Antiplatelets, Anticoagulants & Polypectomy: Evidence & Expert Opinion

Neena S. Abraham MD, MSc (EPID), FASGE, FACG, AGAF

Professor of Medicine, Mayo Clinic

CardioGI clinic, Division of Gastroenterology and Hepatology, Mayo Clinic, Scottsdale, AZ

Division of Gastroenterology and Hepatology, Mayo Clinic, Phoenix/Scottsdale, AZ

Division of Health Care Policy & Research, Department of Health Sciences Research, Mayo Clinic, Rochester, MN

AZ Director, Kern Center for the Science of Health Care Delivery Research

@NeenaSAbrahamMD

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Learning Objectives

1. **Risk of post-polypectomy bleeding (PPB)**
   - Immediate vs. Delayed
   - On and Off Antithrombotic therapy
2. **Polypectomy techniques: does it matter?**
   - Cold Snaring vs. Conventional
   - Prophylactic Clipping
3. **Temporary interruption & resumption**
   - What is the evidence?
4. **Controversies & Knowledge Gaps**
5. **Clinical Takeaways**

Observational Study: Antithrombotics & Delayed PPB

	GIB/PPB within 30 days
DOAC	0.90 (0.44-1.85)
Warfarin	1.90 (1.28-2.83)
Clopidogrel	2.84 (2.6-3.73)
EMR	4.96 (4.36-5.64)
Bridge anticoagulation	3.29 (1.68-6.44)

DOAC, direct-acting oral anticoagulant; EMR, endoscopic mucosal resection; GIB, gastrointestinal bleeding

Study Limitations:

- Few patients on DOACs :
  - 3471 on warfarin
  - 1590 on DOACs ****
  - 6443 on clopidogrel

- Higher PPB on any antithrombotic vs controls ($P < 0.001$)
- DOACs did not increase in the odds of GIB
  - *** likely a sample size effect ***

Yu JX et al, *CGH* 2019

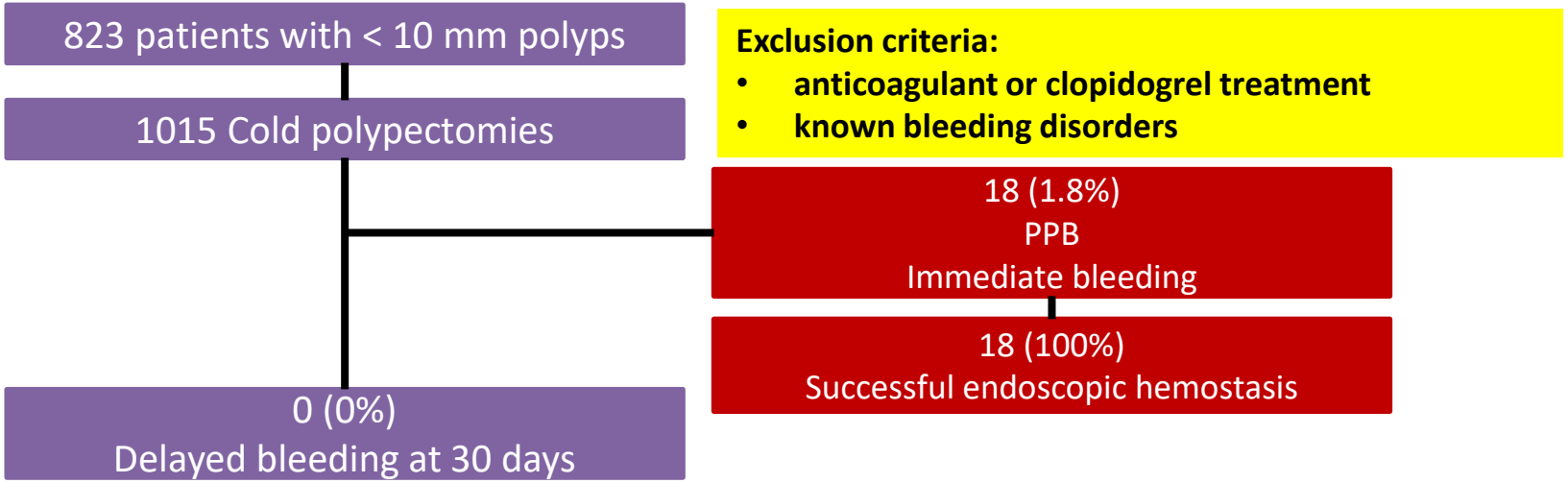
Procedural Risk of Bleeding (w/out AC/AP)

High bleeding risk procedures (30-d risk of major bleed >2 %)	Low/moderate bleeding risk procedures (30-d risk of major bleed ≤ 2%)
Polypectomy (≥ 1cm)	EGD with/without biopsy
PEG/PEJ placement	Colonoscopy with/without biopsy
ERCP with biliary or pancreatic sphincterotomy	Flexible sigmoidoscopy with/without biopsy
EMR/ESD	ERCP with stent (biliary or pancreatic) placement or papillary balloon dilation without sphincterotomy, tissue sampling, or treatment of choledocholithiasis
EUS-FNA	EUS without FNA
Endoscopic hemostasis (excluding APC)	Push enteroscopy and diagnostic balloon-assisted enteroscopy
Radiofrequency ablation	Enteral stent deployment
POEM	Argon plasma coagulation
Treatment of varices (including variceal band ligation)	Balloon dilation of luminal stenoses
Therapeutic balloon-assisted enteroscopy	Polypectomy (<1 cm)
Tumor ablation	ERCP without biliary or pancreatic sphincterotomy
Cystgastrostomy	Marking (including clipping, electrocoagulation, tattooing)
Ampullary resection	Video capsule endoscopy
Pneumatic or bougie dilation for achalasia or esophageal strictures	
Laser ablation and coagulation	

Abraham et al. *AJG* 2022

Cold Polypectomy: <10mm polyps

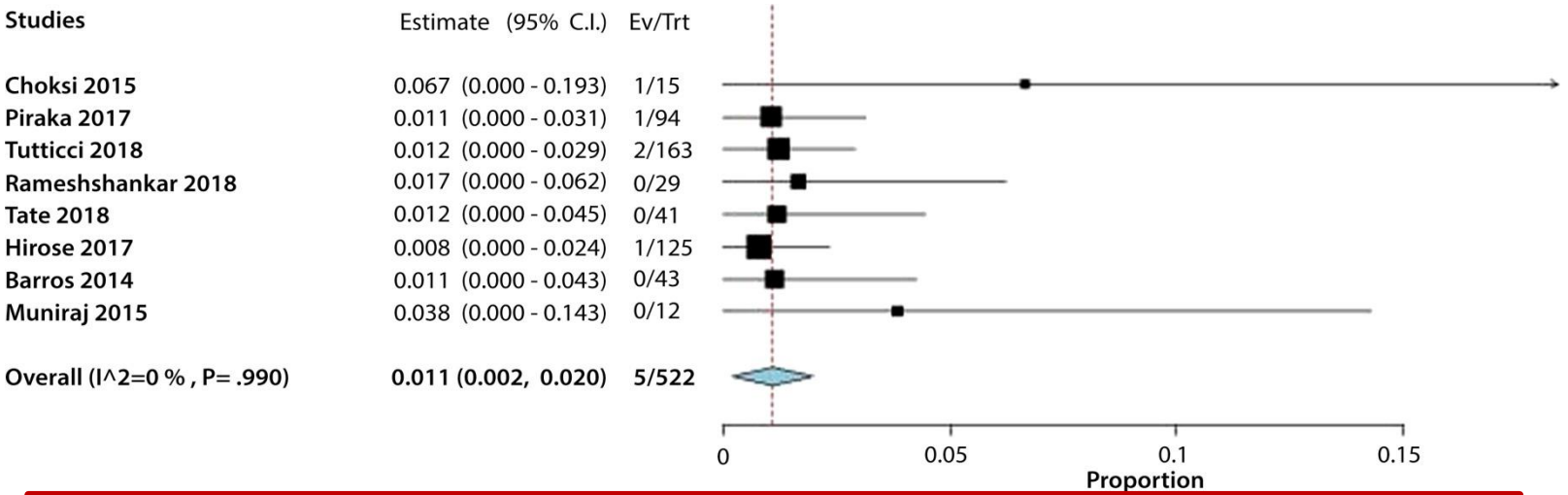
** cold polypectomy (forceps biopsy or cold snare)



- **Immediate PPB: Per-patient bleeding rate: 2.2 % (95% CI 1.2%-3.2%); per-polyp bleeding rate: 1.8% (95% CI 1%-2.6%).**
- **1.8% complication rate also observed in the Munich Polypectomy Study (MUPS) for small polyps.^**
- **Unknown risk with antithrombotic drug use.**

