THROMBOTECT – a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents

Jeanette Greiner,[1] Martin Schrappe,[2] Alexander Claviez,[2] Martin Zimmermann,[3] Charlotte Niemeyer, [4]Reinhard Kolb,[5] Wolfgang Eberl,[6] Frank Berthold,[7] Eva Bergsträsser,[8] Astrid Gnekow,[9] Elisabeth Lassay,[10] Peter Vorwerk,[11] Melchior Lauten,[12] Axel Sauerbrey,[13] Johannes Rischewski,[14] Andreas Beilken,[3] Günter Henze,[15] Wolfgang Korte[16]* and Anja Möricke[2]* for the THROMBOTECT Study Investigators†

[1]Children's Hospital of Eastern Switzerland, Hematology and Oncology Department, St. Gallen, Switzerland; [2]Department of Pediatrics, Christian-Albrechts-University Kiel and University Medical Center Schleswig-Holstein, Kiel, Germany; [3]Department of Pediatric Hematology and Oncology, Hannover Medical School, Germany; [4]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Hematology and Oncology, Medical Center - Faculty of Medicine, University of Freiburg, Germany; [5]Department of Pediatrics, Zentrum für Kinder- und Jugendmedizin, Klinikum Oldenburg GmbH, Germany; [6]Institute for Clinical Transfusion Medicine and Children's Hospital, Klinikum Braunschweig GmbH, Germany; [7]Department of Pediatric Hematology and Oncology, Children's Hospital, University of Cologne, Germany; [8]Department of Pediatric Oncology, University Children's Hospital, Zurich, Switzerland; [9]Hospital for Children and Adolescents, Klinikum Augsburg, Germany; [10]Division of Pediatric Hematology, Oncology and Stem Cell Transplantation, Medical Faculty, RWTH Aachen University, Germany; [11]Pediatric Oncology, Otto von Guericke University Children's Hospital, Magdeburg, Germany; [12]University Hospital Schleswig-Holstein, Department of Pediatrics, University of Lübeck, Germany; [13]HELIOS Children's Hospital GmbH, Erfurt, Germany; [14]Department of Oncology/Hematology, Children's Hospital, Cantonal Hospital Lucerne, Switzerland; [15]Department of Pediatric Oncology/Hematology, Charité Universitätsmedizin Berlin, Germany and [16]Center for Laboratory Medicine and Hemostasis and Hemophilia Center, St. Gallen, Switzerland

**WK and AM share last authorship*

†A complete list of the THROMBOTECT study investigators is provided in the Online Supplementary Appendix

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Correspondence: *JEANETTE GREINER*

jeanette.greiner@kispisg.ch

Supplementary appendix to "THROMBOTECT – a randomized study comparing low molecular weight heparin, antithrombin and unfractionated heparin for thromboprophylaxis during induction therapy of acute lymphoblastic leukemia in children and adolescents"

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List of participating centers (principal investigator; number of patients enrolled)

