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► **To cite this version:**

Jean-Philippe Galanaud, Marie-Antoinette Sevestre, Gilles Pernod, Céline Genty, Cécile Richaud, et al.. Epidemiology and 3-year outcomes of combined oral contraceptive-associated distal deep vein thrombosis. *Research and Practice in Thrombosis and Haemostasis*, 2020, 4 (7), pp.1216-1223. 10.1002/rth2.12409 . hal-03270248

HAL Id: hal-03270248

<https://hal.umontpellier.fr/hal-03270248v1>

Submitted on 24 Jun 2021

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ORIGINAL ARTICLE



Epidemiology and 3-year outcomes of combined oral contraceptive-associated distal deep vein thrombosis

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Funding information

The French Ministry of Health, the Société Française de Médecine Vasculaire, and Sanofi-Aventis provided funding for the study. The funding sources had no

Abstract

Background: Distal deep vein thrombosis (infrapopliteal DVT without proximal DVT or pulmonary embolism [PE]) generally shares the same triggering risks factors as proximal DVT. In women of childbearing age, a frequent triggering risk factor is the use of combined oral contraceptive (COC) pills. However, data on the epidemiology and long-term outcomes of COC-associated distal DVT are lacking.

Objectives: To assess the epidemiology and long-term outcomes of COC-associated distal DVT.

Methods: Using data from the OPTIMEV (Optimisation de l'Interrogatoire dans l'évaluation du risque thrombo-Embolique Veineux [Optimization of Interrogation in the Assessment of Thromboembolic Venous Risk]) multicenter cohort study of patients with objectively confirmed venous thromboembolism (VTE) enrolled between 2004 and 2006, we assessed in nonpregnant or postpartum women aged ≤ 50 years without cancer or history of VTE (i) proportion of COC-associated distal DVTs among women with distal DVTs and among women with COC-associated VTEs (distal DVT, proximal DVT, or PE) and (ii) 3-year incidence of death, bleeding, and VTE recurrence.

Results: COC-associated distal DVTs ($n = 54$) represented 43.9% of all distal DVTs and 51.9% of COC-associated VTEs. All but one woman with a COC-associated distal DVT received therapeutic anticoagulation for a median of 3 months. At 3-year follow-up, all women with COC-associated distal DVTs were alive, and none had bled during anticoagulant treatment or had experienced a DVT or PE recurrence after stopping anticoagulants. Similar results were found in patients with COC-associated proximal DVT and PE: The VTE recurrence rate was 1.7% per patient-year (PY) and 0% PY, respectively, and there were no deaths or major bleeds in either group.

List of OPTIMEV investigators is provided in Appendix 1.

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involvement in the design of the study; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the manuscript for publication.

Handling Editor: Dr Suzanne Cannegieter

Conclusions: Distal DVT was the most frequent clinical presentation of COC-associated VTE and had similarly favorable long-term outcomes as other COC-associated VTE.

KEYWORDS

combined oral contraceptives, deep vein thrombosis, epidemiology, estrogens, risk factors, venous thrombosis

Essentials

- Data on association between combined oral contraceptives (COC) and calf vein thrombosis are scarce.
- We assessed an observational cohort of women aged < 50 years with venous thromboses involving the calf, thigh, or lungs.
- Calf vein thrombosis is the most frequent presentation of COC-associated venous thrombosis.
- The 3-year risk of death, thrombosis recurrence, or bleeding of COC-associated calf thrombosis is low.

1 | INTRODUCTION

In women of childbearing age, venous thromboembolism (VTE) (deep vein thrombosis [DVT] or pulmonary embolism [PE]) occurs in 2–10/10 000 persons per year.¹ In this population, hormones—which includes combined oral contraceptives (COCs), birth control pills containing both estrogen and progestin—play a key triggering role and are usually found to be involved in about half of cases of VTE events.^{2–4} Overall, hormones increase the risk of VTE by 3–6 times, but the risk of VTE recurrence once COC use is stopped is very low.^{5–8} This usually justifies stopping anticoagulants after 3 months of treatment.⁹ As per any woman with previous VTE, further use of COCs is contraindicated.¹⁰

However, data on COC-associated VTE come from studies where the VTE event was either a proximal DVT or a PE or where exact DVT location was not categorized. Little is known about the characteristics and outcomes of women whose COC-associated VTE event was a distal DVT (infrapopliteal DVT without proximal DVT or PE). This is an important knowledge gap as distal DVT represents more than half of all lower-limb DVT,¹¹ that its management is debated^{9,12} and its risk factors, in terms of weight and outcomes (VTE recurrence, death, and bleeding) differ from those of proximal DVT or PE^{13–18}; indeed, if distal DVT and proximal DVT share the same risk factors, distal DVT are more frequently triggered by transient risk factors than proximal DVT and are associated with lower risks of subsequent death, VTE recurrence, and bleeding.

