Anticoagulation in Thrombocytopenic Patients with Hematological Malignancy

A Multi-center, Multinational Decision Making Analysis

Leader A, ten Cate V, ten Cate-Hoek A, Beckers E, Spectre G, Raanani P, Schouten H, Falanga A, ten Cate H

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Maastricht UMC+
Maastricht University
RABIN MEDICAL CENTER
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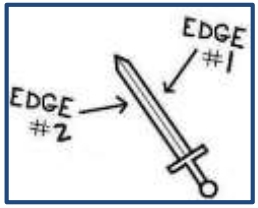
Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

Speaker Disclosure

Nothing to declare

Anticoagulation in thrombocytopenic cancer patients



1. **Not uncommon**[1]

2. **Limited data** on management from retrospective VTE cohorts (n = 47-204)[2-7]
   - Optimal approach not known
   - **Management** practice is **highly variable**
     - » AC was held in 19% to 69%[2-7]

3. VTE guidelines use **VTE acuity and platelet count** to direct management[8-10]

4. No data on AC in atrial fibrillation and thrombocytopenia

[1]Vinholt, Platelets, 2016; [2]Khanal N, Am J Hem, 2016; [3]Kopolovic, Ann Hem 2015; [4]Houghton, Leuk Lymph 2017; [5]Li, Blood Adv 2017; [6]Mantha, J Thr Thrombolysis 2017; [7]Samuelson-Bannow, J Thr Thrombolysis 2017; [8]Carrier, JTH 2013; [9]Easaw, Curr Oncol 2015; [10]NCCN, 1.2017

Understanding factors behind physicians' choice of management

- **Important to identify** these factors:
  - Confounders in analyses assessing management strategies
  - Congruent with guidelines?
  - Can generate hypotheses regarding management
- **Inconsistent associations** between patient variables and management [1-4]
- **Descriptive survey data** on factors affecting management[5,6]
  - Differences between 2 surveys
  - Non-analytical data on single variables

[1]Kopolovic, Ann Hem 2015; [2]Houghton, Leuk Lymph 2017; [3]Li, Blood Adv 2017; [4]Mantha, J Thr Thrombolysis 2017; [5]Samuelson, Thromb Res 2016; [6]Chayaler, Transfusion 2014;

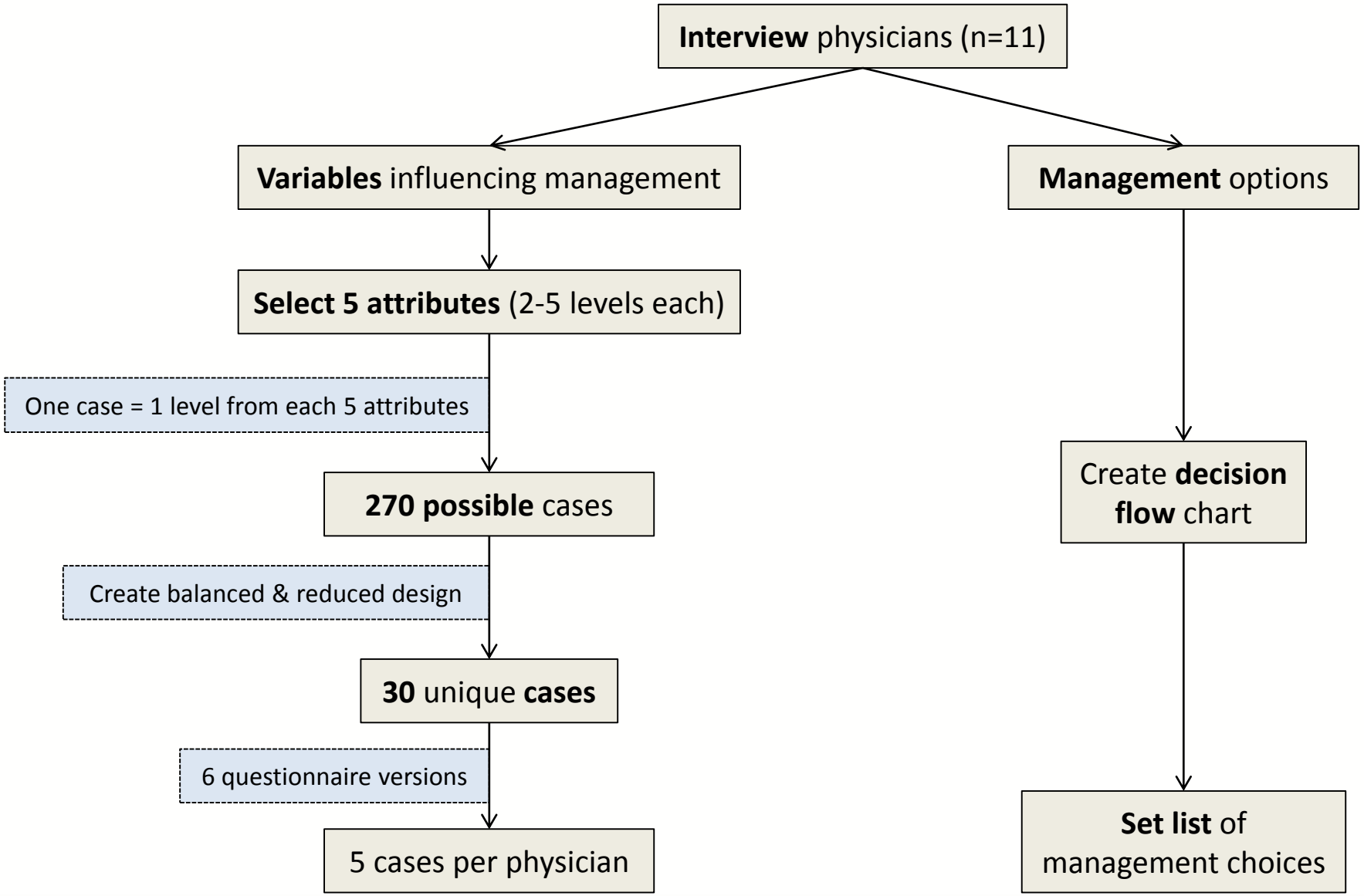
AC in thrombocytopenia: **Knowledge gaps and objectives**