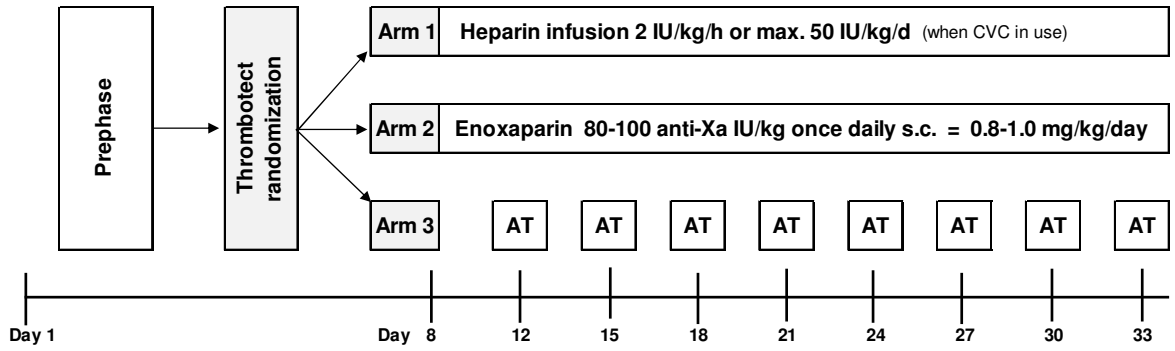
BFM Switzerland

- Luzern, Kantonsspital Luzern, Pädiatrische Klinik, Hämatologie/Onkologie (U. Caflisch, J. Rischewski; n=27)
- St. Gallen, Ostschweizer Kinderspital, Zentrum für Pädiatrische Hämatologie/Onkologie (J. Greiner; n=53)
- Zürich, Universitäts-Kinderklinik, Onkologie (F. Niggli, E. Bergsträsser, N. Bodmer; n=70)

BFM Germany

- Augsburg, I. Kinderklinik des Klinikum Augsburg, Hämatologie/Onkologie (A. Gnekow; n=69)
- Aachen, Kinderklinik der Medizinischen Fakultät der RWTH (R. Mertens, L. Lassay; n=40)
- Bad Mergentheim, Caritas Krankenhaus, Kinder- und Jugendmedizin (R. Buchhorn; n=1)
- Berlin, Charité Campus Virchow-Klinikum Berlin, Klinik für Pädiatrie mit Schwerpunkt Onkologie und Hämatologie (G. Henze, A. von Stackelberg; n=117)
- Braunschweig, Städtisches Klinikum, Klinik für Kinder- und Jugendmedizin (W. Eberl; n=26)
- Erfurt, Helios Klinikum Erfurt GmbH, Klinik für Kinder- und Jugendmedizin (A. Sauerbrey; n=30)
- Frankfurt /Main, Klinikum der Johann Wolfgang Goethe-Universität, Zentrum für Kinder- und Jugendmedizin, Klinik III, Pädiatrische Hämatologie und Onkologie (T. Klingebiel; n=29)
- Freiburg, Universitätsklinikum, Zentrum für Kinderheilkunde und Jugendmedizin, Klinik IV, Pädiatrische Hämatologie und Onkologie (C. Niemeyer; n=108)
- Hannover, Medizinische Hochschule Hannover, Kinderheilkunde IV, Klinik für Pädiatrische Hämatologie und Onkologie (K. W. Sykora, A. Beilken; n=84)
- Homburg/Saar, Universitätsklinik für Kinder- und Jugendmedizin, Pädiatrische Hämatologie und Onkologie (N. Graf, H. Reinhardt; n=24)
- Jena, Universitätsklinikum, Klinik für Kinder- und Jugendmedizin (B. Gruhn; n=1)
- Kassel, Klinikum Kassel, Klinik für Pädiatrische Onkologie/Hämatologie (M. Natrath, n=2)
- Kiel, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Klinik für Kinder- und Jugendmedizin, Pädiatrische Hämatologie und Onkologie (M. Schrappe, A. Claviez; n=70)
- Köln, Klinikum der Universität zu Köln, Kinderonkologie und –hämatologie (F. Berthold, D. Schwamborn; n=56)
- Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck, Klinik für Kinder- und Jugendmedizin, Pädiatrische Hämatologie und Onkologie (P. Bucsky, M. Lauten; n=22)
- Magdeburg, Universitätsklinikum Magdeburg, Kinderklinik, Pädiatrische Hämatologie/Onkologie (U. Mittler, P. Vorwerk; n=28)
- Marburg, Universitätskinderklinik (H. Christiansen; n=2)
- Nürnberg, Cnopf'sche Kinderklinik (W. Scheurlen; n=1)
- Oldenburg, Klinikum Oldenburg GmbH, Zentrum für Kinder- und Jugendmedizin, Allgemeine Kinderheilkunde, Hämatologie/Onkologie (R. Kolb; n=69)
- Siegen, DRK-Kinderklinik (R. Burghard; n=6)
- Ulm, Universitätsklinik für Kinder- und Jugendmedizin (K. M. Debatin, C. F. Classen; n=9))
- Vechta, St. Marienhospital Vechta, Klinik für Kinder- und Jugendmedizin (J. Erkel; n=3)
- Wolfsburg, Klinikum Wolfsburg, Klinik für Kinder- und Jugendmedizin (S. Mukodzi; n=2)

Figure S1. Treatment schedule of the THROMBOTECT study



Arm 1: Unfractionated heparin 2 IU/kg/h or max. 50 IU/kg/d, when CVC is in use

- For documentation purposes, measurement of anti-Xa activity (venous blood sample, not from CVC) if infusion duration exceeds 24 h between day 16 and day 33. No dose adjustment is necessary.