Therefore, we analyzed data from the French, prospective, observational, multicenter OPTIMEV (Optimisation de l'Interrogatoire dans l'évaluation du risque thrombo-Embolique Veineux [Optimization of Interrogation in the Assessment of Thromboembolic Venous Risk]) study to ascertain the epidemiology, management, and long-term outcomes of COC-associated isolated distal DVT.

2 | METHODS

The OPTIMEV study was a large, French, multicenter, prospective, observational study of inpatients and outpatients referred

to vascular medicine physicians for clinically suspected acute VTE and followed for 3 years thereafter. Its primary objective was to assess risk factors for the various clinical presentations of VTE. The study protocol has been described elsewhere¹⁴ and is available at ClinicalTrials.gov (registration number: NCT00670540). In this substudy, the objectives were to ascertain in nonpregnant or postpartum women aged <50 years and without cancer or history of previous VTE, the proportion of COC-associated distal DVTs among COC-associated VTEs and among distal DVTs; secondary objectives were to describe the management of COC-associated distal DVT and to provide, in an exploratory analysis manner, the 3-year incidence of death, bleeding, and VTE recurrence of COC-associated distal DVTs.

2.1 | Patients

In brief, consecutive patients aged at least 18 years, referred for clinically suspected VTE to the vascular medicine physicians of the 41 hospitals and 292 private practices participating in the OPTIMEV study were enrolled, during a prespecified limited period of time, between 2004 and 2006. All VTE events were confirmed or ruled out with objective tests. All patients with suspicion of symptomatic lower-limb DVT underwent a standardized bilateral whole-leg compression ultrasound (CUS) which imaged the entire deep venous network. The diagnosis of DVT was confirmed if there was incompressibility of the vein. Only clots ≥ 5 mm diameter under CUS compression were considered as distal DVTs.¹⁹

For the present substudy, we included only those women whose index VTE event was a first, objectively confirmed, symptomatic, lower-limb distal or proximal DVT or a PE (with or without concomitant DVT).

We considered that women who used estrogen-containing contraceptive pills in the 3 months preceding VTE diagnosis/suspicion as being exposed to estrogens. Women were excluded if they (i) were aged > 50 years; (ii) had active cancer or a newly diagnosed

cancer within 3 months after VTE diagnosis; (iii) used estrogen for menopausal hormone replacement therapy purposes or fertility treatment purposes; (iv) used progesterone-only birth control pills; or (v) were pregnant or postpartum (up to 6 weeks after delivery). In OPTIMEV, women enrolled in overseas territories, living outside of France, or who were homeless were not eligible for follow-up.

2.2 | Study protocol

At inclusion, all demographic characteristics, clinical data, diagnostic test results, and usual medications were collected by the vascular medicine physician using a standardized validated questionnaire. Women were specifically asked questions regarding their fertility (pregnancy, miscarriage, periods, menopause) and whether they were taking or had been recently taking medications for birth control or menopause purposes (including name and date of onset/stop). They were informed to abstain from taking further COCs. At 3 months, and thereafter every year for 3 years, patients were phoned by a clinical research assistant to obtain information on health-related events and their treatment

since inclusion. Medical records were reviewed in the case of potential adverse events (death, VTE recurrence, bleeding, cancer, cardiovascular event), hospitalization, or a new visit to the vascular medicine physician during the follow-up period. All DVT and PE recurrences were confirmed according to ISTH criteria.²⁰ Major bleeding was defined as any bleeding that was either fatal or overt within a critical organ (eg, intracranial, retroperitoneal, intraocular, pericardial, intraspinal, or in adrenal glands) or that was associated with a fall in hemoglobin level ≥ 2 g/dL, or leading to a transfusion ≥ 2 units of packed red blood cells or whole blood. All suspected adverse events (death, major bleeding, VTE recurrence, new cancer) were adjudicated by the study's expert committee. Estrogen exposure and its type were assessed by Drs Bosson and Galanaud after reviewing the list of medications disclosed.

The OPTIMEV study was approved by the Ethics Committee (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé) and the Commission Nationale de l'Informatique et des Libertés. In accordance with French legislation on medical research, we obtained oral informed consent from all patients.

