USE OF DIRECT ORAL ANTICOAGULANTS IN ANTIPHOSPHOLIPID SYNDROME: SYSTEMATIC REVIEW OF LITERATURE

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EUROPEAN FORUM ON ANTIPHOSPHOLIPID ANTIBODIES

CONFLICT OF INTEREST

None

RATIONALE

- The cornerstone of thrombotic APS management is to prevent recurrent thrombosis
  - By long term anticoagulation
  - Gold standard is warfarine

- Conflicting data from several case reports, case series, cross sectional studies and two controlled randomized trials (RAPS, TRAPS)

Dufrost et al. Curr Rheum Review, 2016
Cohen et al. Lancet Haematol. 2016
Pengo et al. Blood 2018

AIMS

Our objectives were :

- **To summarize all literature available about DOACs use in APS patients**
- **To identify risk factors predisposing to thrombotic events**

METHODS

- Search strategy
  - **Systematic literature search** in MEDLINE, EMBASE and Cochrane databases
  - All articles published from 2000 until **March 15th, 2018**
  - Key words : *antiphospholipid antibodies, antiphospholipid syndrome, lupus coagulation inhibitor, antibodies anticardiolipin, familial antiphospholipid syndrome, anti-β2-glycoprotein-I, lupus erythematosus systemic and direct oral anticoagulant, novel oral anticoagulant, rivaroxaban, apixaban, edoxaban, dabigatran*

METHODS

- Inclusion criteria
  - Population: **APS patients** defined according to revised Sapporo criteria
  - Exposure: treatment with **any DOACs**
  - Outcome: **documented thrombosis recurrence** while on DOAC

- Exclusion criteria
  - **Poorly documented** or u**ndocumented** recurrent thrombosis
  - **Absence of follow-up** during DOACs treatment

