Prophylaxis of catheter-related deep vein thrombosis in cancer patients with low-dose warfarin, low molecular weight heparin, or control: a randomized, controlled, phase III study.

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DISCLOSURE SLIDE

The authors declare no Conflict of Interest that may be inherent in their work

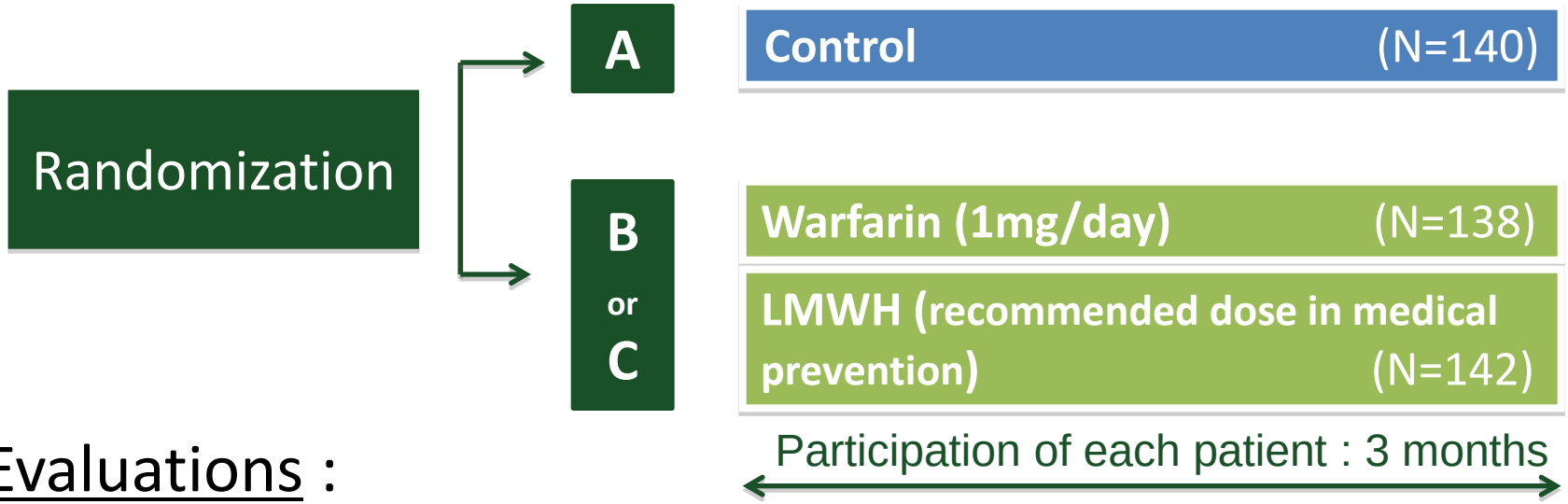
BACKGROUND

- Catheter-related deep vein thrombosis (CRDVT) are known to be an important risk factor of morbidity and mortality in cancer patients
- The incidence ranges from 0.3% to 28.3% in symptomatic patients and from 27% to 66% when asymptomatic CRDVT are included
- Current guidelines of American and European Societies do not recommend prophylactic anticoagulant treatment for cancer outpatients BUT major studies focused on symptomatic CRDVT

ENDPOINTS

- Phase III, open-label, randomized prospective trial (1999-2009, started before guidelines)
- **Main objective** : rate of symptomatic **and** asymptomatic CRDVT of the ipsilateral upper limbs and cervical veins
  - with or without prophylaxis,
  - excluded intra-luminal thrombosis
- **Secondary objectives** :
  - Rate of symptomatic venous thromboembolic events in other venous territories (catheter-unrelated)
  - Feasibility of prophylaxis
  - Comparison between the 2 different anticoagulants in case of positive main objective

STUDY DESIGN



Evaluations :

- D_1 and D_{90} (or sooner in case of symptoms):
  - Systematic Doppler ultrasound (US) of the upper limbs and cervical veins
  - Venography by CVAD
- Clinical and Biological exams: each chemotherapy course (every 3 or 4 weeks)
- Weekly platelets control under LMWH, no other blood coagulation tests

INCLUSION CRITERIA

- Aged 18 years or older
- Life expectancy > 3 months
- Performance status < 3, ambulatory patients
- Solid tumour: locally advanced or metastatic status (excepted cerebral metastasis)
- Subcutaneous central venous catheter inserted for less than 7 days
- Starting a first line of chemotherapy
- No contra-indication to anticoagulation
- No formal indication for anticoagulation or anti-platelets agents in preventive or curative treatments
- No recent history of DVT in the past 6 months