- **No analytical data** on factors influencing management

1) **Identify patient/physician characteristics** associated with AC management
   - in thrombocytopenic patients with hematological malignancy

2) Evaluate whether **physician-assessed bleeding/thrombotic** risk is associated with AC management

Methods (A): **Identify attributes and levels**

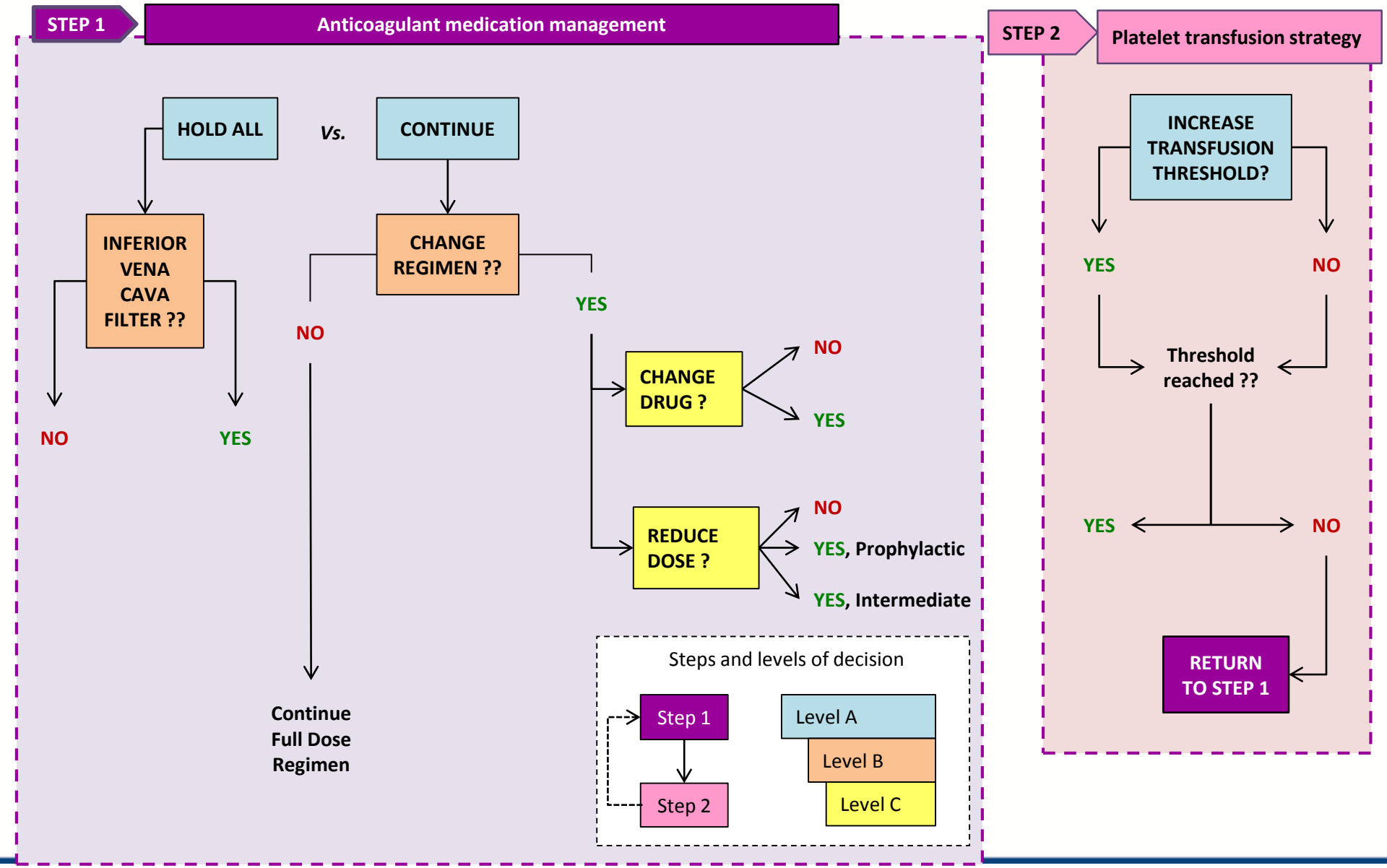


Multinational, multicenter clinical vignette-based choice experiment

Selected attributes and levels

Attribute
Hematological malignancy and treatment
Depth of Thrombocytopenia
Indication and type of antithrombotic regimen
Time since the AC indication-defining event
Major GI bleeding from an unidentified source