Repici A et al, *Endoscopy* 2012; ^Heldwein W et al, *Endoscopy* 2005

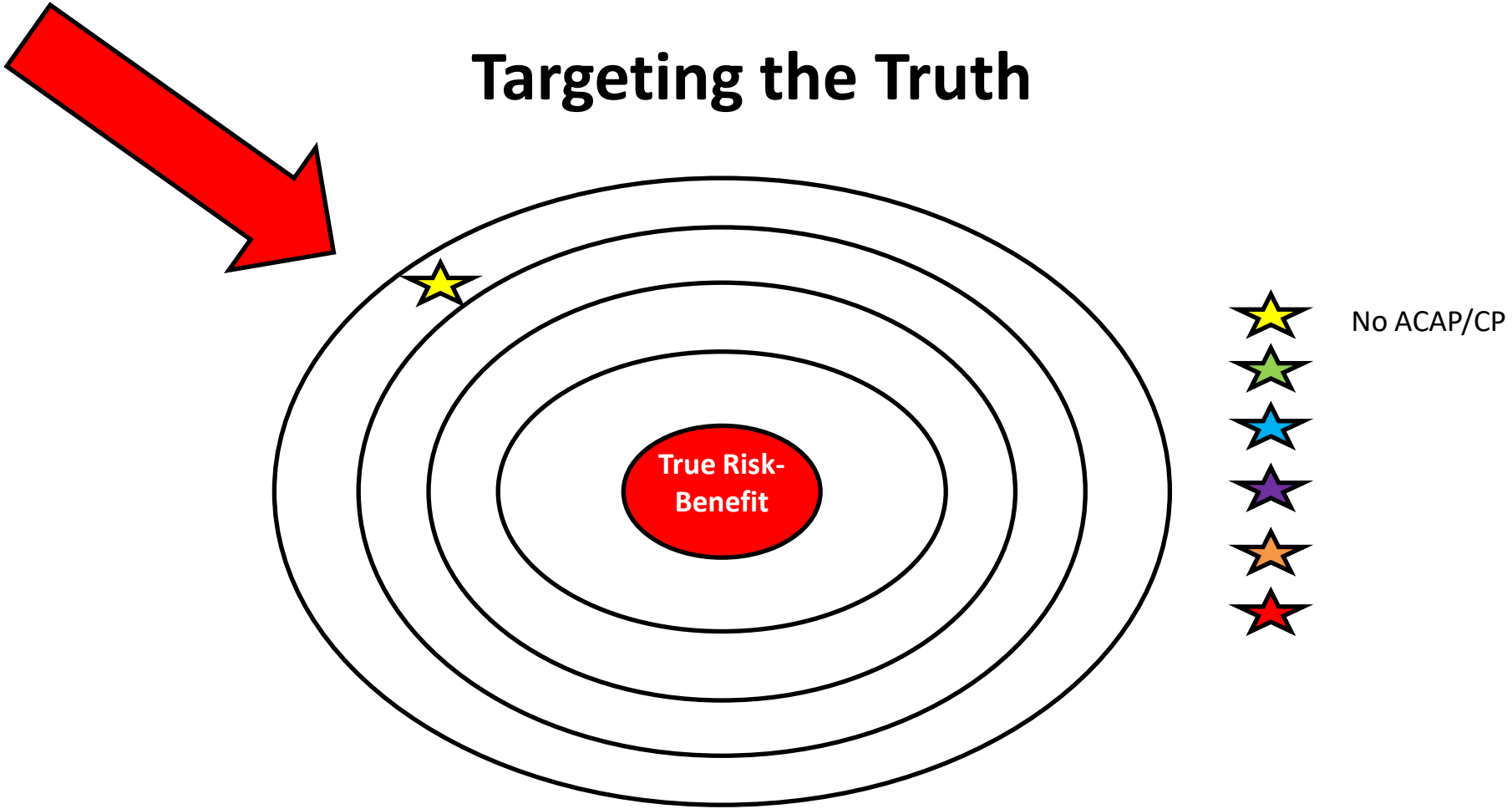
Cold Snare of Polyps >10 mm
Systematic review of 9 case series



- **Patients on antiplatelets & anticoagulants EXCLUDED**
- **Largest polyp removed 22.8 mm**
- **Intraprocedural bleeding rate 0.7% (95% CI: 0%-1.4%)**
- **PPB rate 0.5% (95% CI 0.1%-1.2%)**

Chandrasekar V et al, *Gastrointestinal Endoscopy* 2019

Targeting the Truth



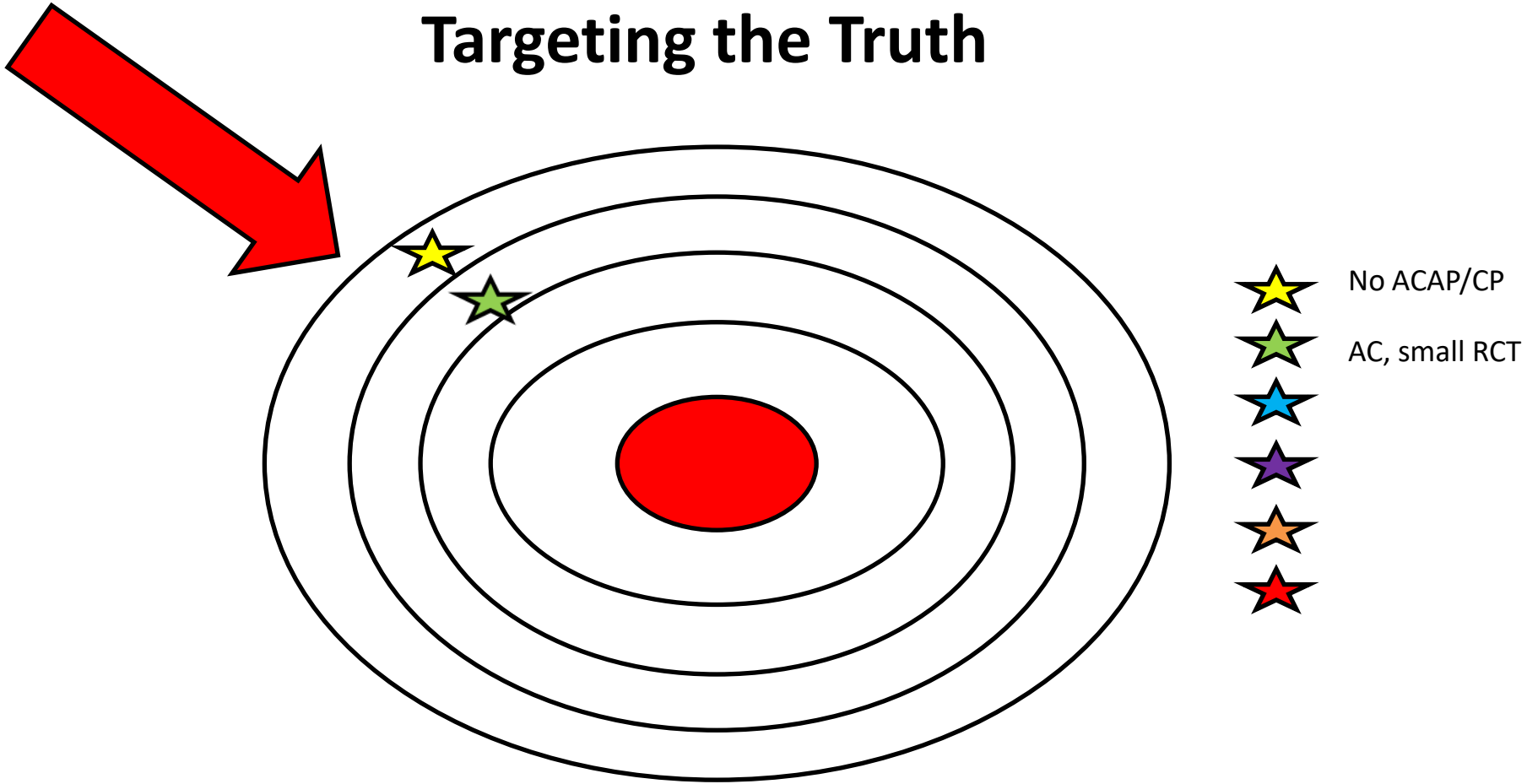
Continuously Anticoagulated Patients: Hot or Cold Polypectomy?