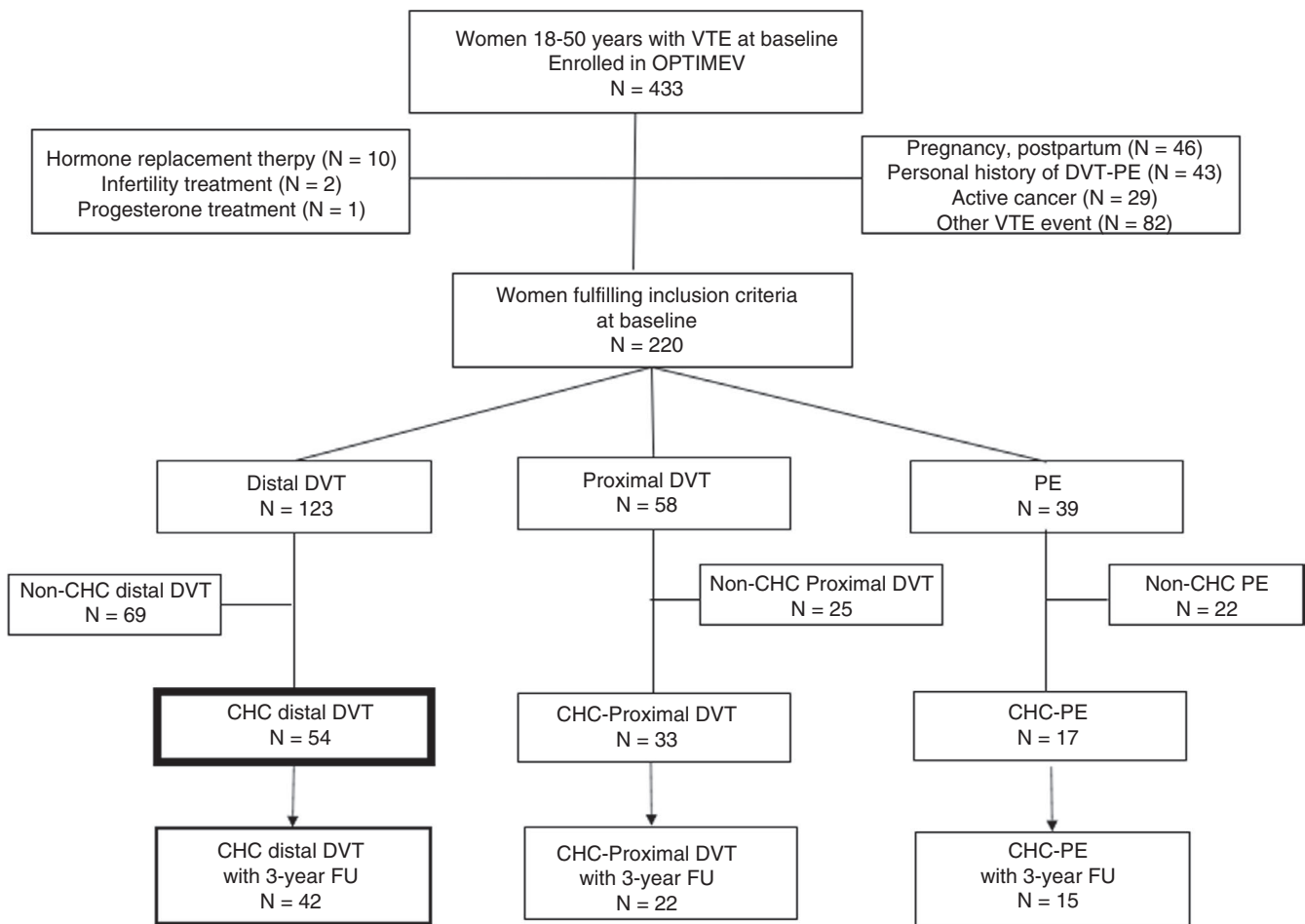


FIGURE 1 Study flow chart

2.3 | Statistical analysis

Categorical variables were expressed as frequencies and percentages; continuous variables were expressed as medians and interquartile ranges and means and standard deviations. Results and comparisons between groups (isolated distal or proximal DVT, PE, COC or non-COC related) were presented as events per 100 patient-years (PY).

Two-sided *P* values of .05 or less were considered to be statistically significant. Data were analyzed using Stata software (version 15.0, StataCorp, College Station, TX, USA).

3 | RESULTS

Between November 2004 and January 2006, 8256 patients were recruited in the study for a suspicion of VTE (Figure 1).

3.1 | Characteristics of VTE events

In OPTIMEV, 220 women were not pregnant or postpartum and were aged ≤ 50 years, without active cancer and had either a first distal DVT ($n = 123$), a first proximal DVT ($n = 58$) or a first PE ($n = 39$). Of

these women, 47.3% ($n/N = 104/220$) were on COC pills at the time of their VTE event.

In 43.9% ($n/N = 54/123$) of cases, women with distal DVT were on COC pill at time of DVT event. The respective proportion of women with proximal DVT and PE while on COC pills was 56.9% ($n/N = 33/58$) and 43.6% ($n/N = 17/39$).

Overall, 51.9% ($n/N = 54/104$) of COC-associated VTEs and 62.1% of COC-associated DVTs ($n/N = 54/87$) were distal DVTs. DVT (distal DVT, proximal DVT) and VTE (distal DVT, proximal DVT, PE) distributions were not statistically different between COC users and nonusers: $P = .1$ and $P = .2$, respectively. In 1.9% of cases ($n/N = 1/54$), the distal DVT was diagnosed in the contralateral asymptomatic leg of a woman with non-COC-associated distal DVT.

In 27.6% ($n/N = 24/87$) of cases, COC pills had been started less than a year before the VTE event: 25.6% ($n/N = 11/43$) in case of distal DVT, 22.6% ($n/N = 7/31$) in case of proximal DVT, and 46.2% ($n/N = 6/13$) in case of PE.

