2017

Progetto Ematologia Romagna

Coagulazione Intravascolare Disseminata: *Terapia*

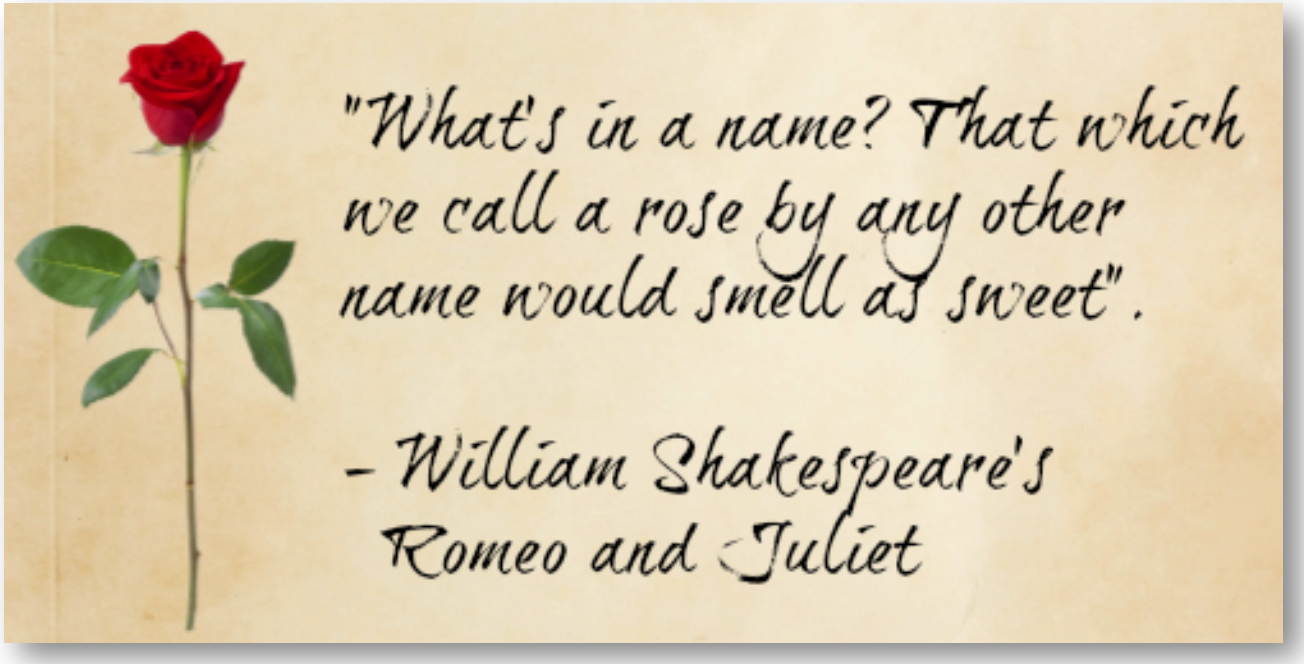
Ambra Paolini- Modena

Relazioni con soggetti portatori di interessi commerciali in campo sanitario

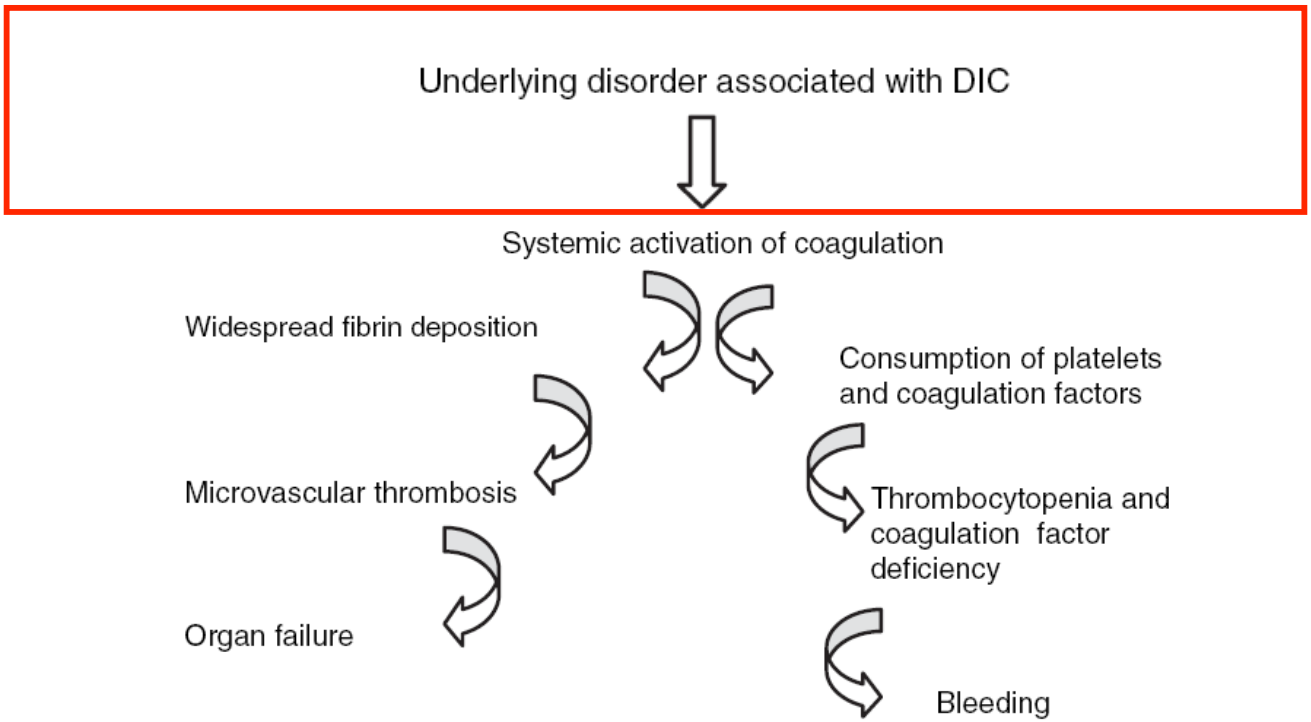
Ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17
del Regolamento Applicativo dell'Accordo Stato-Regione del 5 novembre 2009, io sottoscritta **Dott.ssa Ambra Paolini** dichiaro che negli ultimi due anni ho avuto i seguenti rapporti ricevendo compensi individuali con soggetti portatori di interessi commerciali in campo sanitario:

- Relatore a convegno sponsorizzato Celgene

Disseminated intravascular coagulation (DIC): what's in a name?



Processes in DIC



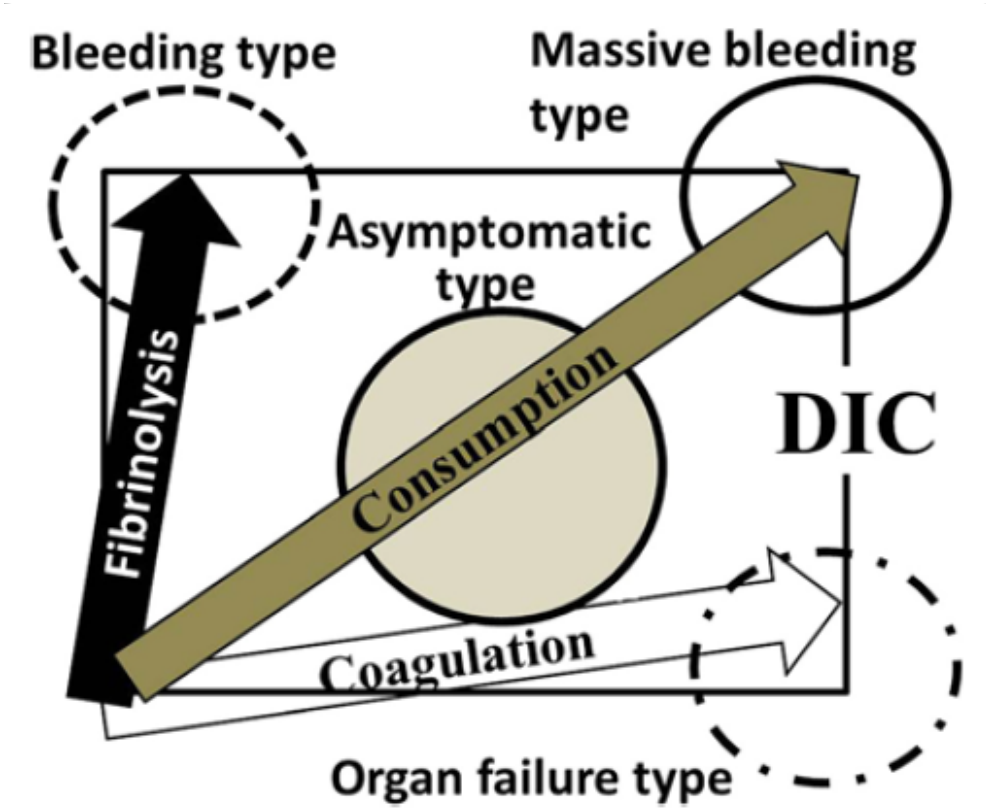
British J Haematol 2009; 145:24-33.

Conditions associated with DIC

- Sepsis and severe infection
- Trauma
- Organ destruction e.g pancreatitis
- Malignancy
  - Solid tumours
  - Leukaemia
- Obstetric
  - Amniotic fluid embolism
  - Placental abruption
  - Pre-eclampsia
- Vascular abnormalities
  - Large haemangiomata
  - Vascular aneurysm
- Severe liver failure
- Toxic and immunological insults
  - Snake bites
  - Recreational drugs
  - ABO transfusion incompatibility
  - Transplant rejection

British J Haematol 2009; 145:24-33.