	Cold group	Conventional group	P	OR (95% CI)
Immediate bleeding	5.7% (2/35)	23% (8/35)	.042	4.9 (.96-25.0)
Hematochezia*	5.7% (2/35)	8.6% (3/35)	.500	1.5 (.24-9.9)
Delayed bleeding*	0% (0/35)	14% (5/35)	.027	
Total	11% (4/35)	46% (16/35)	.0015	6.5 (1.9-22.5)

- **Single Site Japanese RCT (n=70); continuously anticoagulated patients (warfarin); mean INR 2.3**
- **Overall PPB 46% for conventional polypectomy vs 11% for cold group**
  - **Mean polyp size- 6.5 to 6.8 mm**
  - **Delayed bleeding in 14% of the conventional group**
- **Immediate bleeding (> 30 s) in the conventional group (23%) higher than expected**
- **Further studies needed to appropriately define immediate bleeding**

Horiuchi A et al, *Gastrointest Endosc* 2014

Targeting the Truth



Elective Procedures: DAPT

Agent	COX inhibitor		Thienopyridine agents			
	ASA	NSAID	Ticlopidine (Ticlid)	Clopidogrel (Plavix)	Prasugrel (Effient)	Ticagrelor (Brilinta)
Timing of D/C (days)	**N/A**	**N/A**	**10-14**	**5 ***	**7 ***	**5 ***

~ ~ MUST continue the cardiac ASA as monotherapy while other antiplatelets are held
~ RESTART DAPT when immediate hemostasis is achieved!

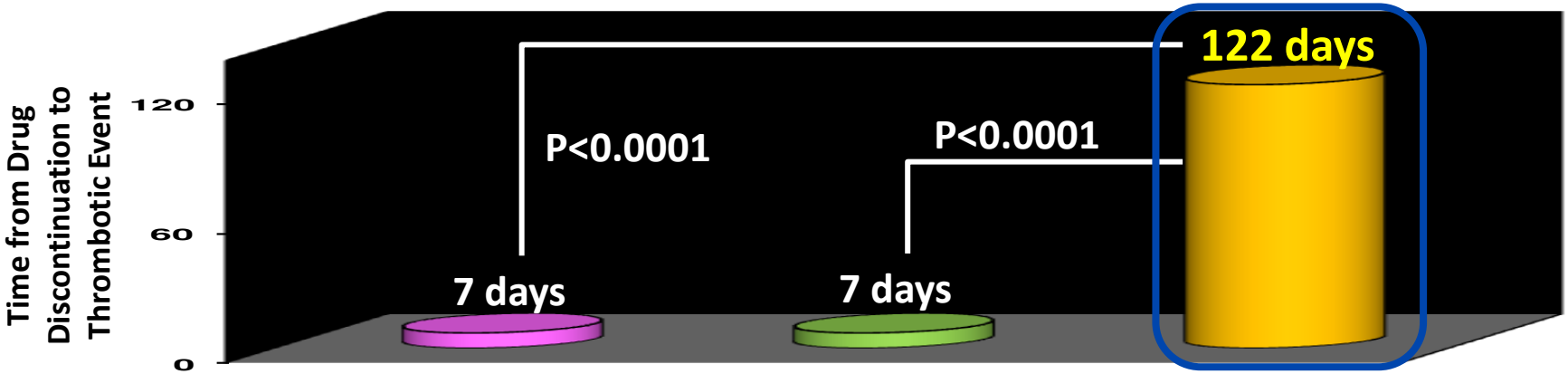
*Based on FDA recommendations

Abraham et al, *AJG* 2022; Barkun et al, *AJG* 2022

CARDIOGASTROENTEROLOGY TIP

Stent Thrombosis Post-DES: Antiplatelet Cessation

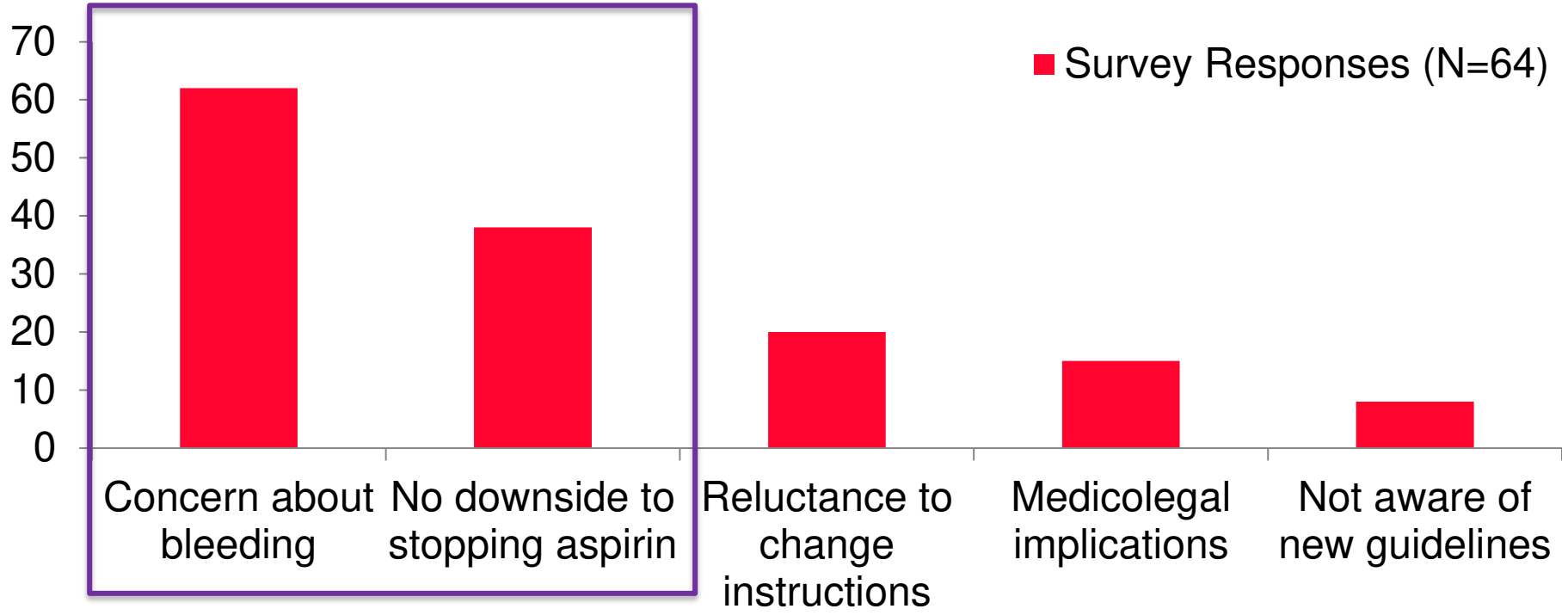
Short-term discontinuation of thienopyridine is safe in if ASA therapy maintained



- ASA and thienopyridine discontinued simultaneously (n=33)
- ASA discontinued after thienopyridine previously discontinued (n=15)
- Only thienopyridine discontinued; ASA continued (n=94)

Eisenberg M et al, *Circulation* 2009

Reasons to Discontinue ASA Pre-Endoscopy



Robbins R et al, *Gastrointest Endosc* 2015

Perceived Risk vs. Actual Risk

"Perceived risk may cause practitioners to make cognitive errors by overemphasizing events that have a limited chance of occurring, while de-emphasizing events that have the *potential* to cause greater actual harm."

Adams MA et al, *Gastrointest Endosc* 2015

CARDIOGASTROENTEROLOGY TIP

Risk of Cardiac ASA Discontinuation

RCT

- Low-dose ASA (n=78) vs. placebo (n=78)
- 30-day recurrent bleeding: 10.3% vs. 5.4%
  - ARR: 4.9%; NNT=20
- 30-day mortality: 1.3% vs. 9.0%
  - ARI: 7.7%; NNH= 13

Hospital-based cohort

- N=118
- Discontinued ASA therapy: Mortality and CV event HR 6.3 (1.3-31.3)

- ❑ Discontinuation of ASA in CV patients is associated with increased mortality.
- ❑ It is reasonable to perform endoscopic procedures in patients taking ASA.