Flow of possible management decisions



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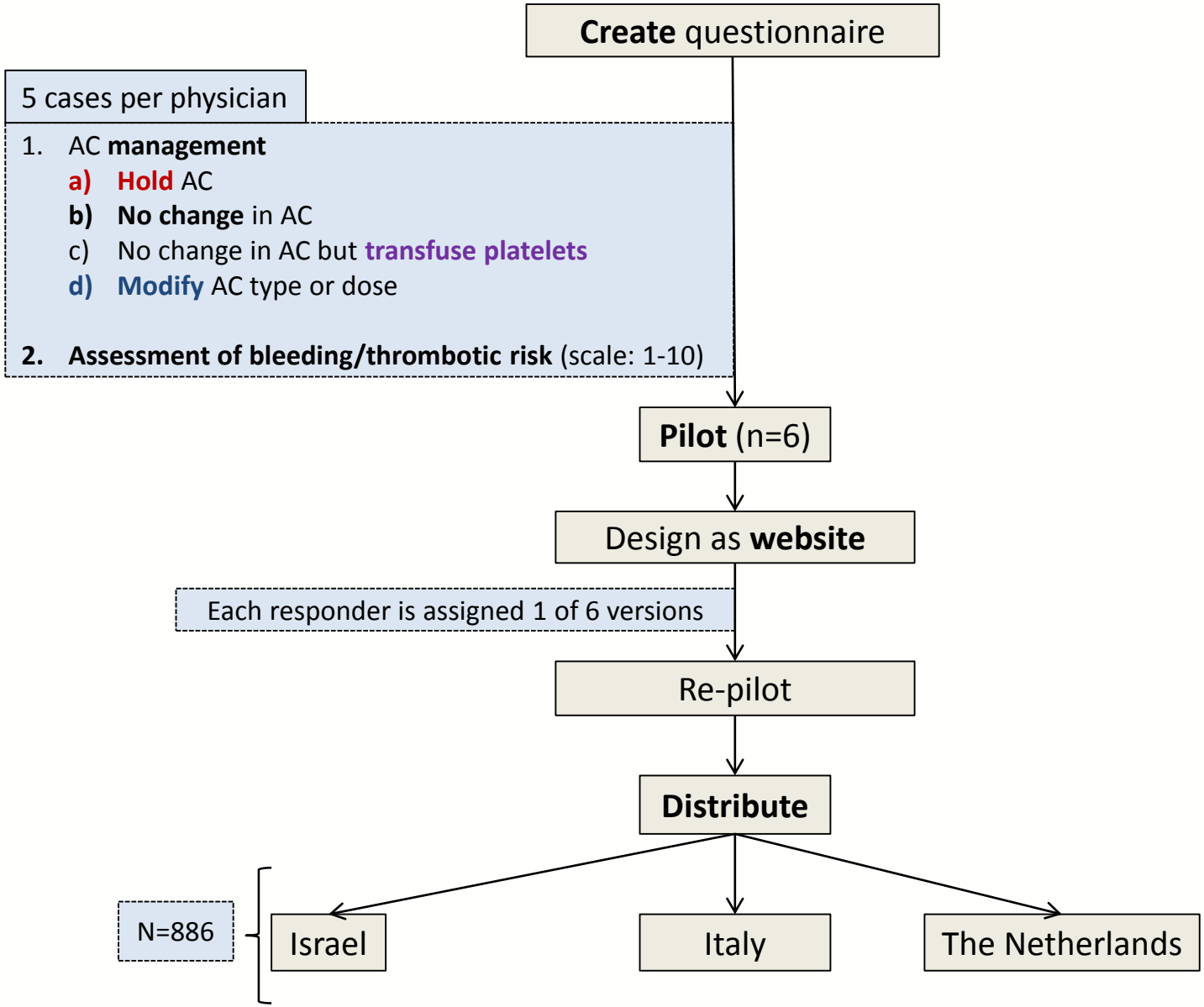
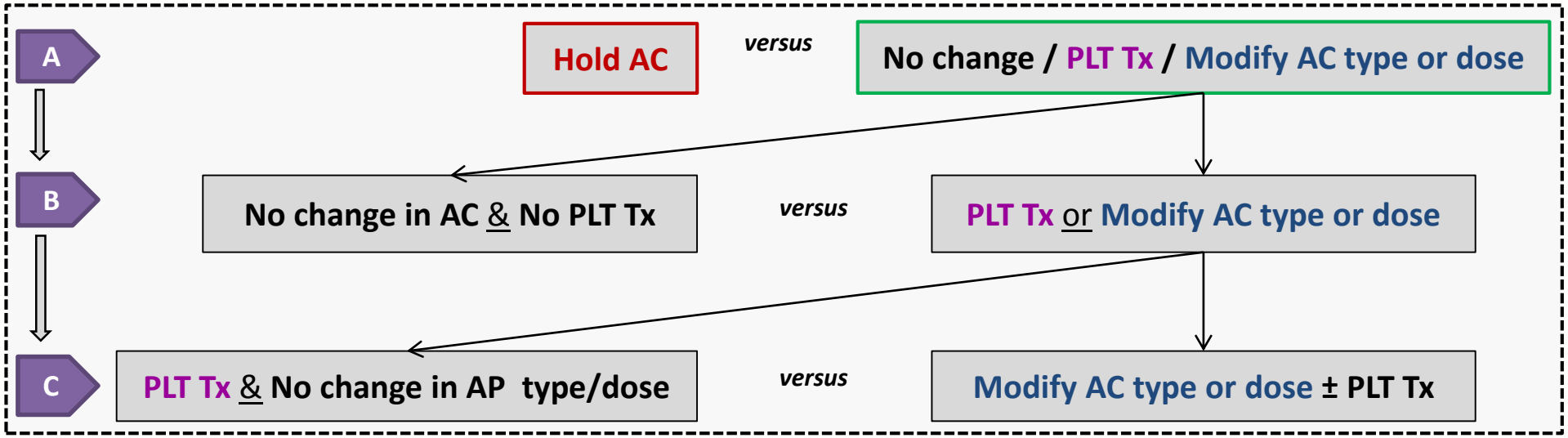
Methods (B): **Creating and piloting vignettes**



Methods (C): **Statistical analysis**

- Comparison between 2 management strategies at each step.



- Mixed effects binomial logistic regression models
- Calculate OR's for using one management option (over the other) for:
  - Each **patient / physician variable**
  - Increasing **thrombotic/bleeding risks**

- Estimated **sample size = 125** (500 X 5 levels / [4 choices X 5 vignettes])