Types of DIC



Journal of Intensive Care 2014 2:15.

DIC therapy


LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED

Journal of Thrombosis and Haemostasis, **11**: 761–767 DOI: 10.1111/jth.12155

OFFICIAL COMMUNICATION OF THE SSC

Guidance for diagnosis and treatment of disseminated intravascular coagulation from harmonization of the recommendations from three guidelines

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**Department of Molecular and Laboratory Medicine, Mie University School of Medicine, Mie, Japan; †Department of Haematology, Manchester Royal Infirmary, Manchester, UK; ‡Department of Medical, Oral and Biotechnological Sciences University 'G. D. Annunzio' of Chieti-Pescara, Chieti, Italy; §Department of Vascular Medicine, Academic Medical Center, Amsterdam, the Netherlands; ¶Department of Pediatrics, University of New Mexico, Albuquerque, NM; **Department of Pathology and Laboratory Medicine, Boston University School of Medicine, Boston, MA, USA; ††Division of Acute and Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Hokkaido University Graduate School of Medicine, Sapporo, Japan; ‡‡Department of Laboratory Medicine, Seoul National University College of Medicine, Seoul, Korea; §§Department of Hematology, Rigshospitalet University Hospital of Copenhagen, Copenhagen, Denmark; ¶¶First Department of Medicine, University Hospital of Mannheim, Mannheim, Germany; ***The Roald Dahl Haemostasis & Thrombosis Centre, Royal Liverpool University Hospital, ; and †††Institute of Infection and Global Health, University of Liverpool, Liverpool, UK*

Table 2 Recommendation levels in the three guidelines

Grade	BCSH	JSTH	SISET
		Consensus: treatment does not have HQ of Ed, but it should be carried out as common sense	
A	Requires at least one RCT as part of a body of literature of overall GQ and consistency addressing specific Rm (EdL Ia, Ib)	Treatment has HQ of Ed, and the CU is clear	EdL 1++ and DATTTP *or* EdL 1+, DATTTP, and DOCOR
B	Requires the availability of well-conducted clinical Sys but no RCT on the topic of Rm (EdL IIa, IIb, III)	B1: treatment has moderately HQ of Ed, or it has HQ of Ed but the CU is not significant. B2: treatment does not have HQ of Ed, but it has few deleterious effects and it is carried out clinically	EdL 2++, DATTTP and DOCOR *or* EEd from Sys (EdL 1++ or 1+)
C	Requires Ed obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical Sys of GQ (EdL IV)	Treatment does not have HQ of Ed or the CU is not clear	EDL 2+, DATTTP and DOCOR *or* EEd from Sys (EdL 2++)
D		Treatment has HQ of Ed, and it has deleterious effects	EdL 3 or 4; *or* EEd from Sys (EdL 2+)

BCSH, British Committee for Standards in Haematology; CU, clinical usefulness; DATTTP, directly applicable to the target population; DO-

Table 3 Quality of evidence and definitions for recommendation in the modified GRADE system

High quality	Further research is very unlikely to change our confidence in the estimate of the effect
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of the effect, and may change the estimate
Low quality	Further research is very likely to have an important impact on our confidence in the estimate of the effect, and is likely to change the estimate

sal, or based on physiology, bench research, or 'first principles. Ed levels in SISET are as follows. 1++: HQ meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias. 1+: well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias. 1−: meta-analyses, systematic reviews, or RCTs with a high risk of bias. 2++: HQ systematic reviews of case-controlled or cohort Sys. HQ case-controlled or cohort Sys with a very low risk of confounding or bias, and a high probability that the relationship is causal. 2+: well-conducted case-controlled or cohort Sys with a low risk of confounding or bias, and a moderate probability that the relationship is causal. 2−: case-controlled or cohort Sys with a high risk of confounding or bias, and a significant risk that the relationship is not causal. 3: non-analytic Sys, e.g. case reports, case series. 4: expert opinion.

J Thromb Haemost 2013; **11**: 761–7

Treatment of the underlying disease

The cornerstone of DIC treatment is the treatment of the underlying condition (moderate quality).

J Thromb Haemost 2013; **11**: 761–7

Asymptomatic type

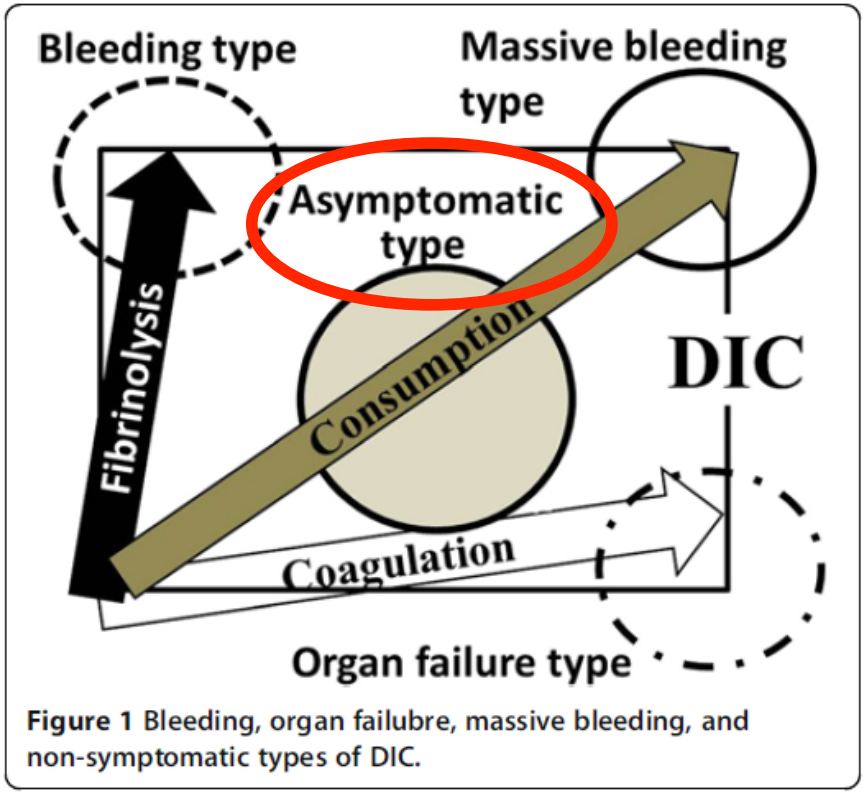


Figure 1 Bleeding, organ failubre, massive bleeding, and non-symptomatic types of DIC.

Journal of Intensive Care 2014 2:15.

Table 1 Scoring system for overt Disseminated Intravascular Coagulation (DIC)

1. Risk assessment: does the patient have an underlying disorder known to be associated with overt DIC?

   If yes: Proceed.

   If no: Do not use this algorithm.

2. Order global coagulation tests (platelet count, prothrombin time, fibrinogen, fibrin-related marker).

3. Score global coagulation test results.

- Platelet count
  (>100 = 0; <100 = 1; < 50 = 2)
- Elevated fibrin related marker (e.g. D-dimers; fibrin degradation products)
  (no increase = 0; moderate increase = 2; strong increase = 3)
- Prolonged prothrombin time
  (< 3 s = 0; > 3 but < 6 s = 1; > 6 s = 2)
- Fibrinogen level
  (>1.0g L^{-1} = 0; < 1.0g L^{-1} = 1)

5. Calculate score

If ≥ 5: compatible with overt DIC: repeat score daily

If < 5: suggestive (not affirmative) for non-overt DIC: repeat next 1–2 days.

British J Haematol 2009; 145:24-33.

Thrombotic phenotype

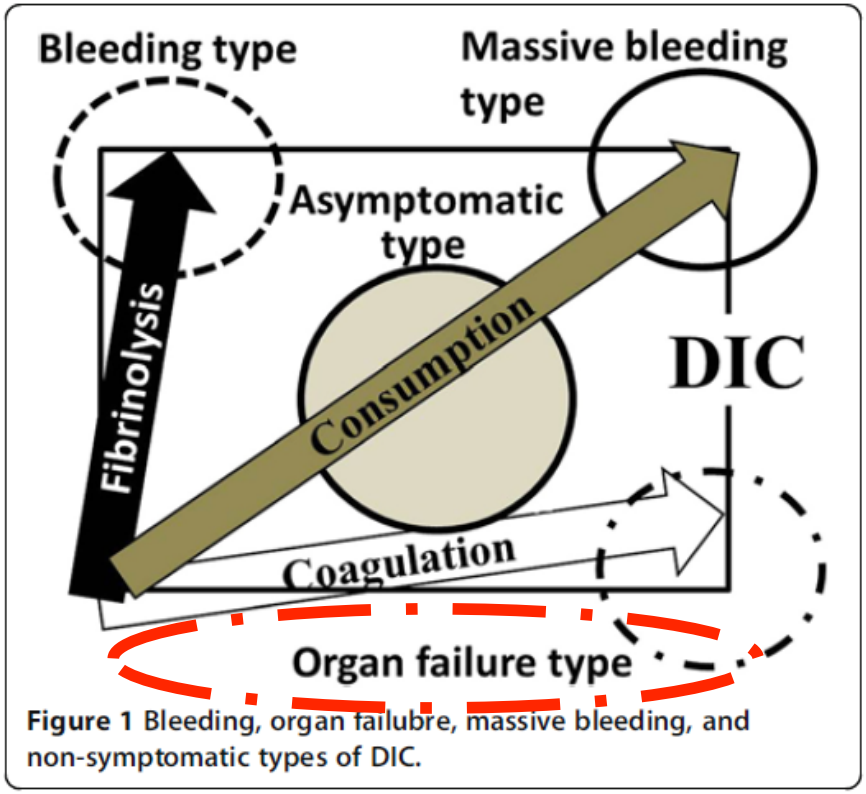


Figure 1 Bleeding, organ failubre, massive bleeding, and non-symptomatic types of DIC.