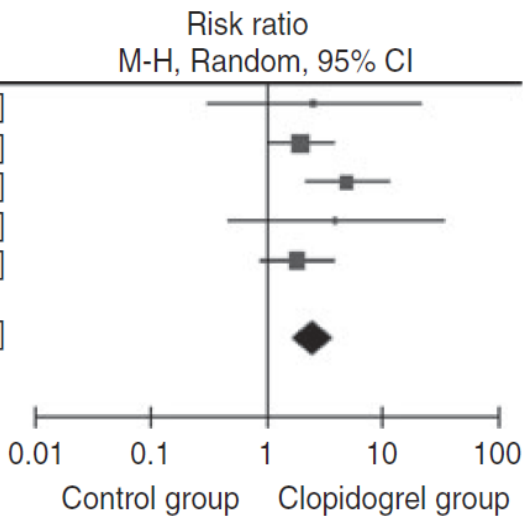
Sung et al, *Ann Intern Med* 2010; Acosta & Abraham, *GIE* 2016; Derogar M et al, *Clin Gastroenterol Hepatol* 2013

Continued Clopidogrel and PPB
Retrospective & Case-Control studies

Study or Subgroup	Clopidogrel Events	Clopidogrel Total	Control Events	Control Total	Weight	Risk ratio M-H, Random, 95% CI
Feagins 2011	1	118	6	1849	3.8%	2.61 [0.32, 21.52]
Feagins and Iqbal 2013	21	219	14	297	38.2%	2.03 [1.06, 3.91]
Grossman 2010	6	70	41	2380	24.4%	4.98 [2.18, 11.33]
Rodino 2011	1	25	4	400	3.6%	4.00 [0.46, 34.47]
Singh 2010	8	142	38	1243	29.9%	1.84 [0.88, 3.87]
Total (95% CI)		574		6169	100.0%	2.54 [1.68, 3.84]
Total events	37		103			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.08$, df = 4 ($P = 0.40$); $I^2 = 2\%$

Test for overall effect: $Z = 4.44$ ($P < 0.00001$)

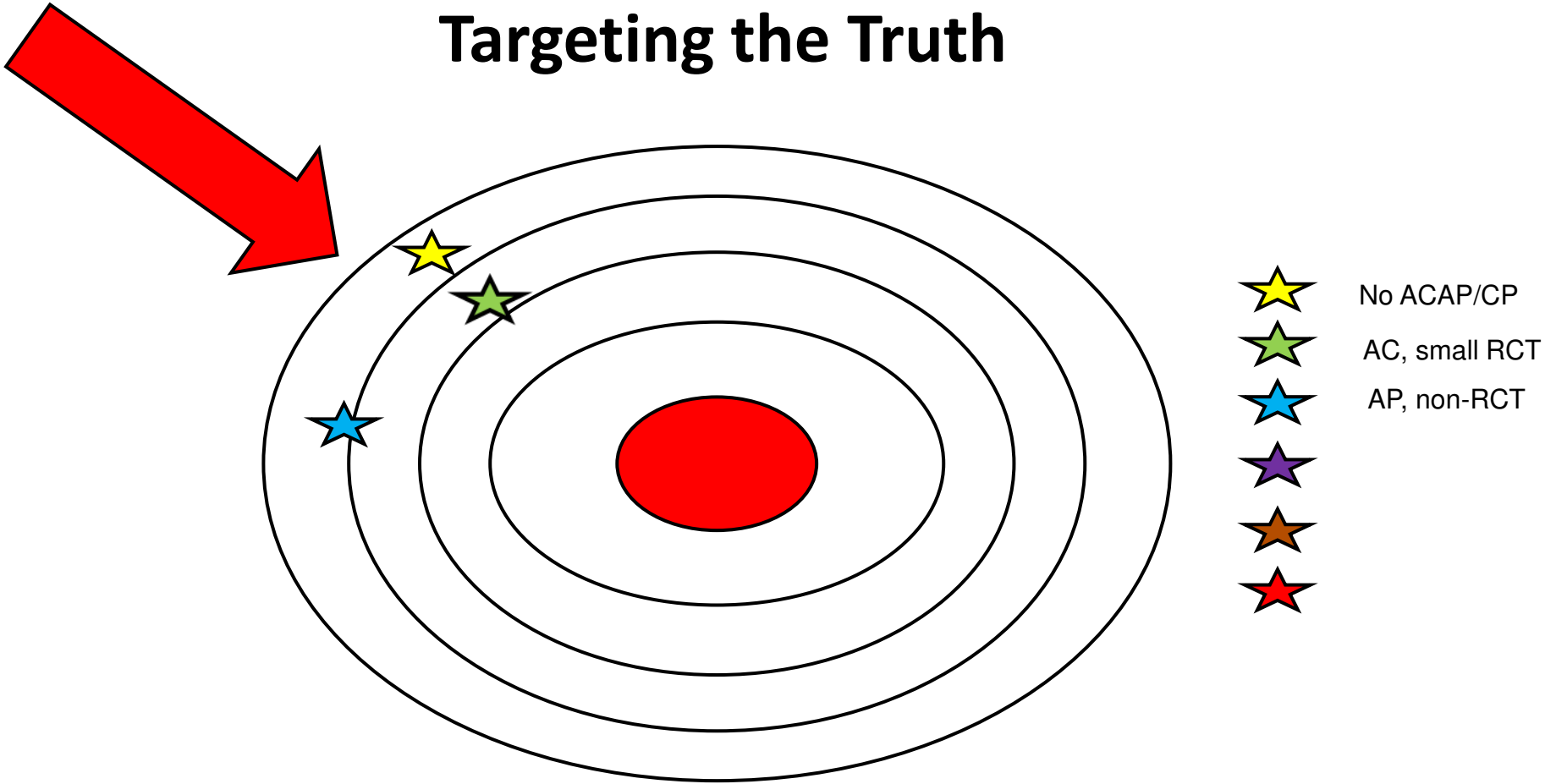


***Delayed PPB = up to 30 days post-polypectomy**

	Clopidogrel group	Control group	Relative risk ratio	Lower 95% CI	Upper 95% CI	P value	I^2%
Immediate PPB (%)	22/431 (5.10)	66/3920 (1.68)	1.76	0.90	3.46	0.10	**30**
Delayed PPB (%)	15/565 (2.65)	37/6158 (0.60)	4.66	2.37	9.17	<0.00001	**0**
Total PPB (%)	**37/574 (6.45)**	**103/6169 (1.67)**	**2.54**	**1.68**	**3.84**	**<0.00001**	**2**

Gandhi S et al, *Aliment Pharmacol Ther* 2013

Targeting the Truth



Clopidogrel Uninterrupted Postpolypectomy Bleeding Trial (CUP Trial)

- **Hypothesis: Uninterrupted clopidogrel therapy increases delayed PPB in patients**
- **Eligibility: Clopidogrel alone or in combination with other antiplatelet agents; colonoscopy for colorectal cancer screening, surveillance, or symptom.**
- **Exclusion: PCI within 30 days, CV event within 3 months, DES within 6 months, concomitant anticoagulants, bleeding diathesis, pregnancy, and terminal illness.**

- **STUDY DESIGN:**
  - **Eligible patients discontinued clopidogrel 7 days before colonoscopy (N=387)**
  - **Randomized (1:1) to 7 days of drug or placebo until the morning of colonoscopy**
  - **All patients resumed clopidogrel when oral intake was allowed**
  - **Primary end point: delayed PPB assessed on days 2, 7 & 30**