3.2 | Characteristics of COC-associated VTE and therapeutic management

Baseline characteristics of women with COC- and non-COC-associated VTEs are presented in Table 1.

TABLE 1 Baseline characteristics and therapeutic management of women with either isolated distal DVT, isolated proximal DVT, or PE according to their COC exposure

	Distal DVT		Proximal DVT		PE	
	COC user N = 54	COC nonuser N = 69	COC user N = 33	COC nonuser N = 25	COC user N = 17	COC nonuser N = 22
Characteristics						
Age, y, mean (SD)	35.7 (8.1)	38.7 (7.3)	32.2 (9.8)	41.2 (7.7)	30.8 (9.3)	42.9 (6.7)
Obesity, % (N)	13.0 (7)	18.8 (13)	15.2 (5)	4.0 (1)	35.3 (6)	18.2 (4)
Varicose veins, % (N)	14.8 (8)	8.7 (6)	0 (0) ^c	20.0 (5)	5.9 (1)	18.2 (4)
Active smoker, % (N)	16.7 (9)	17.4 (12)	18.2 (6)	12.0 (3)	23.5 (4)	9.1 (2)
Family history of VTE, % (N)	40.7 (22)	23.2 (16)	30.3 (10)	16.0 (4)	17.6 (3)	45.5 (10)
Major transient risk factor ^b , % (N)	37.0 (20)	50.7 (35)	39.4 (13)	40.0 (10)	11.8 (2)	40.9 (9)
Therapeutic management ^a						
Anticoagulation, yes, % (N)	N = 42 100.0 (42)	N = 52 98.1 (51)	N = 22 100.0 (22)	N = 19 100.0 (19)	N = 15 93.3 (14)	N = 16 100.0 (16)
Therapeutic dose, % (N)	97.6 (41)	100.0 (51)	100 (22)	100.0 (19)	100.0 (14)	94.8 (15) ^d
Duration, median (IQR)	90 (61-120)	90 (59-120)	182 (120-212)	151 (92-199)	244 (181-546)	365 (182-685)

Abbreviations: COC, combined oral contraceptive; IQR, interquartile range.

^aIn women eligible and agreeable for long-term follow-up.

^bLeg fracture or lower-extremity plaster cast; immobilization for >3 d; surgery with the use of a general anesthesia in the 3 mo before the index of VTE event.

^c*P* value, varicose veins, COC-associated distal DVT vs COC-associated proximal DVT = 0.02.

^dOne missing data.

All women with COC-associated distal DVTs were treated with anticoagulants at therapeutic dose in all but one case (97.6%, $n/N = 41/42$) and for a median duration of 90 days. The woman with a COC-associated distal DVT that was left untreated was 46 years old, an active smoker, and had no additional risk factors for VTE and no risk factors for bleeding (her follow-up was also uneventful). The management of women with non-COC-associated distal DVTs was identical to the management of women with COC-associated distal DVTs, all of whom were treated with a full dose of anticoagulant for a median duration of 90 days. Therapeutic management of COC- and non-COC-associated proximal DVT and PE is also presented in Table 1.

3.3 | Outcomes during the 3-year follow-up (exploratory analyses)

Four (9.5%, $n/N = 4/42$ among women eligible and agreeable to follow-up) patients with COC-associated distal DVT were lost to follow-up.

3.3.1 | COC

All women with COC-associated VTEs stopped taking COCs during follow-up.

3.3.2 | VTE recurrence

No woman with COC-associated distal DVT experienced a DVT or PE recurrence during the 3 years of follow-up. Only one woman with COC-associated distal DVT experienced an isolated superficial vein thrombosis, representing an incidence rate of 0.9% per PY. One woman with a COC-associated proximal DVT experienced a VTE recurrence, representing an incidence rate of 1.7% per PY. No woman with COC-associated PE had a VTE recurrence during follow-up.

Of note, the respective incidence of DVT or PE recurrence in women with non-COC-associated distal DVT, proximal DVT, and PE was 1.3% per PY, 0.0% per PY, and 0% per PY for PE.

3.3.3 | Death

None of the women with COC-associated distal DVT, proximal DVT, or PE died during follow-up.

3.3.4 | Major bleeding

None of the women with COC-associated distal DVT, proximal DVT, or PE experienced a major bleeding during anticoagulant treatment.

4 | DISCUSSION

We found that in unselected nonpregnant or postpartum women aged ≤ 50 years, without active cancer or previous history of VTE and not using estrogen for hormone replacement therapy purposes, managed in routine clinical practice, distal DVT was the most frequent clinical presentation of COC-associated VTE. Its prognosis was favorable, with a very low incidence of adverse outcomes in the long term.

