Prospective studies in ET in the last 10 years – where are we now?

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Conflict of interest

- SHIRE
- NOVARTIS
- AMGEN
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- GLAXOSMITHKLINE

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Prospective, randomized Phase III studies in ET

Author/Trial	Design of trial	Setting & diagnostic criteria	No. of Patients & Follow-up
Cortelazzo *et al* 1995 Bergamo study	HU *vs* no treatment	High risk ET PVSG criteria	n = 114 27 months (median)
Harrison *et al* 2005 MRC-PT1 trial	HU + ASS *vs* ANA + ASS	High risk ET PVSG criteria	n = 809 2400 patient-years
Gisslinger *et al* 2013 Anahydret Study Group	HU *vs* ANA Non-inferiority	High risk ET WHO criteria prevoiusly untreated	n = 259 730 patient-years

HU: hydroxyurea, ANA: anagrelide, ASS: acetylsalicylic acid,
PVSG: Polycythaemia Vera Study Group, WHO: World Health Organisation

Cortelazzo S *et al, N EngJ Med*. 1995;332:1132-6, Harrison C *et al, N EngJ Med*. 2005;353:33-45,
Gisslinger H *et al, Blood*. 2013;121:1720-1728.

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Prospective, randomized Phase III studies in ET

Author/Trial	Design of trial	Definition of high risk	Different definition of events
Cortelazzo *et al* 1995 Bergamo study	HU *vs* no treatment	Age > 60 years Previous Thrombosis	TIA -> major arterial event, Superficial thrombophlebitis -> major venous event
Harrison *et al* 2005 MRC-PT1 trial	HU + ASS *vs* ANA + ASS	Age > 60 years Prevoius Thrombosis or Bleeding Plts > 1000 G/l Hypertension or Diabetes on therapy	TIA and unstable angina -> major arterial event
Gisslinger *et al* 2013 Anahydret Study Group	HU *vs* ANA Non-inferiority	Age ≥ 60 years Prevoius Thrombosis or Bleeding Plts ≥ 1000 G/l, ↑ Plts of ≥ 300 in 3 months Hypertension Diabetes	TIA , A. pectoris, unstable angina -> minor arterial event Superficial thrombophlebitis -> minor venous event

HU: hydroxyurea, ANA: anagrelide, ASS: acetylsalicylic acid, plts: platelets

Cortelazzo S *et al, N EngJ Med*. 1995;332:1132-6, Harrison C *et al, N EngJ Med*. 2005;353:33-45, Gisslinger H *et al, Blood*. 2013;121:1720-1728.

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Prospective, randomized Phase III studies in ET

- Different definition of events -

Minor events (total)	ANA	HU	P value
	No. of events	No. of events	0.18
	45	38	
Minor arterial thrombosis	24	20	0.36
Microcirculatory disturbances (dysesthesia, tingling paresthesia)	9	11	
Other minor arterial eventes	-	-	
TIA, balance disorders, dizziness	7	2	
Scotoma	-	2	
Angina pectoris	3	2	
Erythromelalgia	3	1	
Myocardial ischemia	-	1	
Raynaud	2	1	
Minor venous thrombosis	3	3	0.93
Thrombophlebitis	3	3	
Minor bleeding events	18	15	0.44
Epistaxis	7	9	
Hypermenorrhea	2	-	
Hematoma	1	2	
Bleeding (uterine, nose, skin, anal fissures, gingiva)	6	3	
Other (echymosis, petechiae, blood-staine expectoration)	2	1	

Number of Patients Reaching Principal Study End Points*

Feature	Hydroxyurea plus Aspirin (N = 404)	Anagrelide plus Aspirin (N = 405)	Odds Ratio (95% CI)	P value
	No. of patients			
Primary end point				
Arterial or venous thrombosis, serious hemorrhage, or death from thrombosis or hemorrhage	36	55	1.57 (1.04-2.37)	0.03
Secondary end point				
Arterial thrombosis	17	37	2.16 (1.27-3.69)	0.004
Myocardial infarction	7	13	1.84 (0.76-4.41)	NS
Unstable angina	2	4	1.94 (0.39-9.63)	NS
Stroke	7	9	1.30 (0.49-3.47)	NS
Tansient Ischemic attack	1	14	5.72 (2.08-15.73)	<0.001
Other†	2	0		NE
Venous thromboembolism	14	3	0.27 (0.11-0.71)	0.006
Deep-vein thrombosis	9	1	0.20 (0.06-0.71)	0.009
Pulmonary embolism	5	2	0.43 (0.01-1.87)	NS
Hepatic-vein thrombosis	1	0		NE

* CI denotes confidence interval, NS not significant and NE not able to be evaluated (since one group had no events)