Chan FKL et al, *Gastroenterology* 2019

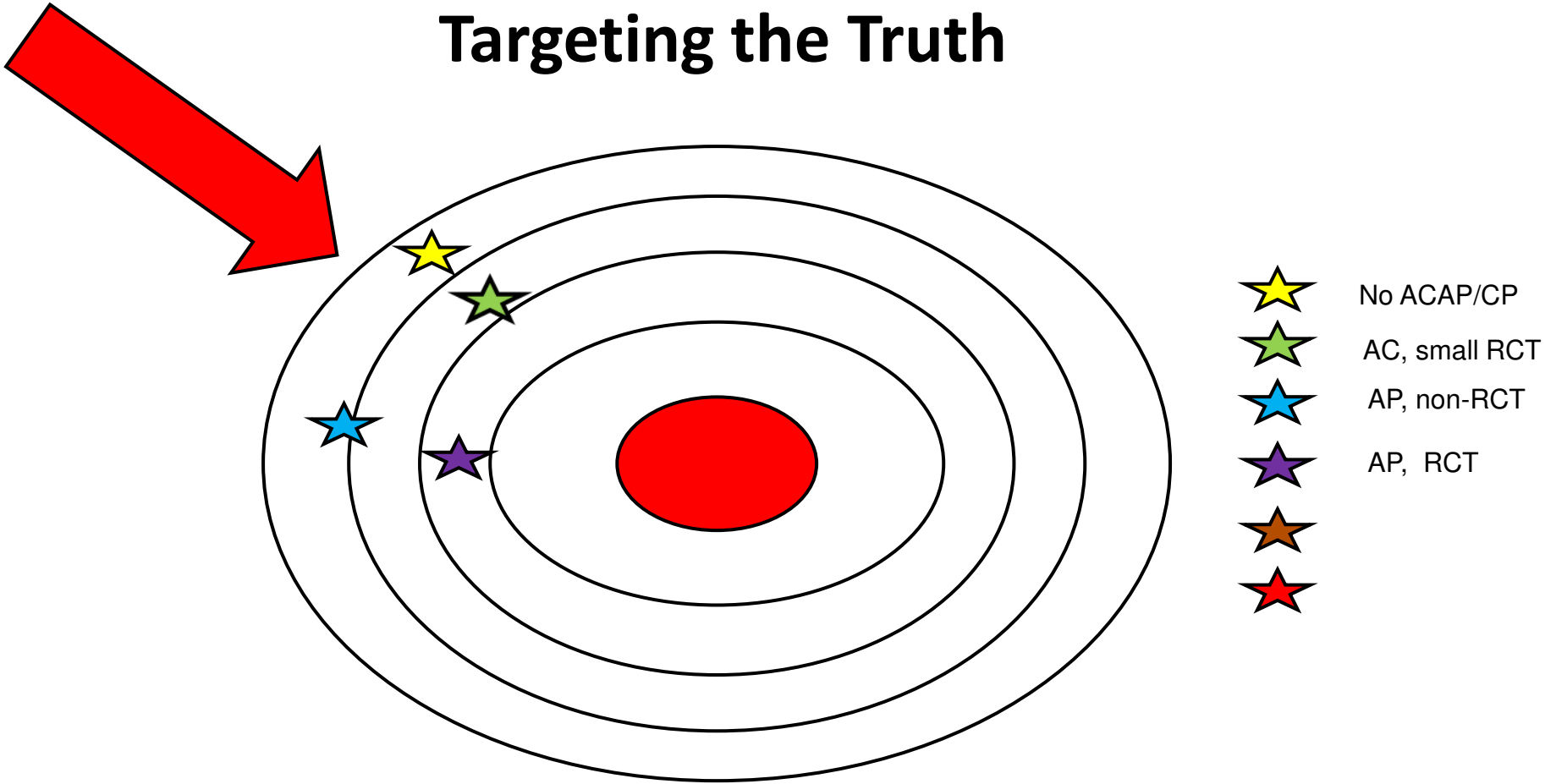
CUP Trial: Outcomes

Outcomes	Clopidogrel	Placebo	P value
Delayed post-polypectomy bleeding (%)	3.8 (1.4–9.7)	3.6 (1.4–9.4)	.945
Immediate post-polypectomy bleeding (%)	8.5 (3.2–13.8)	5.5 (1.2–9.7)	.380
Serious cardio-thrombotic events (%)	1.5 (0.5–4.7)	2.0 (0.8–5.4)	.713

- **Delayed PPB w/continuing clopidogrel similar to previous reports**
  - PPB after interrupting clopidogrel (placebo) was higher than anticipated
  - Resumption of clopidogrel in the placebo group increased PPB due to cauterization-related thermal injuries (40% CSP & 60% electrocautery)
- **Numerical trend toward increased immediate PPB with uninterrupted clopidogrel**
- Limitation: small number of patients with large polyps.

Chan FKL et al, *Gastroenterology* 2019

Targeting the Truth



Elective Warfarin Management & Bridge Anticoagulation

- **Hold 5 days prior to endoscopy; <3% risk of thromboembolism in 30 days ^**
- **To Bridge or Not to Bridge?**

➢ **YES if mechanical valve, CVA/TIA, or VTE/PE within the last 3 months**

- **Prothrombotic patients (cancer, thrombophilia, AFIB w/ CHADS2 >5 or CHA2DS2VASC score ≥ 7) …individualize therapy; *benefit may not outweigh the bleeding risk***
- **AFIB patients on warfarin with mechanical heart valve or recent stroke have high thromboembolic risk– they need LMWH 3 days before endoscopy**

➢ **NO if *only* non-valvular AFIB on warfarin, or non-valvular AFIB on DOACs**

- ***Warfarin*: BRIDGE trial* & ORBIT-AF Trial show increased risk of bleeding with bridged group & no thromboembolic benefit (7.8% vs. 1.5% [bridged vs. no bridge]).**
- ***DOAC*: Sub-study of RE-LY shows similar results to BRIDGE and ORBIT-AF Trial.**

Healey JS et al, *Circulation* 2012; Sherwood MW et al, *J Am Coll Cardiol* 2013; Lopes RD et al, *Can J Cardiol* 2013; Blacker et al, *Neurology* 2003; Garcia et al, *Arch Intern Med* 2008; Douketis JD et al, N*EJM* 2015; Steinberg BA et al, *Circulation* 2015; Douketis JD et al, *Thromb Haemost* 2015; ^Inoue et. al, *Dig Endosc* 2014; January et al, *JACC* 2019; Lip et al, *Chest* 2018

Temporary Interruption & Resumption of DOAC

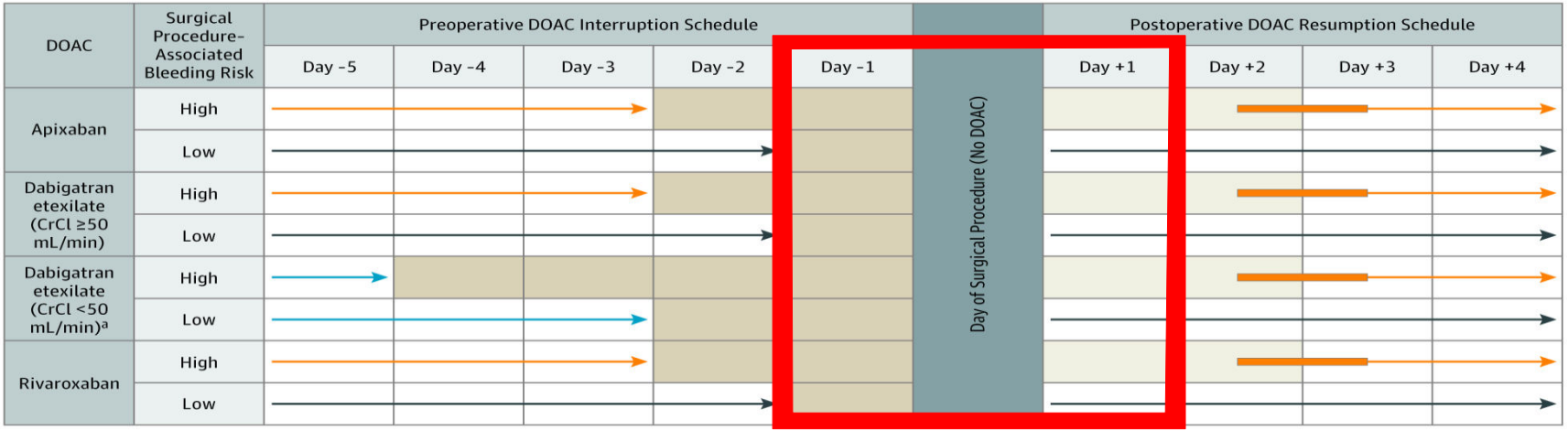
Factor Xa Inhibitor						Direct Thrombin Inhibitor	
Rivaroxaban		Apixaban		Edoxaban		Dabigatran	
CrCl (ml/min)	Last Dose (days)	CrCl (ml/min)	Last Dose (days)	CrCl (ml/min)	Last Dose (days)	CrCl (ml/min)	(days)
>90	≥1					>80	1-3
60-90	2	>60	1-2	>60	≥1	50-80	1-3
30-59	3	30-59	3	30-60	≥1	30-49	1.5-4
15-29	4	15-29	4	15-30	≥1	≤29	2-6

Restart when hemostasis achieved; usually next day at full dose

Acosta & Abraham et al, *GIE* 2016

Perioperative Anticoagulation Use for Surgery Evaluation (PAUSE) Cohort Study

*23 clinical centers in Canada, the United States, and Europe; n = 3007 atrial fibrillation patients



- No DOAC on shaded days & on the day of the elective surgery or procedure.
- Dark blue arrows refer to patients with a low-bleed-risk surgical procedure**.
- **ALL endoscopic procedures considered as low-risk (like the BRIDGE Trial^).