The primary objective of this study was to assess the proportion of COC-associated distal DVT among COC-associated VTE and among distal DVT. Our results evidence that distal DVT was the most frequent clinical presentation of COC-associated VTE. In our population, it accounted for 43.9% of distal DVT, for 51.9% of all COC-associated VTE ($n = 104$) and for 62.1% of all COC-associated DVT. The proportion of COC-associated distal DVT among COC-associated DVT we report seems slightly different than what has been reported in two previous French series of patients from Brest (47.3%, [53/112]) and from Paris (78.3% [1156/1475]), but numbers were small and interpretation should be cautious.^{4,21} In contrast to ours, those studies were single center and hospital based. Furthermore, in OPTIMEV, we used a standardized US protocol that systematically screened the distal deep venous system (deep calf and muscular veins) in case of suspected DVT.

Regarding management and outcomes, all COC-associated distal DVT patients were treated with anticoagulants, and almost always (97.6%) at therapeutic doses, for a median duration of 3 months. This management was identical to the management of women with non-COC-associated distal DVT. It was also in line with the usual routine practice management of distal DVT as reported either in France or in international registries.^{13,15} This suggests that, at the time these patients were enrolled (2004–2006), COC-associated distal DVT was not perceived differently by clinicians from a therapeutic management perspective than other distal DVTs. Furthermore, as previously reported in recently published studies for COC-associated proximal DVT or PE,^{6–8} we found that the risk of recurrence after stopping anticoagulant treatment was extremely low, and lower than OPTIMEV patients with a first distal DVT and without cancer (2.7% per PY [1.9–3.8]).¹⁴ Thus, no patient with a COC-associated distal DVT developed a DVT or PE recurrence, and only one woman developed a superficial vein thrombosis.

Our study has certain strengths and limitations. Given its national design, our results are only generalizable to the French population of women fulfilling our inclusion criteria. Our sample size was small, and we thus cannot draw any definitive conclusions, particularly in terms of long-term rates of adverse outcomes. These latter data should only be considered as exploratory data. Consistent with literature data, we found that a significant proportion of women with COC-associated distal DVT were also exposed to another strong superimposed transient risk factor (37%, which is lower than for women with non-COC distal DVT [eg, 50%]).²² This has certainly also contributed to our low rate of VTE recurrence. Finally, we cannot also exclude

that VTE prevalence and distribution between DVTs and PEs may have changed since 2004, particularly because screening strategies have evolved (D-dimer assays, multislice chest computed tomography pulmonary angiogram, etc.).²³

Among the strengths of our study, we believe that its multicenter design with both community- and university-based recruitment and the use of a standardized whole-leg CUS protocol for suspected DVT provides a reliable estimate of the true contribution of COC-associated distal DVT among distal DVT and COC-associated VTEs in patients seen in routine clinical practice for suspected VTE. All recurrent events were validated by an expert committee after reviewing medical records. We were also able to provide for the first-time data on the therapeutic management and long-term outcomes of this frequent clinical presentation of VTE.

In conclusion, in our study, distal DVT was the most frequent clinical presentation of COC-associated VTE in nonpregnant or postpartum women aged ≤ 50 years without cancer or history of VTE. Clinical characteristics of women with COC-associated distal DVTs and COC-associated proximal DVTs were similar, and DVT and VTE distributions did not appear to be statistically different in COC and non-COC users. The prognosis of COC-associated distal DVT seemed favorable, with a very low incidence of adverse outcomes in the long term. Larger studies are needed to confirm our results and evaluate the most appropriate therapeutic management of COC-associated distal DVT.

ACKNOWLEDGMENTS

Dr Kahn is supported by the Canada Research Chairs Program. Drs Kahn and Galanaud are investigators of the CanVECTOR Network (funded by Canadian Institutes of Health Research CDT-142654).

RELATIONSHIP DISCLOSURES

This study was supported by grants from the French Ministry of Health, the French Society of Vascular Medicine and Sanofi-Aventis. Dr Kahn has received advisory board fees from BMS Pfizer, Sanofi, and Aspen and research grants from Leo-Pharma. Dr Galanaud has received consultant fees from BMS Pfizer, Sanofi, and Servier and research grants from Bayer and Leo-Pharma. All other authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design of the OPTIMEV study: MAS, JLB. Conception and design of the manuscript: JPG, MAS, JLB. Grant funding: MAS, JLB. Data acquisition: JPG, MAS, GP, CG, CR, CR, LW, SRK, IQ, JLB. Data analysis: JPG, CG, JLB. Drafting of the article: JPG. Critical revision for important intellectual content: JPG, MAS, GP, CG, CR, CR, LW, SRK, IQ, JLB. Final approval of the manuscript: JPG, MAS, GP, CG, CR, CR, LW, SRK, IQ, JLB.