Journal of Intensive Care 2014 2:15.

Sepsis and DIC

Table 1. The Sequential Organ Failure Assessment (SOFA) Score*

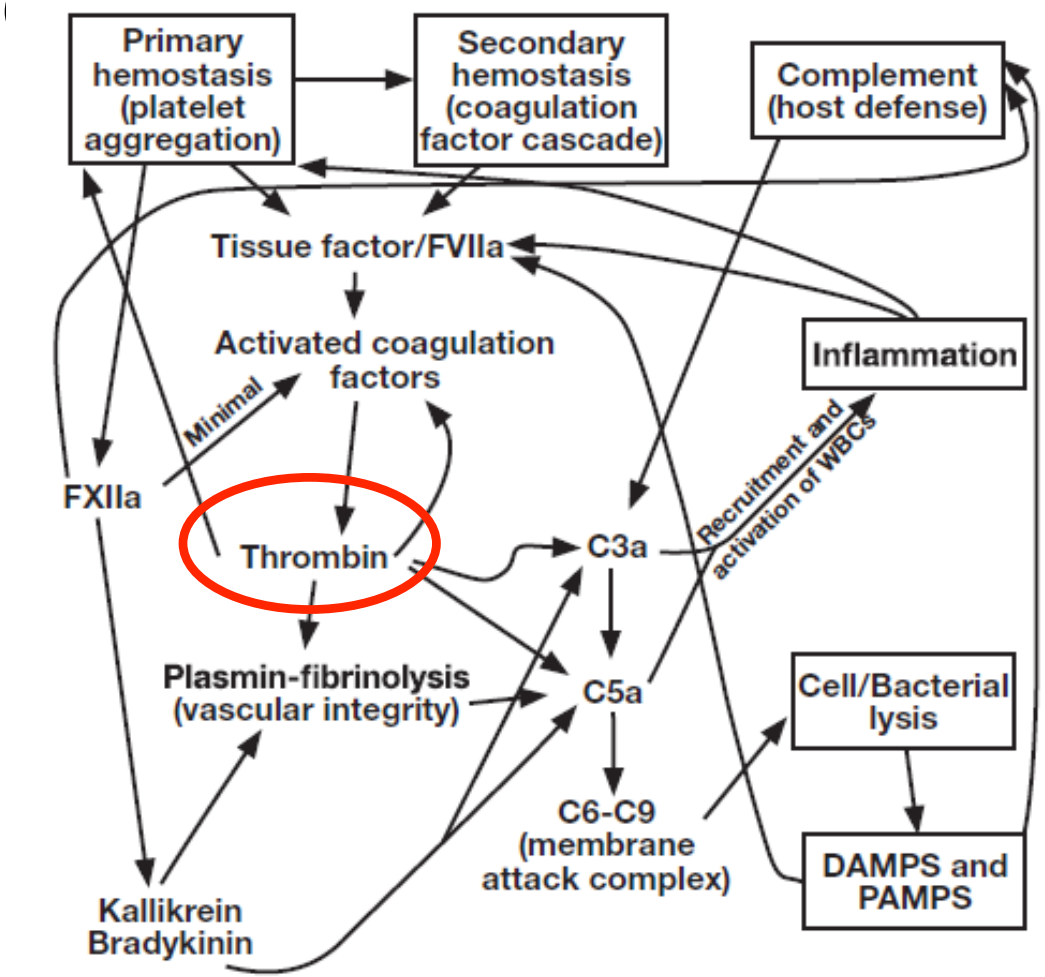
	SOFA Score				
Variables	**0**	**1**	**2**	**3**	**4**
Respiratory Pao_2/FIO_2, mm Hg	>400	≤400	≤300	≤200†	≤100†
Coagulation Platelets $\times 10^3/\mu L$‡	>150	≤150	≤100	≤50	≤20
Liver Bilirubin, mg/dL‡	<1.2	1.2-1.9	2.0-5.9	6.0-11.9	>12.0
Cardiovascular Hypotension	No hypotension	Mean arterial pressure <70 mm Hg	Dop ≤5 or dob (any dose)§	Dop >5, epi ≤0.1, or norepi ≤0.1§	Dop >15, epi >0.1, or norepi >0.1§
Central nervous system Glasgow Coma Score Scale	15	13-14	10-12	6-9	<6
Renal Creatinine, mg/dL or urine output, mL/d‖	<1.2	1.2-1.9	2.0-3.4	3.5-4.9 or <500	>5.0 or <200

*Norepi indicates norepinephrine; Dob, dobutamine; Dop, dopamine; Epi, epinephrine; and FIO_2, fraction of inspired oxygen.
†Values are with respiratory support.
‡To convert bilirubin from mg/dL to µmol/L, multiply by 17.1.
§Adrenergic agents administered for at least 1 hour (doses given are in µg/kg per minute).
‖To convert creatinine from mg/dL to µmol/L, multiply by 88.4.

↓ ANTITHROMBIN
PROTEIN C
TFPI

↑ PAI

M. Levi, T. van der Poll / Thrombosis Research 149 (2017) 38–44



Am J Clin Pathol December 2016;146:670-680

Natural protease inhibitors

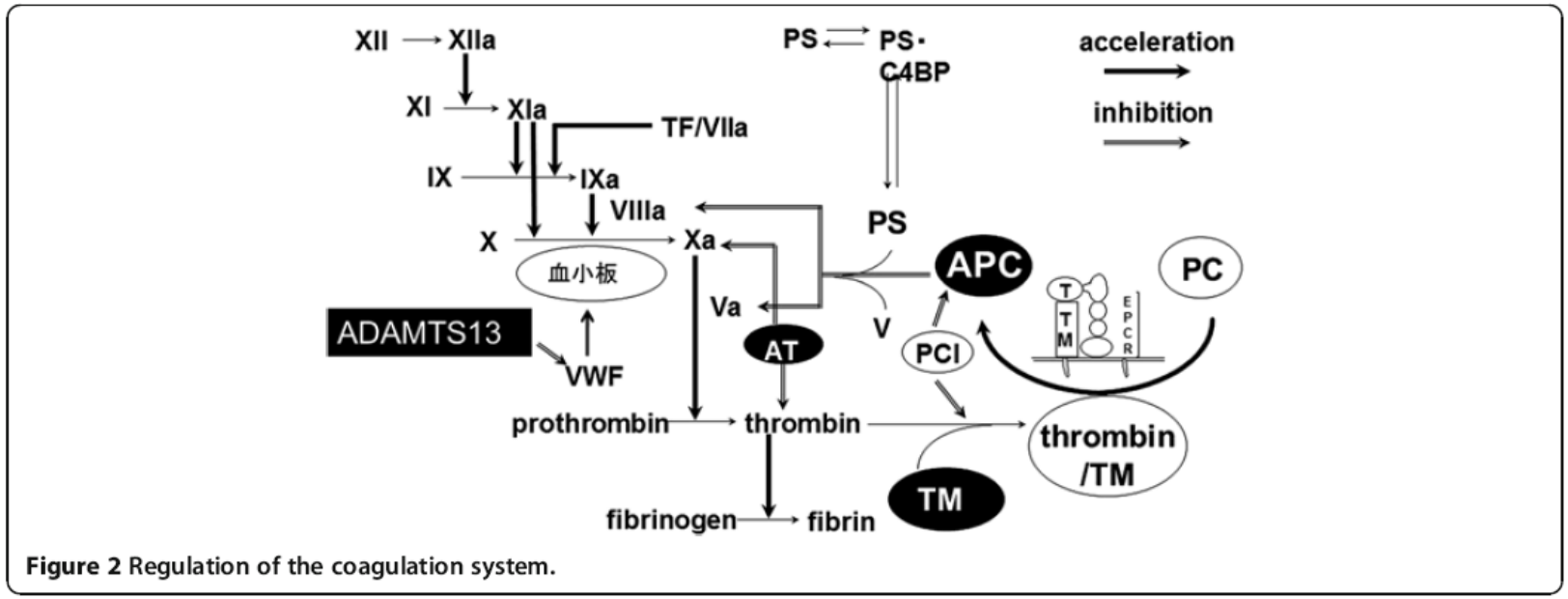
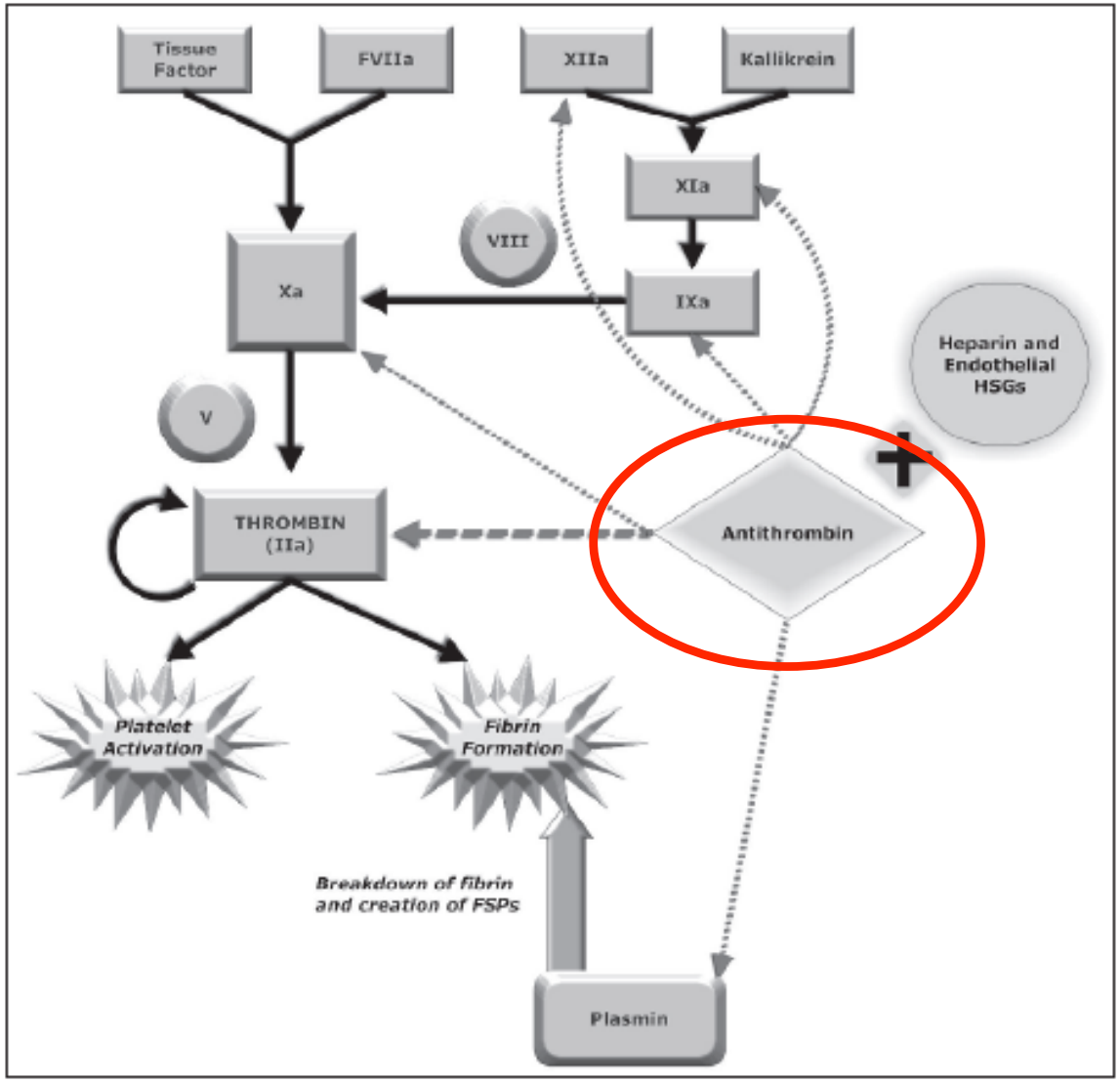


