UPDATE IN HOSPITAL MEDICINE FOR THE FLORIDA INTERNIST

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OCEAN REEF CLUB

KEY LARGO, FL

DISCLOSURE OF FINANCIAL RELATIONSHIPS

Ankush K Bansal

Has disclosed relationships with an entity producing, marketing, reselling, or distributing health care goods or services consumed by, or used on, patients.

- Hospitalist Employment: **Hospitalists Plus**
- Stock Holdings: TelaDoc, iSelectMD
- Telemedicine Independent Contractor: HealthTap, WellnessFX, WellVia Solutions, American Well, Video Medicine

Medical Therapy for Ureteric Colic

Robert Pickard, Kathryn Starr, Graeme MacLennan, Thomas Lam, Ruth Thomas, Jennifer Burr, Gladys McPherson, Alison McDonald, Kenneth Anson, James N'Dow, Terry Clark, Mary Kilonzo, Katie Gillies, Kirsty Shearer, Charles Boachie, Sarah Cameron, John Norrie, Samuel McClinton

Medical expulsive therapy in adults with ureteric colic: a multicentre, randomised, placebo-controlled trial

Lancet 386 (2015): 341-349

DOI: 10.1016/S0140-6736(15)60933-3

Introduction

Ureteric colic: episodic severe abdominal pain due to sustained contraction of ureteric smooth muscle as a kidney stone passes down the ureter into bladder.

2009 USA statistics: 550,000 ER visits at cost of $3 billion

Usual diagnostic & treatment course but may need drainage & stone removal by endoscopy or ESWL

Tamsulosin (α-adrenoceptor antagonist)
Nifedipine (calcium-channel stabilizer)

→ use of either agent termed Medical Expulsive Therapy (MET)

RCTs[1,2] show statistically significant benefit of either agent over placebo for spontaneous stone passage.

Nevertheless, MET adopted as part of routine expectant management - Kidney Intl 83 (2013): 479-86.

1. Campschroer, T et al. Alpha blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev 4 (2014): CD008509.
2. Seitz, C. et al. Medical therapy to facilitate the passage of stones: what is the evidence. Eur Urol 56 (2009): 455-71.

Study Design

- SUSPEND trial – Spontaneous Urinary Stone Passage Enabled by Drugs

- Goal: **Does tamsulosin or nifedipine increase likelihood of spontaneous stone passage with no need for further intervention? If so, which drug was better?**

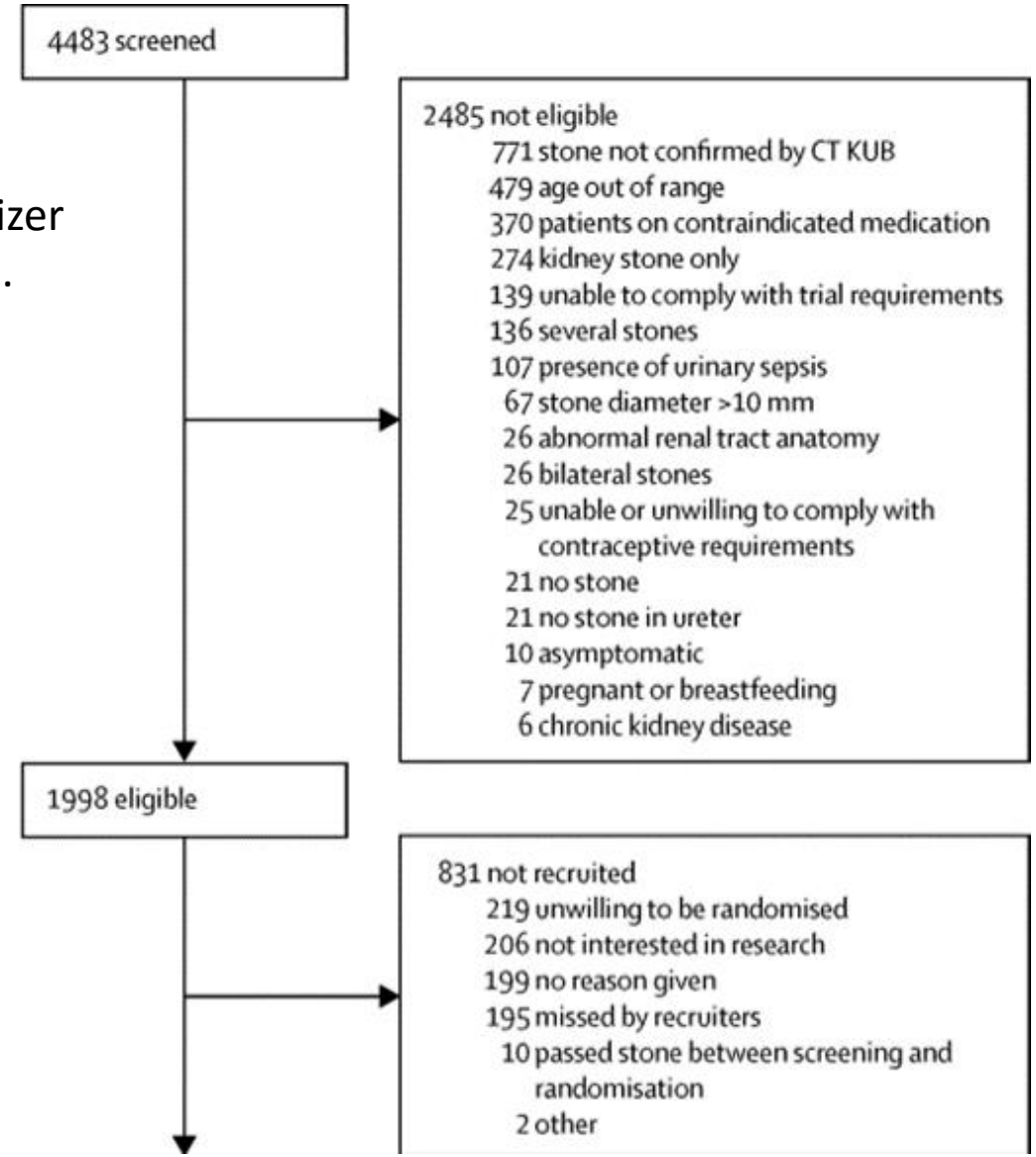
- Multi-center, randomized, placebo-controlled, modified intention to treat (primary outcome)
- Adults aged 18-65 years. Stone ≤10 mm in either ureter on CT KUB.
- 24 hospitals in United Kingdom
- Conducted 11 January 2011 to 20 December 2013 (2.94 years)
- Remote randomization 1:1:1 to :
  - Tamsulosin 0.4 mg
  - Nifedipine 30 mg
  - Placebo
- 28 capsules each participant – all capsules over-encapsulated by one independent source
- Followed up to 4 weeks
- Analyzed by:
  - Center/hospital
  - stone size (≤5 mm or >5 mm)
  - stone location (upper, mid, lower)

