, in this study, the very low incidence of 14.2% vs. 12.7%, favouring the placebo group, was

established with the non-preferred Ginsberg's criteria, while the incidence with the Villalta score was much higher (52.2 vs. 52.3%). Furthermore, the compliance, rather liberally defined as wearing the socks for more than 3 days a week, was only 55%. So there might have been some diagnostic issues, according to Ten Cate. 'Without a proper diagnosis, you won't find an effect of adequate treatment.'

Other options to improve outcome are to watch anticoagulation properly; several studies show that improper anticoagulation (INR below 2 for more than 20% of time) raises the risk of PTS significantly, and LMWH treatment has been shown to lower the risk compared to VKA. Furthermore, according to open vein hypothesis, fast removal of the clot prevents PTS, pleading for invasive treatment as an option to look for. Discussions in the workshops addressed highly various issues such as the possible role for NOACs in PTS prevention and further refining of the diagnosis.



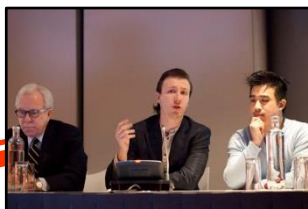
According to vascular surgeon **Cees Wittens**

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the majority of patients has venous claudication, a complaint that is not

mentioned in the Villalta score.



### SESSIONS ON INVASIVE TREATMENT



#### Catheter Directed Thrombolysis in DVT

A method that potentially could lower the incidence of PTS is Catheter Directed Thrombolysis (CDT). The technique was introduced in the early 1990's and adopted in many centres, without its efficacy and safety having been proven by RCT, told **Per Morten Sandset**, university of Oslo. In the CaVent study, performed in South Eastern Norway, CDT with alteplase was added to a standard treatment with anticoagulants and compression stockings in a randomised controlled way. There were two primary effect parameters: post thrombotic

syndrome after 24 months, defined as a Villalta score  $\geq 5$ , and patency after 6 months defined as a compressible vein with restored flow. At the end of the procedure complete lysis was achieved in 48% and partial lysis in 43% (success rate: 89%). After two years PTS was seen in 55.6% of the standard treatment group vs. 41.1% in the CDT group, yielding a

risk reduction of 15% or an NNT of 7. Iliofemoral patency was 65.9% in the PTS group vs. 47.4% with standard treatment. In the TORPEDO-study - using a different definition for PTS - three PTS patients were found in the treatment group vs. 22 in the control group. Adding all patients together

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and applying 'mixed definitions' CDT would yield an RRR of 61%. PTS was much more prevalent amongst patients in whom recanalization had been insufficient, giving support to the open vein hypothesis.

### Removing the clot in PE



**Stavros Konstantinides**, university of Mainz, discussed the 2014 guideline of the ESC, which introduced a

simplified score for risk stratification, distinguishing between intermediate low and intermediate high risk. The PEITHO study established that thrombolysis in the latter group reduced all-cause mortality and the risk of haemodynamic collapse, but raised the risk of stroke to unacceptable proportions.

Interventional treatments for PE such as thrombus fragmentation, rheolytic thrombectomy, suction embolism, catheter directed thrombolysis, etc, have been on the market for decades but evidence for safety and efficacy is meagre. Some combine low dose thrombolytic agents with an interventional treatment. A meta-analysis of catheter-directed

treatment of massive pulmonary embolism concerning 35 non-randomized studies in nearly 600 patients showed 'super results as you might expect from any uncontrolled study' according to Konstantinides, with clinical success rates well above 85% minor complication in 8% and major complications in 2.4%.

### Ultrasound assisted thrombolysis

However, the quality of data improves. In ultrasound assisted catheter directed thrombolysis ultrasound is supposed to destabilise the clot, making it more penetrable for a thrombolytic agent. The technique is applied with a dual catheter, delivers the combination over a period of 15 to 24 hours and is highly expensive. In the ULTIMA study randomizing 59 patients with intermediate risk PE the technique improved right ventricular size within 25 hours and 90 days, without causing extra cases of major bleeding. These results are more or less supported in a single arm study with 150 participants. In this study there was 11% bleeding in 30 days and no intracranial bleeding. Based on these studies, percutaneous catheter directed treatment (PCDT)

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should be considered as an alternative to surgical embolectomy for patients in whom full dose systemic thrombolysis is contra indicated or has failed (IIa) and it may be considered in intermediate high risk patients if the anticipated risk of bleeding under a thrombolytic regimen is high (IIb). Konstantinides also drew attention to a study with a reduced dose of rtPA, which reduced the incidence of pulmonary hypertension from 63 to 16%, with no major or minor bleedings.