Results

- **168** responders
  - **18% of target** population

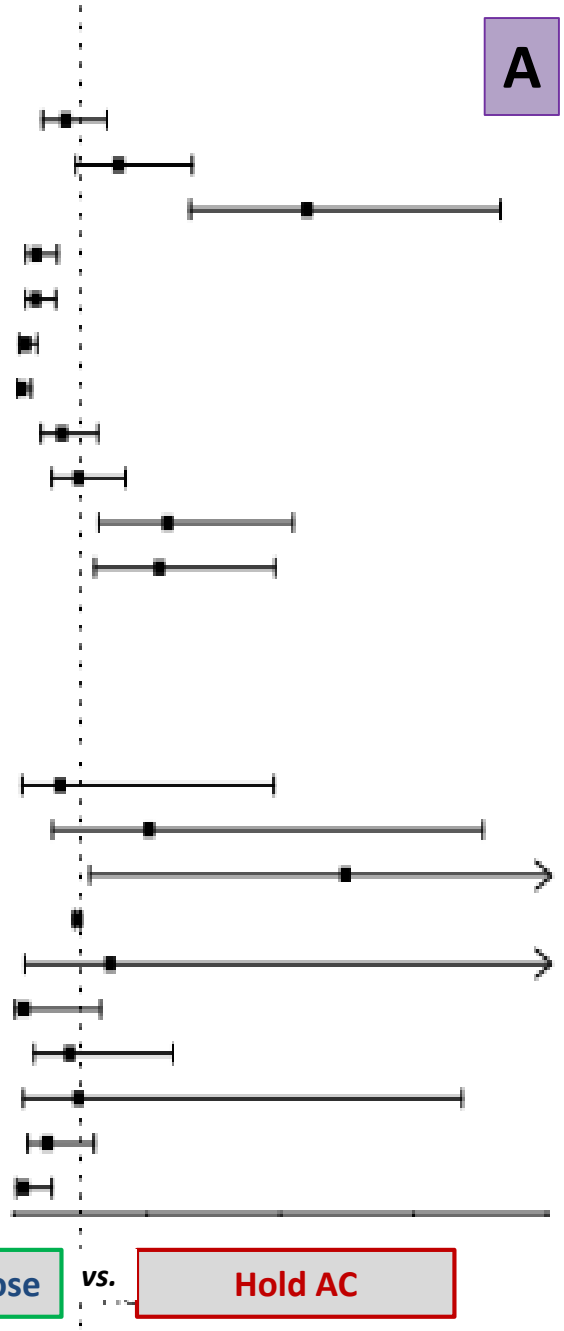
- 774 cases answered

- <u>Physician Characteristics</u>
  - 46% worked at academic tertiary referral centers
  - *Expertise*: Thrombosis, 41%; Transfusion medicine, 12%
  - Estimated median of **5 patients** [IQR 8] **per month**.
  - Institutional guidelines for AC in TCP in 38%
  - **Risk-benefit discussion** with patients: **93%**

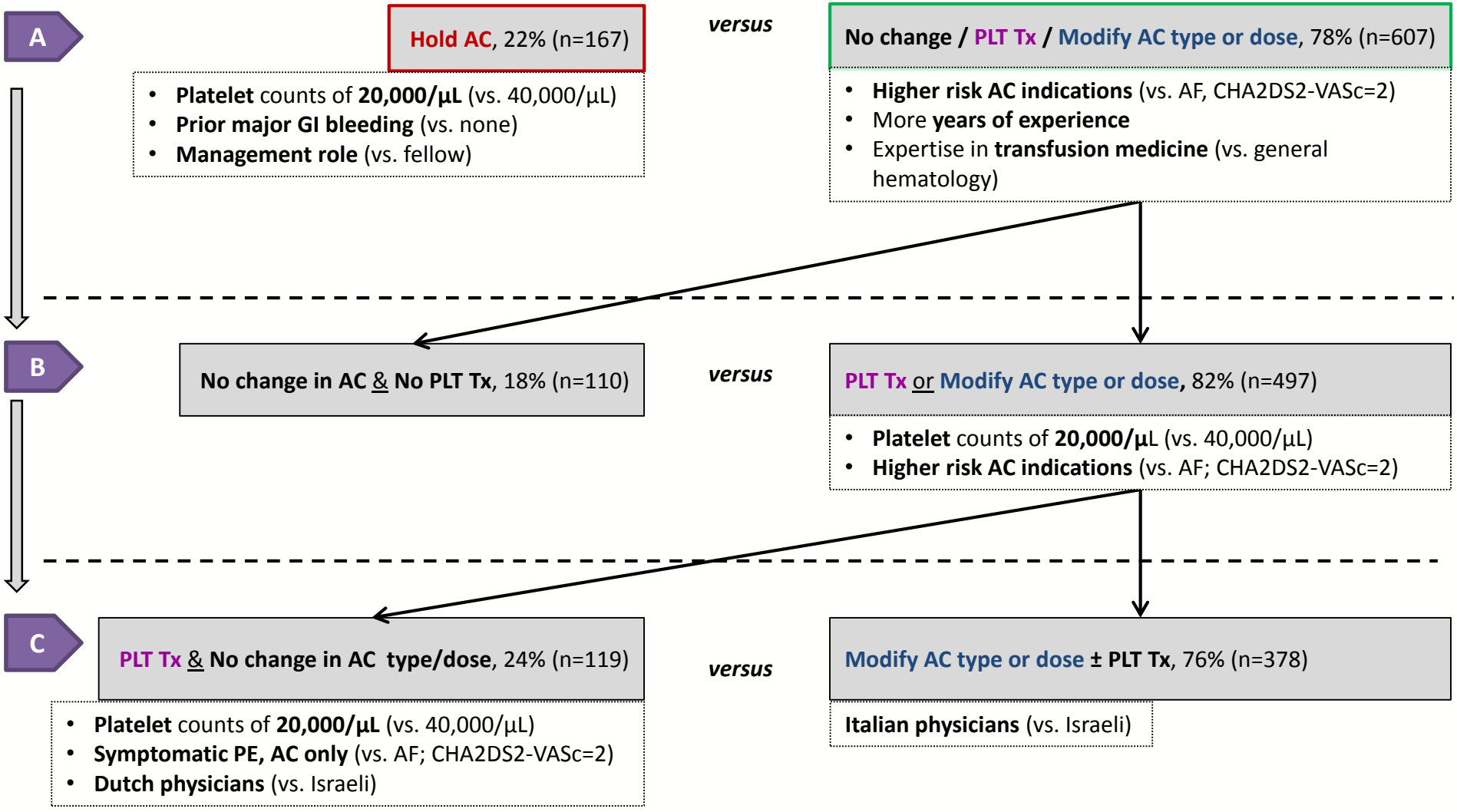
OR for holding AC with each variable (compared to the reference)

Patient attributes		OR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	0.78 (0.43-1.40)	0.0201
AML.High dose Cytarabine consolidation	*	1.58 (0.93-2.68)	0.4005
Platelets: 20,000/microliter	†	4.40 (2.65-7.31)	<0.0001
AF; CHA2DS2-VASc = 6. AC only	‡	0.34 (0.17-0.66)	0.0013
Symptomatic UE-DVT. AC only	‡	0.33 (0.17-0.63)	0.0008
Symptomatic PE. AC only	‡	0.17 (0.08-0.36)	<0.0001
Symptomatic PE. AC. Aspirin treatment	‡	0.12 (0.05-0.26)	<0.0001
Time since indication: 2 weeks	§	0.72 (0.41-1.27)	0.2549
Time since indication: 2 months	§	0.97 (0.57-1.67)	0.9267
Major GI bleeding 3 weeks earlier	||	2.31 (1.27-4.19)	0.0058
Major GI bleeding 4 months earlier	||	2.18 (1.22-3.93)	0.0089

