

# Towards Definition, Clinical and Laboratory Criteria, and a Scoring System for Disseminated Intravascular Coagulation\*

On behalf of the Scientific Subcommittee on Disseminated Intravascular Coagulation (DIC) of the International Society on Thrombosis and Haemostasis (ISTH)

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Already in the 19<sup>th</sup> century some of the first clinical and pathological observations related to DIC were made. A more precise description of DIC and its underlying pathogenesis had to wait until the 20<sup>th</sup> century, when more insight in the mechanism of blood coagulation was attained and better laboratory tests had become available. Although the general picture of DIC is known to most clinicians, a precise description of the syndrome, a good working definition and a useful scoring system are not available. The SSC subcommittee on DIC has worked over the last years to come closer to achieve these goals.

Traditionally DIC is diagnosed in association with the following clinical and pathophysiologic events:

1. Initiation of a massive localized or generalized inflammatory response with release of host proteases, cytokines, and hormones from multiple inflammatory and vascular cell types leading to an extensive damage to microvascular endothelium.
2. This is accompanied by (a) vasodilatation, loss of tight junctions between endothelial cells leading to capillary leak and shock, (b) escape from regulatory control, activation of coagulation pathways and excessive thrombin generation with microthrombus formation locally and at sites remote from the site of original injury, leading to ischemia and multiple organ dysfunction, and (c) subsequent consumption and exhaustion of platelets and coagulation factors leading to bleeding and hemorrhage into tissues.

Considering these premises, the consensual definition of DIC as proposed by the SSC/ISTH subcommittee on DIC and as further explained in this manuscript, is as follows: "DIC is an acquired syndrome characterized by the intravascular activation of coagulation with loss of localization arising from different causes. It can originate from and cause damage to the microvasculature, which if sufficiently severe, can produce organ dysfunction".

In this manuscript the subcommittee on DIC has attempted to put forward a concept of DIC and a scoring system as a first step in the ultimate aim of improving outcome in this area. It therefore has to be useful for those practicing clinical medicine as well as those involved in clinical and basic research, so that progress can be made both in the understanding of pathogenesis and therapy.

## One Concept and Six Conseriations

The assumption under which the subcommittee worked is that DIC is characterized by the generation of fibrin related products (soluble fibrin monomer, fibrin degradation products, D-dimer, etc.) and that it reflects an acquired (inflammatory) or non-inflammatory disorder of the microvasculature. The microvasculature is defined as a transport organ composed of blood and the vascular structures in contact with blood, including mononuclear cells and endothelium (microvasculature). The subcommittee proposes that the microvascular system be viewed as a distinct physiologic organ, the function of which, on injury may be switched from homeostatic regulation to amplification of its own dysfunction ("inflammation gone amok").

In developing a practical diagnostic approach and set of criteria for the diagnosis of DIC and microvascular dysfunction, the DIC subcommittee has operated with six objectives in mind:

1. To establish the importance of the presence of the underlying disorder for the development of overt DIC and to integrate diagnostic criteria for e.g. sepsis and organ failure with the criteria for the evaluation of the severity of DIC (Table 1). Although the microvascular derangement is closely linked to other clinical markers of inflammation and organ dysfunction, we have chosen not to include criteria for organ failure to be part of the DIC score. The main reason for this, is that the DIC score itself is likely to become part of scores for organ failure.
2. To establish diagnostic criteria for the diagnosis of a stressed, but compensated hemostatic system (non-overt DIC) as well as for the diagnosis of a stressed but decompensated hemostatic system (overt DIC).
3. To establish clinical and laboratory criteria, which will aid in distinguishing between (a) "controlled" overt DIC, in which the endo-

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\* A detailed version of this article including 17 references, three tables and a long list of acknowledgements is available at <http://www.isth.org/>