† P values were obtained with the use of log-rank analysis

ANAHYDRET Study

Adapted from Gisslinger H *et al, Blood*. 2013;121:1720-1728

MRC-PT1 trial

Adapted from Harrison C *et al, N EngJ Med.* 2005;353:33-45

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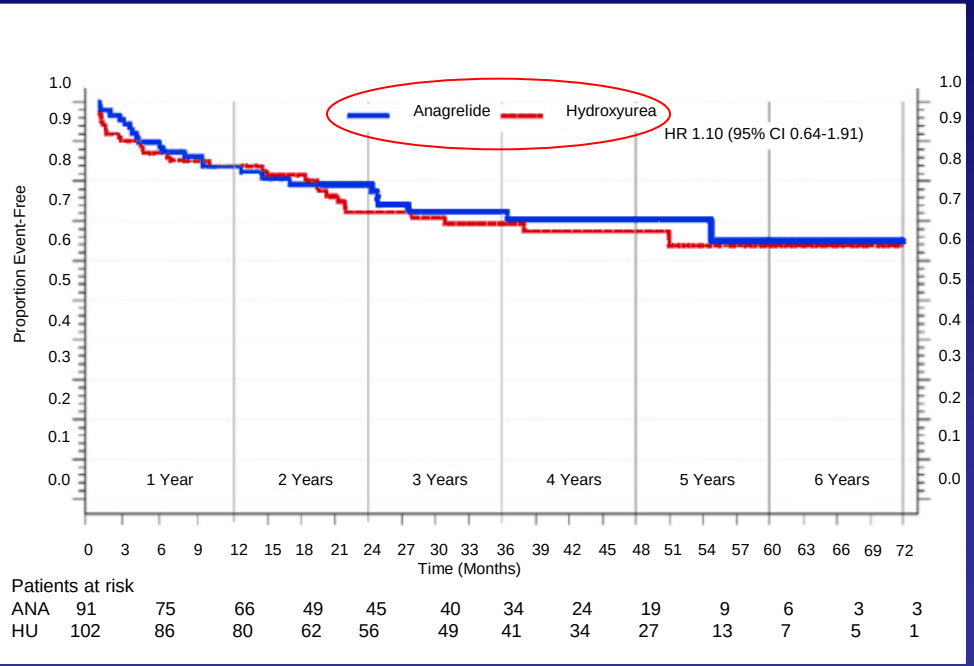
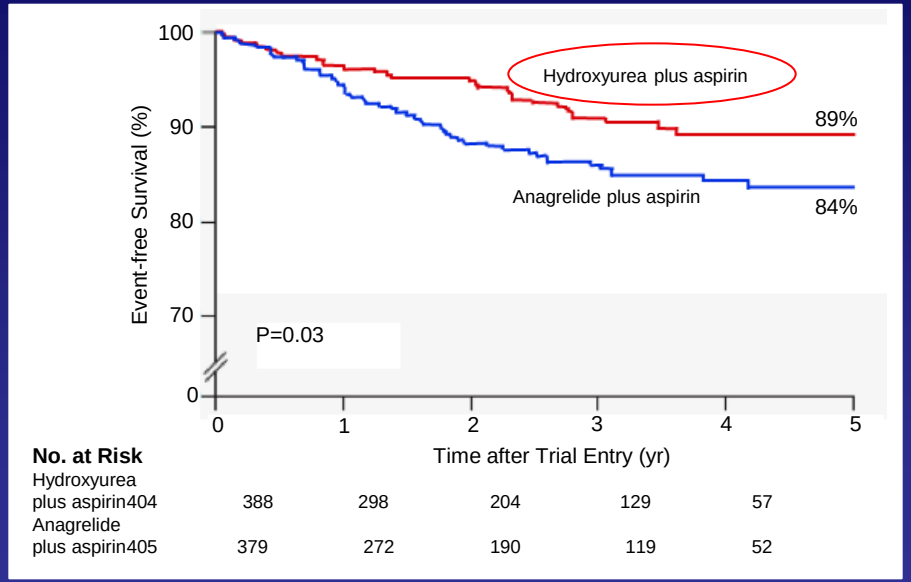
Prospective, randomized Phase III studies in ET

- RESULTS of event-free survival in ANAHYDRET versus MRC-PT1 trial -





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MRC-PT1 trial

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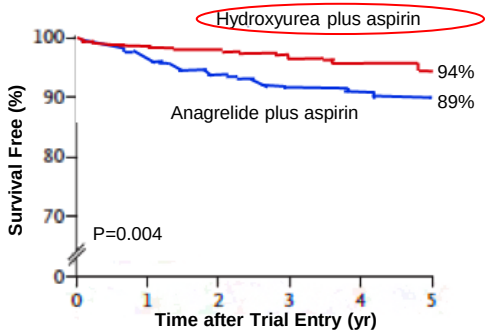
Prospective, randomized Phase III studies in ET