Douketis JD et al, *JAMA Internal Medicine* 2019; ^ Douketis JD et al, *NEJM* 2015

PAUSE Cohort Study (n=3007)

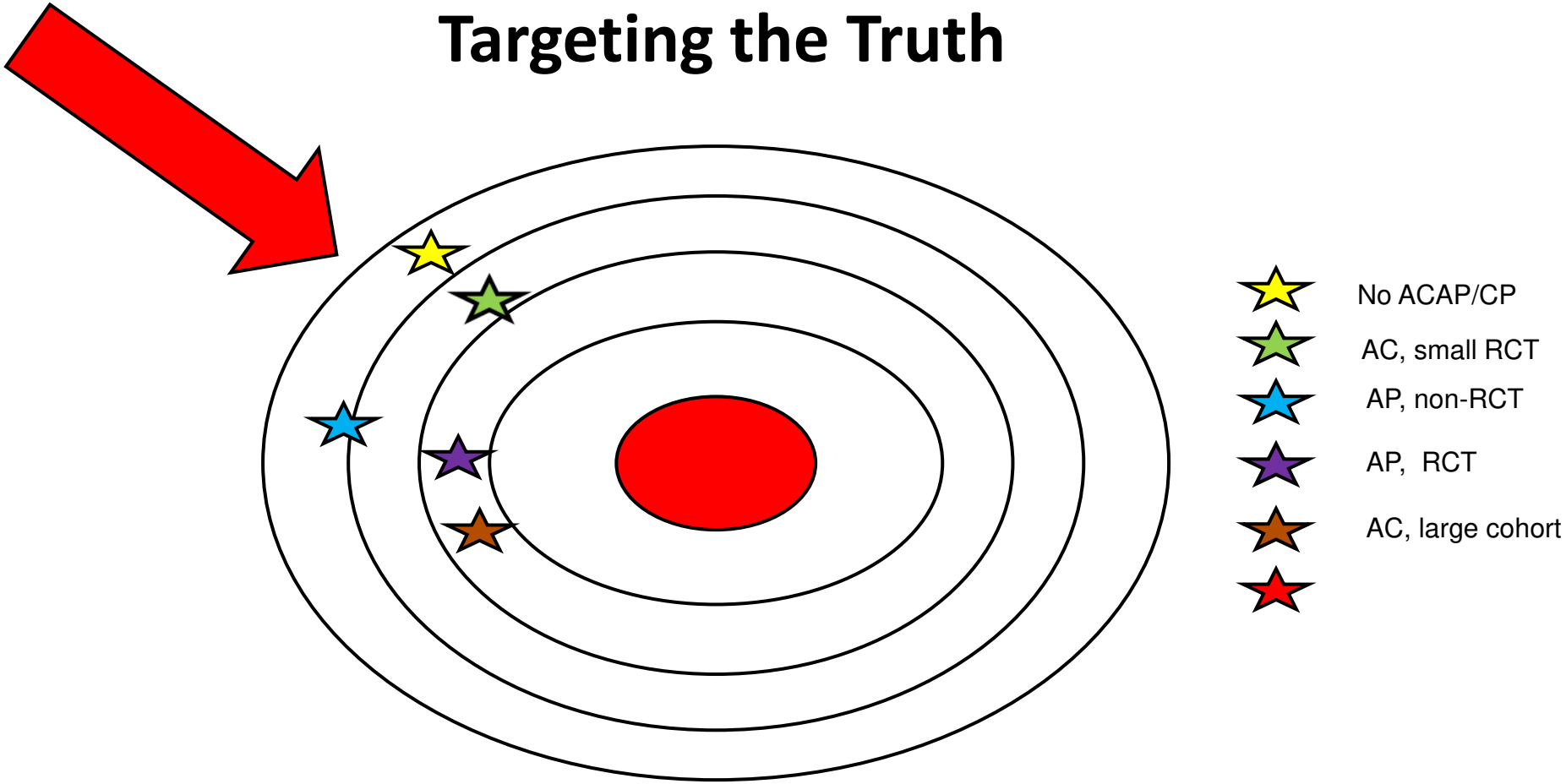
Procedure-associated bleeding risk	Apixaban cohort (n=1257)	Dabigatran etexilate cohort (n=668)	Rivaroxaban cohort (n=1082)
Low bleeding risk			
No. (%)	851 (67.7)	440 (65.9)	709 (65.5)
30-d postoperative rate of major bleeding, % (95% CI)	0.59 (0-1.20)	0.91 (0-2.01)	1.27 (0-2.17)

- Standardized management strategy *did not require heparin bridging or coagulation function testing*
- Low rates of perioperative major bleeding (<2%) and arterial thromboembolism (<1%)
- >90% overall had a minimal or no residual anticoagulant level at the time of the procedure.

- <u>Caveats of this study:</u>
  - Most GI procedures were EGD/colon with or without polypectomy
  - Few advanced endoscopic procedures (ERCP & ES, no EMR/ESD)

Douketis JD et al, *JAMA Internal Medicine* 2019

Targeting the Truth



Prophylactic Hemoclips & Delayed PPB

Dataset	Total N	Hemoclip Group n (%)	No Hemoclip Group n (%)	Important Delayed Bleed Difference, % (90% CI)
Per Protocol	1,050	12/530 (2.26%)	15/520 (2.88%)	-0.62 (2.23 to 0.99)
Intention to Treat	1,098	12/547 (2.19%)	15/551 (2.72%)	-0.53 (-2.07 to 1.01)

Study Limitations:

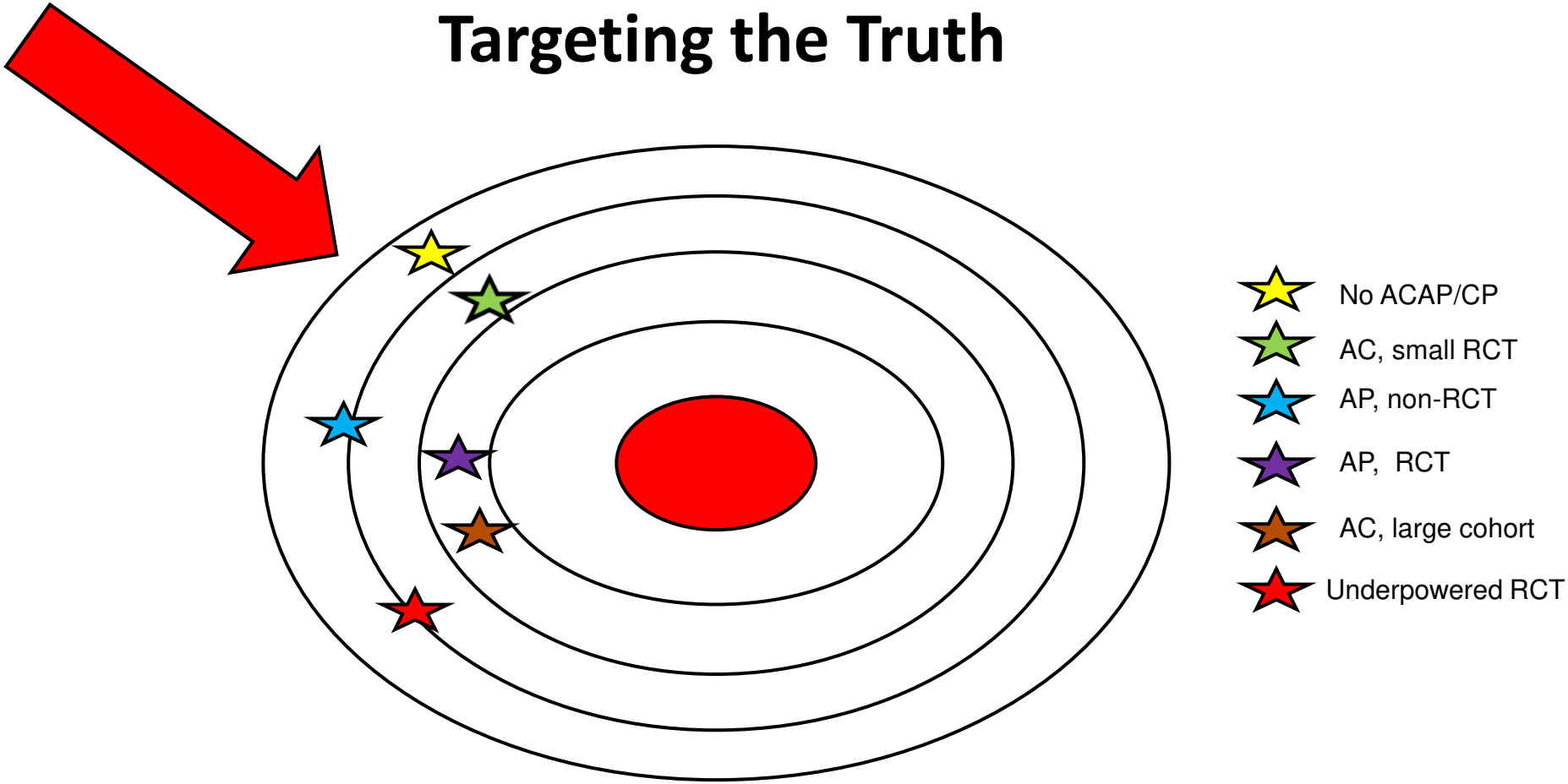
- Early termination of funding & underestimation of rate of delayed PPB (power calculation) -- study underpowered

- Few patients on antithrombotic drugs:
  - 5.7% on thienopyridine agents
  - 6.8% on warfarin
  - 1.7% on DOACs
  - 2.6% on heparin