Arm 2: Low molecular weight heparin (Enoxaparin) 80-100 anti-Xa units once daily s.c.

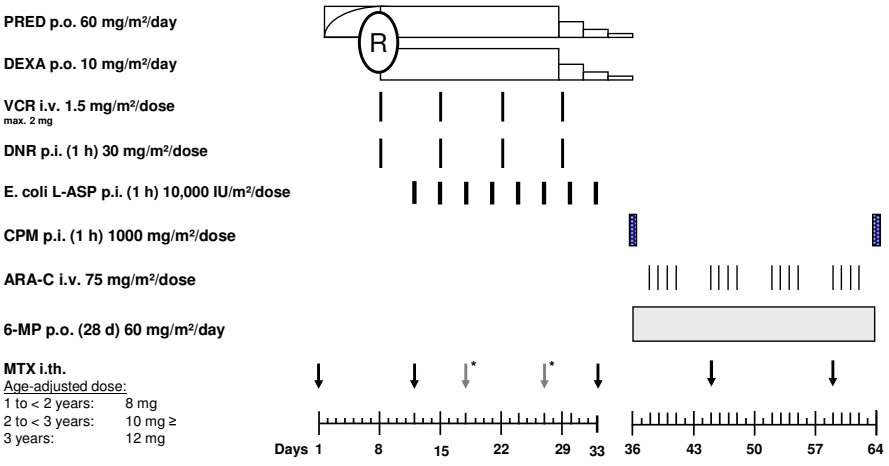
- Measurement of anti-Xa activity on day 12 if LP on day 15, or on day 15 if LP on day 12 (venous blood sample, not from CVC)
- Target value: anti-Xa activity ≤ 0.4 IU/ml [for deviations: dose adjustment of Enoxaparin and repeat measurement of anti-Xa activity after 3 days]
- no concomitant antithrombin replacement

Arm 3: Antithrombin (AT) replacement (Kybernin^{R}), if Antithrombin is < 80%

- Antithrombin measurement before each asparaginase dose (CVC may be used)
- Dosage according to the formula $AT_{nominal\ (100\%)} - AT_{actual} \times kg$
- Antithrombin can also be given on the same day, after the asparaginase

Figure S2. Treatment schedule of induction therapy in ALL-BFM 2000 and AIEOP-BFM ALL 2009

A. ALL-BFM 2000



*additional i.th. MTX on days 19 and 26 if CNS-positive (CNS 3) or presence of blasts in initial cytospin (CNS 2)

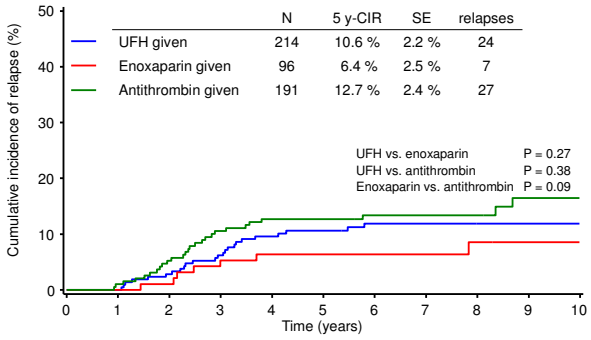
B. AIEOP-BFM ALL 2009

Induction and consolidation therapy (Protocol I) was the same as in ALL-BFM 2000 except for the following differences:

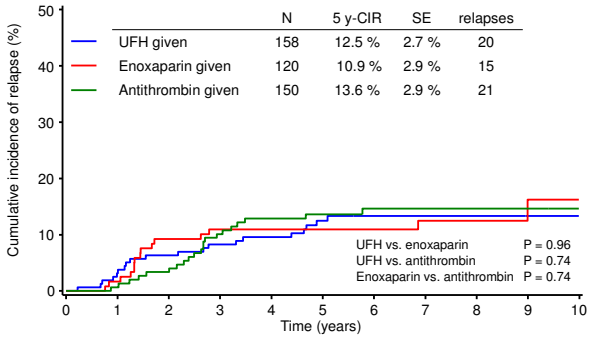
- Dexamethasone was given to good-risk T-ALL only; all other patients received Prednisone.
- Pegylated E. coli L-asparaginase given on day 12 and 26 instead of native E. coli L-asparaginase

Figure S3. Relapse incidence in specific patient subsets in analysed in randomized patients according to the treatment as given

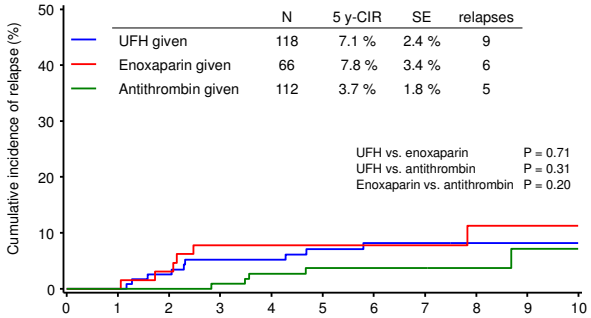
A Age < 6 years



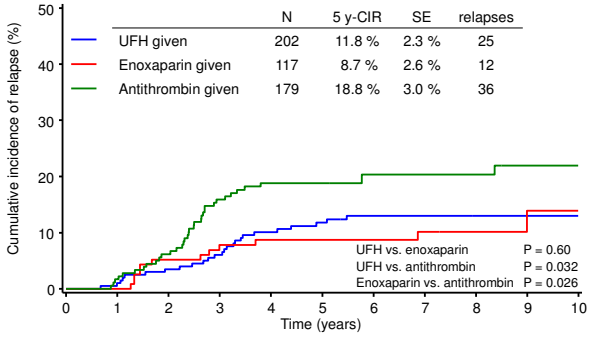
B Age ≥ 6 years



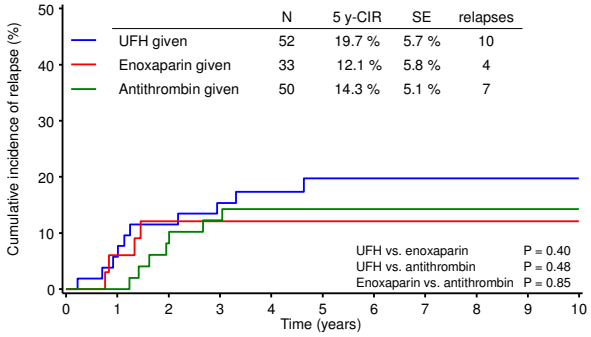
C Risk group SR (Standard Risk)



D Risk group MR (Medium Risk)