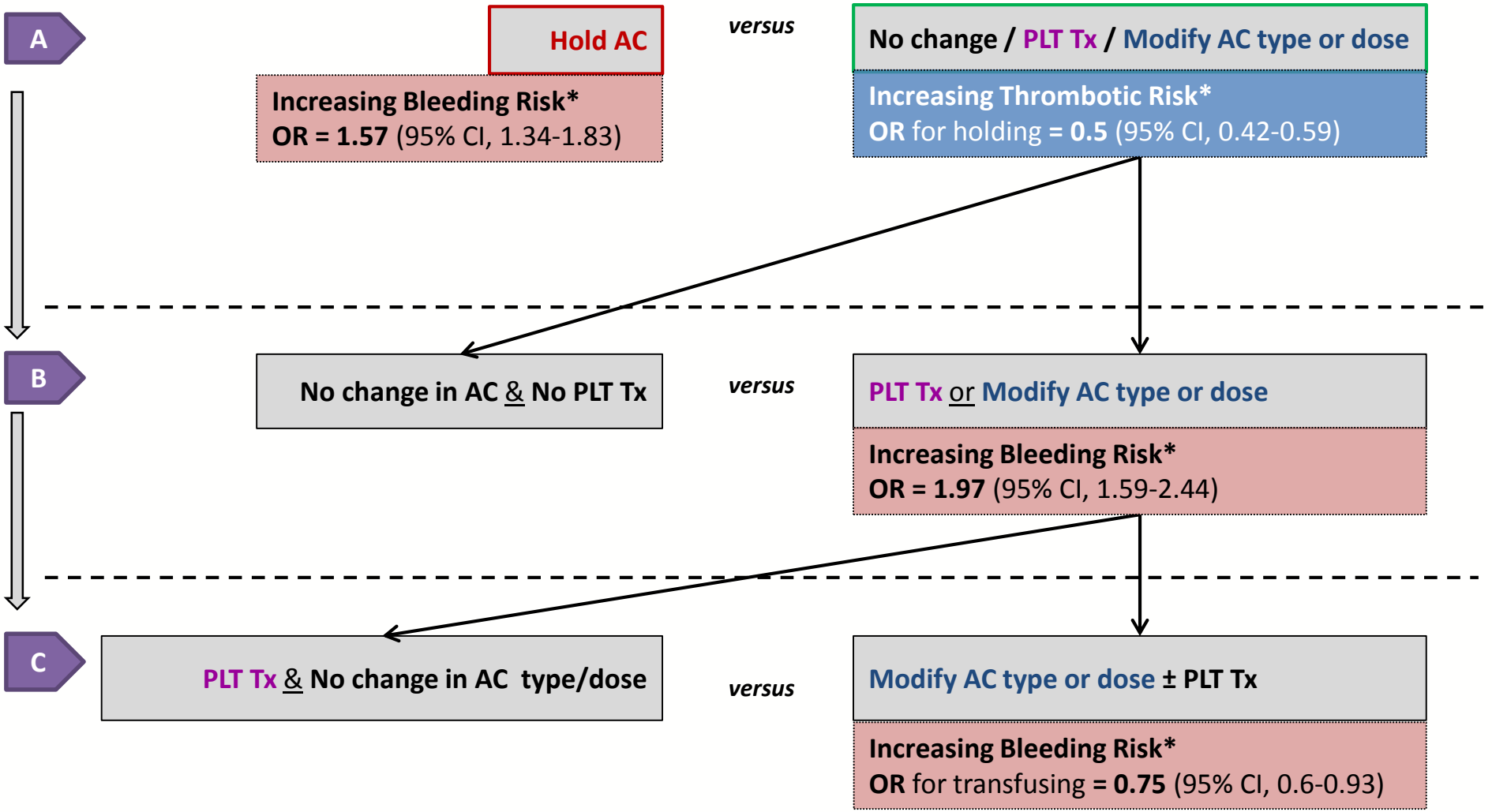
Physician attributes		OR (95% CI)	P
Position: Resident	α	0.70 (0.12-3.90)	0.6804
Position: Senior physician	α	2.03 (0.58-7.04)	0.2664
Position: Senior physician with management	α	4.98 (1.14-21.70)	0.0326
Practicing years	β	0.95 (0.91-0.99)	0.0239
Expertise: Leukemia	γ	1.45 (0.16-12.70)	0.7387
Expertise: Other	γ	0.15 (0.02-1.30)	0.0856
Expertise: Other malignancy	γ	0.84 (0.30-2.39)	0.7456
Expertise: Stem cell	γ	0.97 (0.14-6.72)	0.9791
Expertise: Thrombosis	γ	0.50 (0.21-1.21)	0.1238
Expertise: Transfusion	γ	0.15 (0.04-0.57)	0.0056