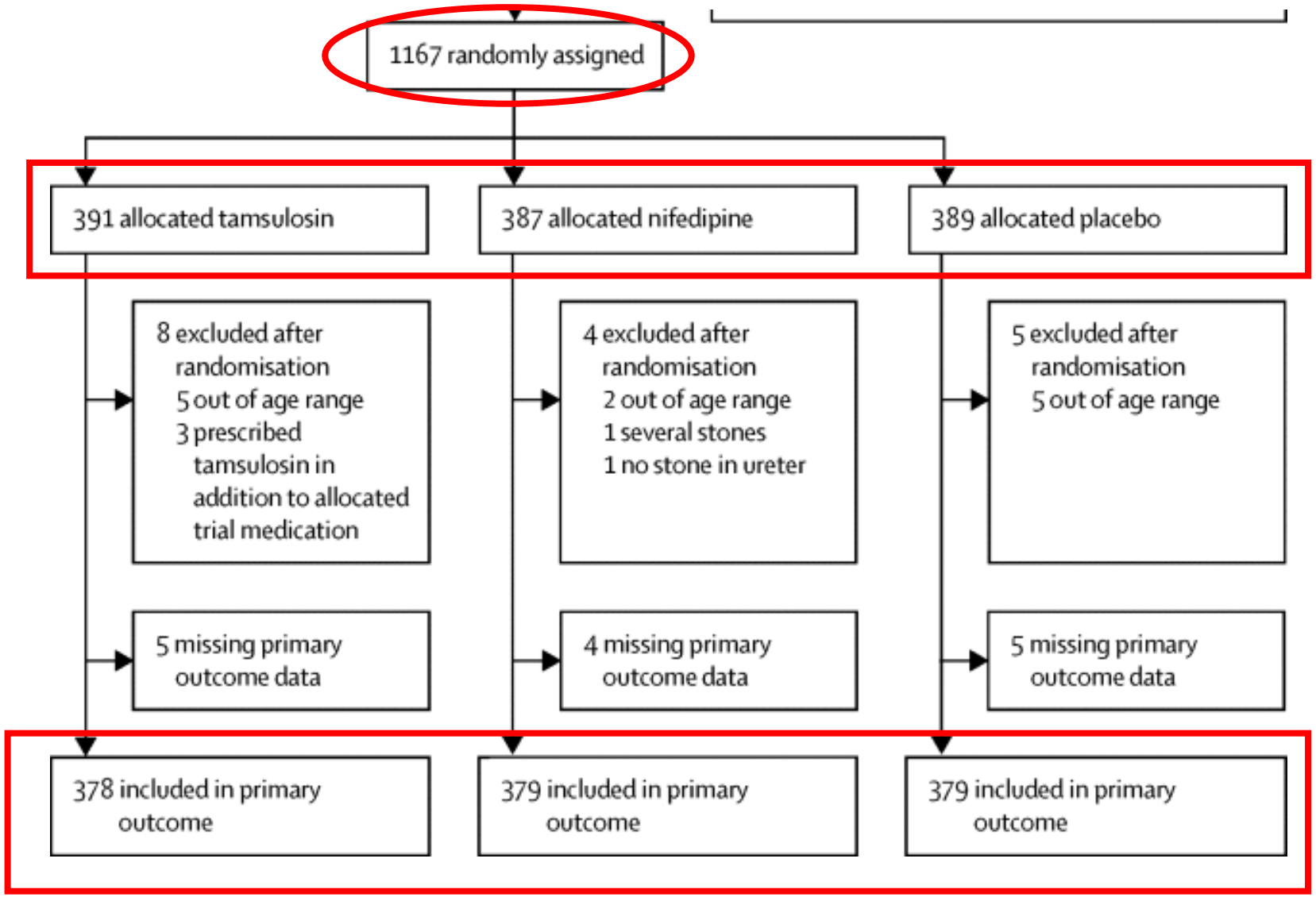
Exclusion Criteria

- Need immediate intervention by clinical assessment
- Sepsis
- eGFR <30 mL/min
- Already on or unable to take α-blocker or calcium-channel stabilizer
- Age >65 because then nifedipine dose-titration is recommended.

Procedure

- Participants self-administered medication until:
  - Spontaneous stone passage
  - Agreed need for intervention
  - 4 weeks passed
- DID NOT verify medication adherence
- Follow up questionnaires at home at 4 and 12 weeks
- Case report forms in clinic or by phone at 4 and 12 weeks
- NO mandatory testing
- Serious adverse effects reported as occurred





Powered for hypothesis that: number of participants with stone passage in tamsulosin group would be 10% higher than in nifedipine group.

Comparisons:

- **MET against placebo**
- **Tamsulosin against nifedipine**
- **Tamsulosin against placebo**
- **Nifedipine against placebo**

90% power, Type 1 error of 5%:
Need 1062 participants (354 in each group) but:
Inflated to 1200 to allow 10% loss to follow up.

17 excluded to ineligibility
14 lost to follow up

= 1136 (97%) in primary analysis

Outcomes

- Primary: spontaneous stone passage at 4 weeks (no need for intervention to assist with stone passage at 4 weeks)

- Secondary:
  - Pain by number of days of analgesic use (participant-reported) and visual analogue scale at 4 weeks
  - Time to stone passage assessed by imaging
  - Health status by SF-36 questionnaire
  - Safety by participant report of medication discontinuation due to adverse effects
  - Health outcomes by EQ-5D questionnaire (not reported in this paper)
  - Health care resource use and participant cost (not reported in this paper)

Baseline Characteristics

	Tamsulosin (n=383)	Nifedipine (n=383)	Placebo (n=384)
Age, years	43·1 (11·5)	42·3 (11·0)	42·8 (12·3)
Women	68 (18%)	66 (17%)	85 (22%)
Stone size, mm	4·6 (1·6)	4·5 (1·6)	4·5 (1·7)
≤5 mm	287 (75%)	286 (75%)	286 (74%)
>5 mm	96 (25%)	97 (25%)	98 (26%)
Stone location			
Upper ureter	94 (25%)	89 (23%)	93 (24%)
Middle ureter	40 (10%)	43 (11%)	44 (11%)
Lower ureter	249 (65%)	251 (66%)	247 (64%)
History of previous stone episode	130 (34%)	118 (31%)	137 (36%)
Duration of pain, days	3·0 (5·1)	2·6 (3·3)	3·2 (5·5)
Pain visual analogue score*	4·0 (3·4)	3·9 (3·4)	3·6 (3·2)
Analgesic medication before admission			
Non-steroidal anti-inflammatory drug	132 (34%)	110 (29%)	117 (30%)
Opiate	63 (16%)	67 (17%)	81 (21%)
Other	79 (21%)	86 (22%)	79 (21%)
Analgesic medication on admission			
Non-steroidal anti-inflammatory drug	279 (73%)	289 (75%)	278 (72%)
Opiate	224 (58%)	230 (60%)	230 (60%)
Other	127 (33%)	141 (37%)	133 (35%)
Antibiotic medication on admission	38 (10%)	46 (12%)	41 (11%)
SF-36 physical score†	47·0 (9·0)	46·5 (9·2)	46·1 (9·7)
SF-36 mental score†	50·2 (10·8)	50·6 (10·8)	49·6 (11·6)