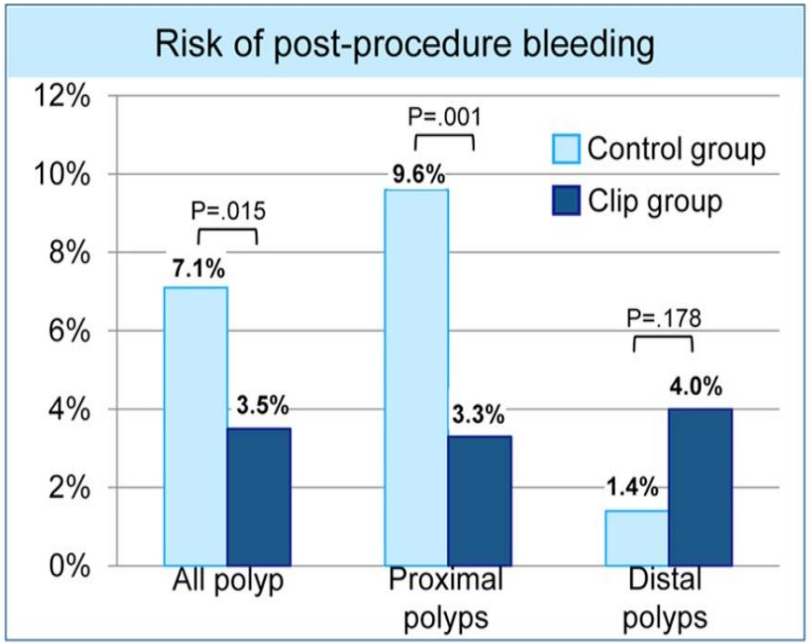
- **^Study protocol failed to standardize:**
  - **Technique (95% hot snare with or without lift technique)**
  - **Number of hemoclips placed**
  - **Bridging strategy**
  - **Strategy for temporary interruption of thienopyridine agents among recruiting sites**

Feagins LA et al, *Gastroenterology* 2019; ^Abraham NS, *GIE* 2019

Targeting the Truth



Clip Closure of Large Polyps Post-EMR



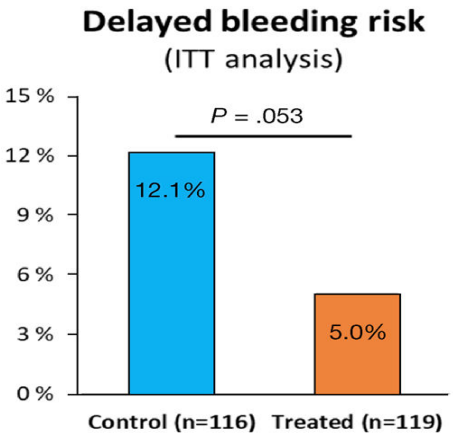
Study Design:

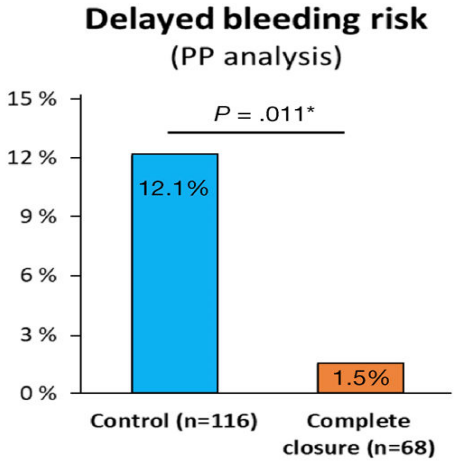
- N=919; randomized to clip vs. no clip & current setting (blended or pure coagulation) following EMR of polyps (>20 mm)
- Outcome = delayed PPB (within 30 days)
- Subgroup analysis of antithrombotic users:
  - Lower rate of delayed PPB in the clip group versus control
  - **Greater antithrombotic use in control group (34.2 %) vs. clip group (26.6%)**
  - Unmeasured confounding variables introduced by failure of randomization cannot be excluded

- **Delayed PPB reduced following clip closure (3.3% PPB with clip *vs* 9.6% without)**
- **4 clips/defect (IQR 3-6)**
- **NNT = 16 patients with proximal lesions & 71 patients with distal lesions**

Pohl H et al, *Gastroenterology* 2019

Clip Closure After Resection of Large Colorectal Lesions (>2 cm)





Crude OR	0.39
(95% CI)	(0.14, 1.04)
P-value	0.061
NNT	14

Crude OR	0.11
(95% CI)	(0.01, 0.85)
P-value	0.034*
NNT	9

Study Design:

Multi-center Spanish RCT

- 235 patients with large non-pedunculated colorectal polyps
- **Temporary interruption of antithrombotic agents** - thienopyridine X 5-7d; VKA X 5 days; DOACs 2-3 days & all AT resumed next day
- No interruption of ASA

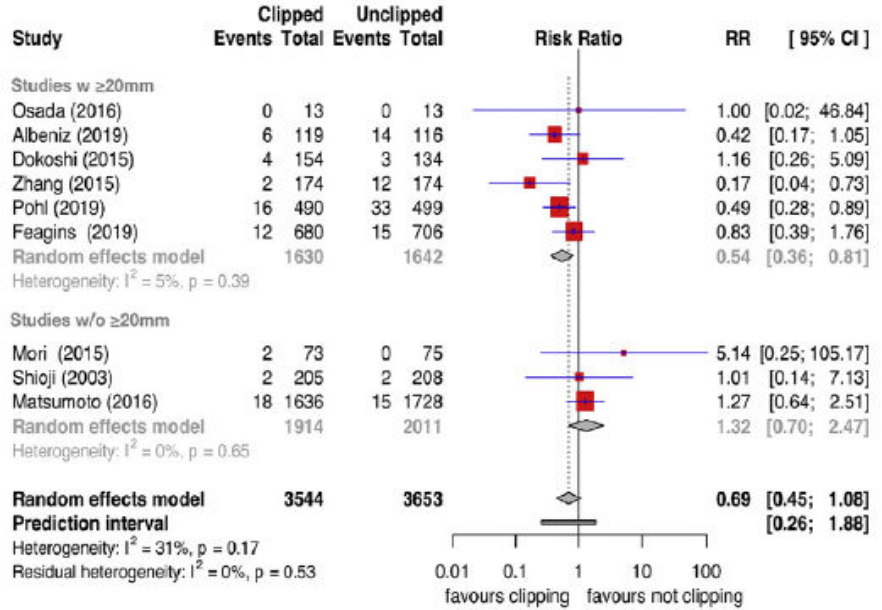
Results:

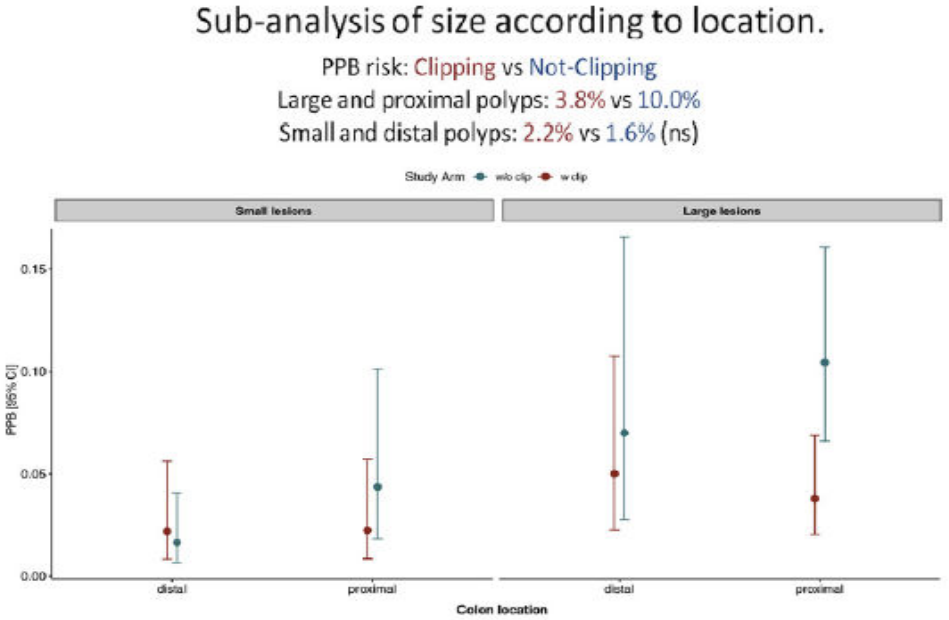
- **Protective effect limited to cases where complete closure was achieved (28.3%).**
- **2X more patients on AP in clip group (42%) vs. control (29%); balanced AC use (25-26%)**

Complete clip closure was not possible in 43% cases due to size or accessibility.