Case and physician variables associated with each management choice



Subjective thrombotic and bleeding risks associated with each management choice



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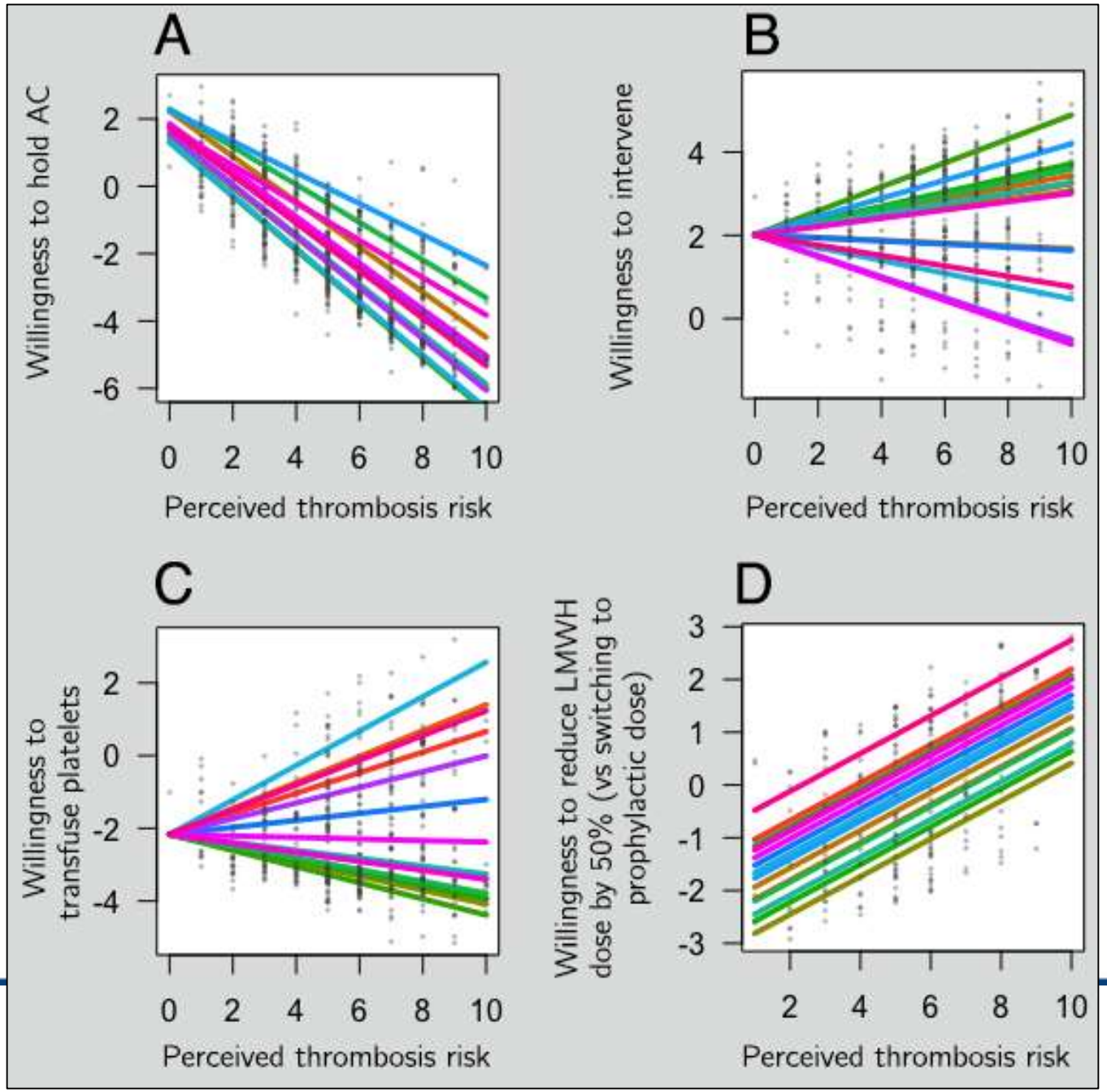
* Physician-assessed risk on a scale of 1-10 (1 = lowest risk; 10 = highest) for a given case

Relationship between perceived thrombotic risk and management varies among physicians



Summary (1)

- **Degree of TCP** is consistently associated with management
  - In line with current guidelines
- **Acuity** of the indication **did not affect** management
  - Implementation of this recommendation (e.g. education) could be improved
- **AC indication** was associated with management
  - Guidelines for atrial fibrillation are needed
- **Bleeding risk** influences management **more than thrombotic risk**
- All findings are clinically plausible

Summary (2)

- **Management varies** between countries and physicians

- **Limitations**
  - Can only discuss the variables chosen for investigation
  - The management choices may not reflect actual practice
  - Current findings are hypothesis-generating

- The **clinical relevance** of these variables should be **assessed in future** studies

- These **clinical variables** should be considered as **confounders**

Study collaborators

Maastricht University / MUMC+

- *Cardiovascular Research Institute (CARIM); Hematology Institute*
- *Thrombosis Expertise Center*
  - **Hugo ten Cate**
  - Vincent ten Cate
  - Arina ten Cate-Hoek
  - Harry Schouten
  - Erik Beckers

Hospital Papa Giovanni XXIII, Bergamo

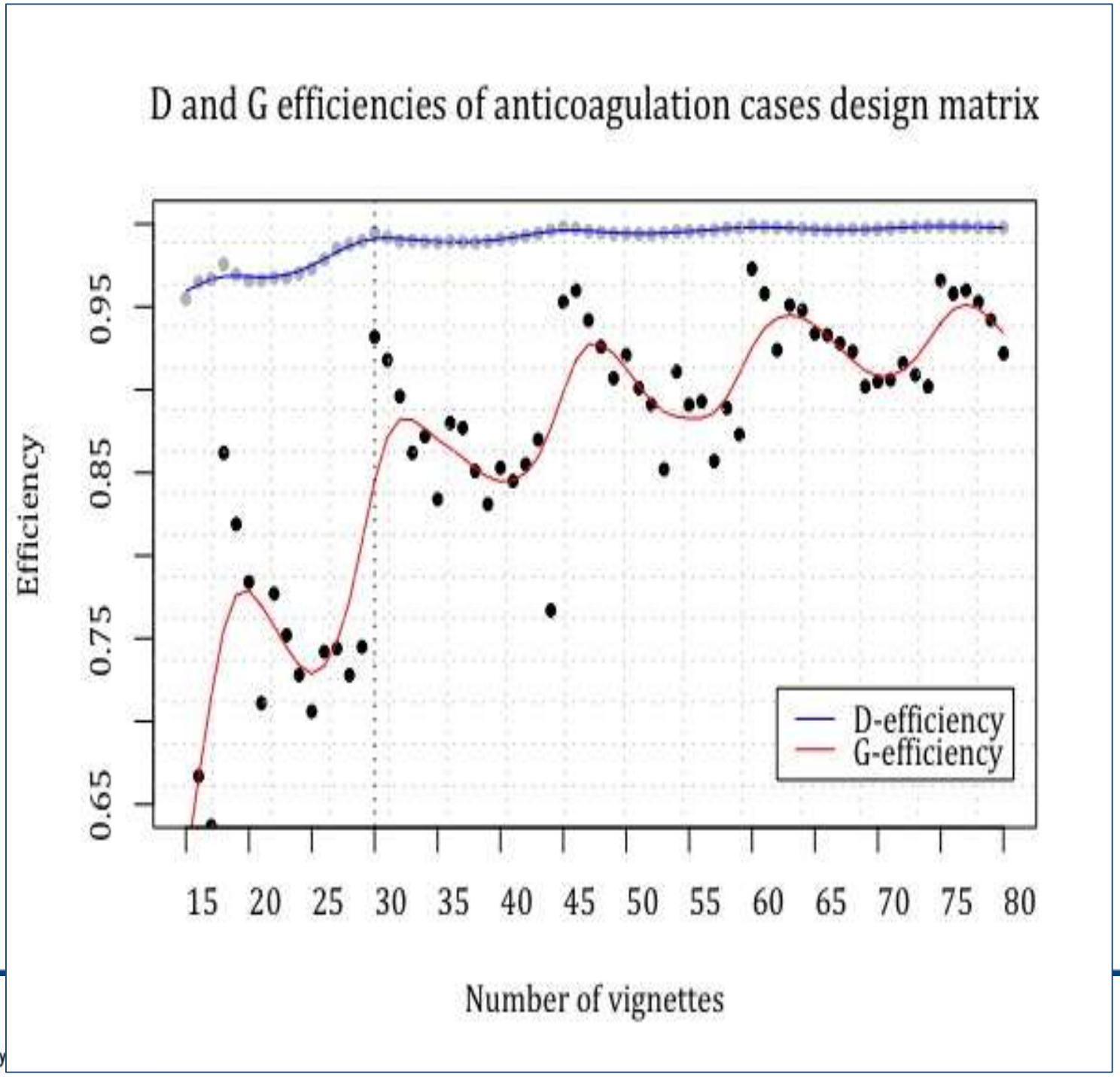
- *Hemostasis and Thrombosis Center*
  - **Anna Falanga**