Results

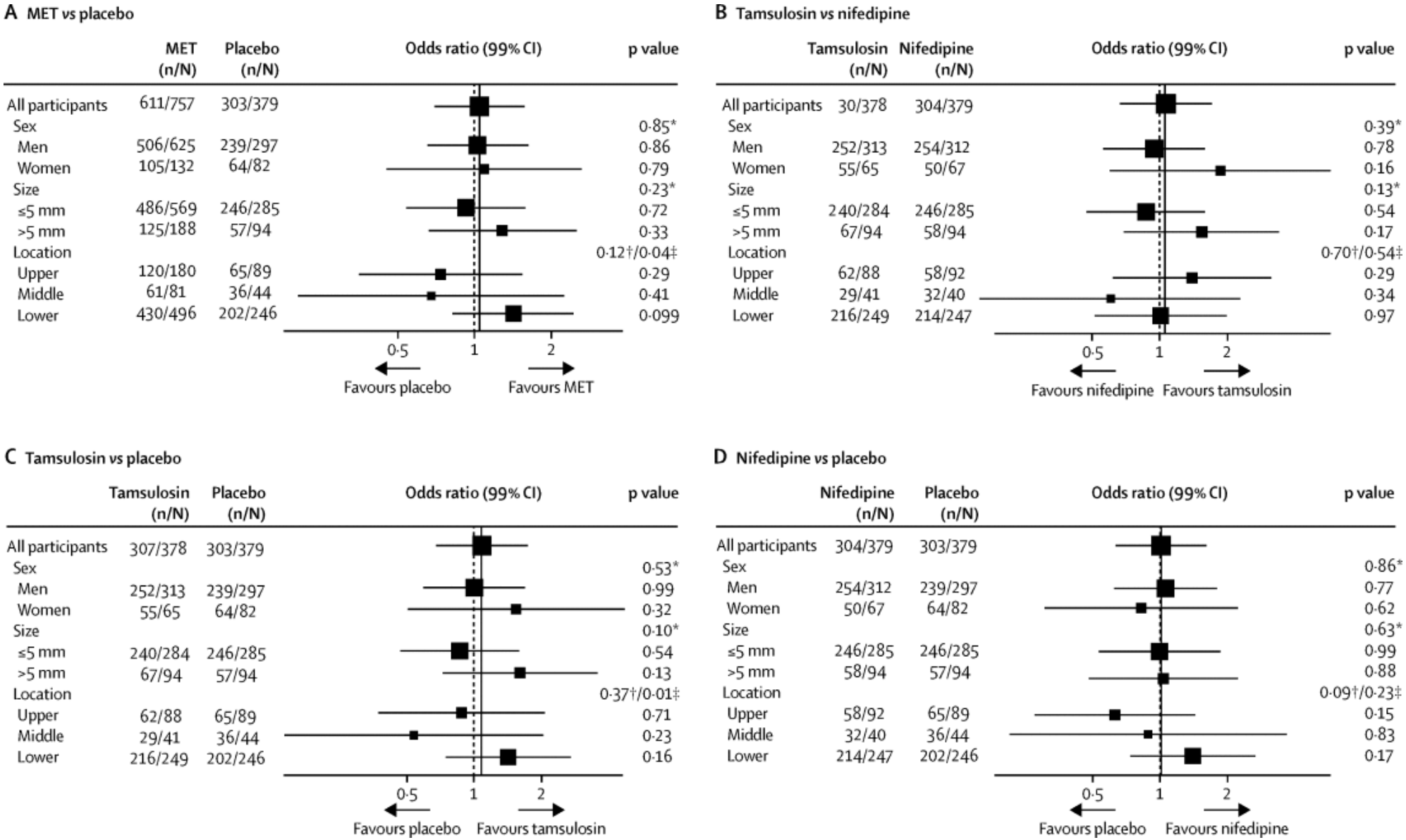
- 80% in placebo group did not need further intervention by 4 weeks
- 81% in tamsulosin group did not need further intervention by 4 weeks (ARR 1.3%, p=0.73) ∴ NNT=77
- 80% in nifedipine group did not need further intervention by 4 weeks (ARR 0.5%, p=0.88) ∴ NNT=200
- Consistent findings across 3 groups (gender, stone size, stone location)
- Between nifedipine or tamsulosin and placebo, p=0.78
- Between nifedipine and tamsulosin, p=0.77
- Also: <u>NO difference in stone passage at 12 weeks</u>
  - 7% in tamsulosin group had intervention planned
  - 6% in nifedipine group had intervention planned
  - 7% in placebo group had intervention planned
- <u>NO differences in secondary outcomes of analgesic use, time to stone passage, health status between groups</u>

- Adverse events:
  - Nifedipine: 3 participants – 1 had right groin pain, diarrhea, vomiting; 1 had malaise, headache, chest pain; 1 had chest pain, dyspnea, left arm pain
  - Placebo: 1 participant – headache, dizziness, lightheadedness

Primary Outcome Results

	Odds ratio (95% CI); p value	Risk difference (95% CI)
MET vs placebo		
Unadjusted	1·04 (0·77–1·43); 0·76	0·8% (–4·1 to 5·7)
Adjusted	1·06 (0·70–1·60); 0·78	0·9% (–5·1 to 6·8)
Tamsulosin vs nifedipine		
Unadjusted	1·07 (0·74–1·53); 0·73	1·0% (–4·6 to 6·6)
Adjusted	1·06 (0·73–1·53); 0·77	0·8% (–4·5 to 6·1)
Tamsulosin vs placebo		
Unadjusted	1·08 (0·76–1·56); 0·76	1·2% (–4·4 to 6·9)
Adjusted	1·09 (0·67–1·78); 0·73	1·3% (–5·7 to 8·3)
Nifedipine vs placebo		
Unadjusted	1·02 (0·71–1·45); 0·93	0·2% (–5·4 to 5·9)
Adjusted	1·03 (0·68–1·56); 0·88	0·5% (–5·6 to 6·5)

Subgroup Analyses



Pain and Time to stone passage (adjusted)

	Tamsulosin	Nifedipine	Placebo	Difference (95% CI); p value
Pain variables				
Number of patients	247	239	231	
Any self-reported use of pain medication in first 4 weeks*	139 (56%)	133 (56%)	136 (59%)	
Number of days pain medication				
Mean (SD)	11·6 (8·7)	10·7 (9·0)	10·5 (8·2)	
Median (IQR)	10 (4–17)	7 (4–14)	7 (4–14)	
MET *vs* placebo†	..	..	..	0·6 (–1·6 to 2·8); 0·45
Tamsulosin *vs* nifedipine†	..	..	..	0·8 (–1·6 to 3·2); 0·50
VAS pain scale at 4 weeks				
Number of patients	233	231	216	
Mean score (SD)	1·0 (2·0)	1·3 (2·2)	1·2 (2·2)	
MET *vs* placebo†	..	..	..	0 (–0·4 to 0·4); 0·96
Tamsulosin *vs* nifedipine†	..	..	..	–0·3 (–0·7 to 0·1); 0·095
Time to stone passage				
Number of patients	79	74	84	
Mean time, days (SD)	16·5 (12·6)	16·2 (14·5)	15·9 (11·3)	
Median time, days (IQR)	14 (5–27)	13 (4–26)	14 (5–25)	
MET *vs* placebo				
Unadjusted	..	..	..	0·5 (–2·9 to 3·9); 0·78
Adjusted	..	..	..	0·6 (–2·6 to 4·0); 0·71
Tamsulosin *vs* nifedipine				
Unadjusted	..	..	..	0·4 (–3·7 to 4·4); 0·86
Adjusted	..	..	..	0·6 (–2·5 to 3·7); 0·72

Conclusion

Tamsulosin 0.4 mg and nifedipine 30 mg are no better than placebo at decreasing need for further treatment for stone clearance at 4 weeks and 12 weeks in those with expectantly managed ureteric colic.

No evidence that either drug reduced pain, hastened time to stone passage, or improved health state.

Therefore, these drugs should not be offered in ureteric colic when managed expectantly.

IVC Filter + AC vs AC alone in PE recurrence

Patrick Mismetti, Silvy Laporte, Olivier Pellerin, Pierre-Vladimir Ennezat, Francis Couturaud, Antoine Elias, Nicolas Falvo, Nicolas Meneveau, Isabelle Quere, Pierre-Marie Roy, Olivier Sanchez, Jeannot Schmidt, Christophe Seinturier, Marie-Antoinette Sevestre, Jean-Paul Beregi, Bernard Tardy, Philippe Lacroix, Emilie Presles, Alain Leizorovicz, Hervé Decousus, Fabrice-Guy Barral, Guy Meyer, PREPIC2 Study Group

Effect of a retrievable inferior vena cava filter plus anticoagulation vs anticoagulation alone on risk of recurrent pulmonary embolism: A randomized clinical trial

JAMA 313 (2015): 1627-1635

DOI: 10.1001/jama.2015.3780

Introduction

- Sharp increase in use of IVC filters in last 30 years, including as add-on to anti-coagulation [1-3]
- Unclear benefit to risk analysis in literature regarding adding retrievable inferior vena cava filter to anti-coagulation for acute venous thromboembolism (DVT, PE)

1. Stein, PD et al. Twenty-one-year trends in the use of inferior vena cava filters. Arch Intern Med 164 (2004): 1541-1545.
2. Stein, PD et al. Increasing use of vena cava filters for prevention of pulmonary embolism. Am J Med 124 (2011): 655-661.
3. Spencer, FA et al. A population-based study of inferior vena cava filters in patients with acute venous thromboembolism. Arch Intern Med 170 (2010): 1456-1462.