Reassuringly he pointed out that 'the approach is off label, so if it goes wrong it is totally your own fault' and warned that the methodology of the study was weak.



### Stenting in PTS

Following any kind of treatment, DVT patients may have permanent obstruction, often of a collagenous type. Surgical bypassing is often effective but dependent on the position and materials used and there are complications such as hematoma and infections. So alternatives are sought in angioplasty and stenting. In

this field also, the evidence is modest according to **Rick de Graaf**, university Maastricht. So far PTS with disabling symptoms and PTS with less severe symptoms have grade 1b and 2b recommendations respectively.

Patency gets worse when the segment gets longer. Longstanding chronic total obstructions also have worse patencies, and self-expandable stents are preferred. Beyond these recommendations, things progressively get murky. Studies have been done in specific indications such as the non-thrombotic iliac vein lesion (NIVL) or May-Thurner syndrome, where the vein is compressed by the overlying artery. Although the diagnosis is on hardly established criteria such as lumen reduction or ill-defined pressure measurements, primary stenting is considered highly effective (patency 100%). Also the post-thrombotic syndrome has high patencies and favourable clinical outcomes such as ulcer healing and relief of pain and swelling.

### Unproven assumptions

Confluence stenting is problematic: where two expandable stents meet, one will often squeeze the other, so



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de Graaf has recently published on crossing the confluence with a balloon expandable stent. Advises on stenting across the inguinal ligament are downright contradictory (should be avoided but reaching a normal segment is even more important). There is little proof on whether or not stenting during thrombolysis improves patency, and studies addressing the subject not always have confirmed an underlying stenosis with MRV or IVUS which would also have given the opportunity to distinguish between fresh and older thrombi. In studies sometimes highly inadequate imaging procedures have been applied. Furthermore there are hardly any comparative studies between different types of stents and although anyone working in the field has ideas about the technical qualities for a venous stent, there are no standardised qualifications. For follow up, duplex ultrasound seems reliable in detecting restenosis, but it doesn't give a clue about the nature of the stenosis. Is it thrombosis and if so, is it self-limiting or is it fibrosis or intimal hyperplasia? And then there is a long list of unproven assumptions that have been repeated over the

years until they ended up in the guidelines. So we should consider, de Graaf concluded, to let the 'house of knowledge' be broken down by fundamental research before rebuilding it on more evidence based foundations.



### Arteriovenous fistula

A much debated technique to improve the chances of patency after thrombectomy is the construction of arteriovenous fistula.

**Anthony Comerota**, university of Michigan, discussed the various designs and hemodynamic issues surrounding this technique.

The theoretical advantage of AVF is to increase flow velocity to avoid thrombosis. Sometimes AVF are constructed in patients with proximal venous obstruction, which are very symptomatic, in order to develop collaterals around the construction. Initially the goal was to maintain patency to allow endothelial healing after thrombectomy. Later on they were constructed to overcome the thrombogenicity of a bypass or stent. However, there are potential adverse effects such as a cardiac overload,

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arterial or venous dilation, vascular steal syndrome, and distal venous hypertension and even venous reflux. So closure of the AVF is an integrated part of the procedure.

The initial idea based on canine models was that the endothelium took about four weeks to heal, resulting in guidelines advising the fistula to be closed some six to eight weeks after the procedure. This led to re-thrombosis in about 16%, where patients not having an AVF showed about 50% re-thrombosis. In a group of 70 patients, presented in 2000, with a mean diameter of the AVF was 50% of the iliac artery, the dilation of the artery was 2.5 mm. Most iliac flow went through the AVF but there was no drop in distal arterial pressure. In patients with normal iliac veins there was no reflux but this did occur in half of the patients with obstruction and three quarters of them developed venous collaterals. Collaterals developed when AVF increased venous pressure  $\geq 6$  mmHg. Infrapopliteal AVF often closed spontaneously but femoral AVF often remained patent. Closing these fistulas appeared very difficult, and patients often did better when the

fistula was open, which provoked the suggestion to keep AVF longer in place than advocated so far.

