

Appendix B.1: Evidence for risk of venous or arterial thrombosis among women with thrombogenic conditions and characteristics using progestin-only contraception

Author, Published, Location, Support	Study Design, Years	Population	Medical condition	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading															
Mintz, 1984 [1] Mexico Funding not stated	Prospective cohort 1981-1983	Ages 18-40 Cohort: using POP (N=15) or NET-EN (N=10) Comparison group (N=18): using IUD, sterilization, no sexual activity Exclusions: liver abnormalities, history thrombosis, abnormal uterine bleeding, breast or uterine neoplasm Follow-up time not reported	Lupus Inactive for at least 6 months Confirmed by study investigators	POP (LNG) NET-EN Timing of use not stated (AMI was within 13 weeks after first NET-EN injection) Study investigators	PE AMI Study investigators	<table><tr><th>Method</th><th>PE N (%)</th><th>AMI N (%)</th></tr><tr><td>POP</td><td>1 (6.7%)</td><td>0</td></tr><tr><td>NET-EN</td><td>0</td><td>1 (10%)</td></tr><tr><td>Comparison</td><td>1 (5.6%)</td><td>0</td></tr></table>	Method	PE N (%)	AMI N (%)	POP	1 (6.7%)	0	NET-EN	0	1 (10%)	Comparison	1 (5.6%)	0	Strengths: Outcomes confirmed by study investigators Limitations: No information on source of study population or response rates Unclear whether contraceptive use was measured only at baseline or throughout study Follow up time for specific events not reported PE and AMI assessment not described Small sample size, no assessment of study power Statistical tests for comparisons of interest not reported; no adjustment for potential confounders Large and differential loss to follow-up: 40% for NET-EN, 80% for POP, and not reported among comparison group	II-2, poor			
Method	PE N (%)	AMI N (%)																					
POP	1 (6.7%)	0																					
NET-EN	0	1 (10%)																					
Comparison	1 (5.6%)	0																					
WHO, 1998 [2] Multiple countries in Africa, Asia, Europe and Latin America World Bank, NIH	Case control 1989-1993	Ages 20-44 Cases (N=1,137 VTE, 2,196 stroke, 364 AMI): admitted to hospital, identified by physicians Controls (hospital) (N=9,997):	HTN Smoking Participant questionnaire [3]	POP POI (most DMPA) Use within 3 months [3] Participant questionnaire	VTE Stroke AMI Ascertained by recruitment system at hospitals [3] Diagnosis verified by medical records and imaging	<table><tr><th>HTN</th><th>POP</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>Yes</td><td>Yes</td><td>1</td><td>2</td><td>1.2 (0.1-23.7)</td></tr><tr><td>Yes</td><td>No</td><td>41</td><td>91</td><td>1.5 (0.98-2.4)</td></tr></table>	HTN	POP	Cases	Controls	VTE aOR* (95% CI)	Yes	Yes	1	2	1.2 (0.1-23.7)	Yes	No	41	91	1.5 (0.98-2.4)	Strengths: Multiple countries Proxy interviews for deceased cases [3] VTE, stroke, and AMI diagnoses confirmed with medical records	II-2, fair
HTN	POP	Cases	Controls	VTE aOR* (95% CI)																			
Yes	Yes	1	2	1.2 (0.1-23.7)																			
Yes	No	41	91	1.5 (0.98-2.4)																			

Author, Published, Location, Support	Study Design, Years	Population	Medical condition	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																																																																																									
