



UMC Utrecht

# Plasma fibrinogen level as a potential predictor of hemorrhagic complications after catheter-directed thrombolysis for peripheral arterial occlusions

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# Introduction

Outcomes after thrombolysis:<sup>1</sup>

- Limb salvage at 6 months: 72-93%
- Survival after 12 months: 80-94%

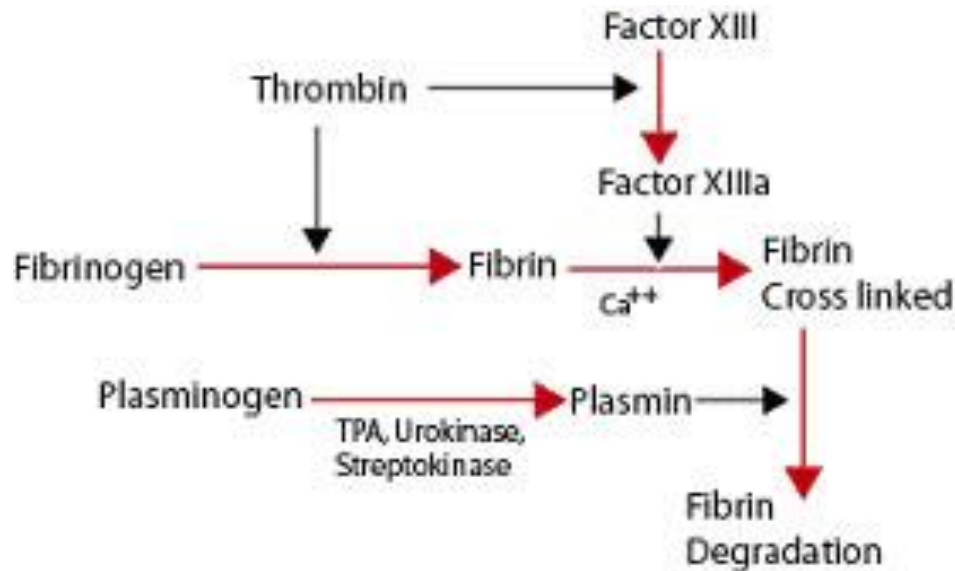
However, **8.8% risk of major hemorrhage within 30-days**

<sup>1</sup> Berridge, Cochrane Database Syst Rev, 2013



# Introduction

- Plasma fibrinogen level (PFL) predictor of hemorrhagic complications<sup>1</sup> ?
- Different thresholds for abortion: <100 mg/dL vs <150 mg/dL



<sup>1</sup> STILE-trial, Ann Surg, 1994



# Objective

Domain: Patients with (sub)acute arterial or arterial bypass occlusions

Determinant: PFL

Outcome: Hemorrhagic complications



# Methods

- Systematic search on PubMed and EMBASE
- January 1, 2017
- Two reviewers independently assessed titles / abstracts / full-texts
- No language restriction
- Authors' definition of outcome was used



# Methods – Inclusion Criteria

- Peer-reviewed journals, not restricted to any language
- Description of original treatment data of thrombolysis of occluded native artery or arterial bypass
- Adults
- Catheter-directed thrombolysis
- Acute (<14 days) or subacute (14 days – 3 months)
- ≥30 patients treated