### Hemodynamic models

So we need some hemodynamic guidance, said Comerota. An in vitro model developed by the MAYO clinic with 8 mm tubing and a pulsatile flow showed that flow from the distal vein quickly goes down when the size of the fistula exceeds 3 mm being zero at 5 mm. In vivo experiments even showed reversal of the flow. Also, in fistula of 4 and 5 mm, exercise had an adverse effect on flow in the distal artery and the distal vein, where in the 3 mm fistula the streaming patterns improved. In a small Swedish study 18% of the AVF closed spontaneously and surgical closure was in 43% followed by thrombosis. So the technique of constructing an AVF is highly important according to Comerota, a small diameter and good pressure are important elements, and if the reconstruction is patent and the AVF remains well tolerated, one may consider to leave it permanently.

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### Inhibition of selectins

In spite of sophisticated techniques, anticoagulation is currently the standard treatment in VTE. Anticoagulation does not lyse the thrombus or prevent the



development of PTS, and it carries a significant risk of bleeding. Intervening at the intersection of thrombosis and inflammation might have better prospects, according to **Thomas Wakefield**, university of Michigan, focussing on the role of selectins. Selectins are cell adhesion molecules: glycoproteins found primarily on endothelial cells, leukocytes and platelets, and involved in trafficking of leukocytes in acute and chronic inflammatory processes. P-selectin is stored in the  $\alpha$  granules of platelets and the Weibel Palade bodies in the endothelium. It mediates cell adhesion in leukocytes and platelets but also in cancer cells. PSGL-1 is the primary ligand stimulating the release of pro-coagulant microparticles and fibrin formation. E-selectin is expressed on endothelial cells only and plays an important role in the recruitment of leukocytes, platelets and red blood cells in states of

inflammation. A polymorphism for the E-selectin gene associated with higher E-selectin levels results in increased risk of recurrent VTE.

In a baboon model of VTE, blocking the P-selectin/ PSGL-1 interaction with an aptamer appeared to promote thrombus resolution and prevented wall fibrosis better than enoxaparin and also better than an inhibitor of the von Willebrand-factor. This suggests that inflammatory interactions dependent on P-selectin are involved in both thrombus formation and resolution. In knock out studies E-selectin also appeared as an attractive target, so an E-selectin inhibitor has been developed as a small molecule. In mice this molecule, GMI-1271, proved as effective as enoxaparin in lowering thrombus weight with much less influence on the tail bleeding time. So far preclinical safety studies have been completed, and a phase 1 study to assess the safety and pharmacokinetics in healthy adult subjects and subjects with calf vein DVT is now ongoing.



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### New roles for imaging

Imaging in VTE is traditionally used to confirm the diagnosis, and according to the standards, duplex ultrasound is technique of choice. However, considering DVT as the starting point



for development of a PTS, there is a lot more to be seen, said **Carsten Arnoldussen**, Maastricht, university and VieCurie

MC. There are dynamic options such as dynamic duplex ultrasound, phlebography and IVUS and there are static options such as MR-venography, CT-venography and CT-PET-scanning. Using MR -venography for instance can visualize a complete overview of the venous system, showing the extend of the disease, and also different stages of the disease process are recognizable. Acutely thrombosed veins are dilated without major anomalies to the vein wall. In later stages there are signs of

inflammation, the wall looks edematous and signs of recanalization appear. In old thrombosis a lumen can often be seen but also parts that are filled with thrombus.

In PTS the patency of the affected vein can be judged by duplex scanning, phlebography can show outflow obstruction and collateral formation. MR gives elucidating pictures of compression in May Thurner's disease. In chronic PTS long strands of fibrosis are visible and a complete map of collaterals can be seen. So what can we do with all this information was the main question in the workshop, yielding a broad range of suggestions for improvement of prediction, prevention and treatment. A general conclusion was that just looking at the duplex-scan is not enough anymore.



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## THROMBOSIS IN PREGNANT WOMAN



**Pulmonary embolism is a number one cause of maternal death in developed countries, taking the lives of 2-3 mothers per 100.000**

**births. Pregnant women are young, the sequels of VTE are serious and these women will have to deal with them for the rest of their lives. So it is a shame that there is hardly any evidence available on the subject, stated Saskia Middeldorp, AMC Amsterdam. Based on common sense however, caring for women on anticoagulants having to deliver is not really complicated, although it does require some experience.**