		hospitalized at same hospitals, matched by 5-year age band Exclusions: TIA, death within 24 hours of admission, history of VTE, stroke or AMI, menopause, pregnancy, bedrest or surgery				<table><tr><td>No</td><td>Yes</td><td>9</td><td>21</td><td>2.0 (0.8-4.7)</td></tr><tr><td>No</td><td>No</td><td>439</td><td>1667</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>Stroke aOR† (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>13</td><td>7</td><td>10.9 (3.6-33.8)</td></tr><tr><td>Yes</td><td>No</td><td>571</td><td>368</td><td>7.2 (6.1-8.5)</td></tr><tr><td>No</td><td>Yes</td><td>14</td><td>53</td><td>0.95 (0.5-1.8)</td></tr><tr><td>No</td><td>No</td><td>1193</td><td>4811</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>AMI aOR‡ (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>1</td><td>1</td><td>1.9 (0.1-38.4)</td></tr><tr><td>Yes</td><td>No</td><td>84</td><td>53</td><td>8.1 (4.9-13.3)</td></tr><tr><td>No</td><td>Yes</td><td>2</td><td>5</td><td>1.7 (0.2-12.5)</td></tr><tr><td>No</td><td>No</td><td>175</td><td>742</td><td>Ref</td></tr></table> * Adjusted for BMI † Adjusted for marital status, smoking ‡ Adjusted for diabetes, smoking <table><tr><th>Smoking</th><th>POP</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>Yes</td><td>Yes</td><td>4</td><td>9</td><td>2.4 (0.7-8.3)</td></tr><tr><td>Yes</td><td>No</td><td>128</td><td>445</td><td>1.3 (0.97-1.6)</td></tr><tr><td>No</td><td>Yes</td><td>6</td><td>14</td><td>1.8 (0.6-5.4)</td></tr><tr><td>No</td><td>No</td><td>353</td><td>1313</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>Stroke aOR† (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>4</td><td>3</td><td>2.5 (0.5-13.2)</td></tr><tr><td>Yes</td><td>No</td><td>445</td><td>1084</td><td>1.5 (1.3-1.8)</td></tr><tr><td>No</td><td>Yes</td><td>23</td><td>57</td><td>0.99 (0.6-1.8)</td></tr></table>	No	Yes	9	21	2.0 (0.8-4.7)	No	No	439	1667	Ref					Stroke aOR† (95% CI)	Yes	Yes	13	7	10.9 (3.6-33.8)	Yes	No	571	368	7.2 (6.1-8.5)	No	Yes	14	53	0.95 (0.5-1.8)	No	No	1193	4811	Ref					AMI aOR‡ (95% CI)	Yes	Yes	1	1	1.9 (0.1-38.4)	Yes	No	84	53	8.1 (4.9-13.3)	No	Yes	2	5	1.7 (0.2-12.5)	No	No	175	742	Ref	Smoking	POP	Cases	Controls	VTE aOR* (95% CI)	Yes	Yes	4	9	2.4 (0.7-8.3)	Yes	No	128	445	1.3 (0.97-1.6)	No	Yes	6	14	1.8 (0.6-5.4)	No	No	353	1313	Ref					Stroke aOR† (95% CI)	Yes	Yes	4	3	2.5 (0.5-13.2)	Yes	No	445	1084	1.5 (1.3-1.8)	No	Yes	23	57	0.99 (0.6-1.8)	Matched on age and adjusted for confounding; excluded women with recent pregnancy Limitations: Hospital controls Participation rate of controls not reported (97% participation rate of cases) [3] Contraceptive use and medical conditions not verified Contraceptive formulations not specified <10 events for some comparisons of interest	
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						<table><tr><td>No</td><td>No</td><td>1319</td><td>4095</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>AMI aOR‡ (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>3</td><td>3</td><td>7.2 (0.7-74.6)</td></tr><tr><td>Yes</td><td>No</td><td>151</td><td>227</td><td>5.0 (3.4-7.3)</td></tr><tr><td>No</td><td>Yes</td><td>0</td><td>3</td><td>NR</td></tr><tr><td>No</td><td>No</td><td>108</td><td>568</td><td>Ref</td></tr></table> * Adjusted for BMI † Adjusted for HTN, marital status ‡ Adjusted for HTN, diabetes <table><tr><th>Smoking</th><th>POI</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>Yes</td><td>Yes</td><td>1</td><td>2</td><td>7.0 (0.4-138)</td></tr><tr><td>Yes</td><td>No</td><td>128</td><td>445</td><td>1.3 (0.97-1.6)</td></tr><tr><td>No</td><td>Yes</td><td>5</td><td>14</td><td>1.9 (0.5-7.0)</td></tr><tr><td>No</td><td>No</td><td>353</td><td>1313</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>Stroke aOR† (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>0</td><td>8</td><td>NR</td></tr><tr><td>Yes</td><td>No</td><td>445</td><td>1084</td><td>1.5 (1.3-1.8)</td></tr><tr><td>No</td><td>Yes</td><td>23</td><td>73</td><td>1.1 (0.6-1.8)</td></tr><tr><td>No</td><td>No</td><td>1319</td><td>4095</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>AMI aOR‡ (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>0</td><td>1</td><td>NR</td></tr><tr><td>Yes</td><td>No</td><td>151</td><td>227</td><td>5.0 (3.4-7.3)</td></tr><tr><td>No</td><td>Yes</td><td>1</td><td>6</td><td>0.95 (0.1-8.9)</td></tr><tr><td>No</td><td>No</td><td>108</td><td>568</td><td>Ref</td></tr></table> * Adjusted for BMI † Adjusted for HTN, marital status ‡ Adjusted for HTN, diabetes	No	No	1319	4095	Ref					AMI aOR‡ (95% CI)	Yes	Yes	3	3	7.2 (0.7-74.6)	Yes	No	151	227	5.0 (3.4-7.3)	No	Yes	0	3	NR	No	No	108	568	Ref	Smoking	POI	Cases	Controls	VTE aOR* (95% CI)	Yes	Yes	1	2	7.0 (0.4-138)	Yes	No	128	445	1.3 (0.97-1.6)	No	Yes	5	14	1.9 (0.5-7.0)	No	No	353	1313	Ref					Stroke aOR† (95% CI)	Yes	Yes	0	8	NR	Yes	No	445	1084	1.5 (1.3-1.8)	No	Yes	23	73	1.1 (0.6-1.8)	No	No	1319	4095	Ref					AMI aOR‡ (95% CI)	Yes	Yes	0	1	NR	Yes	No	151	227	5.0 (3.4-7.3)	No	Yes	1	6	0.95 (0.1-8.9)	No	No	108	568	Ref		
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Heinemann, 1999 [4] Europe Schering AG	Case control 1993-1996	Ages 16-44 Cases (N=394): hospitalized and death reports [5] Controls (hospital and community) (N=2,366): hospital controls and community controls (from general practice or neighborhood) [6], matched on age Exclusions: history thrombosis, hysterectomy, pregnancy, surgery, severe trauma	HTN Smoking Participant questionnaire [6]	POP Use within 3 months Participant questionnaire [5], confirmed by examining pill packs	VTE Ischemic stroke AMI Obtained from hospitals and death reports, confirmed by radiology results and necropsy reports [5]	<table><tr><th>HTN</th><th>POP use</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>Yes</td><td>Yes</td><td>2</td><td>6</td><td>2.3 (0.2-28.1)</td></tr><tr><td>Yes</td><td>No</td><td>21</td><td>88</td><td>1.4 (0.7-2.8)</td></tr><tr><td>No</td><td>Yes</td><td>5</td><td>48</td><td>0.6 (0.2-1.8)</td></tr><tr><td>No</td><td>No</td><td>153</td><td>1258</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>Stroke aOR† (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>0</td><td>1</td><td>-</td></tr><tr><td>Yes</td><td>No</td><td>25</td><td>28</td><td>9.5 (3.7-24.1)</td></tr><tr><td>No</td><td>Yes</td><td>3</td><td>9</td><td>2.8 (0.4-18.7)</td></tr><tr><td>No</td><td>No</td><td>61</td><td>453</td><td>Ref</td></tr><tr><td></td><td></td><td></td><td></td><td>AMI aOR‡ (95% CI)</td></tr><tr><td>Yes</td><td>Yes</td><td>1</td><td>3</td><td>0.8 (0.03-20.4)</td></tr><tr><td>Yes</td><td>No</td><td>37</td><td>39</td><td>8.3 (3.8-18.5)</td></tr><tr><td>No</td><td>Yes</td><td>6</td><td>14</td><td>1.3 (0.4-4.3)</td></tr><tr><td>No</td><td>No</td><td>79</td><td>418</td><td>Ref</td></tr></table> * Adjusted for BMI † Adjusted for alcohol, smoking ‡ Adjusted for diabetes, education, smoking <table><tr><th>Smoking</th><th>POP use</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>Yes</td><td>Yes</td><td>2</td><td>20</td><td>0.95 (0.2-6.0)</td></tr></table>	HTN	POP use	Cases	Controls	VTE aOR* (95% CI)	Yes	Yes	2	6	2.3 (0.2-28.1)	Yes	No	21	88	1.4 (0.7-2.8)	No	Yes	5	48	0.6 (0.2-1.8)	No	No	153	1258	Ref					Stroke aOR† (95% CI)	Yes	Yes	0	1	-	Yes	No	25	28	9.5 (3.7-24.1)	No	Yes	3	9	2.8 (0.4-18.7)	No	No	61	453	Ref					AMI aOR‡ (95% CI)	Yes	Yes	1	3	0.8 (0.03-20.4)	Yes	No	37	39	8.3 (3.8-18.5)	No	Yes	6	14	1.3 (0.4-4.3)	No	No	79	418	Ref	Smoking	POP use	Cases	Controls	VTE aOR* (95% CI)	Yes	Yes	2	20	0.95 (0.2-6.0)	Strengths: Multinational Use of both hospital and community controls (combined, but results similar when examined separately) Proxy interviews for deceased cases [6] POP use verified VTE, stroke and AMI diagnoses confirmed by radiology and necropsy Matched on age and adjusted for confounders; excluded women with recent pregnancy Limitations: <10 POP users for some comparisons of interest	II-2, good