Figure 2 Regulation of the coagulation system.

Wada et al. Journal of Intensive Care 2014 2:15.

A role for anticoagulant factor concentrates?



JTH 2016; 115: 712–728

Intensive Care Med (2016) 42:505–520
DOI 10.1007/s00134-016-4225-7

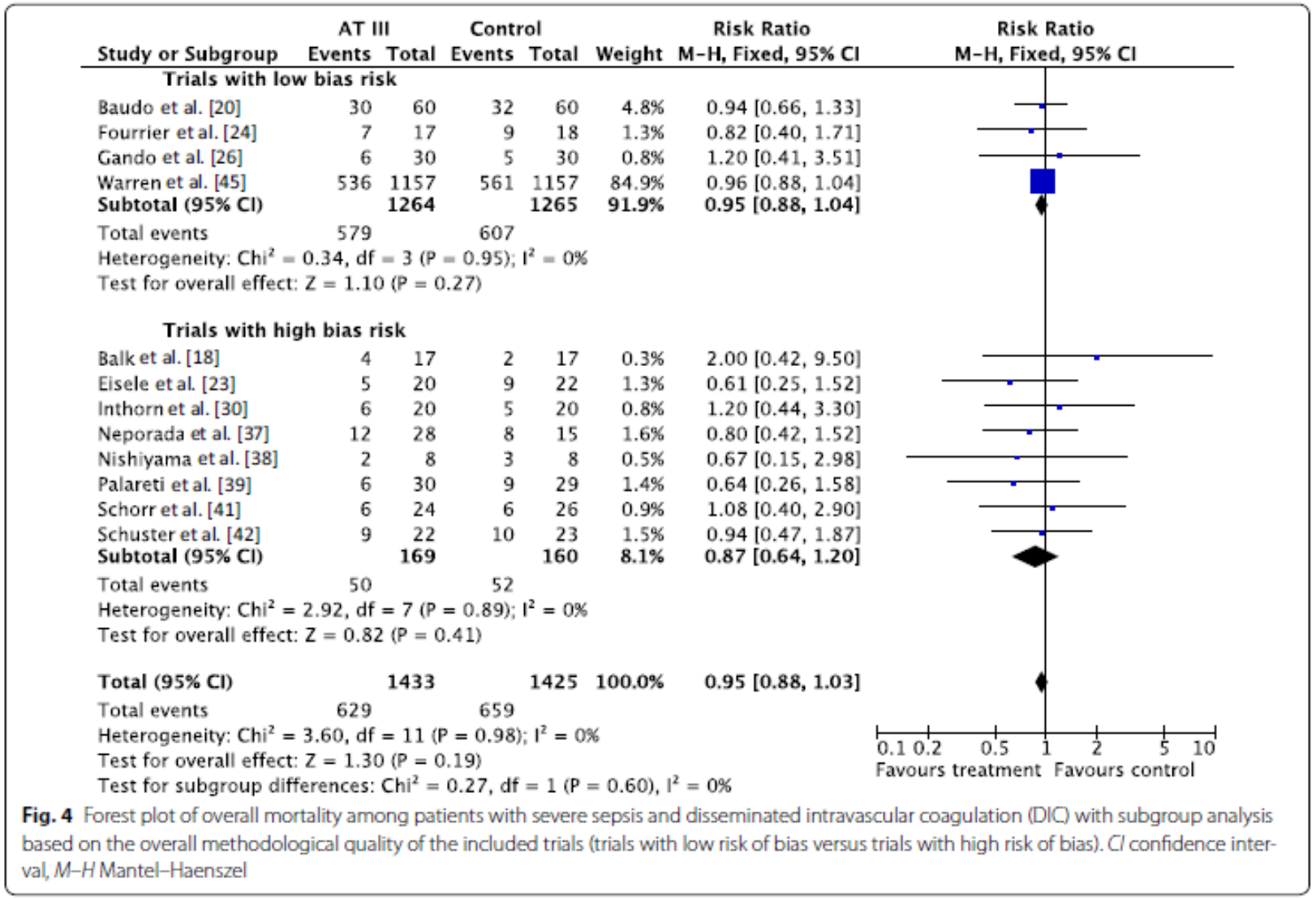
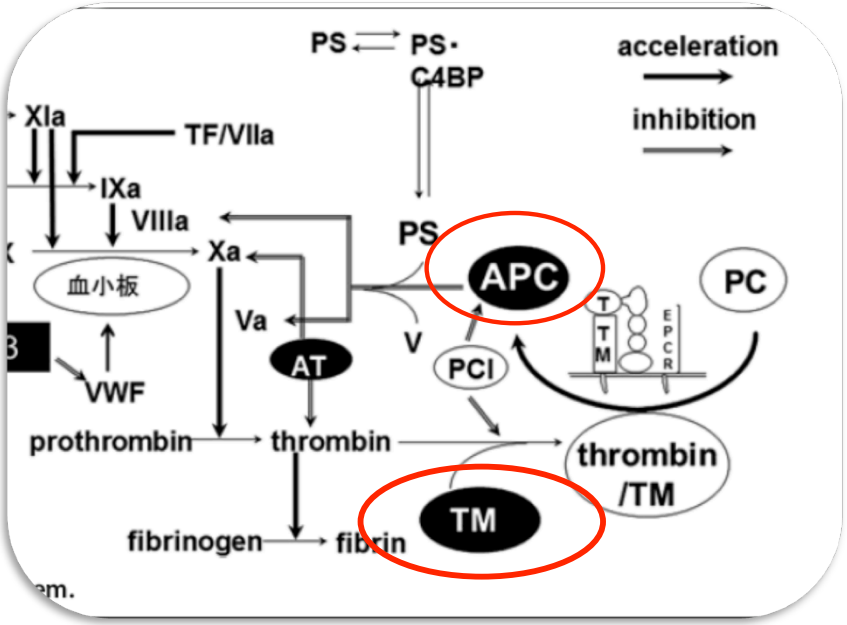


Fig. 4 Forest plot of overall mortality among patients with severe sepsis and disseminated intravascular coagulation (DIC) with subgroup analysis based on the overall methodological quality of the included trials (trials with low risk of bias versus trials with high risk of bias). *CI* confidence interval, *M–H* Mantel–Haenszel

Other anticoagulant factor concentrates..?