The overall rate of VTE in pregnant women is 1.4 /1000 vs. 0.5 for not pregnant women; in the antepartum period it is about 1/1000 but in the postpartum period about 5/1000. Almost 90% of DVT in pregnancy occurs in the left leg, which is 55% in the non-pregnant population. In pregnancy thrombosis often starts very proximal, even in the iliac vein, contributing to the extra high risk of

PTS. The risk is especially high in the first 6 weeks after delivery. The MEGA study showed OR's of 84 and 9 compared to non-pregnant women for the first and second six weeks after delivery respectively. In the Minnesota study 62 of the 64 events occurred in the first 6.5 weeks. Not able to pass the placenta, LMWH are the drugs of choice and there is plenty neonatal safety data on these drugs. UHF is associated with a higher chance of heparin induced thrombocytopenia and osteoporosis, VKA may cause the foetal warfarin syndrome and is restricted to women at extremely high risk, such as those with mechanical heart valves. NOACs are also very likely to cross the placenta and therefore contraindicated.

### **Risk assessment**

Women considered at high risk have a personal history of VTE, are asymptomatic carriers of thrombophilia or have a strong family history. According to the ACCP guidelines, prophylaxis during the post-partum period of six weeks,

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should be confined to an absolute risk reduction of 1% (NNT 100); for prophylaxis antepartum the absolute risk reduction should be 3%. The daily injections with LMWH are not really pleasant, especially because 20 to 40% of the women get skin reactions, some may even develop type IV hypersensitivity reactions.

Furthermore there is higher risk of bleeding, and getting an epidural during delivery becomes complicated. Absolute risks for the first pregnancy in women with hereditary thrombophilia and a first degree relative with a history of VTE vary from 1.5 to 16.3 in FV Leiden, according to a series of cohorts that have been studied lately and, reassuringly, all yielded quite similar risk estimates. Without a family history, multiplications of known risk factors with a relative risk factor must be made. Calculating the NNT, the problem with LMWH-prevention is that the RRR for this indication is unknown. There are just two very old studies with 40 and 16 patients to support clinical decision making. In order to tackle this lack of information the ACCP decided to apply the RRR's known from

orthopedic studies, being some 64%. So LMWH does not prevent every VTE, and it can do harm, which is reason enough for careful decision making.

Based on this approach, prophylaxis during the entire pregnancy and aftermath should be considered in women with a single episode of VTE (provoked or not by the use of oral contraceptives pregnancy or postpartum), women with recurrent VTE, and women homozygous for factor V Leiden or a prothrombin mutation with a first degree relative having experienced VTE. Postpartum prophylaxis for six weeks should be considered in women with a history of *a single* episode of VTE, related to a major non-hormonal transient risk factor, women with hereditary thrombophilia and a family history of VTE, and women who are homozygous for factor V Leiden or a prothrombin mutation without a positive family history of VTE. Women



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with only a positive family history, or women who are heterozygous for factor V Leiden or prothrombin mutation without a family history should not get prophylaxis.

### Multidisciplinary approach

In the AMC there is multidisciplinary team having monthly meetings, setting up individual policies for every patient, which are discussed with the patient and handed over on paper as well. In case of induction of labour the LMWH is stopped 24 hours in advance; patients who await spontaneous labour are instructed to stop injecting themselves as this occurs. Neuraxial anaesthesia is avoided if the last injection is less than 24 hours ago; other types of pain management are offered. With a very recent VTE (2 weeks), UHF is often considered, but Saskia Middeldorp is not very eager because it is not easy to get the APTT right in such a short time. A filter in the VCI is sometimes considered, but there are quite some reports about migration of these filters: flow patterns in women giving birth are not that predictable. LMWH is restarted from 12 to 24 hours after delivery and

assessment of bleeding. Middeldorp prefers to keep to the safe side with regard to bleeding. Especially in caesarean section the risk of severe bleeding on LMWH is 2.5 times higher.

### Switching

Women on VKA for recurrent VTE or mechanical heart valves do not have to switch prior to pregnancy, because the window of safety goes up to six weeks after the last period. However it is save to do regular pregnancy tests and to discontinue VKA immediately after a positive result, take 10 mg vitamin K on three consecutive days and start LMWH at the same time. Women on fenprocoumon are switched to a shorter acting alternative, or the dosing of vitamin K is prolonged. Women on NOACs should switch to VKA prior to pregnancy and of course fertile women using NOACs should be informed. There are no contraindications for breastfeeding, except for the NOACs.