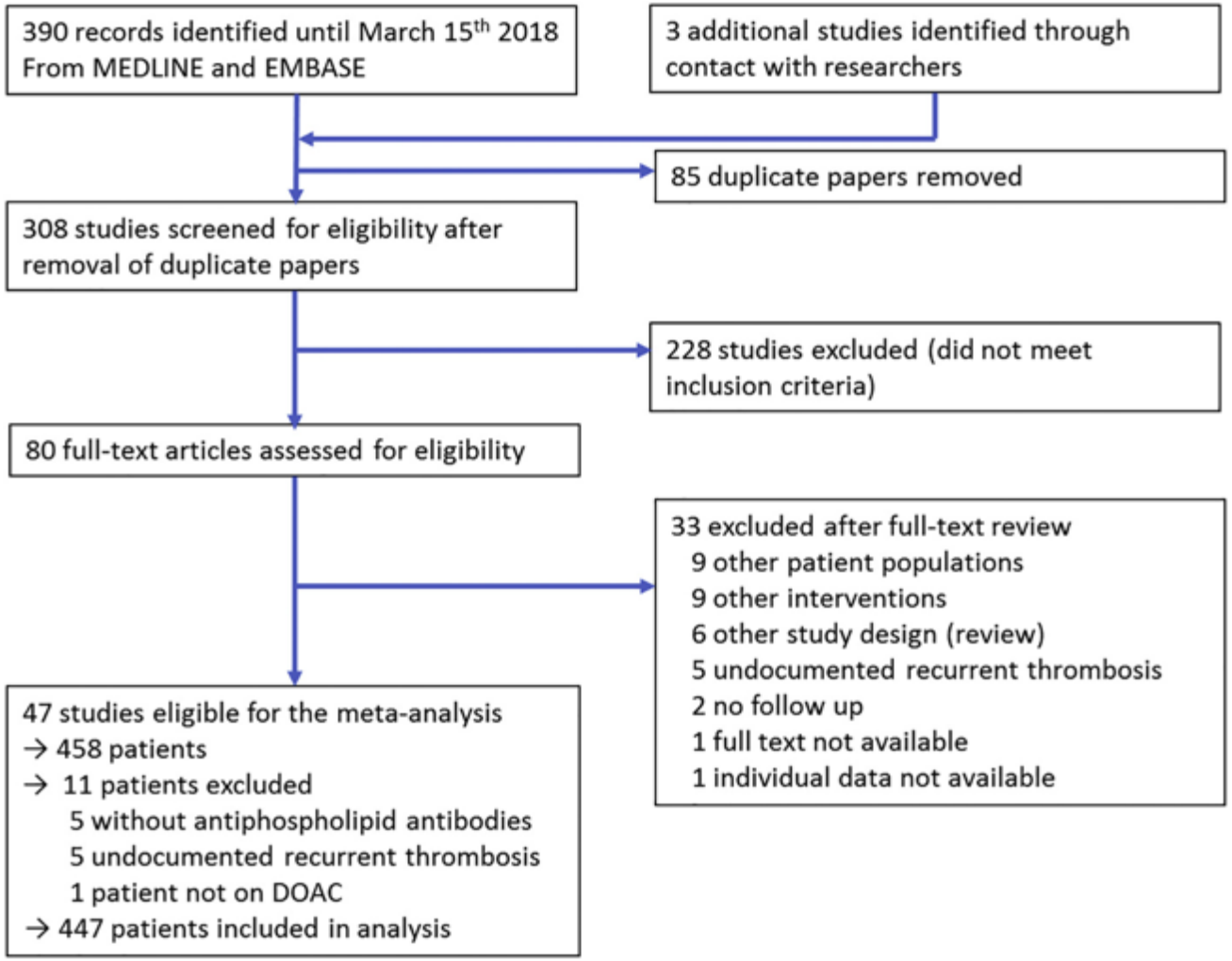
METHODS

- Individual data extraction
  - Among included case series, patients were excluded if :
    - Recurrent thrombosis undocumented
    - No DOACs used
    - APL tests negative
  - Authors were contacted if needed
  - **Variables** collected were : demographics, past thrombotic history, aPL profile, presence of any underlying autoimmune disease, previous anticoagulant treatment and reason of the switch, DOAC used, characteristic of recurrent thrombosis, bleeding and duration of follow-up

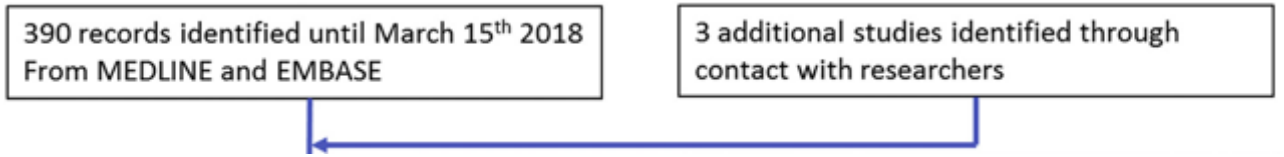
METHODS

- Statistical analyses
  - Outcome : **recurrent thrombosis** documented by appropriate imaging or histology occurring while on DOACs treatment
  - Patients were categorized according to this outcome to determine associated factors
  - **Non-parametric tests** were used : Wilcoxon test for quantitative variables and Fisher's exact test for qualitative variables
  - Missing data were excluded from analyses

RESULTS


390 records identified until March 15th 2018
From MEDLINE and EMBASE
3 additional studies identified through contact with researchers
85 duplicate papers removed
308 studies screened for eligibility after removal of duplicate papers
228 studies excluded (did not meet inclusion criteria)
80 full-text articles assessed for eligibility
33 excluded after full-text review
9 other patient populations
9 other interventions
6 other study design (review)
5 undocumented recurrent thrombosis
2 no follow up
1 full text not available
1 individual data not available
47 studies eligible for the meta-analysis
→ 458 patients
→ 11 patients excluded
5 without antiphospholipid antibodies
5 undocumented recurrent thrombosis
1 patient not on DOAC
→ 447 patients included in analysis