STATISTICAL CONSIDERATIONS

Sample size

–Based an incidence of DVT of 40%* in absence of prophylaxis versus 20% in presence of prophylaxis during the 3-month period

–Allowing also a comparison between the 2 regimens of prophylaxis

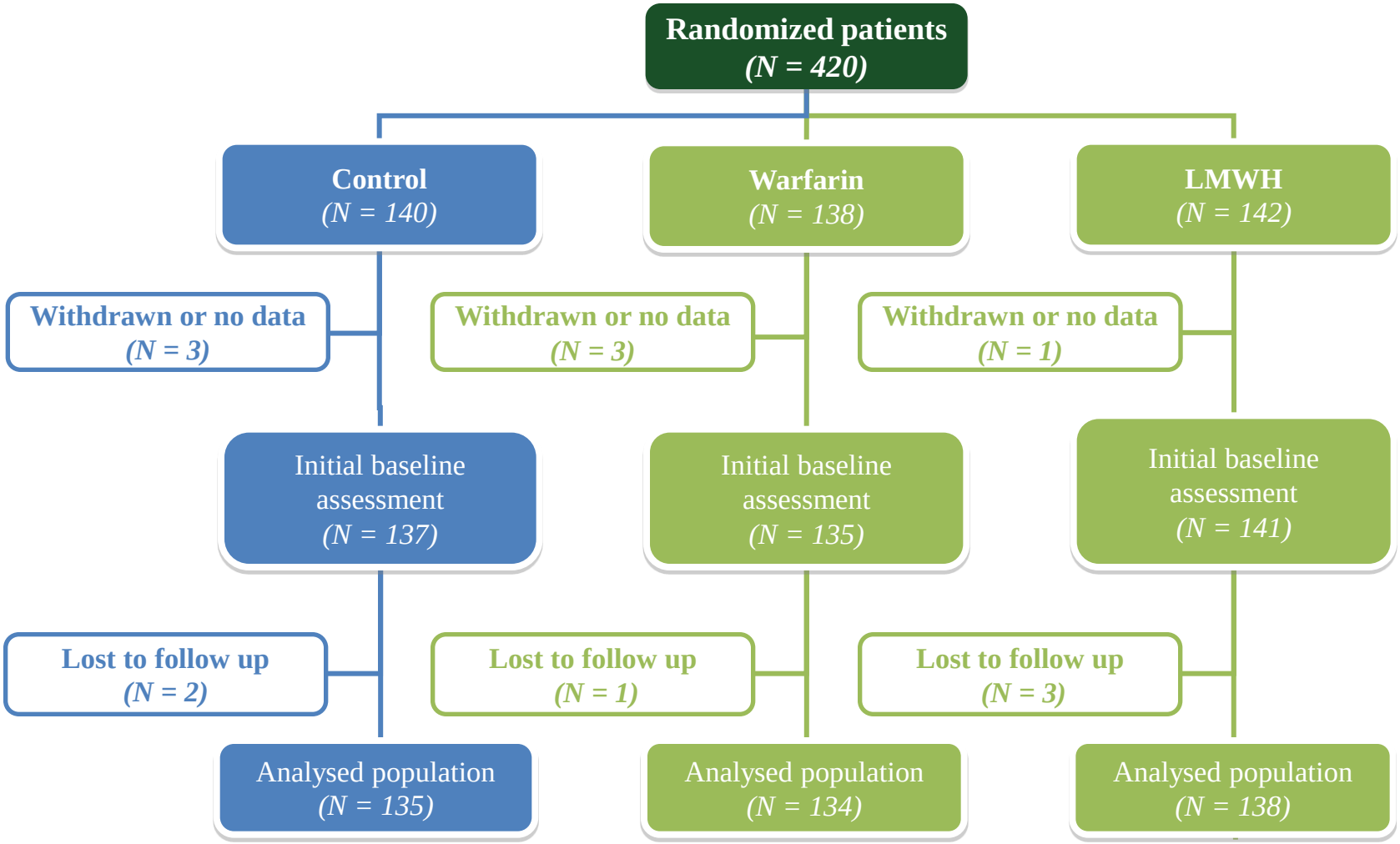
→**420 patients** (α=5%, β=10%)