HTN	POP use	Cases	Controls	VTE aOR* (95% CI)																																																																																									
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						Yes	No	94	517	1.9 (1.2-2.9)														
						No	Yes	5	34	1.5 (0.4-5.7)														
						No	No	80	829	Ref														
										Stroke aOR† (95% CI)														
						Yes	Yes	2	4	-														
						Yes	No	54	198	2.6 (1.3-4.9)														
						No	Yes	1	6	0.4 (0.03-6.5)														
						No	No	33	284	Ref														
										AMI aOR‡ (95% CI)														
						Yes	Yes	5	11	10.4 (1.1-98.8)														
						Yes	No	92	167	10.2 (5.0-20.6)														
						No	Yes	2	6	3.9 (0.5-32.0)														
						No	No	24	290	Ref														
						* Adjusted for BMI † Adjusted for HTN, alcohol ‡ Adjusted for HTN, diabetes, education																		
Rosenberg, 2001 [7] United States NIH	Case control 1985-1999	Ages <45 Cases: hospitalized Controls (hospital): admission lists or patient files from same hospitals, admitted with diagnosis unrelated to OC use	Smoking ≥25 cigarettes per day	POP Use within 1 month before admission Participant questionnaire Inpatient interviews prompted with pictures Validation of some participants	AMI Phone call to collaborating hospitals, confirmed by review of records	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>AMI %</th></tr><tr><td>POP</td><td>1</td><td>1</td><td>50</td></tr><tr><td>Past and never users</td><td>591</td><td>2710</td><td>17.9</td></tr></table>							Method	Cases	Controls	AMI %	POP	1	1	50	Past and never users	591	2710	17.9
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				by physicians (86% agreement for hospital interviews, 81% agreement for phone interviews)													
Conard, 2004 [8] France Funding source not stated	Retrospective cohort 1992-1997	Ages 15-50 Cohort (N=102): women using POP referred to thrombosis clinic, mean follow-up 31.2 months Comparison group (N=102): non-hormonal, matched on age, date of first visit, and thrombosis risk factors; mean follow-up 35 months	Thrombophilia (blood test by study investigators) History VTE (questionnaire)	POP (chlormadinone acetate) Current use at beginning of follow-up Participant questionnaire	VTE Ascertained by study investigators in thrombosis clinic	<table><tr><th>Method</th><th>VTE (N)</th><th>VTE aRR* (95% CI)</th></tr><tr><td>POP</td><td>3</td><td>0.8 (0.2-3.9)</td></tr><tr><td>Comparison</td><td>6</td><td>Ref</td></tr></table> *Adjusted for age, thrombophilia, BMI	Method	VTE (N)	VTE aRR* (95% CI)	POP	3	0.8 (0.2-3.9)	Comparison	6	Ref	Strengths: Exposed and unexposed from same clinic population VTE diagnoses confirmed by follow up in clinic Matched on age and probable personal VTE history; adjusted for age, BMI, thrombophilia Limitations: <10 VTEs in users and non-users Did not account for recent pregnancy Did not measure contraceptive use during follow-up Unable to examine risk separately for thrombophilias or history VTE, due to small numbers No information on initial response rates; median follow-up times similar between groups	II-2, poor
Method	VTE (N)	VTE aRR* (95% CI)															
POP	3	0.8 (0.2-3.9)															
Comparison	6	Ref															