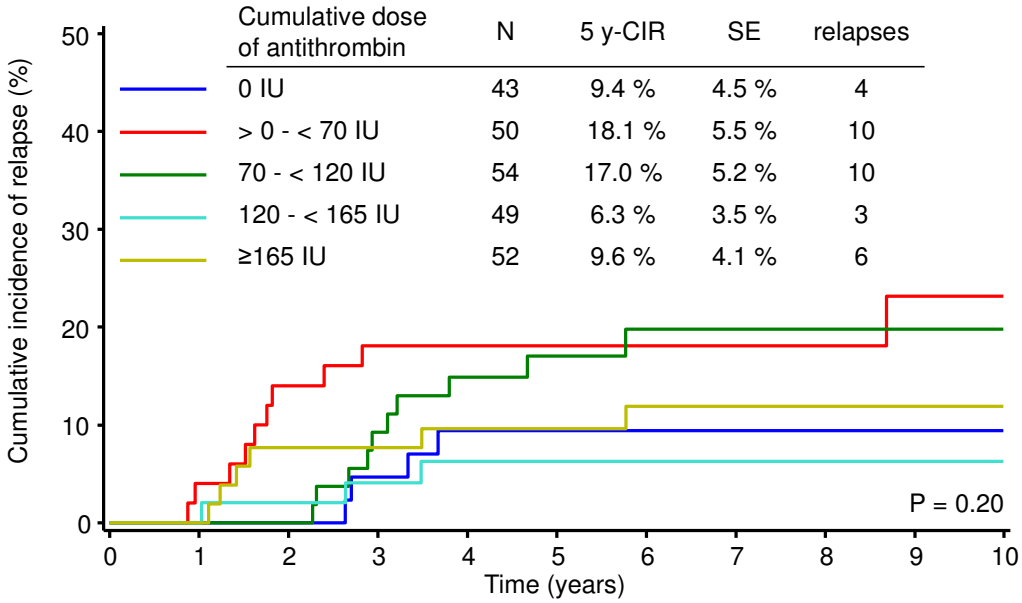
E Risk group HR (High Risk)



P values were calculated with the Gray's test.

Abbreviations: 5 y-CIR, 5-year cumulative incidence of relapse; SE, standard error; UFH, unfractionated heparin.

Figure S4. Relapse incidence of randomized patients treated in the antithrombin arm according to the cumulative antithrombin dose actually substituted per KG body weight



The P value was calculated with the Gray's test.

Abbreviations: 5 y-CIR, 5-year cumulative incidence of relapse; SE, standard error.

Table S1. Recommended diagnostic procedures for suspected thrombosis

Suspected diagnosis	Diagnostic procedures
Deep vein thrombosis	Conventional and/or pulse-wave ultrasound, and/or color Doppler ultrasound, if not conclusive ⇨ phlebography
Sinus vein thrombosis	(angio)magnetic resonance imaging
Atrial thrombosis	Echocardiography
Catheter occlusion	Imaging of the catheter tip using contrast medium (Note: identifies only thrombi at the tip of the central venous catheters (CVC), does **not** identify thrombi along the intravascular part of the catheter (sheath clot). If strong clinical suspicion of CVC-related thrombosis, perform phlebography)
Pulmonary embolism	(Ventilation) perfusion scintigraphy

Abbreviations: ALL, acute lymphoblastic leukemia

Table S2. Definition of major and minor haemorrhage [1-3]

Major hemorrhage	This category covers hemorrhages meeting one or more of the following criteria: • clinically evident • fatal • requiring erythrocyte replacement (10-20 ml/kg body weight) • hemorrhage located within the cranium/spine, or eye, or retroperitoneum (diagnosis using magnetic resonance imaging, computed tomography and/or ultrasound) • severe or life-threatening event resulting from the hemorrhage, therefore requiring intensive care
Minor hemorrhage	This category covers hemorrhages which, although clinically evident, do not meet the criteria for a major hemorrhage. Minor hemorrhages includes: • epistaxis (irrespective of platelet count) lasting more than 5 minutes, whether or not treatment is necessary • nonmechanical hematuria (i.e. not caused by urinary catheter, nephrolithiasis) • nonmechanical hemorrhages in the gastrointestinal tract (i.e. not caused by gastric tube, endoscopy, intubation) • hemorrhage of the skin and mucous membranes • subconjunctival hemorrhage • wound hematoma or minor bleeding from a new wound, as they do not satisfy the criteria for a major hemorrhage