Issues to be resolved are the assumed efficacy of the intermediate (orthopaedic) dose of LMWH, and the several treatment failures (up to 8%) that have been described. These



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issues were a rationale behind the design of the now recruiting international High Low study in which

the efficacy and safety of two doses of LMWH are studied in pregnant women with a history of VTE.

### THROMBOSIS IN PATIENTS WITH CANCER

**Patients with cancer have a four to seven fold increased risk for VTE, up to 20% of cancer patients are confronted with VTE and post-mortem studies suggest**



**incidences up to 50%. In daily practice of VTE treatment the cancer patient is also Quite prevalent for 15 to 20% of the cases concern cancer patients and these patients have more complications such as recurrence of VTE or bleeding on anticoagulant therapy. According to Anna Falanga, Hospital Papa Giovanni XXIII, Bergamo, Italy, the NOACs are an attractive alternative for the so far advised LMWH. However more research is needed.**

Tumor cells apply highly variable mechanisms to influence coagulation, such as the release of inflammatory cytokines and the expression of angiogenic or cell adhesion factors.

According to the ASCO guideline, LMWH is the preferred treatment in cancer patients on the short and the longer term, although on longer term, VKA can also be considered. The most well-known study on this topic is the CLOT study dating from 2003, showing dalteparin to be superior over warfarin in preventing VTE without raising the risk of bleeding. Recently a similar study was performed; the CATCH-study. In the study tinzaparin lowered the risk of recurrent VTE to comparable levels as warfarin, meaning a significant reduction in symptomatic DVT and clinically relevant non-major bleeding compared to baseline.

### NOACs in cancer patients

However, there are some drawbacks of LMWH, such as recurrent thrombosis and major bleeding being still significant; the fact that

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subcutaneous injections are more or less uncomfortable and the potential for toxicity in patients with renal failure. NOACs offer an attractive option because of their oral administration, fixed-dose, and freedom from routine laboratory monitoring. The results of phase III trials support their efficacy and safety, but the number of participating cancer patients was far too low for conclusions. Patients with cancer have multiple factors to consider such as an increased risk of hemorrhage from chemotherapy-

induced thrombocytopenia or antiangiogenic drugs. Furthermore, NOACs might have drug interactions with anticancer drugs. So they could be promising drugs but very little is known. Subgroup analysis from the MAGELLAN-study, testing rivaroxaban vs. enoxaparin in more than 8000 medically ill patients, even showed a sobering result: rivaroxaban, performing better in most patients did worse in the subgroup of cancer patients. However a series of clinical trials in this field is now underway.

### VTE PREVENTION STRATEGIES IN MEDICALLY ILL PATIENTS



**VTE-prophylaxes in medical ill patients is often underused and the explanations are diverse. However recent studies on the subject will shake up**

**the guidelines stated Martin Prins, University Maastricht.**

Dealing with the acute medically ill patients, VTE-prevention is often a

neglected aspect. Prophylaxis is highly underused, caused by lack of awareness and fear of bleeding in these ill and often elderly patients having to undergo invasive tests and procedures. Hospital staff is not familiar with existing guidelines, and

these guidelines are frequently too complex to follow, presenting huge lists of ailments and risk factors which are not always known in the acute ill patients.

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### Abundancy of risk factors

However, risk factors for VTE are highly prevalent in hospitalised patients and often quite obvious. This was recently confirmed by the ENDORSE registry, showing chronic pulmonary disease in 27%, heart failure in a quarter, obesity in 11% and so on. During hospitalisation a third was completely immobilised, another third was more or less immobile, 28% was admitted to the ICU. In about 70% of cases of VTE there is an attributable risk factor: a quarter had undergone surgery, but about half of the patients had a medical condition. VTE-prevention trials show VTE-incidences of 11 to 15% in the placebo group, based on venography. Sub analysis of the MEDENOX study revealed that also infection is an independent risk factor for VTE, increasing the relative risk by nearly 50%. Placebo-controlled trials have shown that acute infection is associated with VTE rates of 11-16% in the placebo groups; in patients with heart failure incidences of 4 to 15% are found and in respiratory diseases incidences up to 28%.

VTE is huge scale-problem; the yearly dead toll in six countries (UK, Italy, Spain, Germany, Sweden & France)

was estimated at 370.000: 70% of them in hospitals. So the risk of VTE is high; little is done to address the problem, and a more systematic application of protocols with a generic character - for instance based on laboratory tests - might increase adequate prophylaxis.