Christiansen, 2010 [9] The Netherlands Netherlands Heart Foundation, Prevention Fund/ZonMW	Prospective cohort 1998-2000	Ages 16-48 Cohort (N=12): POC users with previous VTE during OC use or pregnancy, followed in anticoagulant clinic; total follow up 52 WY	History VTE while using COC or pregnant Initial VTE confirmed by imaging	POP DMPA Use within 1 month Participant questionnaire	Recurrent VTE Ascertained by participant questionnaire, confirmed by medical records and radiology results	<table><tr><th>Method</th><th>VTE (N)</th><th>Recurrent VTE IRR* (95% CI)</th></tr><tr><td>POC</td><td>2 (both in women using DMPA)</td><td>3.6 (0.7-17.3)</td></tr><tr><td>Comparison</td><td>8</td><td>Ref</td></tr></table> * Adjusted for age	Method	VTE (N)	Recurrent VTE IRR* (95% CI)	POC	2 (both in women using DMPA)	3.6 (0.7-17.3)	Comparison	8	Ref	Strengths: Exposed and unexposed from same clinic population Contraceptive use confirmed by provider VTE diagnoses confirmed by imaging	II-2, poor
Method	VTE (N)	Recurrent VTE IRR* (95% CI)															
POC	2 (both in women using DMPA)	3.6 (0.7-17.3)															
Comparison	8	Ref															

Author, Published, Location, Support	Study Design, Years	Population	Medical condition	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																			
		Comparison group (N=80): currently not using hormonal and not pregnant, previous VTE during OC use or pregnancy, followed in anticoagulant clinic; total follow up 760 WY Exclusions: recent cancer					Limitations: Small numbers and no power calculations POP formulations not specified All POC methods analyzed together																																				
Vaillant-Roussel, 2011 [10] France Public funds	Retrospective cohort 1995-2008	Ages 17-53 Cohort (N=34): POP users, with previous VTE during COC use, from hospital records and referred to clinic Comparison group (N=126): non-users, with previous VTE from same hospital Median follow-up 74 months	History VTE while using COC Hospital records	POP Use within 1 month Participant questionnaire	Recurrent VTE Ascertained by hospital or office records, confirmed by radiology results	<table><tr><th>Method</th><th>VTE (N)</th><th>Recurrent VTE HR (95% CI)</th></tr><tr><td>POP</td><td>7</td><td>1.3 (0.5-3.0)</td></tr><tr><td>Comparison</td><td>24</td><td>Ref</td></tr></table>	Method	VTE (N)	Recurrent VTE HR (95% CI)	POP	7	1.3 (0.5-3.0)	Comparison	24	Ref	Strengths: Exposed and unexposed from same patient population VTE diagnoses confirmed with radiology results Limitations: POP use not confirmed; type unknown <10 recurrent VTE among POP users Did not adjust for potential confounders	II-2, poor																										
Method	VTE (N)	Recurrent VTE HR (95% CI)																																									
POP	7	1.3 (0.5-3.0)																																									
Comparison	24	Ref																																									
Bergendal, 2014 [11] Sweden Janssen-Cilag, Novartis, Organon, Schering, Wyeth, AFA Insurance, Karolinska Institutet, Medical Products Agency	Case control 2003-2009	Ages 18-54 Cases: inpatient and outpatient Controls (community): from population register, matched on age Exclusions: history thrombosis, pregnancy within 3 months, current cancer	Thrombogenic mutations Blood sample by investigators	POP DMPA Implant (ETG or LNG) [12] LNG-IUD POC combined Use within 3 months Participant questionnaire	VTE Diagnosis confirmed by medical records and imaging Included only if initiated anticoagulation	<table><tr><th>Factor V Leiden carrier</th><th>Method</th><th>Cases</th><th>Controls</th><th>VTE OR* (95% CI)</th></tr><tr><td>Yes</td><td>DMPA</td><td>NR</td><td>NR</td><td>16.7 (2.4-714)</td></tr><tr><td>Yes</td><td>LNG-IUD</td><td>NR</td><td>NR</td><td>3.2 (1.2-10.4)</td></tr><tr><td>Yes</td><td>POC combined</td><td>35</td><td>9</td><td>5.4 (2.5-13)</td></tr><tr><td>Yes</td><td>No HC</td><td>101</td><td>55</td><td>2.6 (1.8-3.7)</td></tr><tr><td>No</td><td>POC combined</td><td>107</td><td>54</td><td>1.0 (0.7-1.3)</td></tr><tr><td>No</td><td>No HC</td><td>378</td><td>525</td><td>Ref</td></tr></table> *Matched on age	Factor V Leiden carrier	Method	Cases	Controls	VTE OR* (95% CI)	Yes	DMPA	NR	NR	16.7 (2.4-714)	Yes	LNG-IUD	NR	NR	3.2 (1.2-10.4)	Yes	POC combined	35	9	5.4 (2.5-13)	Yes	No HC	101	55	2.6 (1.8-3.7)	No	POC combined	107	54	1.0 (0.7-1.3)	No	No HC	378	525	Ref	Strengths: Population-based VTE diagnoses confirmed with medical records Limitations: Differential participation rate between cases (90%) and controls (69%) [13] Contraceptive type self-reported, not verified <10 POC users for some comparisons of interest	II-2, fair