Study Design

- PREPIC2 trial – Prévention du Risque d'Embolie Pulmonaire par Interruption Cave 2

- Goal of this study: **Evaluate efficacy and safety of retrievable IVC filters + anti-coagulation vs anti-coagulation alone for preventing PE recurrence in patients with acute PE and high risk of recurrence.**

- Multi-center, randomized, open-label, blinded end-point, intention to treat trial with 6 month follow up
- 17 centers (hospital & ambulatory follow up) in France
- Conducted August 2006 to January 2013 (6.5 years)

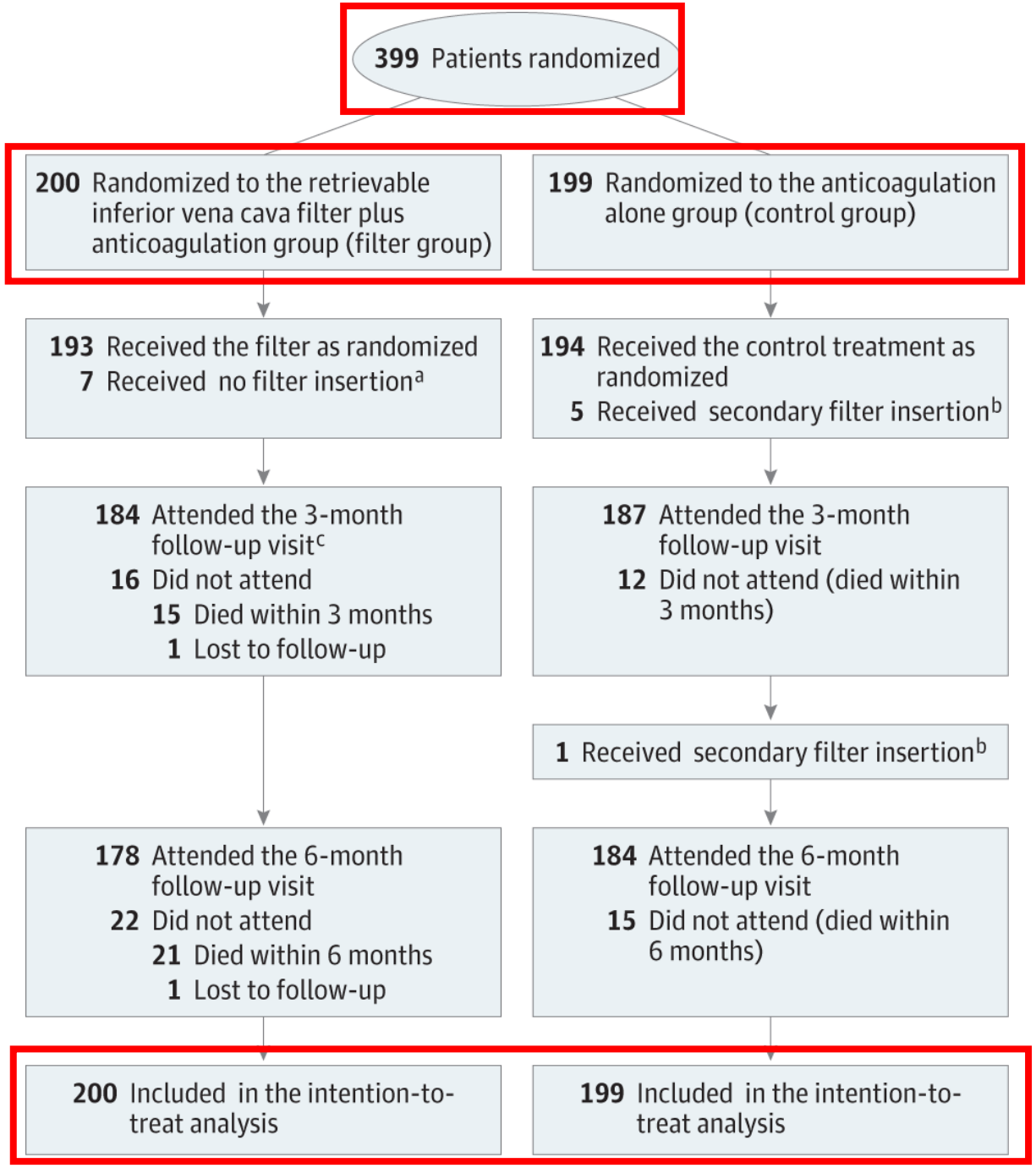
- Hospitalized patients, aged ≥18
- **Acute, symptomatic PE with LE vein thrombosis (deep or superficial)** and ≥1 severity criterion:
  - Age >75 • Active cancer • Chronic cardiac or respiratory insufficiency
  - Ischemic stroke with leg paralysis 3 days to 6 months before randomization
  - DVT involving iliocaval segment or bilateral
  - 1 sign of RV dysfunction or myocardial injury
    - RV dilation or pulmonary HTN on echo or abnormal BNP, N-terminal pro-BNP, troponin T or I
- Diagnosis by:
  - PE – spiral CT, V/Q, or pulmonary angio • DVT of LE – bilateral compression ultrasound or venography
- Randomization to:
  - Retrievable IVC filter implantation + anti-coagulation (200) • Anti-coagulation alone without IVC filter (199)

Exclusion Criteria

- Transient or permanent contraindication to anti-coagulation
- Recurrent VTE despite adequate anti-coagulant therapy
- IVC filter already inserted or could not insert filter due to vena caval thrombosis
- Patient already on full-dose anti-coagulation >72 hours before randomization
- Non-cancer surgery in prior 3 months or cancer surgery in prior 10 days
- Allergy to iodinated contrast • Serum creatinine >2.04 mg/dL • Life expectancy <6 months • Pregnant

Procedure

- Randomization by central IVR for concealed allocation, stratified by center and CrCl (Cockgroft-Gault)
- Full-dose anti-coagulation for minimum 6 months for all patients (thereafter at investigator discretion)
- Used any injectable anti-coagulant followed by vitamin K antagonist ASAP (unless cancer)
- Placement of retrievable IVC filter in filter group (randomized) within 72 hours (36 hours delay if thrombolyzed) - by IR
- Filter retrieval at 3 months from placement in filter group – by vascular/interventional radiology (IR)
- Cavography before and after filter placement • Abdominal x-ray 24-48 hours after placement
- Ultrasound or venography prior to filter retrieval to detect filter thrombosis • Cavography after retrieval
- Follow up visits at 3 and 6 months
- Immediate reporting of S/S suggesting VTE or bleeding between visits



- **8% incidence** in primary efficacy outcome based on prior studies on rates of recurrent fatal PE and case fatality rates of VTE.
- Prior study – 82% risk reduction in recurrent PE with permanent IVC filter + AC vs AC alone.

Powered for hypothesis: 75% risk reduction of primary outcome in filter group.

80% power:
Need 200 patients per group.