DATA AVAILABILITY STATEMENT

JP Galanaud had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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REFERENCES

1. Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol.* 2015;12(8):464–74.
2. Roach RE, Lijfering WM, Rosendaal FR, Cannegieter SC, le Cessie S. Sex difference in risk of second but not of first venous thrombosis: paradox explained. *Circulation.* 2014;129(1):51–6.
3. Blanco-Molina A, Trujillo-Santos J, Tirado R, Canas I, Riera A, Valdes M, et al. Venous thromboembolism in women using hormonal contraceptives. Findings from the RIETE Registry. *Thromb Haemost.* 2009;101(3):478–82.
4. Hugon-Rodin J, Horellou MH, Conard J, Flaujac C, Gompel A, Plu-Bureau G. First venous thromboembolism and hormonal contraceptives in young French women. *Medicine.* 2017;96(34):e7734.
5. Stegeman BH, de Bastos M, Rosendaal FR, van Hylckama VA, Helmerhorst FM, Stijnen T, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. *BMJ.* 2013;347:f5298.
6. Kearon C, Spencer FA, O'Keefe D, Parpia S, Schulman S, Baglin T, et al. D-dimer testing to select patients with a first unprovoked venous thromboembolism who can stop anticoagulant therapy: a cohort study. *Ann Intern Med.* 2015;162(1):27–34.
7. Rodger MA, Le Gal G, Anderson DR, Schmidt J, Pernod G, Kahn SR, et al. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. *BMJ.* 2017;356:j1065.
8. Tosetto A, Testa S, Martinelli I, Poli D, Cosmi B, Lodigiani C, et al. External validation of the DASH prediction rule: a retrospective cohort study. *J Thromb Haemost.* 2017;15(10):1963–70.
9. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest.* 2016;149(2):315–52.
10. Black A, Guilbert E, Costescu D, Dunn S, Fisher W, Kives S, et al. No. 329-Canadian contraception consensus part 4 of 4 chapter 9: combined hormonal contraception. *J Obstet Gynaecol Can.* 2017;39(4):229–68.e5.
11. Johnson SA, Stevens SM, Woller SC, Lake E, Donadini M, Cheng J, et al. Risk of deep vein thrombosis following a single negative whole-leg compression ultrasound: a systematic review and meta-analysis. *JAMA.* 2010;303(5):438–45.
12. Righini M, Galanaud JP, Guennegeux H, Brisot D, Diard A, Faisse P, et al. Anticoagulant therapy for symptomatic calf deep vein thrombosis (CACTUS): a randomised, double-blind, placebo-controlled trial. *Lancet Haematol.* 2016;3(12):e556–e562.
13. Galanaud JP, Sevestre-Pietri MA, Bosson JL, Laroche JP, Righini M, Brisot D, et al. Comparative study on risk factors and early outcome of symptomatic distal versus proximal deep vein thrombosis: results from the OPTIMEV study. *Thromb Haemost.* 2009;102(3):493–500.
14. Galanaud JP, Sevestre MA, Genty C, Kahn SR, Pernod G, Rolland C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. *J Thromb Haemost.* 2014;12(4):436–43.
15. Galanaud JP, Quenet S, Rivron-Guillot K, Quere I, Sanchez Munoz-Torrero JF, Tolosa C, et al. Comparison of the clinical history of symptomatic isolated distal deep-vein thrombosis vs. proximal deep vein thrombosis in 11 086 patients. *J Thromb Haemost.* 2009;7(12):2028–34.

16. Barco S, Corti M, Trinchero A, Picchi C, Ambaglio C, Konstantinides SV, et al. Survival and recurrent venous thromboembolism in patients with first proximal or isolated distal deep vein thrombosis and no pulmonary embolism. *J Thromb Haemost.* 2017;15(7):1436–42.
17. Barco S, Klok FA, Mahe I, Marchena PJ, Ballaz A, Rubio CM, et al. Impact of sex, age, and risk factors for venous thromboembolism on the initial presentation of first isolated symptomatic acute deep vein thrombosis. *Thromb Res.* 2019;173:166–71.
18. Baglin T, Douketis J, Tostetto A, Marcucci M, Cushman M, Kyrle P, et al. Does the clinical presentation and extent of venous thrombosis predict likelihood and type of recurrence? A patient-level meta-analysis. *J Thromb Haemost.* 2010;8(11):2436–42.
19. Bosson JL, Riachi M, Pichot O, Michoud E, Carpentier PH, Franco A. Diameters of acute proximal and distal deep venous thrombosis of the lower limbs. *Int Angiol.* 1998;17(4):260–7.
20. Ageno W, Squizzato A, Wells PS, Buller HR, Johnson G. The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH. *J Thromb Haemost.* 2013;11(8):1597–602.
21. Le Moigne E, Delluc A, Tromeur C, Nowak E, Mottier D, Lacut K, et al. Risk of recurrent venous thromboembolism among young women after a first event while exposed to combined oral contraception versus not exposed to: a cohort study. *Thromb Res.* 2013;132(1):51–5.
22. Blanco-Molina A, Rota LL, Di Micco P, Brenner B, Trujillo-Santos J, Ruiz-Gamietea A, et al. Venous thromboembolism during pregnancy, postpartum or during contraceptive use. *Thromb Haemost.* 2010;103(2):306–11.
23. Delluc A, Tromeur C, Le Ven F, Gouillou M, Paleiron N, Bressollette L, et al. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. *Thromb Haemost.* 2016;116(5):967–74.