Table S3. Patient characteristics of randomized versus eligible non-randomized patients

	randomized patients (N=949) N (%)	patients not randomized (N=577) N (%)	P (Fisher's exact)
Study			
ALL-BFM 2000	815 (85.9)	412 (71.4)	< 0.001
AIEOP-BFM ALL 2009	134 (14.1)	165 (28.6)	
Sex			
Male	537 (56.6)	335 (58.1)	0.59
Female	412 (43.4)	242 (41.9)	
Age			
1 – < 6 years	512 (54.0)	311 (53.9)	0.99
6 – < 10 years	188 (19.8)	113 (19.6)	
≥ 10 years	249 (26.2)	153 (26.5)	
WBC at diagnosis [x10^9/L]			
< 20	599 (63.1)	344 (63.4)	0.21
20 - < 100	249 (26.2)	151 (25.6)	
100 - < 200	53 (5.6)	41 (6.0)	
≥ 200	47 (5.0)	40 (5.0)	
No information	1 (0.1)	1 (0.2)	
CNS status			
CNS negative	872 (91.9)	519 (89.9)	0.88
CNS positive	30 (3.2)	19 (3.3)	
no information	47 (5.0)	39 (5.0)	
Immunophenotype			
Non-T-ALL	827 (87.1)	491 (85.1)	0.22
T-ALL	120 (12.6)	86 (14.9)	
no information	2 (0.2)	0 (0.0)	
Genetics			
t(12;21) / *TEL-AML1*			
negative	722 (76.1)	455 (78.9)	0.36
positive	199 (21.0)	110 (19.1)	
no information	28 (3.0)	12 (2.1)	
t(9;22) / *BCR-ABL*			
negative	924 (97.4)	559 (99.3)	0.63
positive	25 (2.6)	18 (0.7)	
no information	0 (0.0)	0 (0.0)	
t(4;11) / *MLL-AF4*			
negative	942 (99.3)	573 (99.3)	1.0
positive	7 (0.7)	4 (0.7)	
no information	0 (0.0)	0 (0.0)	
Peripheral blast count on day 8 (Prednisone Response)			
< 1x10^9/L (PGR)	880 (92.7)	500 (86.7)	< 0.001
≥ 1x10^9/L (PPR)	65 (6.8)	71 (12.3)	

	randomized patients (N=949) N (%)	patients not randomized (N=577) N (%)	P (Fisher's exact)
no information	4 (0.4)	6 (1.0)	
Risk group according to ALL-BFM 2000 criteria			
SR	301 (31.7)	178 (30.8)	0.003
MR	512 (54.0)	278 (48.2)	
HR	136 (14.3)	121 (21.0)	
MRD at end of induction			
negative	303 (31.9)	140 (24.3)	0.017
$< 5 \times 10^{-4}$	316 (33.3)	201 (34.8)	
$\geq 5 \times 10^{-3}$	184 (19.4)	126 (21.8)	
no information	146 (15.4)	110 (19.1)	
MRD at week 12			
Negative	579 (61.0)	278 (48.2)	0.013
$< 5 \times 10^{-4}$	146 (15.4)	98 (17.0)	
$\geq 5 \times 10^{-3}$	43 (4.5)	35 (6.1)	
no information	181 (19.1)	166 (28.8)	

Abbreviations: AT, antithrombin; CNS, central nervous system; HR, high risk, MR, medium risk; MRD, minimal residual disease; PGR, Prednisone Good-Response; PPR, Prednisone Poor-Response; SR, standard risk; WBC, white blood cell count.