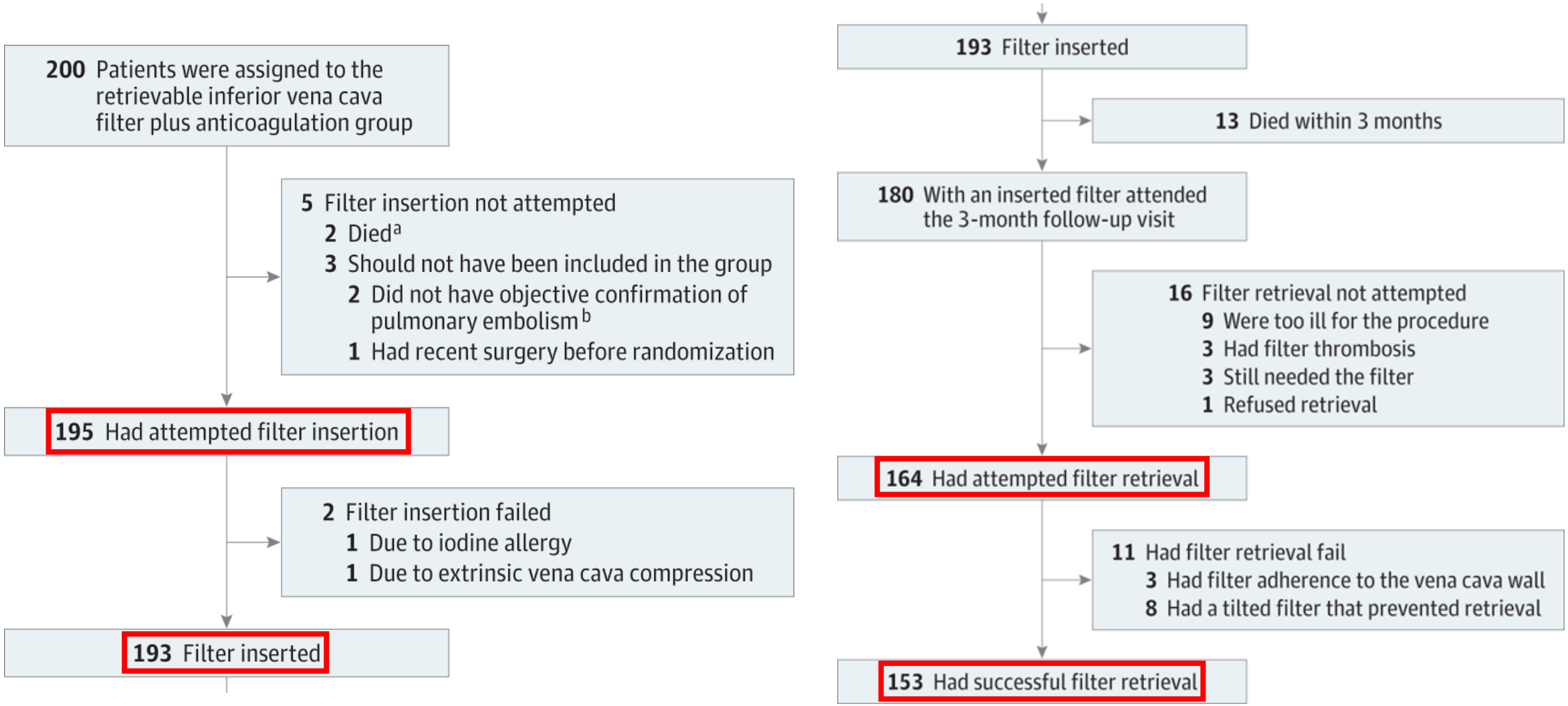
Mean time from randomization to filter insertion attempt:
1.5 days ± 0.6

Table 1. Baseline Characteristics of the Patients in the PREPIC2 Trial[a]

	Group, No. (%)	
	Filter (n = 200)	Control (n = 199)
Age, mean (SD), y	74.2 (10.8)	72.7 (12.4)
Women	102 (51.0)	105 (52.8)
BMI ≥30	52 (27.7)	48 (25.0)
Creatinine clearance category, mL/min		
<30	1 (0.5)	5 (2.5)
30-<50	41 (20.5)	34 (17.1)
≥50	158 (79.0)	160 (80.4)
Risk factors for venous thromboembolism		
Personal history of venous thromboembolism	70 (35.0)	71 (35.7)
History of cancer (excluding active cancer)[b]	15 (7.5)	23 (11.6)
Hormone therapy[c]	18 (9.0)	13 (6.5)
Known thrombophilia	2 (1.0)	2 (1.0)
Main characteristics of the index pulmonary embolism		
Unprovoked[d]	148 (74.0)	158 (79.4)
Objectively confirmed	198 (99.0)	199 (100.0)
With a systolic blood pressure <100 mm Hg at least once	35 (17.9)	20 (10.9)
Concurrent Symptomatic Venous Thrombosis		
Vein thrombosis		
Proximal deep	137 (68.8)	138 (69.7)
Isolated distal deep	57 (28.6)	54 (27.3)
Isolated superficial	5 (2.5)	6 (3.0)
Severity criteria for eligibility		
Aged >75 y	110 (55.0)	99 (49.7)
Active cancer[b]	33 (16.6)	29 (14.6)
Chronic respiratory failure[e]	35 (17.5)	19 (9.5)
Chronic heart failure[e]	18 (9.0)	17 (8.5)
Ischemic stroke with leg paralysis within the past 6 mo	4 (2.0)	4 (2.0)
Deep vein thrombosis involving the iliocaval segment	18 (9.0)	17 (8.5)
Bilateral deep vein thrombosis	26 (13.0)	27 (13.6)
At least 1 sign of right ventricular dysfunction or myocardial injury[f]	126 (66.7)	120 (65.2)

Table 2. Characteristics of Antithrombotic Treatment Received During the PREPIC2 Trial

	Group, No. (%)	
	Filter (n = 200)	Control (n = 199)
Thrombolytic therapy	4 (2.0)	2 (1.0)
Main initial parenteral anticoagulation[a]	200 (100.0)	199 (100.0)
Low-molecular-weight heparin	120 (60.0)	113 (56.8)
Unfractionated heparin	46 (23.0)	44 (22.1)
Fondaparinux	34 (17.0)	42 (21.1)
Duration in patients receiving subsequent vitamin K antagonist therapy, median (IQR), d[b,c]	12 (8-24)	11 (7-22)
Long-term parenteral therapy	34 (17.0)	22 (11.1)
Duration in patients not receiving subsequent vitamin K antagonist therapy, median (IQR), d[b]	184 (171-196)	183 (171-187)
Vitamin K antagonist[d]	166 (83.0)	177 (88.9)
INR at the time initial parenteral therapy was stopped, median (IQR)[e]	2.3 (2.0-2.7)	2.3 (2.1-2.7)
Duration, median (IQR), d[b,c]	182 (170-187)	181 (171-187)
Median percentage of time spent with INR in a given range, %		
<2.0	19.7	15.9
2.0-3.0	58.3	61.5
>3.0	11.8	13.7


200 Patients were assigned to the retrievable inferior vena cava filter plus anticoagulation group
5 Filter insertion not attempted
2 Died[a]
3 Should not have been included in the group
2 Did not have objective confirmation of pulmonary embolism[b]
1 Had recent surgery before randomization
195 Had attempted filter insertion
2 Filter insertion failed
1 Due to iodine allergy
1 Due to extrinsic vena cava compression
193 Filter inserted
193 Filter inserted
13 Died within 3 months
180 With an inserted filter attended the 3-month follow-up visit
16 Filter retrieval not attempted
9 Were too ill for the procedure
3 Had filter thrombosis
3 Still needed the filter
1 Refused retrieval
164 Had attempted filter retrieval
11 Had filter retrieval fail
3 Had filter adherence to the vena cava wall
8 Had a tilted filter that prevented retrieval
153 Had successful filter retrieval

Outcomes

- Primary: fatal or symptomatic, recurrent pulmonary embolism at 3 months

- Secondary:
  - Fatal or symptomatic, recurrent PE at 6 months
  - New or recurrent, symptomatic DVT at 3 or 6 months
  - Major bleeding
  - Death from any cause at 3 and 6 months
  - Filter complications (from insertion to retrieval)
    - Thrombosis
    - Migration
    - Tilting
    - Penetration of vena cava wall
    - Access site hematoma
    - Infection