Analysis

- Intention to treat
- Using consort guidelines
- Chi square tests

* *Monreal M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices-prophylaxis with low molecular weight heparin (Fragmin). Thromb Haemost 1996; 75:251-253.*

FLOWCHART



407 patients were evaluable

PATIENT CHARACTERISTICS

Characteristics		Control (N=135)	Warfarin (N=134)	LMWH (N=138)
Mean Age, years (range)		60 (21-85)	59 (24-81)	61 (21-84)
(SD)		(+/-11.8)	(+/-10.9)	(+/-10.6)
Male		84 (62 %)	81 (60 %)	78 (56 %)
Metastatic setting		42%	45%	51%
Locally advanced setting		28%	28%	28%
Resected metastatic or locally advanced disease		30%	27%	21%
Lower extremity of catheter higher than T5		7 (5.5%)	7 (5.5%)	8 (5.8%)
Hb < 10 g/dl		4 (3.0%)	8 (6.0%)	14 (10%)
Very high or high risk thrombogenic tumour		50 (37%)	40 (30%)	48 (35%)
	Pancreas	*6*	*8*	*6*
	Stomach	*14*	*7*	*14*
	Lung	*16*	*16*	*13*
	Pelvic gynaecological	*7*	*3*	*10*
	Testicle	*2*	*2*	*2*
	Bladder	*5*	*4*	*3*
Other		85	94	90
Platelets $\geq 350x10^9/L$		42 (31%)	53 (40%)	49 (35%)
BMI ≥ 35 (kg/m^2)		4 (3.0%)	2 (1.5%)	3 (2.0%)

RESULTS

	Control (N=135)	Anticoagulation (N=272)	*P-value*
CRDVT thrombosis *Symptomatic (N=12)* *Asymptomatic (N=30)*	**20 (14.8%)** *9 (6.7%)* *11 (8.1%)*	**22 (8.1%)** *3 (1.1%)* *19 (7.0%)*	**0.0357** **RR=0.55 , $IC_{0.95}$ (0.31-0.96)**
Mean delay, days (range)	45 (1-90)	54 (1-90)	NS
Unrelated DVT thrombosis *Symptomatic (N=8)* *Asymptomatic (N=1)*	**7 (5.1%)** *6 (4.4%)* *1 (0.7%)*	**2 (0.7%)** *2 (0.7%)* *0*	**0.007**
Symptomatic thrombosis / Both DVT thrombosis	**15/27 (55.6%)**	**5/24 (20.8%)**	**0.09**

→ 2 arterial thrombosis (myocardial infarction) in control arm

→ No difference between Warfarin and LMWH (*p*=0.2 for CRDVT, *p*=1 for unrelated DVT)

ADVERSE EVENTS

Adverse event (under chemotherapy)	Control (N=135)	Warfarin (N=134)	LMWH * (N=138)	p-value
Bleeding	1 (0.7%)	6 (4.5%)	3 (2.2%)	0.1361
Thrombocytopenia Grade 3-4 (NCI CTC v3.0)	12 (8.8%)	4 (3%)	7 (5.0%)	0.1039
Allergy	0	2 (1.5%)	0	0.1290

→ No treatment-related death

* *3 patients developed renal failure under chemotherapy*

DISCONTINUATION

	Control N=135	Warfarin N=134	LMWH N=138
% of discontinuation	34 (25%)	36 (27%)	45 (33%)
Mean delay of discontinuation (days)	37 (1-82)	36 (1-81)	38 (1-82)
Reasons :			
Concomitant event	15 (11.1%)	20 (15%)	20 (14.5%)
Thrombosis event	17 (12.5%)	3 (2.2%)	3 (2.2%)
Non compliance	2 (1.5%)	3 (2.2%)	9 (6.5%)
Protocol deviation	0	4 (3.0%)	8 (5.8%)
Toxicity	0	6 (4.5%)	5 (3.6%)

→ No difference between allocated arms

LIMITS

- Monocentric study
- Long-term inclusion
- Multiple chemotherapy protocols, no antiangiogenic drug
- Univariate analysis
- CRDVT rate less than scheduled initially

CONCLUSION

- Efficacy on symptomatic and asymptomatic CRVT of anticoagulation prophylaxis in ambulatory cancer patients with locally advanced or metastatic tumours
  - No difference between Warfarin and LMWH
  - No bleeding increase
- Burden of subcutaneous prophylaxis for patients

FUTURE

- Optimization of identification of high-risk hyper-clotting patients
- Testing of short-term prophylaxis
- Assessment of new oral anticoagulants