Factor V Leiden carrier	Method	Cases	Controls	VTE OR* (95% CI)																																							
Yes	DMPA	NR	NR	16.7 (2.4-714)																																							
Yes	LNG-IUD	NR	NR	3.2 (1.2-10.4)																																							
Yes	POC combined	35	9	5.4 (2.5-13)																																							
Yes	No HC	101	55	2.6 (1.8-3.7)																																							
No	POC combined	107	54	1.0 (0.7-1.3)																																							
No	No HC	378	525	Ref																																							

Author, Published, Location, Support	Study Design, Years	Population	Medical condition	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																									
						<table><tr><th>PT gene mutation</th><th>Method</th><th>Cases</th><th>Controls</th><th>VTE OR* (95% CI)</th></tr><tr><td>Yes</td><td>POC combined</td><td>6</td><td>10</td><td>0.7 (0.2-2.2)</td></tr><tr><td>Yes</td><td>No HC</td><td>21</td><td>15</td><td>1.7 (0.8-3.6)</td></tr><tr><td>No</td><td>POC combined</td><td>133</td><td>154</td><td>1.0 (0.8-1.4)</td></tr><tr><td>No</td><td>No HC</td><td>459</td><td>556</td><td>Ref</td></tr></table> *Matched on age	PT gene mutation	Method	Cases	Controls	VTE OR* (95% CI)	Yes	POC combined	6	10	0.7 (0.2-2.2)	Yes	No HC	21	15	1.7 (0.8-3.6)	No	POC combined	133	154	1.0 (0.8-1.4)	No	No HC	459	556	Ref	All POC combined for some comparisons	
PT gene mutation	Method	Cases	Controls	VTE OR* (95% CI)																													
Yes	POC combined	6	10	0.7 (0.2-2.2)																													
Yes	No HC	21	15	1.7 (0.8-3.6)																													
No	POC combined	133	154	1.0 (0.8-1.4)																													
No	No HC	459	556	Ref																													
Le Moigne, 2016 [14] France Support not stated	Prospective cohort 1992-2013	Ages ≤50 Cohort (N=163): POC users, with previous VTE, from hospital records; median duration of follow up 5.1 years after stopping anticoagulation Comparison group (N=256): non-users, with previous VTE from same hospital; median duration of follow up 3.8 years after stopping anticoagulation Exclusions: active cancer, hormone replacement, anticoagulant therapy, periods of exposure to combined hormonal contraception or pregnancy	History VTE Hospital records	POP (LNG or DSG) Implant (ETG) LNG-IUD Timing of use not stated Ascertainment not stated	Recurrent VTE Ascertained by review of hospital diagnoses, confirmed by imaging	<table><tr><th>Method</th><th>VTE (N)</th><th>Recurrent VTE IRR* (95% CI)</th></tr><tr><td>POC</td><td>6</td><td>0.6 (0.3-1.5)</td></tr><tr><td>Comparison</td><td>29</td><td>Ref</td></tr></table> *Adjusted for age	Method	VTE (N)	Recurrent VTE IRR* (95% CI)	POC	6	0.6 (0.3-1.5)	Comparison	29	Ref	Strengths: Exposed and unexposed from same patient population VTE diagnoses confirmed by imaging Limitations: Method of ascertainment of POC use not stated Timing of POC use relative to VTE not stated Comparison group may have used POCs during follow up All POC methods analyzed together <10 recurrent VTE among POC users	II-2, poor																
Method	VTE (N)	Recurrent VTE IRR* (95% CI)																															
POC	6	0.6 (0.3-1.5)																															
Comparison	29	Ref																															