Completed clinical trials in medically ill patients comprise eight trials with LMWH and one with fondaparinux. The MEDENOX comparing enoxaparin with placebo showed 65% reduction in VTE, although many detected by venography, and very little extra risk of bleeding with comparable results in different subgroups of disease. In the PREVENT-trial dalteparine significantly reduced the rate of proximal VTE from nearly 5 to less than 3%, and in the ARTEMIS study fondaparinux nearly halved VTE without a rise in bleeding incidence. So, overall one can conclude that high (orthopaedic) doses of LMWH or fondaparinux reduce symptomatic and asymptomatic VTE by 50 to 70 %.

### Long term prevention

Longer term administration of enoxaparin in the EXCLAIM study also reduced the incidence of VTE from 4

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to 2,5 % in 28 days, but induced almost as many bleedings, making it not really worthwhile according to Prins, especially considering the burden of daily injections for patients. In the MAGGELAN, comparing rivaroxaban for 35 days to enoxaparin for ten days followed by placebo, rivaroxaban met the criteria for non-inferiority at day ten and was superior to placebo in the 25 days to follow but the risk of clinically relevant and major bleedings was more than doubled. So the drug was not registered for long term prevention in medically ill patients. In the ADOPT trial testing apixaban against enoxaparin in the same setting as MAGGELAN, the criteria for non-inferiority were not met at day ten, after day 35 there was some reduction in primary efficacy outcome, although not statistically significant, but there was a

statistically significant increase in the number of bleedings.

### D-dimer test

However, in a subgroup analysis of the MAGGELAN patients with a D-dimer level higher than twice the upper limit had a significantly raised risk of VTE and ultimately an absolute risk reduction of 3% (from 6,4 to 3,4 percent over the period from day 11 to 35), versus a raise of less than 1% in the risk of major bleeding. So, according to Prins, the D-dimer test might possibly prove to be a tool for identification of patients who can profit from longer VTE protection with a new oral agent, replacing the complicated guidelines. So far two trials are now focussing on patients with a D-dimer level more than twice the upper limit.



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### SUPPORTING THROMBOSIS PREVENTION



**Authors of guidelines and protocols should apprentice themselves to the Dutch tax authorities,**

**said Pieter Kubben, neurosurgeon at Maastricht UMC, who is not very fond of bleeding complications during his surgical procedures.**

More than 700.000 medical research articles are published each year. Somehow this information should find its way into medical practice. Guidelines are the instrument for the practitioner not being able to read all of this, but still these documents are bulky stacks of information, not very helpful to the clinician having to make a series of decisions on the individual patient. 'So the computer must not be used as an e-reader', says Kubben, 'it can do better than that'.

'Flowcharts are the next step for implementing guidelines into practice, but the format you actually want can be cribbed from the Dutch

tax authorities' says Kubben. You just fill in some personal data, based on that you get some additional questions applicable to your situation and so on. That is the format you want your guidelines in.

Surgeons for instance are not highly skilled in anticoagulation but often have to make decisions on these drugs. The tool they need to decide on perioperative management should just start with the drug used, followed by the risk factors leading to sub questions, resulting in an estimation of the risk level, followed by an advise. Decision making in personalised medicine can be made as complex as you want, as long as the interface is kept simple. It is essential however that the practitioner is able to consult the flowchart steering the system: being responsible for the decision he or she will want to know what's going on 'behind the curtains'. Of course the system won't be able to tackle any problem and there is nothing against the outcome being a phone number of the vascular internist.

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### Nothing against a cookbook

In his plea for accessibility of tailored information, Kubbens emphasised that level I evidence for improving guideline adherence exists for the 2 minutes rule: evidence based advice should be accessible within two minutes. He rejected the opposition against what often is referred to as cookbook medicine. 'A cookbook just gives you the recipe for a good chance of success. It is not mandatory or a prison law; it just spares you the time of information gathering, especially in individualised medicine.' Further discussions focussed on

where to place expert systems and apps for decision making.

A professor in clotting issues suggested they should be integrated in the EMR/EPD, for putting something on the intranet is not good enough. However, it was also felt that EMRs providing a lot of automatic suggestions create 'alert fatigue'

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## Committee MUMC



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Arina ten Cate



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Paola van der Meijden



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Cees Wittens

**Deze highlights worden mede mogelijk gemaakt door Pfizer bv**

### Colofon

De inhoud van deze publicatie geeft een impressie  
van een gedeelte van het MCCT 2015

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