RESULTS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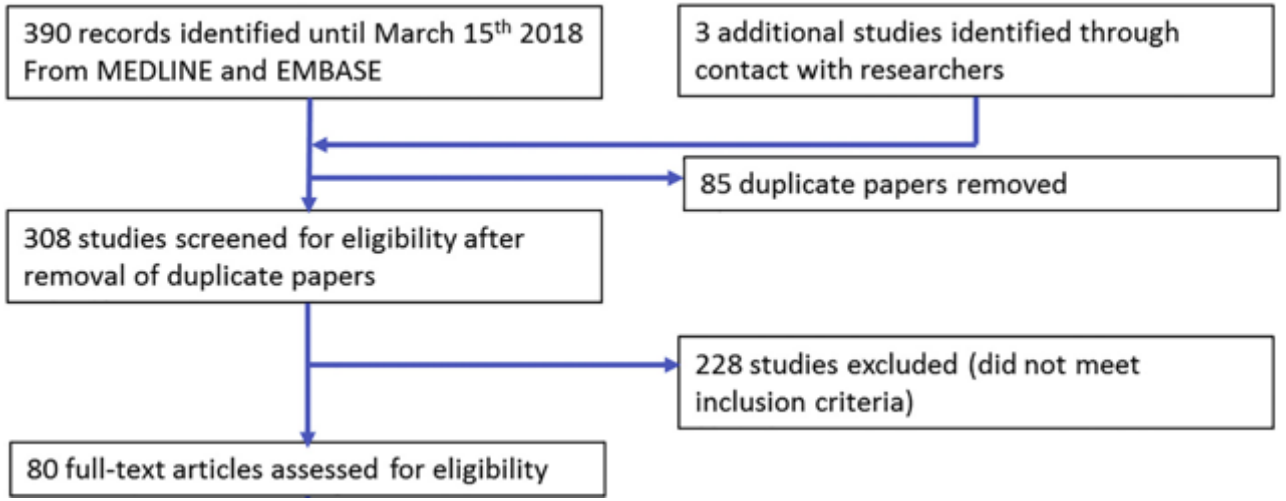
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