How to cite this article: Galanaud J-P, Sevestre M-A, Pernod G, et al; for the OPTIMEV-SFMV Investigators. Epidemiology and 3-year outcomes of combined oral contraceptive-associated distal deep vein thrombosis. *Res Pract Thromb Haemost.* 2020;4:1216–1223. <https://doi.org/10.1002/rth2.12409>

APPENDIX 1

OPTIMEV-SOCIÉTÉ FRANÇAISE DE MÉDECINE VASCULAIRE INVESTIGATORS

Luc Bressollette; Antoine Diard; Jean-Pierre Laroche; Hélène Paradis; Anne Tambosco; Odile Paillard; Claire Grange; Florence Lenoir; Jean-Luc Bosson; Catherine Gaillard; Olivier Pichot; Stéphane Dupas; Christian Escoffier; Bernard Morzol; Jean-Louis Bosselut; Paul Hervé Kuntz; Richard Cayman; Yann-Valéry Lelimouzin; Jean-Michel Baud; Nicolas Neaume; Jean-Manuel Kubina; Michèle Flambart; Catherine Bettarel-Binon; Frederic Haroche; Vincent Hugon; Toufek Berremili; Christophe Seinturier; Véronique Dehant; Philippe Coget; Jean-Marc Diamand; Gilles Miserey; Marie Therese Barrellier; Philippe Le Roux; Patrick Lanoye; Olivier Genre; Maryse Degeilh; Joel Constans; Marie-Anne Roset-Cacciuttolo; Corinne Elharar Bergo; Véronique Le Francq; Christophe Duc-Mauge; Alain Petit; Laurence Beyssier

Weber; Bruno Tribout; Jean-Philippe Lamouroux; Muriel Sprynger; Carole Bazzi; Pascale Chamu; Didier Lebrun; Dorothée Masson-Calvayrac; Agnes Schenone-Witmeyer; Francine Ponchaux-Crepin; Hélène Thiel; Christian Carlo; Sabine Durero; Stéphanie Tran Van; Christine Bequerel; Sylvie Buisson-Braly; Yesim Dargaud; Jacques Ninet; Myriam Vaudaine; Jean-Michel Monsallier; Jean Pierre Audin; Luc Toffin; Benoit Roger; Myriam Martin; Marie Christine Ginestet Auge; Marie-Laure Martin-Poulet; Michel Lausecker; Janellie Raponsky; Didier Colson; François Poirault; Bénédicte Grognet-Lenne; Georges Pares; Nicole Dubois-Pacque; Marie Françoise Pean; Pierre-François Goy; Geneviève Madec-Bougard; Mounir Filali; Dominique Brisot; Mathias Canaple; Chantal Elbhar; Yann Roussin; Constant Quashie; Marlène Coupe; Bertrand Penet; Michel Dadon; Jean Louis Barriere; Marie-Pierre De Heredia; François Buccì; François Xavier De Heredia; Alain Duprey; Alain Viard; Bertrand Deltombe; Olivier Rouyer; Béatrice Sannier; Didier Rastel; Anne Marie Cuenot; Joelle Yvette Laffont; Serge Couzan; Anne Colonna; Gérard Coppe; Annie Hecquet; Joelle Decamps Le Chevoir; Isabelle Vavasseur; Philippe Capoulade; Sophie Cazaillon; Alexandra Zech-Gelb; Dominique Delhoume Lajoie; Isabelle Tourvieille; Philippe Bailly; Virginie Soulier-Sotto; Michelle Sauvet Oliviero; Françoise Ganichot; Christine Jurus; Charles Nedey; Anne Tissot; Florence Garnier; Geneviève Barbe-Rottier; Cheikhou Thioub; Philippe Gasparini; Géraldine Gasparini; Pierre Ouvry; Christian Boissier; Séverine Feasson; Antoine Gosselin; Isabelle Defouilloy; Vincent Knauer; Béatrice Terriat; Bernadette Satger; Jacqueline Yver; Michelle Fontaine; Delphine Mahoux; Dominique Bryon; Christine Aviles; Jean Luc Gerard; Philippe Huguin; Jean-Pierre Vaglio; Georges Leftheriotis; Bruno Perrier; Fabienne Petetin; Monique Mexme; Stéphane Pulci; Roselyne Nazeyrollas Luporsi; Patrice Baudoïn; Caroline Boutami; Yves Tachot; Isabelle De Seze Godefroy; Jean Marie Marchand; Dominique Couture-Gerardin; Véronique Cacareigt-Bourdenx; Jean Michel Lecocq; Sylvie Delattre; Isabelle Quere; Gérard Bravetti; Marie Christine Gagniere-Marsoin; Véronique Raczka Moreau; Alain Cazanave; Anne Jeufraux; Jean Claude Saby; Jean Patrice Camuzat; Claudette Delhoume; Virginia Sassim-Marquez; Paul Aidane; Brigitte Feraud; Philippe Chantereau; Claude Haller; Pascal Thebaut; Michel Fesolowicz; Odile Godillon Praloran; Jean Bernard Dessirier; Mébarka Tiaïr; Symon Sadoun; Sophie Mollet; Anne Monnin Jacquot; Olivier Champion; Pascale Drouet; Jean François Lemoine; Bertrand Viard; Samina Rattani; Christine Stirnemann; Marie Claude Vincenti; Catherine Puget; Bénédicte Zultak; Pascal Deudon; Jean Halligon; Isabelle Terver; Christine Zappulla; Marie Charlotte Cumin; Claude Antoine; Agnes Brachet; Fatsah Baloul; Laurent Marcy; Daniel Rocca; Eric Pavéc; Cyrille Moirant; Pascale Bureau Du Colombier; Marie Boyadjian; Jacques Bouchet; Franco Tonti; Hervé Riom; Joseph Haimovici; Martine Boucher; Dominique Poumaredé; Patrick Louis; Stéphanie Louis-Verger-Hiard; Hélène Renaut Hovasse; Marion Lampel; Mostafa Douche; Isabelle Morin; Philippe Ronceray; Irene Verhulsel; Catherine Brunel; Nicolas Matelot; Patrick Genay; Sylvie Richard; Annie Bannier; Laurence Jeanteur Gonzalez; Hamid