Rabin Medical Center

- *Thrombosis Unit, Hematology Institute*
  - Galia Spectre

avileader@yahoo.com

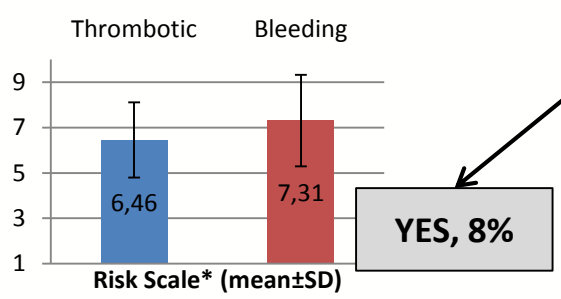
RESERVE SLIDES


D and G efficiencies of anticoagulation cases design matrix
Efficiency
0.65
0.75
0.85
0.95
15
20
25
30
35
40
45
50
55
60
65
70
75
80
Number of vignettes
D-efficiency
G-efficiency

Descriptive analyses of sub-levels of decisions

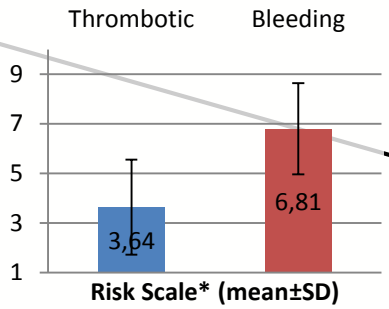
A

IF AC held, then was **an IVC FILTER** recommended? (n=167)



YES, 8%

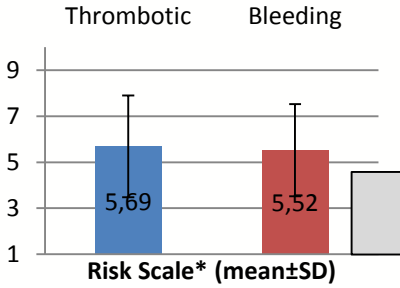
versus



NO, 92%

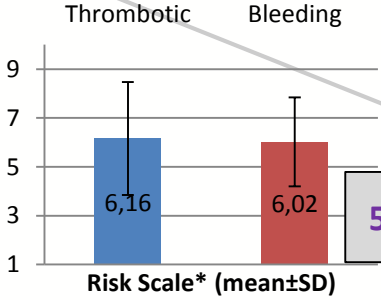
B

IF PLT Tx & no change in AC type/dose, what was the Tx Threshold?



30 x 10^9/L in **45%** (n=54)

versus



50 x 10^9/L in **48%** (n=57)

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* Physician-assessed risk on a scale of 1-10 (1 = lowest risk; 10 = highest) for a given case

C

IF AC type or dose was **modified**, then **which changes were made?**

IF LMWH

42% halve the dose (n=116)

Symptomatic PE, AC only
(vs. AF; CHA2DS2-VASc=2)

Increasing Thrombotic Risk*
OR = 1.43 (95% CI, 1.15-1.79)

versus

40% use **prophylactic doses** (n=112)

Platelet counts of **20,000/µL**
(vs. 40,000/µL)

IF DOAC

13% continue DOAC at any dose (n=37)

87% change to LMWH at any dose (n=240)

IF VKA

5% continue VKA at any dose (n=13)

92% change to LMWH at any dose (n=255);
3% change to DOAC

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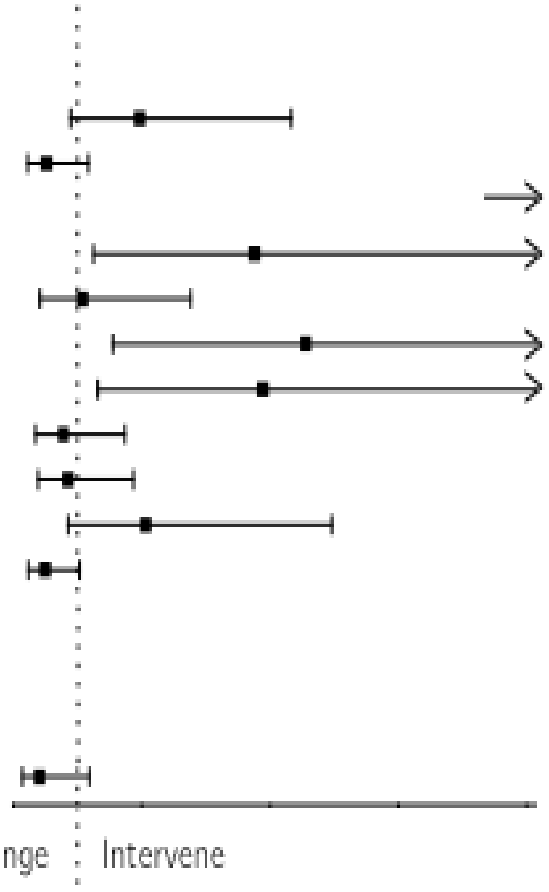
Intervene versus no change in management