Results

- Filters placed in 193 patients. Retrieved in 153 of 164 in those attempted
- At 3 months:
  - 3% of those in filter group had recurrent PE – all were fatal
  - 1.5% of those in no filter group had recurrent PE – 2 of 3 cases were fatal
  - No difference between two groups (p=0.50)
- Results same at 6 months
- 1 additional PE recurrence in each group between 3 and 6 months
- No difference between two groups in other outcomes (DVT, major bleeding, all-cause death)

- Adverse events:
  - Filter thrombosis – 1.6%
  - Access site hematoma – 2.6%
  - Retrival failure – 5.7%
  - Cardiac arrest during filter insertion – 1 patient

  - In control group: 6 required filter insertion
    - 4 because of planned procedure/surgery
    - 2 because of bleeding complication

Table 3. Clinical Outcomes For Patients With at Least 1 Event in the PREPIC2 Trial

Clinical Outcomes	Group, No. With Events (%)		Relative Risk, % (95% CI)	*P* Value[b]
	Filter (n = 200)[a]	Control (n = 199)		
At 3 Months				
Recurrent pulmonary embolism (primary efficacy outcome)[c]	6 (3.0)	3 (1.5)	2.00 (0.51-7.89)	.50
Fatal	6 (3.0)	2 (1.0)		
Nonfatal	0 (0.0)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	1 (0.5)	1.00 (0.06-15.9)	>.99
Recurrent venous thromboembolism	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.36
Major bleeding	8 (4.0)	10 (5.0)	0.80 (0.32-1.98)	.63
Death	15 (7.5)	12 (6.0)	1.25 (0.60-2.60)	.55
At 6 Months				
Recurrent pulmonary embolism[c]	7 (3.5)	4 (2.0)	1.75 (0.52-5.88)	.54
Fatal	6 (3.0)	3 (1.5)		
Nonfatal	1 (0.5)	1 (0.5)		
Recurrent deep vein thrombosis	1 (0.5)	2 (1.0)	0.50 (0.05-5.47)	>.99
Recurrent venous thromboembolism	8 (4.0)	6 (3.0)	1.33 (0.47-3.77)	.59
Major bleeding	13 (6.5)	15 (7.5)	0.87 (0.42-1.77)	.69
Death	21 (10.6)	15 (7.5)	1.40 (0.74-2.64)	.29

Conclusion

Compared with anti-coagulation alone, placement of a retrievable inferior vena cava filter for 3 months in addition to anti-coagulation provided no benefit in terms of pulmonary embolism recurrence or mortality in patients presenting with acute symptomatic pulmonary embolism.

Previous studies showed that filters do not reduce overall mortality – NEJM 338 (1998): 409-415; Circulation 112 (2005): 416-422.

Therefore, use of a retrievable filter when the patient can be treated with anti-coagulation is not supported.

Notes:

- Low rate of events in control group was consistent with contemporary care so full-dose anti-coagulation is likely effective in patients at high risk for recurrence. Further, those at high risk for recurrence are often also at high risk of major bleeding.
- Single source & model of filter. Lack of evidence of efficacy difference between retrievable filter models.
- Excluded those with anti-coagulation contraindication or recurrence due to ethical considerations.
- But included those with hemodynamic instability.

Screening for Occult Cancer in First Unprovoked VTE

Marc Carrier, Alejandro Lazo-Langner, Sudeep Shivakumar, Vicky Tagalakis, Ryan Zarychanski, Susan Solymoss, Nathalie Routhier, James Douketis, Kim Danovitch, Agnes Lee, Gregoire Le Gal, Philip Wells, Daniel Corsi, Timothy Ramsay, Doug Coyle, Isabelle Chagnon, Zahra Kassam, Hardy Tao, Marc Rodger, SOME Investigators

Screening for occult cancer in unprovoked venous thromboembolism

NEJM 373 (2015): 697-704

DOI: 10.1056/NEJMoa1506623

Introduction

- VTE (DVT and PE) is 3rd most common cardiovascular disorder [1-3]

- Provoked: transient risk factor (trauma, surgery, prolonged immobility, pregnancy, puerperium)
- Unprovoked: no strong transient risk factor or overt cancer

- 10% patients with unprovoked VTE are diagnosed with cancer within 1 year. 60% are diagnosed soon after DVT.
- Then, incidence of cancer diagnosis declines and returns to general population rate after 1 year.

- Some studies have shown that adding CT abdomen & pelvis and/or tumor marker measurement to standard testing (labs, CXR) may significantly increase occult cancer detection rate.

1. Cohen, AT et al. Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 98 (2007): 756-764.
2. White, RH. The epidemiology of venous thromboembolism. Circulation 107 (2003): S1: I4-I8.
3. Anderson, FA et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism: the Worcester DVT study. Arch Intern Med 151 (1991): 933-938.

Study Design

- SOME trial – Screening for Occult Malignancy in patients with idiopathic venous thromboEmbolism

- Goal of this study: **Assess efficacy of screening strategy for occult cancer including comprehensive CT of abdomen & pelvis in patients with first, unprovoked VTE.**

- Multi-center, randomized controlled, open-label, intention to treat, with sensitivity analysis (exclude non-adherent)
- 9 centers (hospital & ambulatory follow up) in Canada
- Conducted October 2008 to April 2014 (5.5 years)

- Patients with new diagnosis of first, unprovoked, symptomatic VTE referred to a thrombosis clinic
- Unprovoked:
  - No known overt cancer • Not currently pregnant • No thrombophilia (acquired or hereditary)
  - No previous unprovoked VTE
  - In last 3 months did not have:
    - Paralysis • Paresis • Plaster immobilization of LE • Confinement to bed ≥3 days • Major surgery

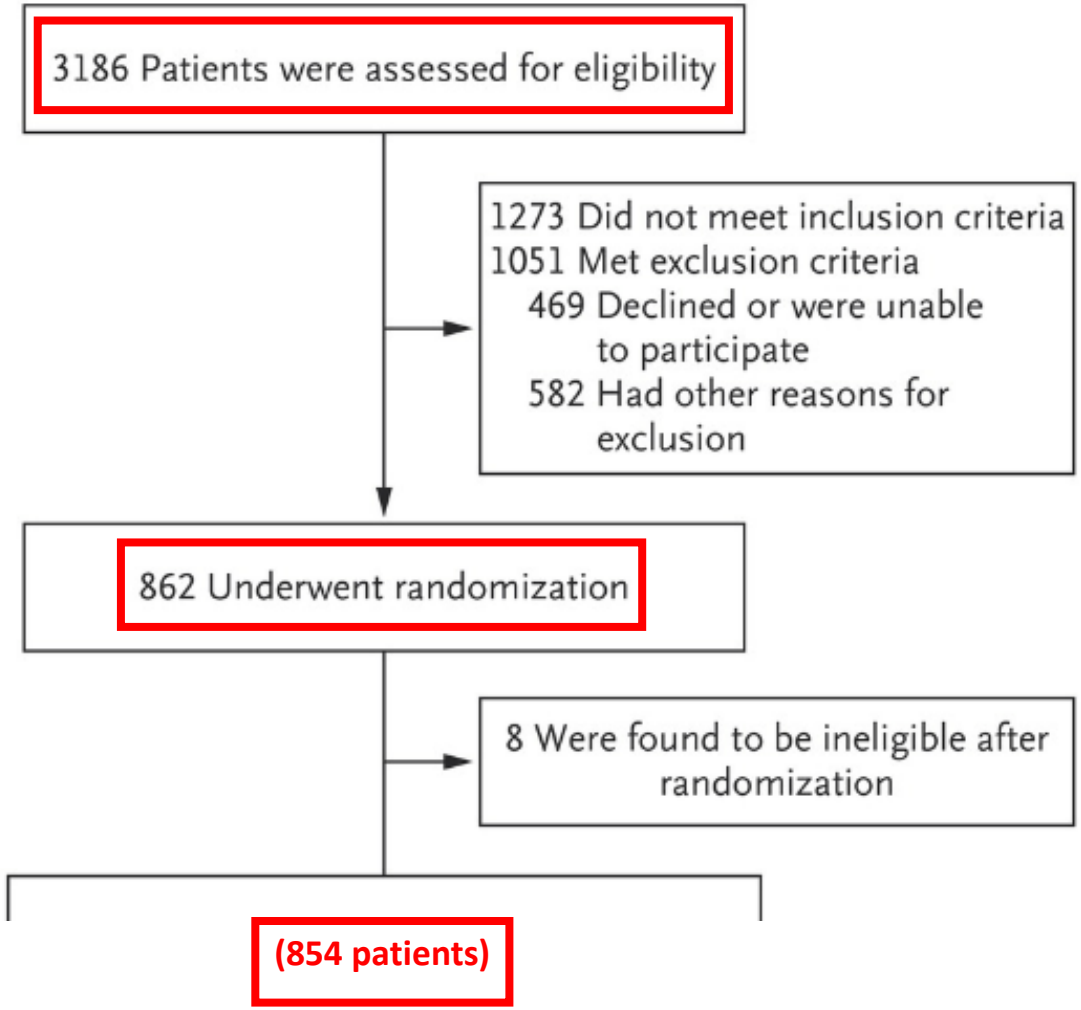
- Randomization with stratification according to center and age (<50, ≥50) within 21 days of VTE diagnosis.