Albeniz E et al, *Gastroenterology* 2019

Prophylactic Clipping: Size Matters





- **Clipping beneficial after resection of large (> 2 cm) proximal lesions.**
- **Lack of data concerning antithrombotic therapy limit ability to infer benefit.**

Spadaccini M et al, *Gastroenterology* 2020

Prophylactic Clip Placement

You have removed a 2 cm polyp & a 1 cm polyp in a 66-year-old patient on chronic anticoagulation for non-valvular atrial fibrillation. Hemostatic clips were placed (2-3) on both mucosal defects to prevent post-polypectomy bleeding. What is the cost of prophylactic clipping to prevent a post-polypectomy bleed?

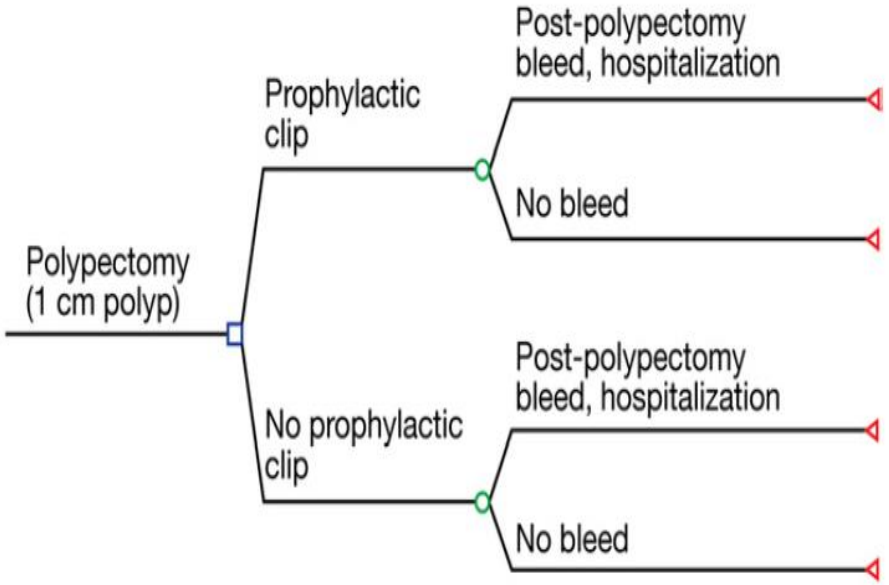
A. $1500

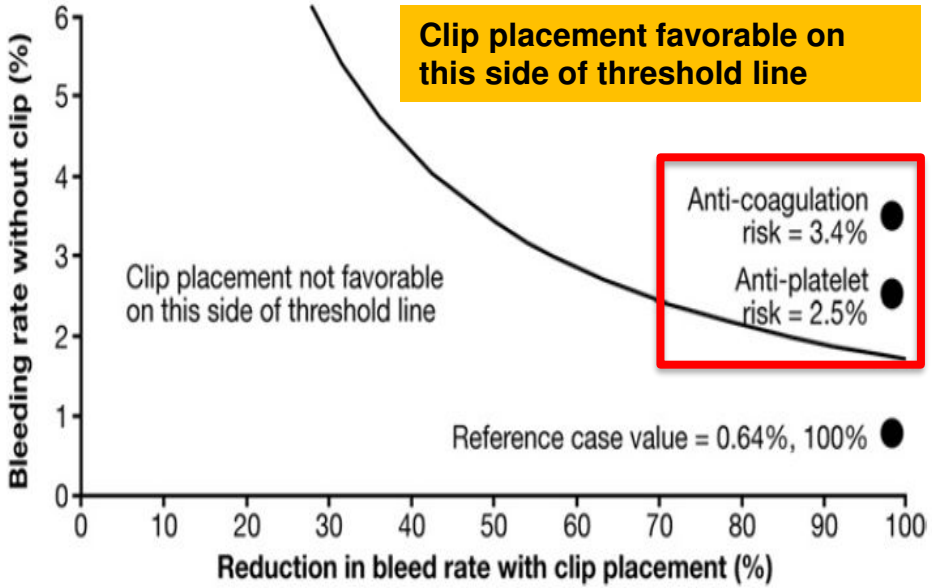
B. $3500

C. $7000

D. $11,000

Cost-effectiveness of Prophylactic Clip Use

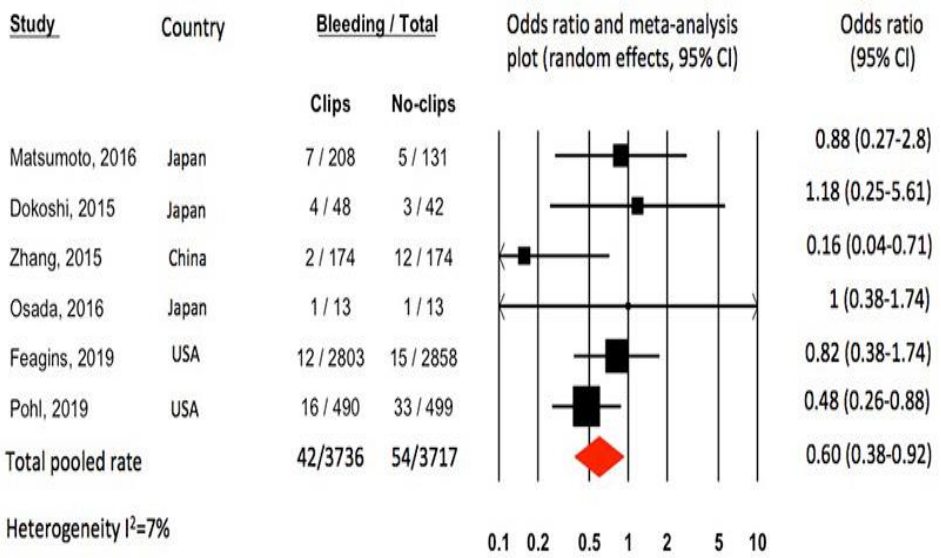




Model sensitive to the probability of PPB and cost of clips & number of clips placed

Parikh ND et al, *Clinical Gastroenterology and Hepatology* 2013

Efficacy & Cost-Effectiveness of Prophylactic Clip Closure Post-EMR (>1 cm)



Study Design:

- 6 studies
  - 2002 patients with 3736 polyps (clipping arm)
  - 1996 patients with 3717 polyps (no clipping arm)
- **Results:**
- No significant difference; antithrombotic use (p=0.57) or lesion size (p=0.79)
- **Base case of 3 clips placed in the clipping arm (=$522/clip)**
  - $1517.91 clipping
  - $1179.69 no clipping

- **Post-Polypectomy Bleeding: clip 2.3% (95% CI 0.8-6.1%) vs. no-clip 3.6% (95% CI 1.2-10.3%)**
- **Number Needed to Treat (NNT) = 77**
- **$11,274 for each PPB prevented; similar cost if the total cost of clipping is lower than $183.**

Yu J et al, *Abstract ACG* 2019

Limitations of Existing Data

- **Few studies include patients on antithrombotic agents**
- **Absence of standardization influences the PPB rate:**
  - Definition of immediate bleeding
  - Polypectomy techniques
  - Hemostatic clip placement without defined criteria
- **Rigorous observational studies & RCTs required to quantify:**
  - Baseline risk of bleeding from high-risk endoscopic GI procedures
  - Reduction of bleeding risk from discontinuation of antithrombotic therapy
  - The optimal duration of antithrombotic interruption
  - Potential benefit of non-cautery, standardized techniques

Leontiadis G et al, *Pol Arch Med Wewn* 2010; Singh M et al, *Gastrointestinal Endoscopy* 2009

Antithrombotics & Polypectomy Take-Aways

- **Estimates of immediate and delayed PPB vary widely in the literature**
  - With AC/AP held: 3.5% to 10% & with continuous AC/AP: 0.5% to 11%
  - **Insufficient quality evidence among antithrombotic patients: lack of standardization of technique & outcome definition**
- **Cold Snare Polypectomy PPB**
  - 1.8%* to 7.0%^ (no AC/AP) to 11%** (w/AC) & 3.8% to 8.5% (w/AP)^^
- **Prophylactic clipping *could be cost-effective* with the following caveats:**
  - Cost-effectiveness declines with >1 clip placed
    - 3-4 clips/polyp >1-2 cm in published RCTs (Albeniz et al. & Pohl et al. *Gastro* 2019)
  - PPB reduction depends on successful clip placement; **$11,274/PPB prevented#**

Ferlitsch, *Endoscopy* 2017; *Repici, *Endoscopy* 2012; Horiuchi, *GIE* 2014**; ^Kawamura, *GUT* 2018; ^^Chan, *Gastroenterology* 2019; Parikh, *CGH* 2013, #Yu J et al, *Abstract ACG* 2019

Questions & Discussion