Table 1 Clinical conditions that may be associated with overt DIC

- sepsis/severe infection (any micro-organism)
- trauma (e.g. polytrauma, neurotrauma, fat embolism)
- organ destruction (e.g. severe pancreatitis)
- malignancy
  - solid tumors
  - myeloproliferative/lymphoproliferative malignancies
- obstetrical calamities
  - amniotic fluid embolism
  - abruptio placentae
- vascular abnormalities
  - Kasabach-Merrit Syndrome
  - large vascular aneurysms
- severe hepatic failure
- severe toxic or immunologic reactions
  - snake bites
  - recreational drugs
  - transfusion reactions
  - transplant rejection

thelial regulatory network (e.g. activation of protein C by endothelial thrombomodulin) is temporarily overridden and which will reverse quickly when the predisposing condition or cause is removed or

stopped (e.g. transfusion reaction, or abruptio placentae), and (b) “uncontrolled” overt DIC, in which there is both an override of the regulatory factors and degradation of the endothelial regulatory network (e.g., sepsis, trauma).

4. To establish the importance of continuing to use readily available laboratory tests (e.g. global coagulation tests) in diagnostic screening for DIC. It is clear that global coagulation tests primarily reflect ongoing consumption and impaired synthesis rather than directly assess activation of coagulation. Assessment of a low and/or decreasing platelet count more accurately reflects both consumption and thrombin generation and is helpful in establishing the presence and severity of DIC. Additionally, tests for the presence of fibrin (either directly or indirectly by measuring fibrin degradation products) are helpful in establishing intravascular fibrin formation. However, for the diagnosis of non-overt DIC these global tests may be insufficiently sensitive.
5. In considering molecular markers, it should be emphasized that (a) these tests have great value in looking at both endothelial injury and hemostatic activation, (b) these tests constitute important means for diagnosing non-overt DIC, and (c) serial measurement of these parameters are important to quantitatively assess the progression and extent of microvascular injury and the progression from non-overt to overt DIC. However, since these markers can only be measured in specialized laboratories and can generally not be available on a daily basis in routine care, they will not form part of the scoring system for overt DIC.
6. To realize that the design of a system to score the presence and severity of DIC may be of importance for clinical practice as well as clinical trials on the effect of interventions directed at pathways or components of the coagulation system to improve DIC and/or the underlying disorder (e.g. sepsis). However, the ultimate aim of the treatment is not directed at the amelioration of the DIC itself. Rather, the improvement of organ function or mortality should be regarded