# Methods - Outcomes

Outcome: hemorrhagic complications

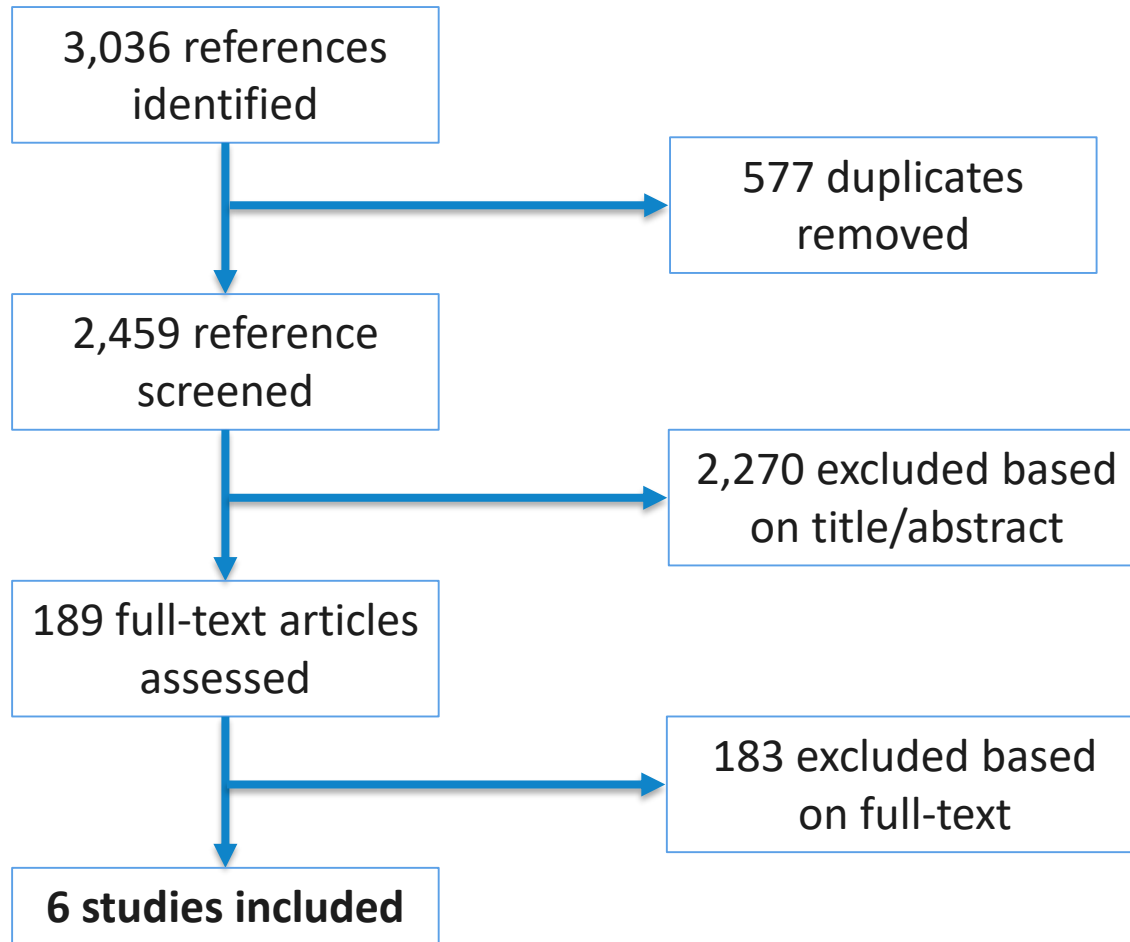
Determinant: absolute PFL or decrease in PFL

Determinant-outcome relation:

- Risk estimates (risk ratios or odds ratios)
- Associations



# Results - Flowchart





# Results – Included Studies

- 2 RCTs and 4 cohorts
- 613 patients underwent 623 procedures.
- Study size ranged from 35 – 228 patients
  
- Thrombolytic Agents
  - Recombinant t-PA (reteplase, tenecteplase, plasmin),
  - r-ProUK
  - UK.



# Results – Predictive Value

First author, year of publication	Type of PFL and moment of measurement
STILE, 1994	PFL at end of infusion
Ouriel, 1999	Threshold level of PFL <100mg/dL vs. ≥100mg/dL
	Threshold level of PFL <100mg/dL vs. ≥100mg/dL
Arepally, 2002	PFL nadir
	Absolute change in PFL
	Percentage change in PFL
Hull, 2004	Threshold level of PFL <100mg/dL
	PFL nadir
	Percentage change in PFL
Hull, 2006	Percentage change in PFL
Marder, 2012	PFL at end of infusion