Exclusion Criteria

- Age <18
- Refusal/inability to provide informed consent
- Contrast allergy
- GFR <60
- Claustrophobia/agoraphobia
- Mass >130 kg
- Ulcerative colitis
- Glaucoma

Procedure

- Randomization by web to ensure concealment
- Limited screening: H&P, CBC, CMP, CXR
  - Also sex-specific screening if not done in previous year per USPSTF and CTFPHC
    - Female: Breast exam, mammography if age >50, Pap & pelvic for age 18-70
    - Male: Prostate exam, PSA if age >40
- Limited + CT
  - Bowel prep followed by:
  - Virtual colonoscopy & gastroscopy
  - Biphasic enhanced CT liver & pancreas
  - Uniphasic unenhanced CT bladder
  - Abnormal findings investigated by local physician
- Followed for 1 year, assessed at fixed intervals
  - Checklist – new cancer diagnosis, recurrent VTE, other adverse events
  - If suspected cancer, required biopsy confirmation
  - If recurrent VTE, objective tests for confirmation



Previous studies: 6.1% have occult cancer at time of diagnosis of unprovoked VTE

At 12 months, prevalence was 10%

Power: 80% to detect RR of 75% (ARR 3%) if CT added
Null: limited + CT would miss as many as limited alone
Need sample size of 798. Assumed 8% non-adherence, so **sample = 862**

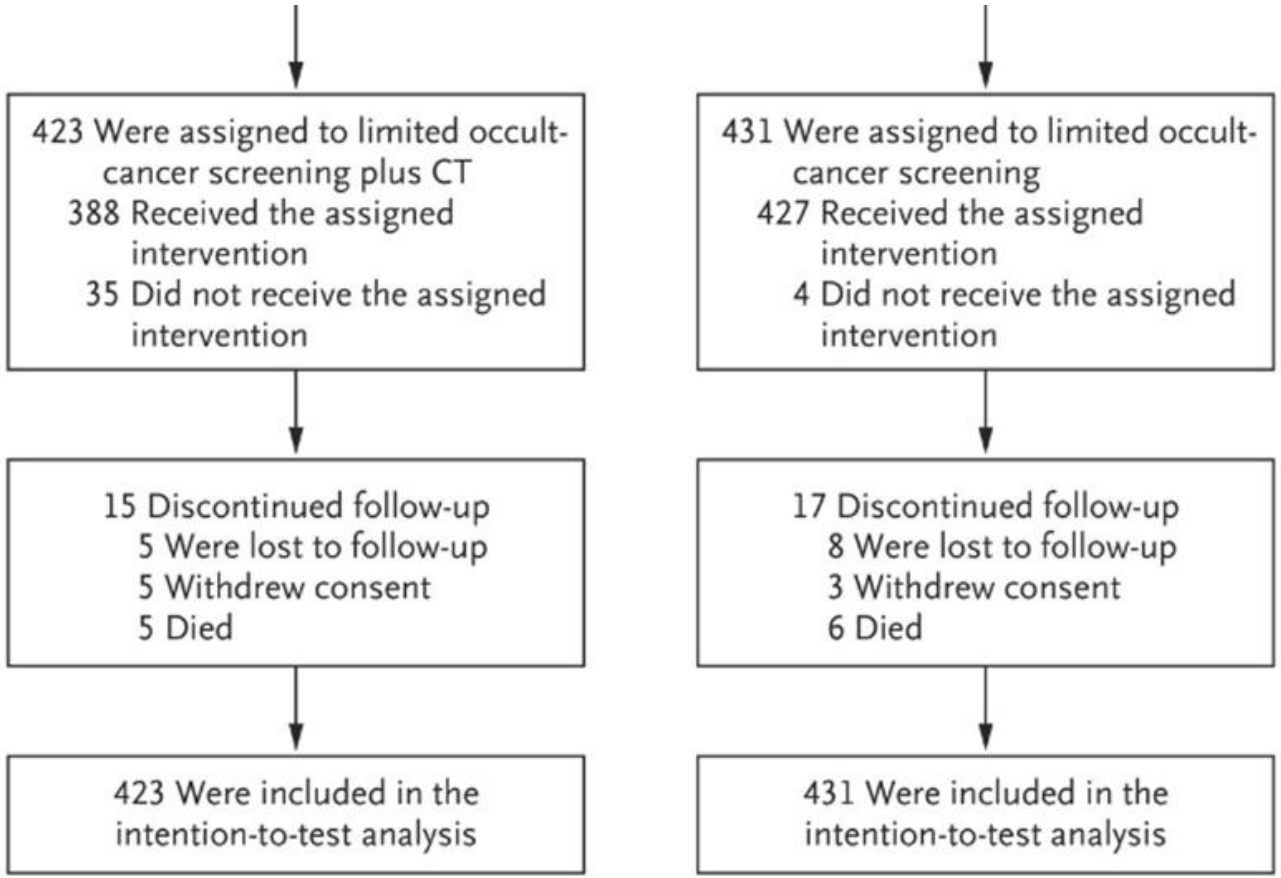


Table 1. Baseline Characteristics of the Intention-to-Test Population.*

Characteristic	Limited Occult-Cancer Screening (N=431)	Limited Occult-Cancer Screening plus CT (N=423)
Age — yr	53.7±13.8	53.4±14.2
Male sex — no. (%)	277 (64.3)	299 (70.7)
White race — no. (%)†	395 (91.6)	397 (93.9)
Weight — kg	89.8±18.3	90.4±17.7
Medical history — no. (%)		
Hypertension	86 (20.0)	101 (23.9)
Myocardial infarction	13 (3.0)	9 (2.1)
Stroke	5 (1.2)	6 (1.4)
Congestive heart failure	2 (0.5)	0
Diabetes	17 (3.9)	22 (5.2)
Previous cancer	20 (4.6)	30 (7.1)
Prior provoked venous thromboembolism	29 (6.7)	18 (4.3)
Current smoker	69 (16.0)	63 (14.9)
Past smoker	140 (32.5)	144 (34.0)
Venous thromboembolism — no. (%)		
Deep-vein thrombosis	289 (67.1)	287 (67.8)
Pulmonary embolism	142 (32.9)	136 (32.2)
Deep-vein thrombosis and pulmonary embolism	52 (12.1)	53 (12.5)
Medications — no. (%)		
Oral contraceptive	29 (6.7)	19 (4.5)
Exogenous estrogen	8 (1.9)	11 (2.6)
Antiplatelet agent	21 (4.9)	19 (4.5)