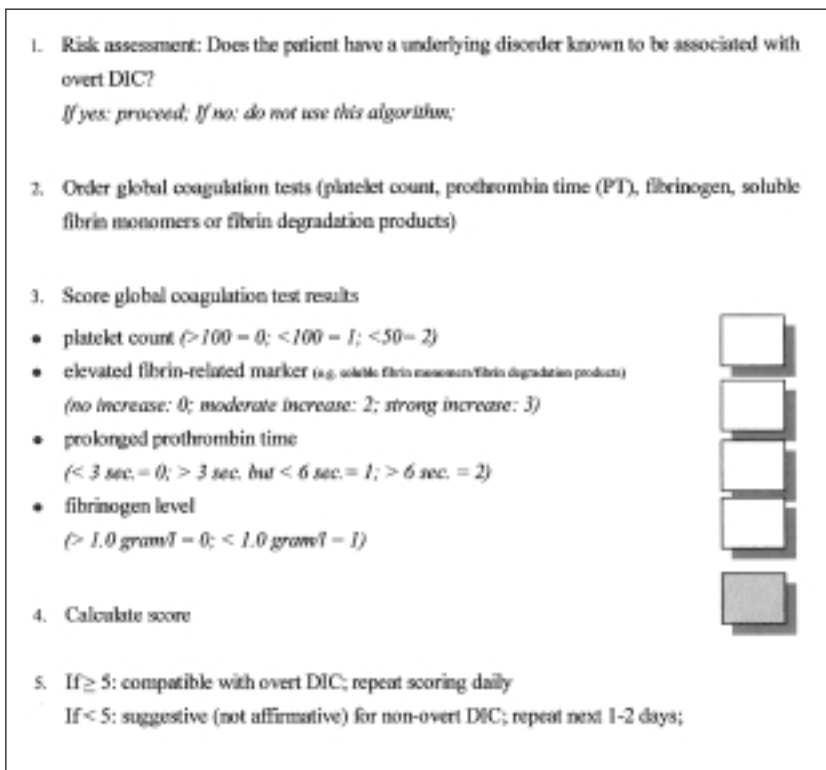


Table 2 Diagnostic algorithm for the diagnosis of overt DIC

Table 3 Template for scoring system for non-overt DIC

|   |                             |                             |  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
|---|-----------------------------|-----------------------------|--|---|--|--------------------------|--------------------------|--|-----------------|------------|-----------|---|--|--------------------------|--------------------------|--|-------------------------|------------|----------|---|--|--------------------------|--------------------------|--|---|-------------|--------------|-------------|---|--------------------------|--------------------------|--------------------------|---|--------------|------------|------------|---|--|--------------------------|--------------------------|--------------------------|--------------|------------|------------|---|--|--------------------------|--------------------------|--------------------------|---|
| <p>1. Risk assessment: Does the patient have a underlying disorder known to be associated with DIC?<br/>yes = 2, no=0</p>   |                             |                             | <p>score</p> <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div>               |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
| <p>2. Major criteria</p>  |                             |                             |  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
| <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">platelet count</td> <td style="padding: 2px; text-align: center;">&gt;100x10<sup>9</sup>/l = 0</td> <td style="padding: 2px; text-align: center;">&lt;100x10<sup>9</sup>/l = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">PT prolongation</td> <td style="padding: 2px; text-align: center;">&lt; 3 sec=0</td> <td style="padding: 2px; text-align: center;">&gt; 3 sec=1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">soluble fibrin or FDP's</td> <td style="padding: 2px; text-align: center;">normal=0</td> <td style="padding: 2px; text-align: center;">raised=1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> </table>   | platelet count              | >100x10 <sup>9</sup> /l = 0 | <100x10 <sup>9</sup> /l = 1  | + |  | <input type="checkbox"/> | <input type="checkbox"/> |  | PT prolongation | < 3 sec=0  | > 3 sec=1 | + |  | <input type="checkbox"/> | <input type="checkbox"/> |  | soluble fibrin or FDP's | normal=0   | raised=1 | + |  | <input type="checkbox"/> | <input type="checkbox"/> |  | <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">rising = -1</td> <td style="padding: 2px;">stable = 0</td> <td style="padding: 2px;">falling = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td style="padding: 2px;">falling = -1</td> <td style="padding: 2px;">stable = 0</td> <td style="padding: 2px;">rising = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> </tr> <tr> <td style="padding: 2px;">falling = -1</td> <td style="padding: 2px;">stable = 0</td> <td style="padding: 2px;">rising = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> </tr> </table> | rising = -1 | stable = 0   | falling = 1 | + |                          | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>  | falling = -1 | stable = 0 | rising = 1 | + |  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | falling = -1 | stable = 0 | rising = 1 | + |  | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> |
| platelet count  | >100x10 <sup>9</sup> /l = 0 | <100x10 <sup>9</sup> /l = 1 | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
|   | <input type="checkbox"/>    | <input type="checkbox"/>    |  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
| PT prolongation   | < 3 sec=0                   | > 3 sec=1                   | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| soluble fibrin or FDP's   | normal=0                    | raised=1                    | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| rising = -1   | stable = 0                  | falling = 1                 | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| falling = -1  | stable = 0                  | rising = 1                  | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| falling = -1  | stable = 0                  | rising = 1                  | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| <p>3. Specific criteria</p>   |                             |                             |  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
| <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="padding: 2px;">antithrombin</td> <td style="padding: 2px; text-align: center;">normal =-1</td> <td style="padding: 2px; text-align: center;">low = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">protein C</td> <td style="padding: 2px; text-align: center;">normal =-1</td> <td style="padding: 2px; text-align: center;">low = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">TAT-complexes</td> <td style="padding: 2px; text-align: center;">normal =-1</td> <td style="padding: 2px; text-align: center;">high = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> <tr> <td style="padding: 2px;">.....</td> <td style="padding: 2px; text-align: center;">normal =-1</td> <td style="padding: 2px; text-align: center;">abnormal = 1</td> <td style="padding: 2px; text-align: center;">+</td> </tr> <tr> <td style="padding: 2px;"></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px; text-align: center;"><input type="checkbox"/></td> <td style="padding: 2px;"></td> </tr> </table> | antithrombin                | normal =-1                  | low = 1  | + |  | <input type="checkbox"/> | <input type="checkbox"/> |  | protein C       | normal =-1 | low = 1   | + |  | <input type="checkbox"/> | <input type="checkbox"/> |  | TAT-complexes           | normal =-1 | high = 1 | + |  | <input type="checkbox"/> | <input type="checkbox"/> |  | .....   | normal =-1  | abnormal = 1 | +           |   | <input type="checkbox"/> | <input type="checkbox"/> |                          | <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> <div style="border: 1px solid black; width: 40px; height: 40px; margin: 0 auto;"></div> |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
| antithrombin  | normal =-1                  | low = 1                     | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
|   | <input type="checkbox"/>    | <input type="checkbox"/>    |  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
| protein C   | normal =-1                  | low = 1                     | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| TAT-complexes   | normal =-1                  | high = 1                    | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| .....   | normal =-1                  | abnormal = 1                | +  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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| <p>4. Calculate score</p>   |                             |                             |  |   |  |                          |                          |  |                 |            |           |   |  |                          |                          |  |                         |            |          |   |  |                          |                          |  |   |             |              |             |   |                          |                          |                          |   |              |            |            |   |  |                          |                          |                          |              |            |            |   |  |                          |                          |                          |   |
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as more relevant outcome parameter. Nevertheless, a DIC score may be of relevance if it can be validated as a suitable intermediate outcome parameter. Prospective validation of the proposed criteria for DIC is mandatory, to determine more precisely the value of these criteria.