# Results – Predictive Value

First author, year of publication	Type of PFL and moment of measurement	Type of hemorrhagic complication
STILE, 1994	PFL at end of infusion	Major hemorrhage
Ouriel, 1999	Threshold level of PFL <100mg/dL vs. ≥100mg/dL	Major bleeding
	Threshold level of PFL <100mg/dL vs. ≥100mg/dL	Any bleeding complication
Arepally, 2002	PFL nadir	Minor or major hemorrhage
	Absolute change in PFL	Minor or major hemorrhage
	Percentage change in PFL	Minor or major hemorrhage
Hull, 2004	Threshold level of PFL <100mg/dL	Major complications
	PFL nadir	Major complications
	Percentage change in PFL	Major complications
Hull, 2006	Percentage change in PFL	Major bleeding
Marder, 2012	PFL at end of infusion	Bleeding complications



# Results – Predictive Value

First author, year of publication	Type of PFL and moment of measurement	Type of hemorrhagic complication	Risk ratio or association
STILE, 1994	PFL at end of infusion	Major hemorrhage	Significant $P = 0.01$
Ouriel, 1999	Threshold level of PFL <100mg/dL vs. $\geq 100$ mg/dL	Major bleeding	<b>RR 0.33 (0.05-2.25)</b>
	Threshold level of PFL <100mg/dL vs. $\geq 100$ mg/dL	Any bleeding complication	<b>RR 1.39 (1.06-1.81)</b>
Arepally, 2002	PFL nadir	Minor or major hemorrhage	Not significant $P > 0.05$
	Absolute change in PFL	Minor or major hemorrhage	Not significant $P > 0.05$
	Percentage change in PFL	Minor or major hemorrhage	Not significant $P > 0.05$
Hull, 2004	Threshold level of PFL <100mg/dL	Major complications	Significant $P = 0.024$
	PFL nadir	Major complications	Significant $P = 0.000007$
	Percentage change in PFL	Major complications	Significant $P = 0.00003$
Hull, 2006	Percentage change in PFL	Major bleeding	Not significant: not quantified
Marder, 2012	PFL at end of infusion	Bleeding complications	Not significant $P = 1.0$



# Results - Risk of bias assessment

First author, year of publication	Study participation	Prognostic factor measurement	Outcome measurement	Other possible predictors	Statistical analysis and reporting
STILE, 1994	M	M	H	H	H
Ouriel, 1999	M	M	M	H	H
Arepally, 2002	L	L	M	H	H
Hull, 2004	M	H	M	H	H
Hull, 2006	M	L	M	H	H
Marder, 2012	L	L	M	H	H

- No study had as its aim to study predictive value of fibrinogen



# Discussion

- Laboratory monitoring during thrombolysis: *“Although monitoring of serum fibrinogen levels is thought by some to predict adverse bleeding, no pivotal study has validated this belief.”*<sup>1</sup>
- Proposed thresholds: <100 mg/dL<sup>2</sup> and <150 mg/dL<sup>3</sup>

<sup>1</sup> Patel, Quality improvement guidelines, J Vasc Interv Radiol, 2013

<sup>2</sup> Ouriel, PURPOSE, J Vasc Interv Radiol, 1999

<sup>3</sup> Skeik, Vasc Endovasc Surg, 2013



## Discussion – Limitations of literature

- Small case series, individually underpowered
- No adjustment for other predictors
- 80 (!) studies measuring fibrinogen were excluded because no association was provided
- Comparability of studies is hampered by the use of different agents, doses, duration of symptoms, type of occlusion, moment of measurement, definition of outcome



# Conclusion

- Predictive value of PFL in unproven





# Future directions

- Clinical prediction rules, using multiple predictors, to assist treatment decisions during thrombolysis are awaited



# Definition of hemorrhagic complication

- Major hemorrhage
  - Intracranial hemorrhage of any size
  - Hemorrhages that result in death
  - Hemorrhage of sufficient magnitude that it leads to (i) extended or unexpected hospitalization, (ii) surgery to arrest the hemorrhage, or (iii) the need for blood transfusion of two or more units.