- **Activated protein C (APC)**
- **Recombinant human trombomodulin (rhTM)**



Further prospective evidence from RCTs confirming a benefit is required.

The administration of ***AT***, recombinant human TM (***rhTM***) or activated protein C (***APC***) ***may be considered*** in DIC patients.

J Thromb Haemost 2013; **11**: 761–7

Anticoagulants: heparin

Therapeutic doses of heparin should be considered in cases of DIC where thrombosis ***predominates*** **(low quality).**

The use of low molecular weight heparin (LMWH) is preferred to the use of unfractionated heparin (UFH) in these cases **(low quality).**

Prophylaxis for VTE with prophylactic doses of UFH or LMWH is recommended in critically ill, non-bleeding patients with DIC **(moderate and high quality, respectively)**, but ***there is no direct evidence of the effects of anticoagulants on DIC.***

J Thromb Haemost 2013; **11**: 761–7

Fibrinolytic phenotype

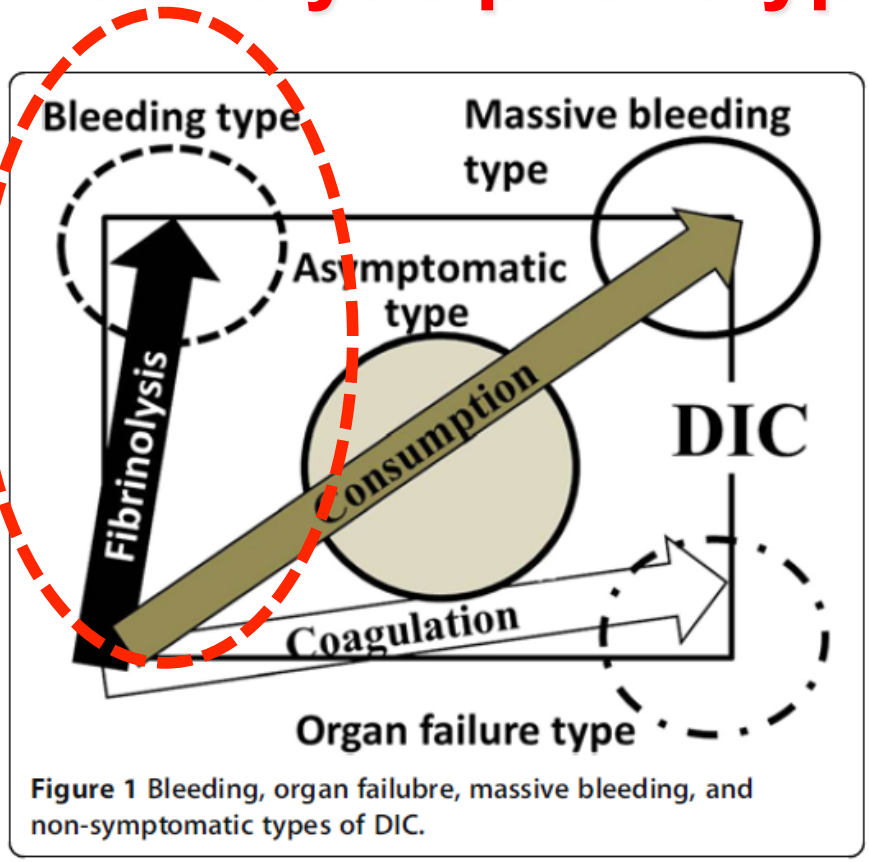


Figure 1 Bleeding, organ failubre, massive bleeding, and non-symptomatic types of DIC.

Journal of Intensive Care 2014 2:15.

Trauma-associated coagulopathy

	Fibrinolytic phenotype
Representative cause	Acute phase of trauma
Coagulation	Activated
Fibrinolysis	Activated
PAI-1	Low
Clinical symptom	Bleeding