a score equal or more than 5 is compatible with DIC, whereas a score of less than 5 may be indicative (but is *not* affirmative) for non-overt DIC (see further). It is the recommendation of the subcommittee that scoring proceeds daily in order to characterize the severity and the course of the overt DIC.

**Criteria for Overt DIC**

Following these objectives the committee proposes a 5-step diagnostic algorithm to calculate a DIC score, as summarized in Table 2. In line with the previous comments, the presence of an underlying disorder known to be associated with DIC (Table 1) is a *conditio sine qua non* for the use of the algorithm. We decided not to include the clinical assessment of organ failure and bleeding as a part of the score, since the DIC score itself may form part of scores for organ failure. The results of routine laboratory tests contribute to the DIC score. Presumably, all laboratory tests required for the score will be available in most hospitals on a daily basis. Dependent of the type of test used, cut-off values for a “severely” or “moderately” elevated result of the test for soluble fibrin monomers or fibrin degradation products have to be established. Tentatively, and awaiting further prospective validation,

**Criteria for Non-overt DIC**

To define and score the presence and severity of non-overt DIC using a “standard” scoring system is much more complicated. Nevertheless, it is of importance to delineate the criteria for the presence of hemostatic dysfunction when it is not yet at the stage of frank decompensation. As mentioned before, the global coagulation parameters will be of limited value in the assessment of non-overt DIC. These tests are in general insufficiently sensitive whereas simultaneously subtle changes may be too non-specific. On the other hand, more sensitive tests for this diagnosis will not be widely available. Hence, it is difficult to accomplish a scoring system that is universally applicable. The subcommittee proposes a framework for a scoring system for non-overt DIC that can be specified and refined according to local potential and/or using essential tests in the context of a clinical trial (Table 3).

This format will also enable one to incorporate any future advancement in either technology or pathophysiological understanding. In the proposed scoring system for non-overt DIC more emphasis on the trend over time of these results is given, thereby increasing the sensitivity of the parameters. Therefore, the subcommittee recommends that measurements proceed daily. Specific criteria will be established by the results of more specialized coagulation tests, such as the determination of antithrombin or protein C or thrombin-antithrombin (TAT) complexes. According to local availability of tests and/or criteria that are defined in the framework of a clinical trial a selection of tests can be

made and a score can be calculated. Also here, prospective validation of a given score is needed.

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