Table S4. Patient characteristics by thromboprophylaxis group as treated

	total N (%)	UFH N (%)	E N (%)	AT N (%)	no treatm. N (%)
all	949	372	216	341	20
Study					
ALL-BFM 2000	815 (85.9)	321 (86.3)	188 (87.0)	290 (85.0)	16 (80.0)
AIEOP-BFM ALL 2009	134 (14.1)	51 (13.7)	28 (13.0)	51 (15.0)	4 (20.0)
Sex					
Male	537 (56.6)	202 (54.3)	136 (63.3)	189 (55.4)	10 (50.0)
Female	412 (43.4)	170 (45.7)	80 (37.0)	152 (44.6)	10 (50.0)
Age					
1 – < 6 years	512 (54.0)	214 (57.8)	96 (44.4)	191 (56.0)	11 (55.0)
6 – < 10 years	188 (19.8)	68 (18.3)	53 (24.5)	65 (19.1)	2 (10.0)
≥ 10 years	249 (26.2)	90 (24.2)	67 (31.0)	85 (24.9)	7 (35.0)
Central venous catheter					
CVC in site	896 (94.4)	355 (95.4)	200 (92.6)	327 (95.9)	14 (70.0)
No CVC	53 (5.6)	17 (4.6)	16 (7.4)	14 (4.1)	6 (30.0)
WBC at diagnosis [x10^9/L]					
< 20	599 (63.1)	247 (66.4)	135 (62.5)	205 (60.1)	12 (60.0)
20 - < 100	249 (26.2)	94 (25.3)	57 (26.4)	93 (27.3)	5 (25.0)
100 - < 200	53 (5.6)	16 (4.3)	10 (4.6)	24 (7.0)	3 (15.0)
≥ 200	47 (5.0)	15 (4.0)	13 (6.0)	19 (5.6)	0 (0.0)
CNS status					
CNS negative	872 (91.9)	337 (90.6)	203 (94.0)	315 (92.4)	17 (85.0)
CNS positive	30 (3.2)	14 (3.8)	5 (2.3)	10 (2.9)	1 (5.0)
no information	47 (5.0)	21 (5.6)	8 (3.7)	16 (4.7)	2 (10.0)
Immunophenotype					
Non-T-ALL	827 (87.1)	321 (86.3)	189 (87.5)	301 (88.3)	16 (80.0)
T-ALL	120 (12.6)	49 (13.2)	27 (12.5)	40 (11.7)	4 (20.0)
no information	2 (0.2)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Genetics					
t(12;21) / *TEL-AML1*					
negative	722 (76.1)	279 (75.0)	170 (78.7)	258 (75.7)	15 (75.0)
positive	199 (21.0)	78 (21.0)	40 (18.5)	76 (22.3)	5 (25.0)
no information	28 (3.0)	0 (0.0)	15 (4.0)	6 (2.8)	7 (2.1)
t(9;22) / *BCR-ABL*					
negative	924 (97.4)	361 (97.0)	210 (97.2)	333 (97.7)	20 (100.0)
positive	25 (2.6)	11 (3.0)	6 (2.8)	8 (2.3)	0 (0.0)
no information	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
t(4;11) / *MLL-AF4*					
negative	942 (99.3)	370 (99.5)	215 (99.5)	338 (99.1)	19 (95.0)
positive	7 (0.7)	2 (0.5)	1 (0.5)	3 (0.9)	1 (5.0)
no information	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral blast count on day 8 (Prednisone Response)					
< 1x10^9/L (PGR)	880 (92.7)	349 (93.8)	198 (91.7)	314 (92.1)	19 (95.0)
≥ 1x10^9/L (PPR)	65 (6.8)	21 (5.6)	18 (8.3)	25 (7.3)	1 (5.0)
no information	4 (0.4)	2 (0.5)	0 (0.0)	2 (0.6)	0 (0.0)
Risk group					
SR	301 (31.7)	118 (31.7)	66 (30.6)	112 (32.8)	5 (25.0)
MR	512 (54.0)	202 (54.3)	117 (54.2)	180 (52.8)	13 (65.0)
HR	136 (14.3)	52 (14.0)	33 (15.3)	49 (14.4)	2 (10.0)
MRD at end of induction					
negative	303 (31.9)	127 (34.1)	66 (30.6)	103 (30.2)	7 (35.0)
< 5 x 10^{-4}	316 (33.3)	126 (33.9)	81 (37.5)	103 (30.2)	6 (30.0)
≥ 5 x 10^{-3}	184 (19.4)	67 (18.0)	41 (19.0)	72 (21.2)	4(20.0)
no information	146 (15.4)	52 (14.0)	28 (13.0)	63 (18.5)	3 (15.0)

	total N (%)	**UFH N (%)**	**E N (%)**	**AT N (%)**	**no treatm. N (%)**
MRD at week 12					
Negative	579 (61.0)	228 (61.3)	136 (63.0)	206 (59.5)	12 (60.0)
$< 5 \times 10^{-4}$	146 (15.4)	61 (16.4)	35 (16.2)	48 (14.1)	2 (10.0)
$\geq 5 \times 10^{-3}$	43 (4.5)	18 (4.8)	9 (4.2)	16 (4.7)	0 (0.0)
no information	181 (19.1)	65 (17.5)	36 (16.7)	74 (21.7)	0 (0.0)
Randomized in induction in AIEOP-BFM ALL 2000*					
Randomized					
assigned to PDN	125 (13.2)	54 (14.5)	22 (10.2)	47 (13.8)	2 (10.0)
assigned to DXM	136 (14.3)	58 (15.6)	31 (14.4)	44 (12.9)	3 (15.0)
Not randomized	688 (72.5)	260 (69.9)	163 (75.5)	250 (73.3)	15 (75.0)