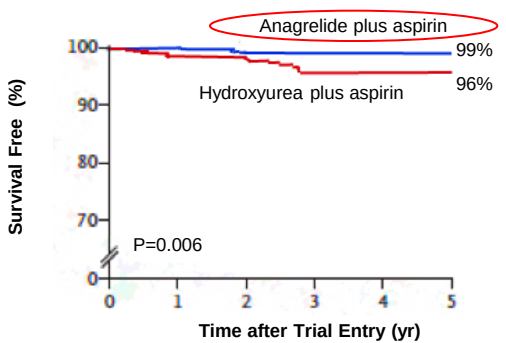
- MRC-PT1 trial: Arterial and venous thrombosis, serious hemorrhage and myelofibrotic transformation -

Arterial Thrombosis



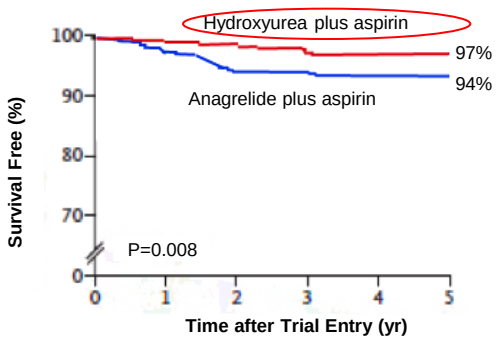
No. at Risk						
Hydroxyurea plus aspirin	404	393	305	214	137	58
Anagrelide plus aspirin	405	385	284	199	127	53

Venous Thrombosis



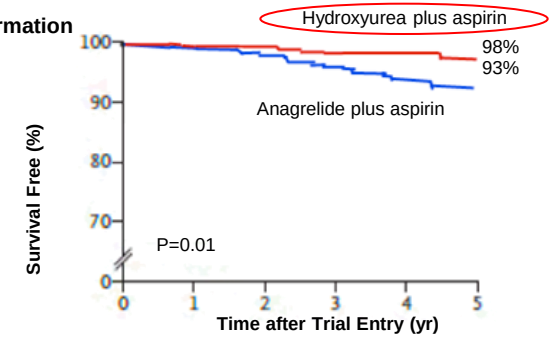
No. at Risk						
Hydroxyurea plus aspirin	404	394	304	207	130	57
Anagrelide plus aspirin	405	399	297	216	135	54

Serious Hemorrhage



No. at Risk						
Hydroxyurea plus aspirin	404	397	307	214	135	58
Anagrelide plus aspirin	405	391	286	206	126	53

Myelofibrotic Transformation



No. at Risk						
Hydroxyurea plus aspirin	404	397	308	213	136	58
Anagrelide plus aspirin	405	398	293	211	127	50

MRC-PT1 trial

Adapted from Harrison C *et al, N EngJ Med.* 2005;353:33-45

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Prospective, randomized Phase III studies in ET

- ANAHYDRET trial: Arterial and venous thrombosis, serious hemorrhage and myelofibrotic transformation -

	Anagrelide group (n=122)	Hydroxyurea group (n=131)	*P* value
Major events (total)	No. of events	No. of events	.86
	14	16	
Major arterial thrombosis	7	8	0.90
Claudication	1	-	
Myocardial infarction	3	2	
Peripheral arterial disease	-	2	
Coronary arterial disease (bypass surgery)	1	-	
Obstruction of subclavian artery	-	1	
Cerebrovascular event/stroke	2	2	
Carotid artery stenosis	-	1	
Major venous thrombosis	2	6	0.18
Thrombosis of mesenteric venocaval shunt	1	-	
Thrombosis of V. ileofemoralis	1	4	
Pulmonary embolism	-	1	
Lower limb thrombosis	-	1	

	Anagrelide (n=122)	Hydroxyurea (n=131)	*P* value
	No. of events	No. of events	
Severe Bleeding events	5	2	0.21
Rectal bleeding	1	-	
Bleeding into gluteal muscle	1	-	
Severe hypermenorrhea	1	-	
Bleeding of esophageal varices	-	1	
Metrorrhagia	-	1	
Severe bleeding after cyst puncture	1	-	
Other major bleeding events	1	-	

Disease transformation into myelofibrosis or secondary leukemia was not reported

ANAHYDRET Study

Adapted from Gisslinger H *et al, Blood*. 2013;121:1720-1728

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ANAHYDRET- Study vs. PT1 Study - major differences -

	ANAHYDRET-Study	PT1-Trial
Treatment	Anagrelide *vs.* Hydroxyurea	Anagrelide +Aspirin *vs.* Hydroxyurea +Aspirin
Patients	Newly diagnosed	Inclusion of pretreated patients allowed
Diagnosis	WHO-classification	PVSG criteria

Harrison C *et al, N EngJ Med*. 2005;353:33-45, Gisslinger H *et al, Blood*. 2013;121:1720-1728.