Amara; Jacqueline Hanrion-Duval; Laurence Moret; Jean Marc Renaudin; Christine Briant Leger; Monique Brun; Richard Kiszelnik; Dominique Bois Janicot; Jean-Cristophe Steinbach; Jean Marc Mollard; Patrice Legarcon; Eric Mouillot; Jean André Porcene; Muriel Muffet; Gérard Leturcq; Saveria Dehaut; Michèle Vionnet-Fuasset; Roger Le Goff; Didier Lurel; Frédéric Chantrel; Bernard Jeangeorges; Jean Yves Boutin; Frédéric Bosler; Yves Lamaiziere; Klaus Walter; Véronique Tarabay; Tahar Mersel; Valérie Lumineau Gilbert; Philippe Quehe; Anne Long; Francois Memeteau; Philippe Caillard; Joel Lucas; Laurence Danchaud; Cathie Schmitt; Philippe Leger; Mario Sica; Jean Francois Londe; Vincent Balme; Maryse Caminzuli; Beatrice Villemur; Bernard Imbert; Elisabeth Chevrier; Géraldine Paoli-Cazanave; Agnes Cadene; Jean Noël Poggi; Brigitte Defives; Christel Reigniez; Corinne Salama; Nathalie Guilhem Cantala; Anne Laure Baldassini-Esquis; Regis Philippe; Jean-claude Roullet; Annie Legagneux; Michel Legagneux; Danièle Le Bescond; Claudine Tran Barbier; Raynald Delannoy; Marie Christine Pierru; Philippe Carriere; Christine Charreyron; Christine Garbit; Nicolas Lemoussu; Danielle Vautard Vigan; Jean Luc Daussin; Christophe De Mirman; Marie Noëlle De La Lance; Hubert Yvorra; Geneviève Bruckert; Catherine Chastagner; Sophie Blaise; Wassim Mazloum; Philippe Caillard; Béatrice Simon Momege; Marie Antoinette Sevestre; Léon Claude Bensoussan; Pierre Martinot; Anne Marie

Perrin; Claudine Invernizzi; Claude Alan; Alix Benard Nuber; Marina Baietto; Pascal Meicler; Pascale Gilbert; Valérie Nguyen Van; Annie Vallecalle Shintu; Bernard Demiot; Valérie Parpeix; Didier Touchard; Bernard Hiltbrand; Elisabeth Joubin; Nathalie Bauvin Goasguen; Hubert Gautier; Aude Agache; Corinne Poulain Veyre; Hervé Benoit; Ingrid Auguste; Adeline Garcia Serrano; Christian Frechinos; Thierry Dutartre; Pascal Giordana; Didier Dumesnil; Violaine Zizka; Stephan Weibel Shah; Claire Dufresne De Virel; Xavier Iscovici; Jean François Damour; Catherine Husson; Gerard Dumont; Eric Jouen; Paul Wallon; Yves Lehodey; Christiane Chabod; Manuela Santacreu; Christian Seiller; Jean Paul Rocchi; Emmanuel Custozza; Christine Cueff; Paul Fava; Clarisse Choquet; Patrick Heleine; Charles Saint Cyr; Jean Charles Boulanger Weill; Didier Marie; Pascale Beaugrand; Isabelle Roussin Pignerol; Jean Francois Bracon; Natacha Touati; Christine Biro; Khalid Amri; Anne Keller; Marianne Quellier Moulis; Christine Purser; Jean Luc Gillet; Pascale Faïsse; Jean François Taveau; Ange Marc Saadoun; Antoine Eid; Laurence Kharboutli; Sandrine Saïdani; David Ferre Bonet; Jean Dominique Allart; Sebastien Muller; Sandrine Murat; Claire Vasseur; Muriel Hercek; Karine Olive; Christine Gadenne; Jean Pierre Cambou; Michel Davinroy; Christian Darie; Marie Steidel; Caroline Poulain; Claire Vesin.