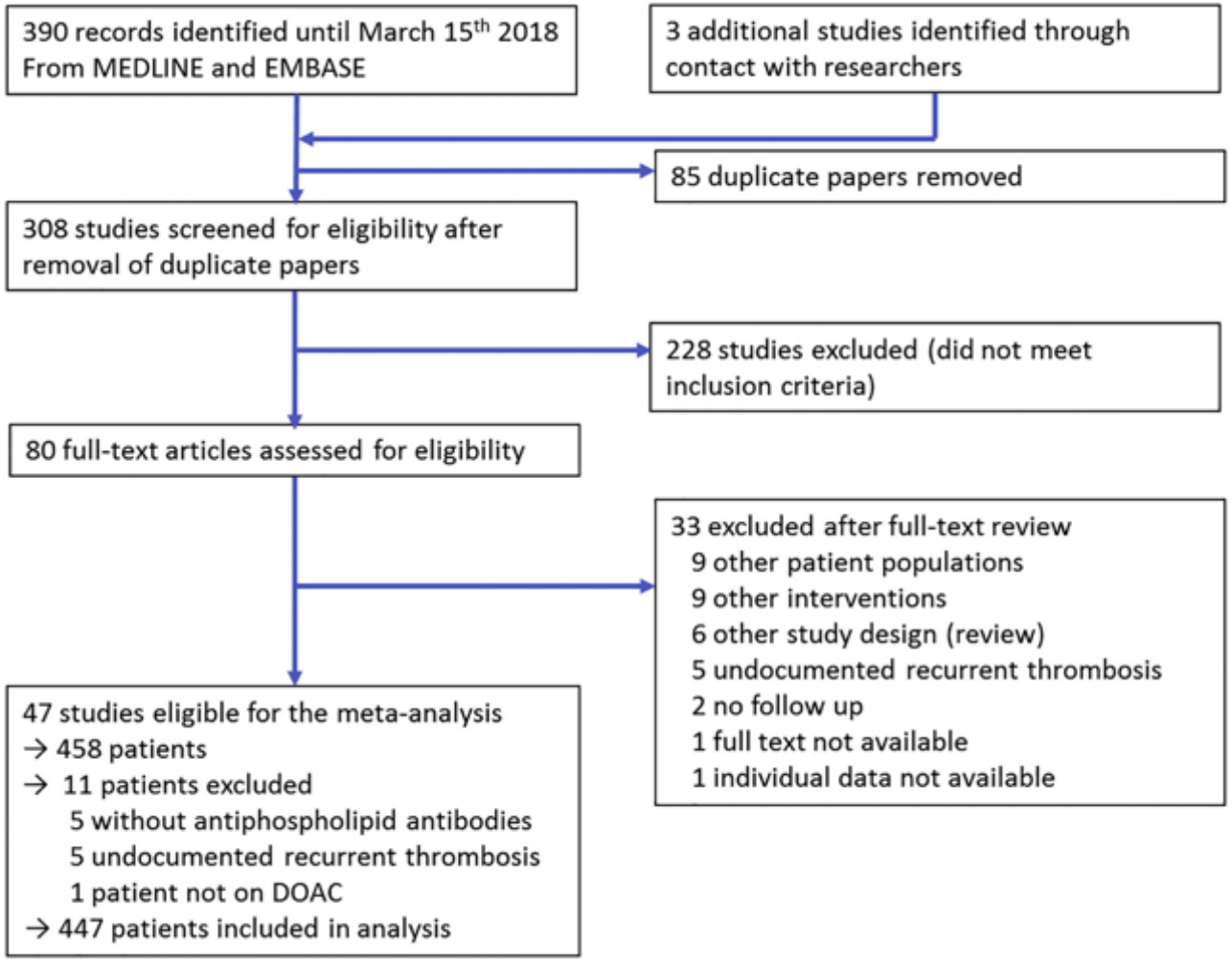
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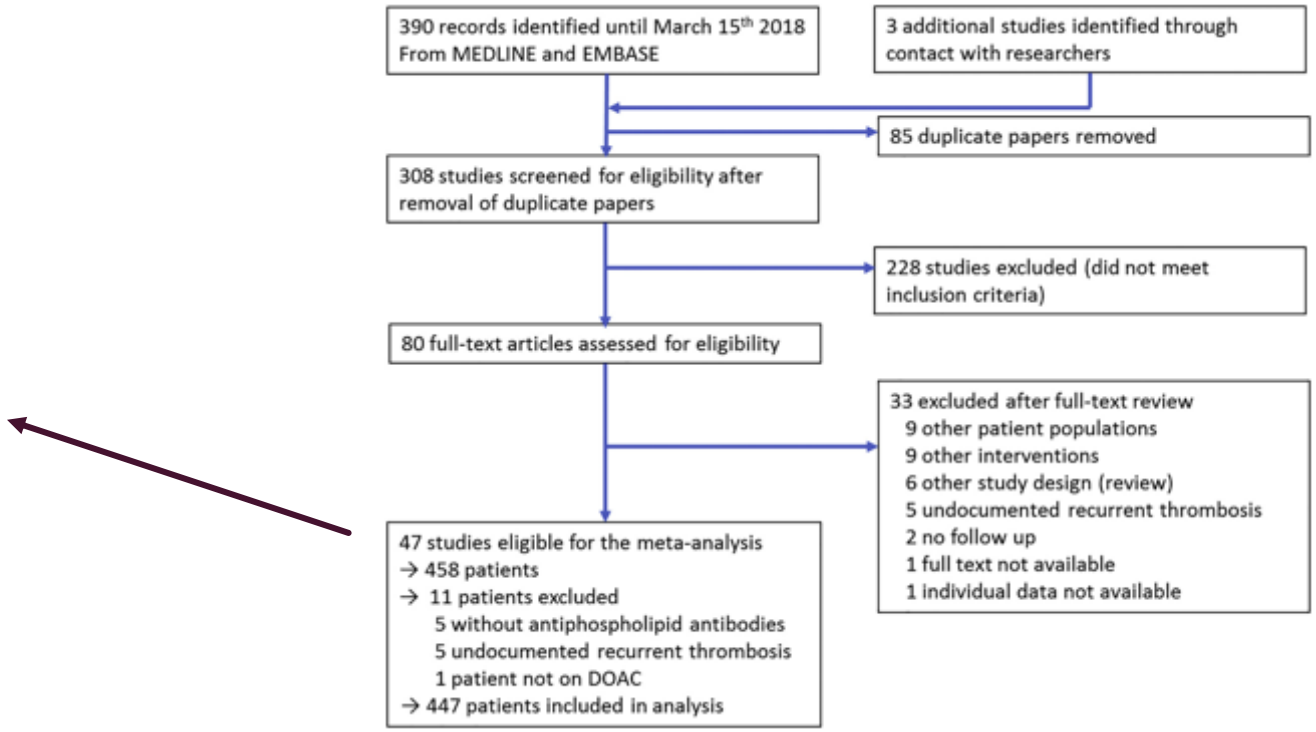
RESULTS