Hayakawa *Journal of Intensive Care* (2017) 5:14

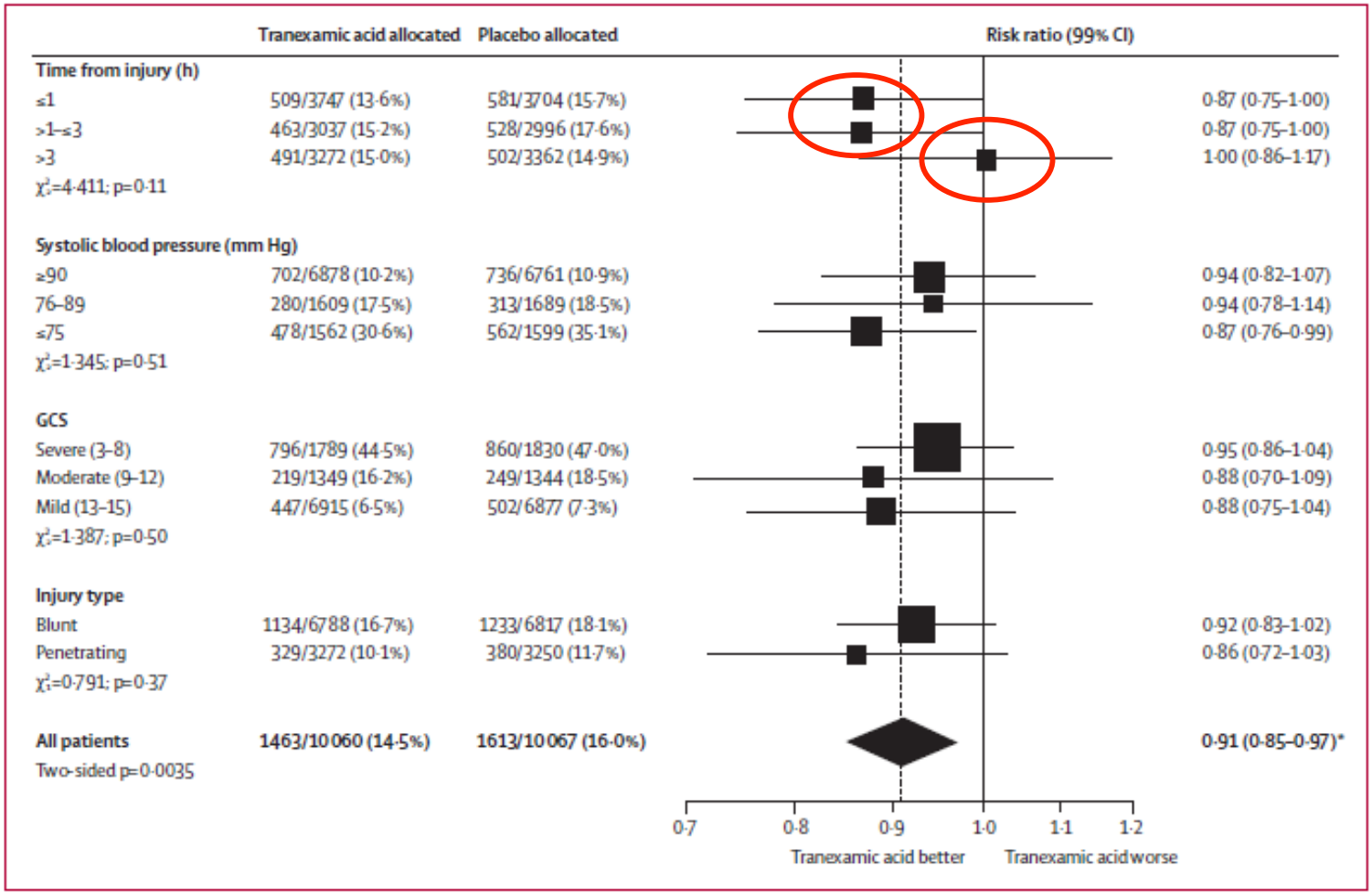


***Figure 3*: All-cause mortality by subgroups**
GCS=Glasgow Coma Score. *95% CI.

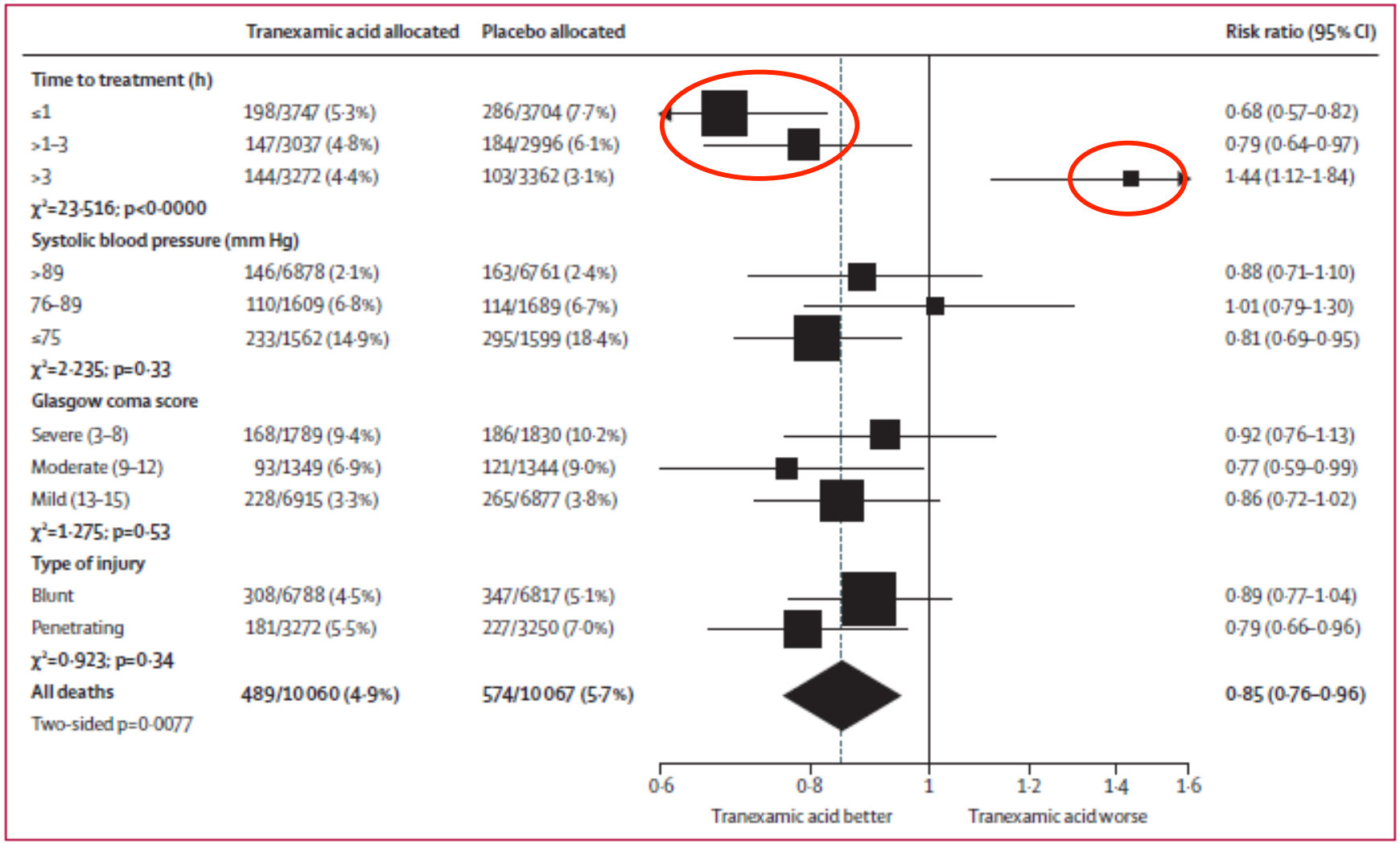
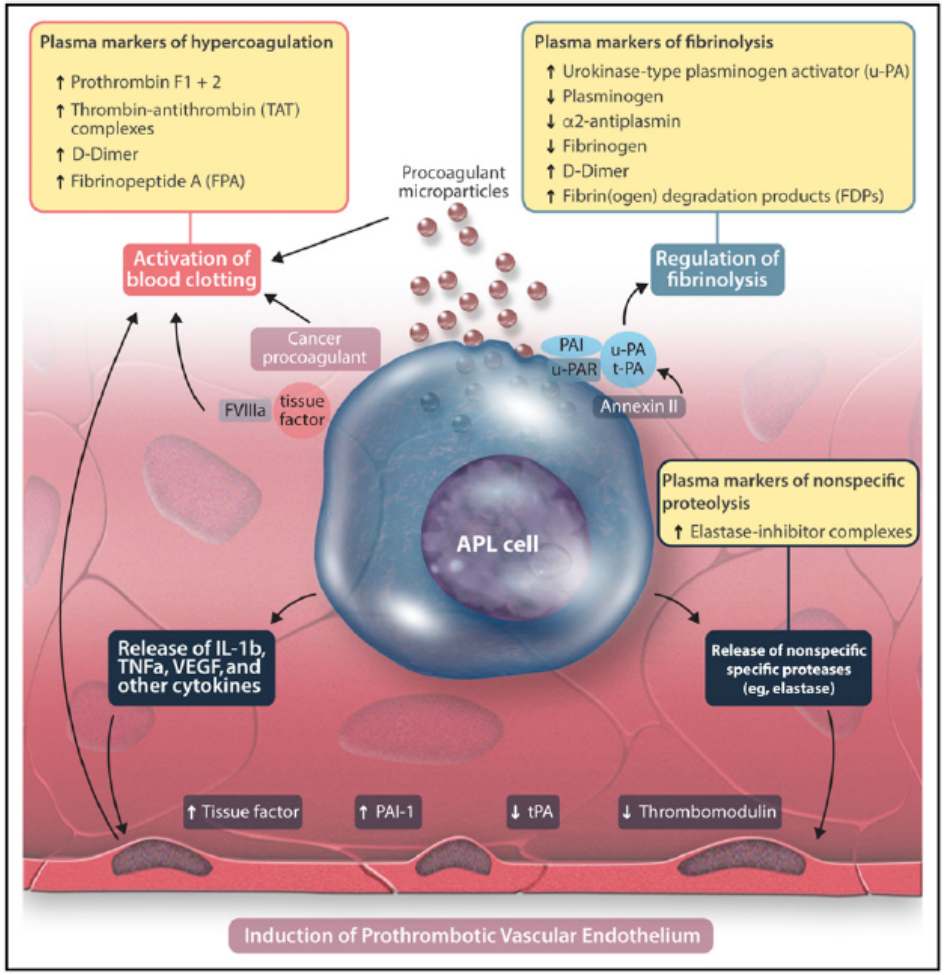


Figure 1: **Mortality due to bleeding by subgroups**

Coagulopathy associated with APL

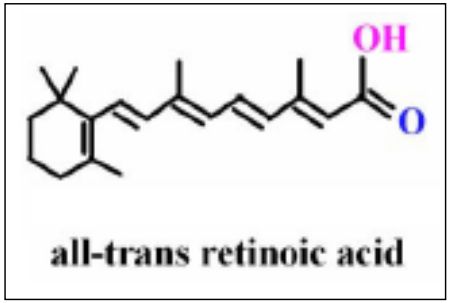


Blood 2017;129(13):1739-40.

blood®
2008 111: 2505-2515
doi:10.1182/blood-2007-07-102798

Acute promyelocytic leukemia: from highly fatal to highly curable

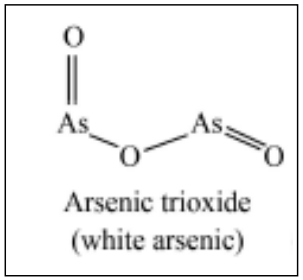
Zhen-Yi Wang and Zhu Chen



all-trans retinoic acid

Chemotherapy (CT; daunorubicin, idarubicin and cytosine arabinoside) was the front-line treatment of APL with a complete remission (**CR**) rate of **75% to 80%** in newly diagnosed patients. Despite all these progresses, the median duration of remission ranged from 11 to 25 months and only 35% to 45% of the patients could be cured by CT.

Since the introduction of **all-*trans* retinoic acid (ATRA)** in the treatment and optimization of the ATRA-based regimens, the **CR** rate was raised up to **90% to 95%** and **5-year** disease free survival (**DFS**) to **74%**.



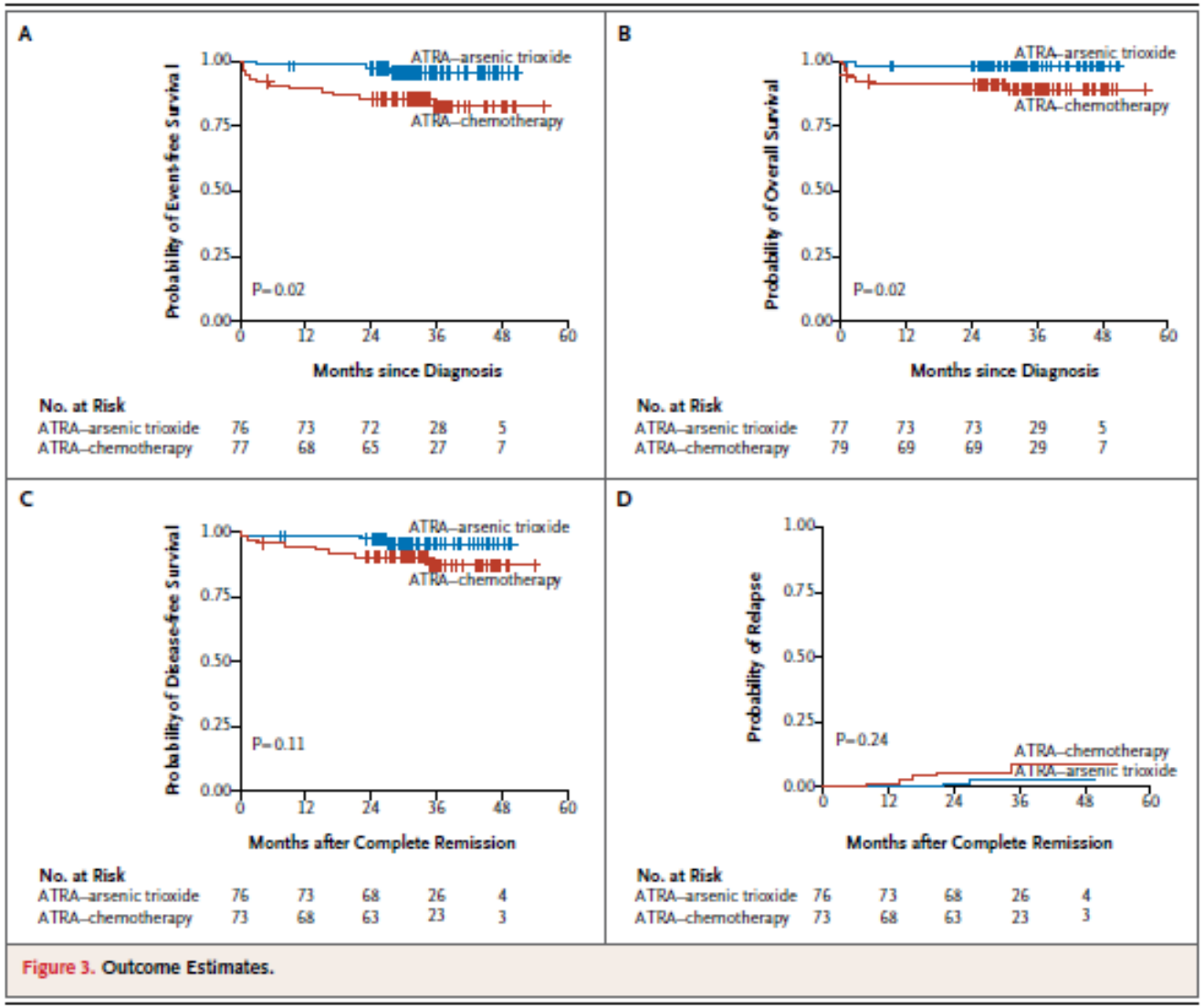


Figure 3. Outcome Estimates.