*For details see Fig S2 in the Supplementary Appendix and Reference Möricke, Blood (2016).[19]

Abbreviations: AT, antithrombin; CNS, central nervous system; CVC, central venous catheter; DXM, dexamethasone; E, enoxaparin; HR, high risk, MR, medium risk; MRD, minimal residual disease; PDN, prednisone; PGR, Prednisone Good-Response; PPR, Prednisone Poor-Response; SR, standard risk; UFH, unfractionated heparin; WBC, white blood cell count.

Table S5. Randomly assigned versus given treatment with respect to age groups

		Arm as treated			
	All patients N (%)	UFH N (%)	Enoxaparin N (%)	Antithrombin N (%)	No treatment N (%)
Age < 6 years					
All patients	512 (100.0)	214 (41.8)	96 (18.8)	191 (37.3)	11 (2.1)
Arm as assigned					
UFH	174 (100.0)	169 (97.1)	0 (0.0)	2 (1.1)	3 (1.7)
Enoxaparin	157 (100.0)	43 (27.4)	95 (60.5)	14 (8.9)	5 (3.2)
Antithrombin	181 (100.0)	2 (1.1)	1 (0.6)	175 (96.7)	3 (2.1)
Age ≥ 6 years					
All patients	437 (100.0)	158 (36.2)	120 (27.5)	150 (34.3)	9 (2.1)
Arm as assigned					
UFH	138 (100.0)	133 (96.4)	3 (2.2)	0 (0.0)	2 (1.4)
Enoxaparin	160 (100.0)	23 (14.4)	117 (73.1)	16 (10.0)	4 (2.5)
Antithrombin	139 (100.0)	2 (1.4)	0 (0.0)	134 (96.4)	3 (2.2)

Abbreviations: UFH, unfractionated heparin

Table S6. Multivariate Cox regression analyses on leukemia-related event-free survival in the randomization groups by intention to treat and as treated

	THROMBOTECT arms by intention to treat				THROMBOTECT arms as treated			
	N (%)	**Hazard ratio**	**95% CI**	***P***	**N (%)**	**Hazard ratio**	**95% CI**	***P***
Risk group								
SR	293 (31.9)	0.44	0.28-0.71	0.001	288 (32.0)	0.43	0.27-0.70	0.001
MR	496 (53.9)	1			483 (53.7)	1		
HR	131 (14.2)	1.62	1.10-2.40	0.015	129 (14.3)	1.54	1.03-2.30	0.034
TEL-AML1								
negative	721 (78.4)	1			706 (78.4)	1		
positive	199 (21.6)	0.54	0.32-0.93	0.026	194 (21.6)	0.57	0.34-0.99	0.044
WBC (x10^9/L)								
< 50	718 (78.0)	1			702 (78.0)	1		
≥ 50	202 (22.0)	1.30	0.91-1.86	0.146	198 (22.0)	1.38	0.96-1.97	0.082
Age								
< 6 years	495 (53.8)	1			484 (53.8)	1		
6 - < 10 years	183 (19.9)	0.80	0.50-1.28	0.351	181 (20.1)	0.85	0.53-1.36	0.500
≥ 10 years	242 (26.3)	1.31	0.91-1.89	0.147	235 (26.1)	1.36	0.93-1.98	0.110
THROMBOTECT arm								
UFH/enoxaparin	607 (66.0)	1			566 (62.9)	1		
antithrombin	313 (34.0)	1.38	0.99-1.91	0.054	334 (37.1)	1.19	0.86-1.66	0.296

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