47 studies :

- 4 RCT (RAPS and patients from RE-COVER, RE-COVER II and REMEDY studies)
- 14 case series
- 21 case reports
- 9 abstracts (national or international congresses)



447 patients included in the analysis

RESULTS

447 patients analyzed ➔ 73 thrombotic events (16%)

- Mean age : 43.6±10.9
- History of venous TE event : 405/445 (91%)
- History of arterial event : 82/350 (23%)
- Triple positivity : 94/326 (29%)
- Associated autoimune disease : 42 % of APS (82% of SLE)
- DOAC most used was rivaroxaban (65%) followed by dabigatran etexilate (32%) and apixaban (3%)
  - No APS patients treated with edoxaban were reported

RISK FACTORS FOR RECURRENT THROMBOSIS DURING DOACs TREATMENT (1)

	APS without recurrent thrombosis (n= 374)	APS with recurrent thrombosis (n= 73)	p value
Mean age, year±SD	**43.9±10.1**	**42±14.3**	**0.006**
Male	**64/229 (28)**	**31/70 (44)**	**0.013**

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Number of clinical criteria for APS classification, number±SD	1.2±0.5	1.5±0.6	< 0.0001

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Number of clinical criteria for APS classification, number±SD	**1.2±0.5**	**1.5±0.6**	**< 0.0001**
History of clinical manifestations, n/N (%)			
Venous thrombosis	336/372 (90)	69/73 (95)	0.369
Arterial thrombosis	61/284 (21)	21/66 (32)	0.078
Small vessels thrombosis	6/131 (5)	5/43 (12)	0.1424
Obstetrical morbidity	36/160 (23)	10/63 (16)	0.358

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Small vessels thrombosis	6/131 (5)	5/43 (12)	0.1424
Obstetrical morbidity	36/160 (23)	10/63 (16)	0.358
Underlying autoimmune disease, n/N (%)			
Primary APS	107/190 (56)	38/58 (66)	0.227
Secondary APS	83/190 (44)	20/58 (34)	0.227

RISK FACTORS FOR RECURRENT THROMBOSIS DURING DOACs TREATMENT (1)

	APS without recurrent thrombosis (n= 374)	APS with recurrent thrombosis (n= 73)	p value
aPL profile			
LA	168/248 (68)	44/59 (75)	0.35
aCL	**152/245 (62)**	**53/60 (88)**	**< 0.0001**
aβ$_2$-GPI	**109/244 (45)**	**45/58 (78)**	**< 0.0001**
Triple positivity			**.0001**

Odd Ratio = 4.3 [95% CI; 2.3–7.7]

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aβ_2-GPI	**109/244 (45)**	**45/58 (78)**	**< 0.0001**
Triple positivity	**61/267 (23)**	**33/59 (56)**	**< 0.0001**
DOAC, n/N (%)			
AntiXa	252/374 (67)	51/73 (70)	0.784
Rivaroxaban	240/374 (64)	50/73 (68)	0.506
Apixaban	12/374 (3)	1/73 (1)	0.703
Dabigatran	122/374 (33)	22/73 (30)	0.784

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aPL profile			
LA			
aC			**001**
aβ			**001**
Tripl			**001**
DOA			
Anti			4
Rivaroxaban	240/374 (64)	50/73 (68)	0.506
Apixaban	12/374 (3)	1/73 (1)	0.703
Dabigatran	122/374 (33)	22/73 (30)	0.784
Duration of follow-up, month±SD	**17±11.2**	**12.5±12.1**	**<0.0001**

Main risk factors :

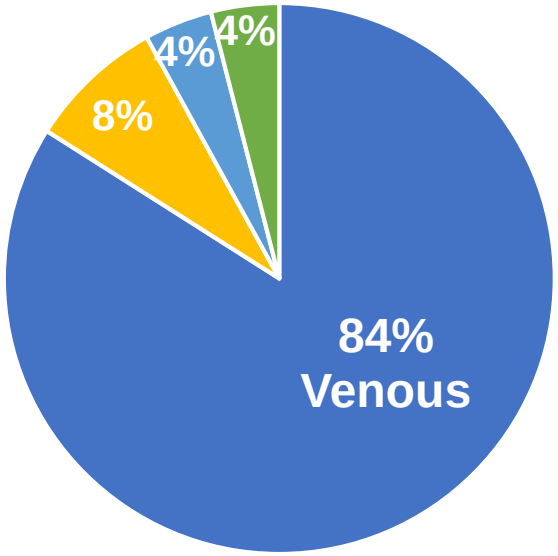
Low age
Male
High number of clinical criteria for APS classification
Triple positivity