blood®
2008 111: 3395-3402
doi:10.1182/blood-2007-07-100669 originally published online January 14, 2008

Causes and prognostic factors of remission induction failure in patients with acute promyelocytic leukemia treated with *all-trans* retinoic acid and idarubicin

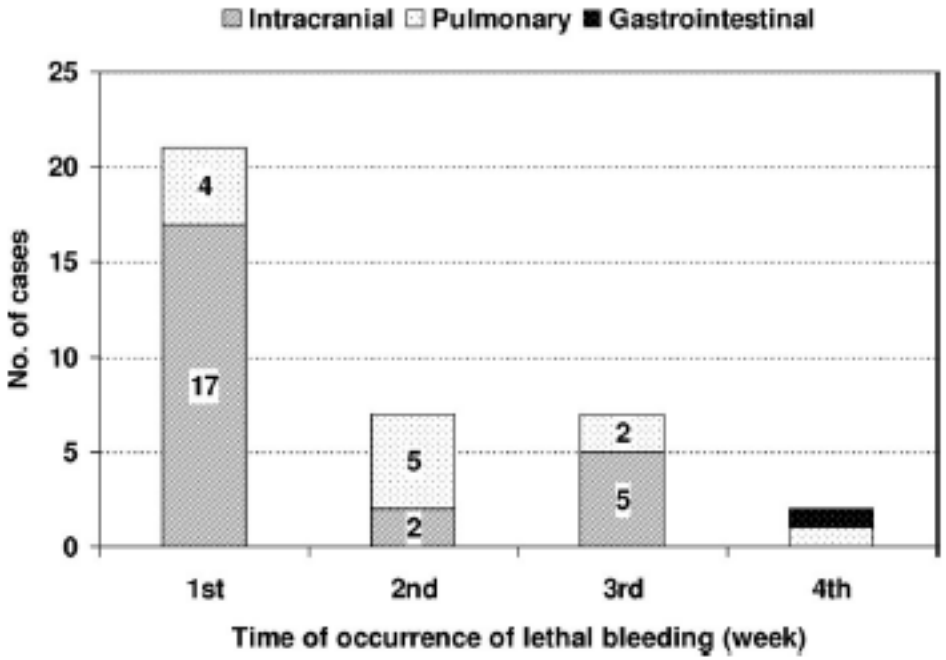
Javier de la Serna, Pau Montesinos, Edo Vellenga, Chelo Rayón, Ricardo Parody, Angel León, Jordi Esteve, Juan M. Bergua, Gustavo Milone, Guillermo Debén, Concha Rivas, Marcos González, Mar Tormo, Joaquín Díaz-Mediavilla, Jose D. González, Silvia Negri, Elena Amutio, Salut Brunet, Bob Lowenberg and Miguel A. Sanz

732 patients of all ages (range, 2-83 years)

Complete remission 91% (666 pts)

All the 66 induction failures were due to induction death.

Hemorrhage was the most common cause of induction death (5%),
followed by infection (2.3%)
and differentiation syndrome (1.4%).



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2017 129: 1763-1767
doi:10.1182/blood-2016-10-747170 originally published online January 12, 2017

Determinants of fatal bleeding during induction therapy for acute promyelocytic leukemia in the ATRA era

Simon Mantha, Debra A. Goldman, Sean M. Devlin, Ju-Whei Lee, Diana Zannino, Marnie Collins, Dan Douer, Harry J. Iland, Mark R. Litzow, Eytan M. Stein, Frederick R. Appelbaum, Richard A. Larson, Richard Stone, Bayard L. Powell, Susan Geyer, Kristina Laumann, Jacob M. Rowe, Harry Erba, Steven Coutre, Megan Othus, Jae H. Park, Peter H. Wiernik and Martin S. Tallman

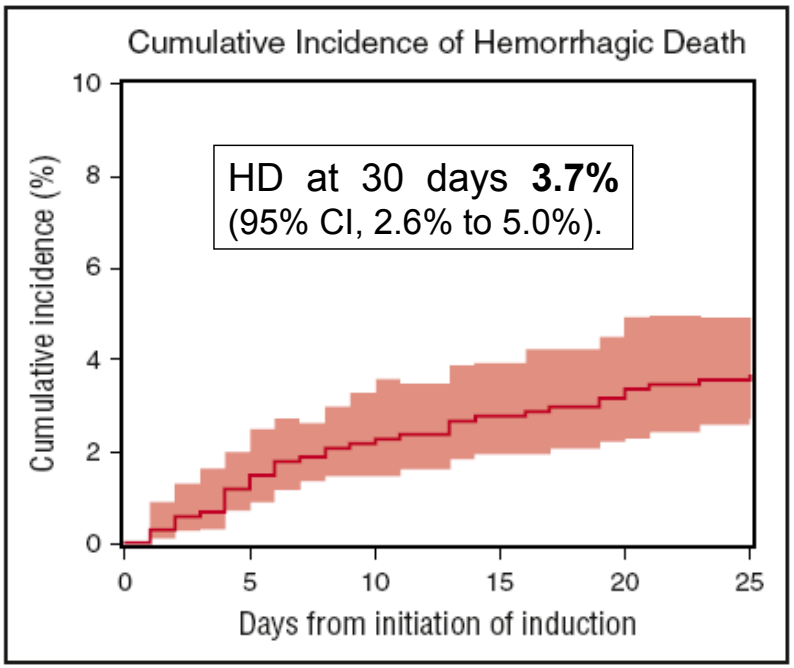


Table 2. Univariate Cox proportional hazards models for the risk of bleeding death in the first 30 days

	No. included (no. of HD)	HR (95% CI)	*P* value
Age, y*	1009 (37)	1.07 (0.89-1.30)	.463
PT, s*	837 (33)	1.07 (1.00-1.14)	.054
WBC count, 1000 cells/μL*	999 (37)	1.07 (1.03-1.10)	**<.001**
WBC count (grouped)			
High risk (≥20)	129 (16)	5.49 (2.86-10.52)	**<.001**
Low risk (<20)	870 (21)	REF	
Platelet count, 1000 cells/μL*	999 (37)	0.91 (0.81-1.02)	.107
Platelet count (grouped)			
High risk (<30)	484 (21)	1.41 (0.74-2.71)	.297
Low risk (≥30)	515 (16)	REF	
Peripheral blast count, 1000 cells/μL*	870 (34)	1.12 (1.05-1.19)	**<.001**
PTT, s*	882 (37)	0.95 (0.79-1.15)	.627
Fibrinogen, mg/dL	861 (35)	1.00 (1.00-1.00)	.689
Hemoglobin, g/dL*	996 (37)	0.54 (0.10-2.83)	.464
Creatinine clearance, mL/min*	869 (36)	0.96 (0.86-1.07)	.495
ECOG performance status			
Poor (3-4)	56 (5)	2.76 (1.07-7.08)	**.035**
Good (0-2)	939 (32)	REF	
FAB classification			
M3v	125 (8)	2.28 (0.99-5.29)	.054
M3	592 (17)	REF	

Key Points

- High WBC is an independent predictor of early HD in APL.