B

Patient attributes		OR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	1.97 (0.90-4.33)	0.0921
AML.High dose Cytarabine consolidation	*	0.52 (0.23-1.17)	0.1128
Platelets: 20,000/microliter	†	25.98 (9.79-68.97)	<0.0001
AF; CHA2DS2-VASc = 6. AC only	‡	3.76 (1.25-11.26)	0.0180
Symptomatic UE-DVT. AC only	‡	1.07 (0.42-2.76)	0.8807
Symptomatic PE. AC only	‡	4.55 (1.55-13.35)	0.0058
Symptomatic PE. AC. Aspirin treatment	‡	3.89 (1.32-11.45)	0.0137
Time since indication: 2 weeks	§	0.78 (0.35-1.74)	0.5420
Time since indication: 2 months	§	0.85 (0.39-1.87)	0.6906
Major GI bleeding 3 weeks earlier	||	2.06 (0.86-4.96)	0.1061
Major GI bleeding 4 months earlier	||	0.49 (0.24-1.03)	0.0598
Physician attributes		**OR (95% CI)**	**P**
Discussion of protocols	δ	0.41 (0.14-1.18)	0.0995

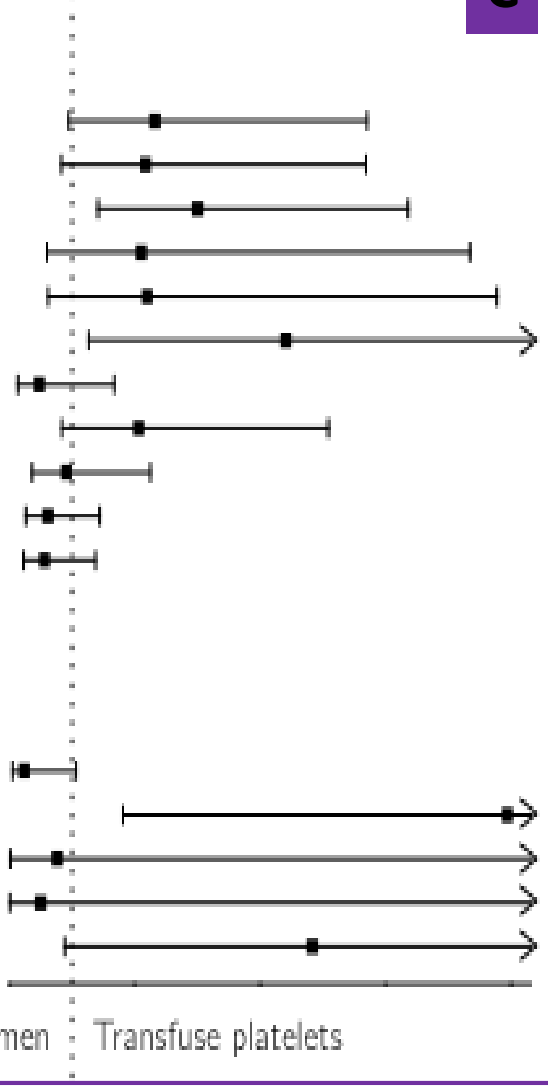


Transfuse platelets versus modify AC regimen

C

Patient attributes		OR (95% CI)	P
ALL. Asparaginase-based intensive chemotherapy	*	2.32 (0.94-5.70)	0.0663
AML.High dose Cytarabine consolidation	*	2.17 (0.83-5.68)	0.1142
Platelets: 20,000/microliter	†	3.00 (1.42-6.36)	0.0041
AF; CHA2DS2-VASc = 6. AC only	‡	2.10 (0.60-7.34)	0.2443
Symptomatic UE-DVT. AC only	‡	2.20 (0.62-7.77)	0.2229
Symptomatic PE. AC only	‡	4.41 (1.26-15.40)	0.0199
Symptomatic PE. AC. Aspirin treatment	‡	0.48 (0.14-1.68)	0.2483
Time since indication: 2 weeks	§	2.06 (0.84-5.08)	0.1159
Time since indication: 2 months	§	0.91 (0.37-2.25)	0.8319
Major GI bleeding 3 weeks earlier	||	0.61 (0.26-1.44)	0.2610
Major GI bleeding 4 months earlier	||	0.56 (0.23-1.37)	0.2057

Physician attributes		OR (95% CI)	P
Country: Italy	ζ	0.24 (0.05-1.06)	0.0602
Country: Netherlands	ζ	7.94 (1.81-34.80)	0.0060
Country: Spain	ζ	0.76 (0.02-34.41)	0.8891
Country: United States	ζ	0.50 (0.01-28.19)	0.7368
Expertise: Stem cell	γ	4.83 (0.88-26.45)	0.0697



Lower LMWH dose by roughly 50% versus to prophylactic dose

Patient attributes		OR (95% CI)	*P*
ALL. Asparaginase-based intensive chemotherapy	*	0.54 (0.21-1.35)	0.1852
AML.High dose Cytarabine consolidation	*	0.55 (0.20-1.53)	0.2507
Platelets: 20,000/microliter	†	0.22 (0.09-0.58)	0.0019
AF; CHA2DS2-VASc = 6. AC only	‡	1.32 (0.46-3.82)	0.6027
Symptomatic UE-DVT. AC only	‡	1.60 (0.54-4.76)	0.3991
Symptomatic PE. AC only	‡	4.18 (1.38-12.66)	0.0115
Time since indication: 2 weeks	§	1.73 (0.64-4.72)	0.2822
Time since indication: 2 months	§	1.27 (0.49-3.25)	0.6224
Major GI bleeding 3 weeks earlier	||	0.72 (0.26-1.96)	0.5173
Major GI bleeding 4 months earlier	||	0.75 (0.28-2.05)	0.5799

Physician attributes		OR (95% CI)	*P*
Hospital: University-affiliated community hospital	η	2.34 (0.78-7.07)	0.1300
Hospital: Community hospital	η	3.72 (0.85-16.27)	0.0806
Discussion of protocols	δ	2.65 (0.95-7.44)	0.0638