RISK FACTORS FOR RECURRENT THROMBOSIS DURING DIRECT FACTOR XA INHIBITORS (2)

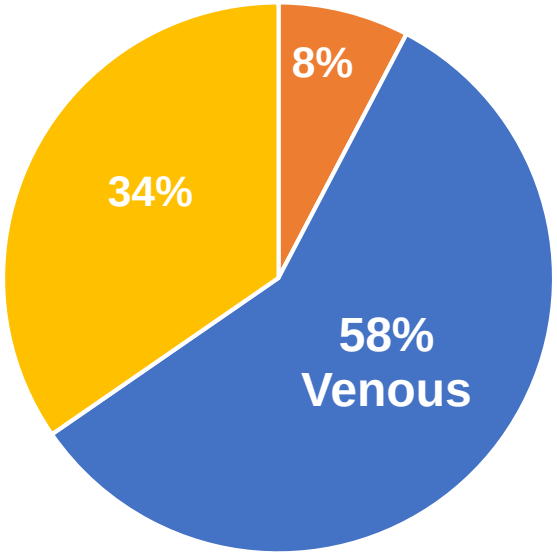
	APS without recurrent thrombosis (n= 252)	APS with recurrent thrombosis (n= 51)	p value
Mean age, year±SD	44.5±10.3	47.8±16.5	0.086
Male	**49/175 (28)**	**23/51 (45)**	
Number of clinical criteria for APS classification, number±SD	**1.22±0.4**	**1.43±0.6**	**0.014**
History of clinical manifestations, n/N (%)			
Venous thrombosis	234/250 (94)	47/51 (92)	0.757
Arterial thrombosis	**33/230 (14)**	**15/47 (32)**	**0.006**
Small vessels thrombosis	**3/117 (3)**	**5/41 (12)**	**0.028**
Obstetrical morbidity	20/106 (19)	4/44 (9)	0.22
Triple positivity			
Duration of follow-up, month±SD	**15.1±9.6**	**9.3±9.9**	**<0.0001**

Odd Ratio = 6.9 [95% CI; 3.4–13.9]

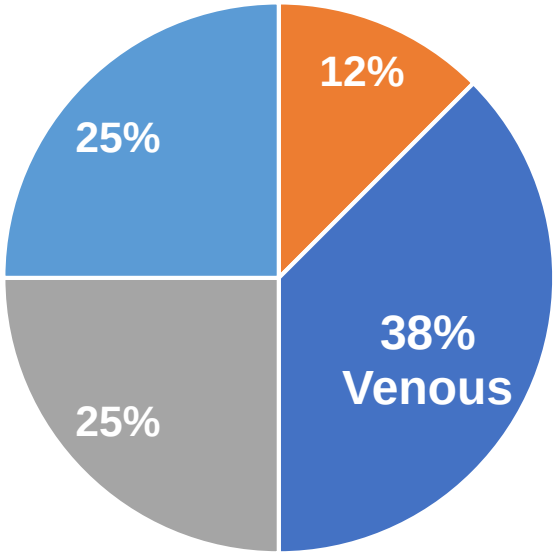
DISTRIBUTION OF PREVIOUS EVENT IN PATIENT WITH RECURRENT THROMBOSIS



A : Recurrent venous thrombosis



B : Recurrent arterial thrombosis



C : Recurrent small vessels thrombosis

- Arterial
- Venous
- Small vessels
- Venous and arterial
- Venous, arterial and small vessel
- Venous and small vessel

3 CAPS ➔ 100% of previous venous events only

CONCLUSIONS

- High-risk APS patients with triple positivity have a **4-fold increased risk** of thrombosis recurrence while on DOACs
- Previous Arterial and small vessel manifestations are associated with thrombotic recurrence
  - But single VTE is also associated with 14% of thrombotic recurrence
- Thus, **DOACs should be used with caution in APS patients**
- Future randomized controlled trials should determine :
  - Which factors are associated with a poor prognosis while on DOACs
  - Which APS patients could be treated safely with these drugs

THANK YOU FOR YOUR ATTENTION

You can find these results in : *Dufrost and al.* *Autoimmun Rev.* *2018 Aug 11*

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