blood®
2017 129: 1744-1745
doi:10.1182/blood-2017-01-761619

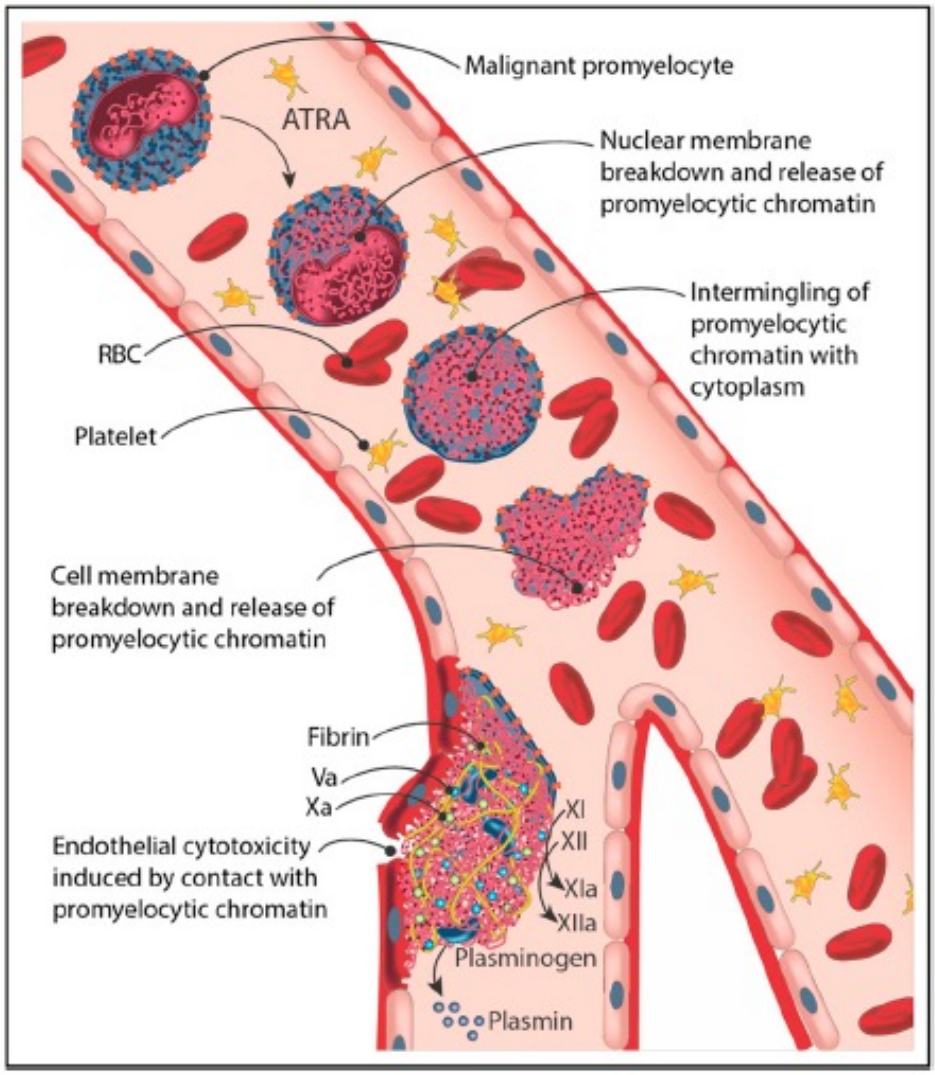
APL: Oh! What a tangled web we weave

Vikram Mathews

ATRA promotes ***ETosis*** leading to procoagulant promyelocytic extracellular chromatin.

Extracellular chromatin fosters excess thrombin production and fibrin deposition, increases plasmin and causes endothelium damage.

Blood 2017 Mar 30;129(13):1855-1864



ALL-*TRANS* RETINOIC ACID (ATRA) AND TRANEXAMIC ACID: A POTENTIALLY FATAL COMBINATION IN ACUTE PROMYELOCYTIC LEUKAEMIA

Table I. Relationship between treatment parameters and death.

Treatment	Number in group	Total number of deaths	Number of early deaths	Number of deaths assigned to thrombotic events
A + T	4	4	4	3
A + C	9	1	0	0
A + T + C	15	2	0	0
T + C	2	1	1	1
C	1	0	0	0
Total	31			4 (13%)

A, ATRA; T, tranexamic acid; C, chemotherapy.
Early deaths are defined as deaths on or before day 42.

Br J Haematol. 2000 Sep;110(4):1010-2.

Antifibrinolytic treatment

Patients with DIC should generally not be treated with antifibrinolytic agents **(low quality).**

DIC patients who present with severe bleeding, characterized by a *marked hyperfibrinolytic state* such as *leukemia* **(low quality)** or *trauma* **(moderate quality),** could be treated with antifibrinolytic agents.

J Thromb Haemost 2013; **11**: 761–7

Blood transfusion

Platelet transfusions

The transfusion of platelets is recommended in DIC patients with ***active bleeding and a platelet count of <50 x10^9/L*** or in those with a ***high risk of bleeding and a platelet count of <20 x 10^9/L*** **(low quality).**

J Thromb Haemost 2013; **11**: 761–7

Fresh frozen plasma (FFP)

The administration of FFP may be useful in patients with *active bleeding* with either prolonged PT/APTT (>1.5 times normal) or decreased fibrinogen (<1.5 g d/L).

It should be considered in *DIC patients requiring an invasive procedure* with similar laboratory abnormalities **(low quality).**

J Thromb Haemost 2013; **11**: 761–7

Coagulation factors

The administration of fibrinogen concentrate or cryoprecipitate may be recommended in *actively bleeding* patients *with persisting severe hypofibrinogenemia* (<1.5 g L1) despite FFP replacement **(low quality).**

Prothrombin complex concentrate (PCC) may be considered in actively bleeding patients if FFP transfusion is not possible.

J Thromb Haemost 2013; **11**: 761–7

Massive bleeding type

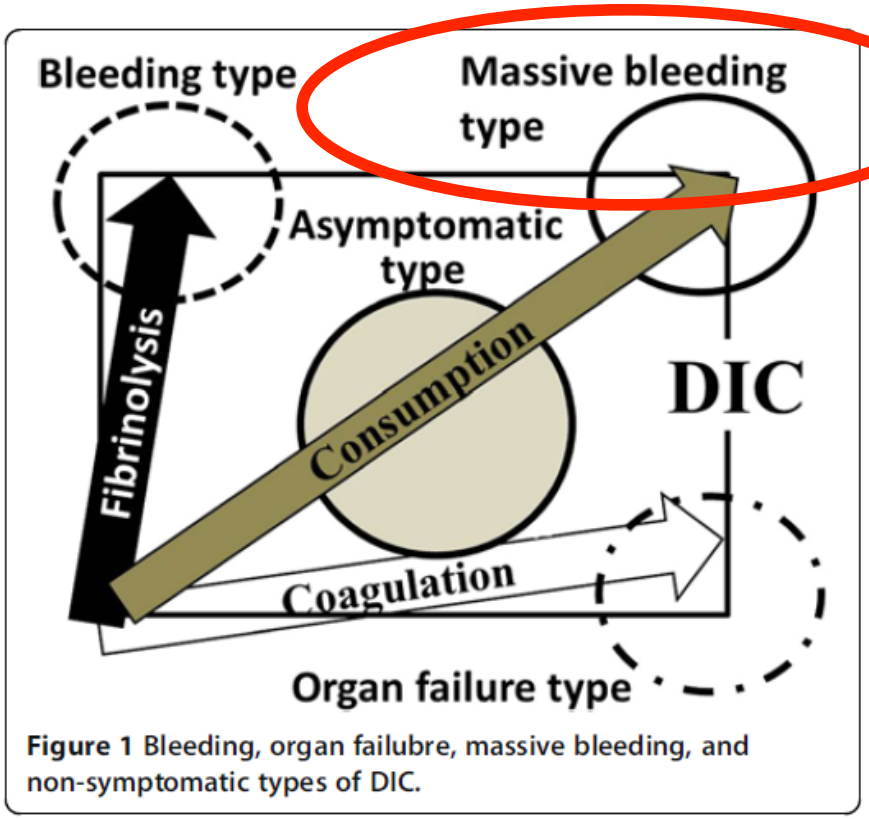


Figure 1 Bleeding, organ failubre, massive bleeding, and non-symptomatic types of DIC.

- **After major surgery**
- **Obstetric diseases**

Journal of Intensive Care 2014 2:15.

Guidelines and reccomendations: state of the art

	BCSH	JSTH	SISET	ISTH/SSC (evidence level and definitions for R)
Scoring system for DIC	R; grade C	R	R; grade C	R (moderate quality)
Single test analysis for DIC	NR	NR	NR; grade D	NR (moderate quality)
Treatment of underlying disease	R; grade C	R; consensus	R; cornerstone	R (moderate quality)
Platelet concentration	R; grade C	R; consensus	R; grade D	R (low quality)
FFP	R; grade C	R; consensus	R; grade D	R (low quality)
Fibrinogen, cryoprecipitate	R; grade C	NM	R; grade D	R (low quality)
Prothrombin complex concentrate	NM	NM	NM	NM
FVIIa	NR	NM	NR; grade D	NR (low quality)
UFH (treatment for thrombosis)	R; grade C	R; level C	NR; grade D	R (low quality)
UFH (prophylaxis for VTE)	R; grade A	NM	R; grade D?	R (moderate quality)
LMWH (treatment for thrombosis)	R; grade C	R; level B2	R; grade D	R; preferred to UFH (low quality)
LMWH (prophylaxis for VTE)	R: grade A	NM	R; grade D?	R (high quality)
Heparin sulfate	NM	R; level C	NM	NM
Synthetic protease	NM	R; level B2	NR; grade D	NM
rhAPC	R; grade A→D	NM	R; grade D	PR
Protein C concentrate	NM	NM	NR; grade D	NM
AT	NR; grade A	R; B1	NR; grade D	PR
rhTM	NM	NM	NR; grade B	PR
Antifibrinolytic agents	R; grade C	NR; level D	NM	R (low quality)
Plasma exchange	NM	NM	NR; grade D	NM

AT, antithrombin; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; LMWH, low molecular weight heparin; NM, not mentioned; NR, not recommended; PR, potentially recommended, needs further evidence; R, recommended; rhAPC, recombinant human activated protein C; rhTM, recombinant human thrombomodulin; UFH, unfractionated heparin; VTE, venous thromboembolism.

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