Outcomes

- Primary: confirmed cancer that was missed by screening and detected by end of 1-year follow up period

- Secondary:
  - Total number of cancers diagnosed
  - Total number of early cancers (by TNM system of WHO) diagnosed by:
    - Occult cancer screening
    - Subsequent 1-year follow up
  - 1-year cancer-related mortality
  - 1-year overall mortality
  - Time to cancer diagnosis (Kaplan-Meier analysis)
  - Incidence of recurrent VTE

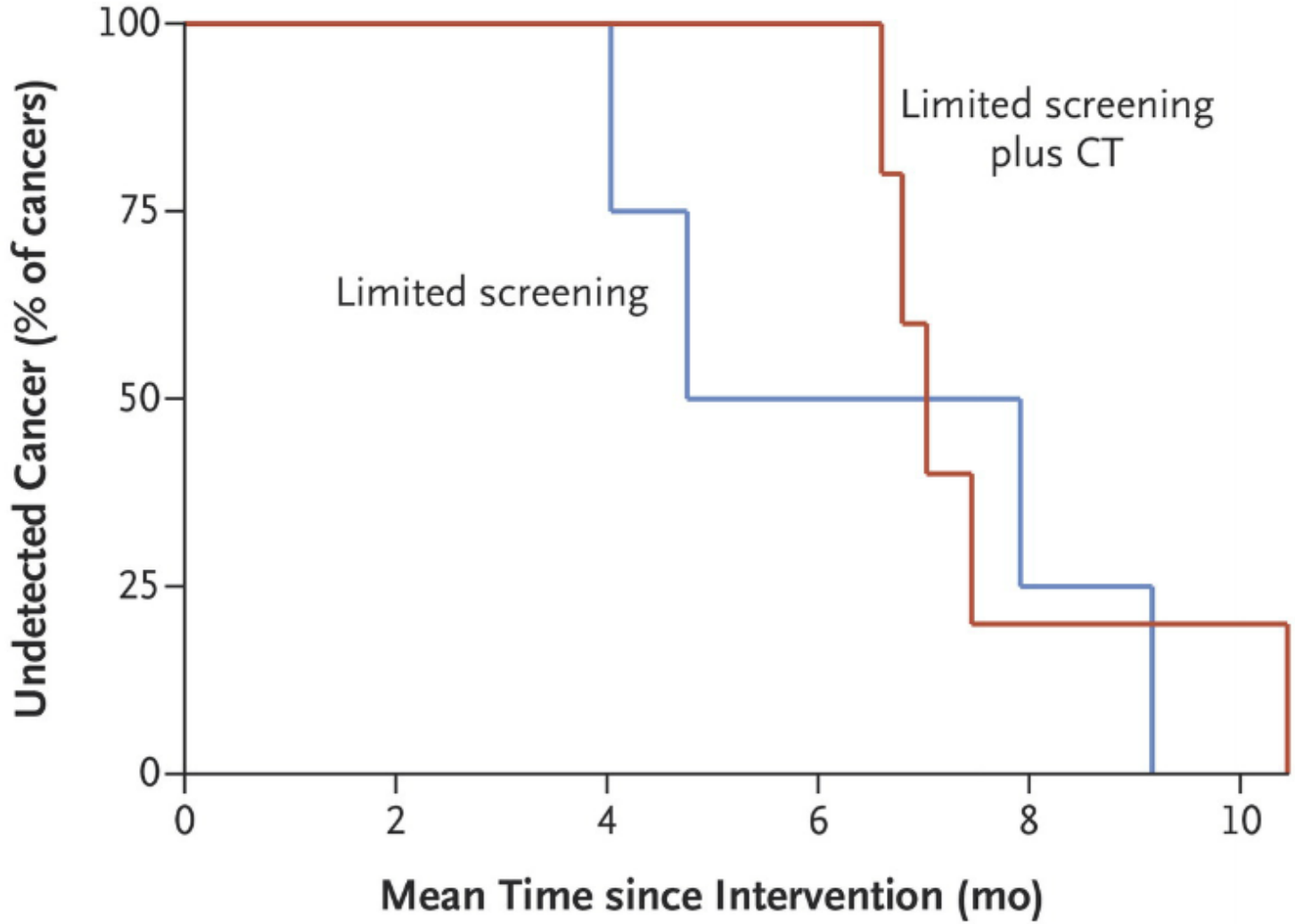
Results

- Of 854 total randomized subjects, 3.9% had new diagnosis of occult cancer by 1-year follow up.
  - 3.2% in limited screening group
  - 4.5% in limited screening plus CT group
  - No difference between groups (p=0.28)

- Analysis:
  - 20% of occult cancers were missed by limited screening strategy.
  - 26% of occult cancers were missed by limited screening plus CT
  - No difference between groups (p=1.0)
  - The best case with CT added to limited screening: NNT = 91

- No difference between groups in mean time to cancer diagnosis
  - 4.2 months in limited screening vs 4.0 months in limited screening plus CT (p=0.88)

- No difference in cancer-related mortality (1.4% vs 0.9%, p=0.75)



No. at Risk

Limited screening	4	4	4	2	1	0
Limited screening plus CT	5	5	5	5	1	1

Table 2. Occult Cancer Tumor Types.

Tumor Type	Limited Occult-Cancer Screening (N=14)	Limited Occult-Cancer Screening plus CT (N=19)
	no. of tumors/total no. (%)	
During screening period		
Acute leukemia	0/10	0/14
Gynecologic	3/10 (30)	0/14
Skin: melanoma	1/10 (10)	0/14
Colorectal	0/10	3/14 (21)
Prostate	2/10 (20)	0/14
Pancreatic	2/10 (20)	0/14
Cholangiocarcinoma	1/10 (10)	2/14 (14)
Lymphoma	1/10 (10)	3/14 (21)
Breast	0/10	2/14 (14)
Urologic	0/10	3/14 (21)
Unknown primary	0/10	1/14 (7)

Tumor Type	Limited Occult-Cancer Screening (N=14)	Limited Occult-Cancer Screening plus CT (N=19)
	no. of tumors/total no. (%)	
During follow-up period		
Acute leukemia	1/4 (25)	1/5 (20)
Gynecologic	1/4 (25)	1/5 (20)
Skin: melanoma	0/4	1/5 (20)
Colorectal	1/4 (25)	1/5 (20)
Prostate	0/4	1/5 (20)
Pancreatic	1/4 (25)	0/5

Conclusion

Routine screening with CT abdomen & pelvis did not provide clinical benefit.

Prevalence of occult cancer was low in first, unprovoked VTE.

Summary

- For expectantly managed ureteric colic, neither tamsulosin nor nifedipine reduced the chance of needing further treatment for stone passage at 4 and 12 weeks.
    - Additionally, neither reduced pain, hastened time to stone passage, or improved health.

- In patients with acute, symptomatic pulmonary embolism who have no contraindication to anti-coagulant therapy, retrievable inferior vena cava filters added no benefit with respect to recurrence or mortality.

- In patients with first, unprovoked venous thromboembolism, screening for occult cancer with CT beyond an H&P, basic labs, age-specific screening, and chest x-ray provided no clinical benefit with respect to time to cancer diagnosis or cancer-specific mortality.

Moral of the story: Less IS More.

Questions?

Thank You.

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