Martinelli, 2016 [15] Canada, France, Germany, Italy, the Netherlands.	Prospective cohort (secondary analysis of RCT) 2007-2011	Women ages <60, mean age 41.3 years (n=1888) Rivaroxaban (n=925) or enoxaparin/	History of VTE, currently on anticoagulation Confirmed by investigators	Estrogen-containing therapy (n=306), defined as use of estrogen in estrogen-only pills or CHC	Recurrent VTE Incidence during at-risk period, objective diagnostic tests were required	Recurrent VTE during at-risk period: <table><tr><th>Method</th><th>Incidence density %/year (95% CI)</th><th>Events/patient-years</th></tr><tr><td>EE-containing</td><td>4.0 (1.1-10.2)</td><td>4/100.3</td></tr><tr><td>POC</td><td>3.8 (0.8-11.2)</td><td>3/78.0</td></tr></table>	Method	Incidence density %/year (95% CI)	Events/patient-years	EE-containing	4.0 (1.1-10.2)	4/100.3	POC	3.8 (0.8-11.2)	3/78.0	Strengths: Large sample size Objective and validated measurement of VTE	II-2, fair																
Method	Incidence density %/year (95% CI)	Events/patient-years																															
EE-containing	4.0 (1.1-10.2)	4/100.3																															
POC	3.8 (0.8-11.2)	3/78.0																															

Author, Published, Location, Support	Study Design, Years	Population	Medical condition	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																				
United Kingdom, USA Bayer HealthCare Pharmaceuticals	Multi-site, multi-country	vitamin K antagonist (n=963)	before RCT enrollment	POC (n=217) LNG-IUD (n not reported) No hormonal therapy (n=1413) Verified by investigators	At-risk period defined as period between randomization and last intake of rivaroxaban or enoxaparin/vitamin K antagonist	<table><tr><td>LNG-IUD</td><td>0 (0.0-24.0)</td><td>0/15.3</td></tr><tr><td>No hormones</td><td>4.7 (3.3-6.4)</td><td>38/811.0</td></tr></table> POC vs no hormonal use: relative risk 0.81 (hand-calculated)	LNG-IUD	0 (0.0-24.0)	0/15.3	No hormones	4.7 (3.3-6.4)	38/811.0	Prospective data collection of medications Limitations: Post-hoc analysis, RCT was open-label trial that could have biased outcome assessment POC group not further defined by type Did not account for age																															
LNG-IUD	0 (0.0-24.0)	0/15.3																																										
No hormones	4.7 (3.3-6.4)	38/811.0																																										
O'Brien, 2017 [16] USA American Diabetes Association	Retrospective cohort 2002-2011 Claims database	Women ages 14-44 (n=146,080) 478,650 woman-years of observation	Diabetes, type 1 or type 2 ICD-9-CM codes for diabetes and prescription for a diabetic medication or device	POC (n=8250) -POP (n=3306) -DMPA (n=2266) -Implant (ETG) (n=124) -IUD (type not specified) (n=2730) No HC (n=139,358) ICD-9-CM codes and filled prescriptions	Thromboembolism (combined VTE [DVT, PE] and ATE [stroke, MI]) VTE patients required to have been dispensed an anticoagulant within 30 days of index date	<table><tr><th>Method</th><th colspan="2">Risk of VTE/ATE, aHR* (95% CI)</th></tr><tr><td></td><td><35 years</td><td>≥35 years</td></tr><tr><td>POC</td><td>2.02 (1.51-2.70)</td><td>1.33 (0.99-1.79)</td></tr><tr><td>No HC</td><td>Ref</td><td>Ref</td></tr></table> <table><tr><th>Method</th><th colspan="3">Risk of VTE/ATE</th></tr><tr><td></td><th>Cases</th><th>Events/1000 WY</th><th>aHR* (95% CI)</th></tr><tr><td>POP</td><td>26</td><td>14.5</td><td>3.69 (2.10-6.48)</td></tr><tr><td>DMPA</td><td>52</td><td>12.5</td><td>4.69 (2.51-8.77)</td></tr><tr><td>Implant</td><td>0</td><td>0</td><td>--</td></tr><tr><td>IUD</td><td>17</td><td>3.4</td><td>Ref</td></tr></table> *Adjusted for age, advanced diabetes, hyperlipidemia, HTN, cancer, obesity, smoking	Method	Risk of VTE/ATE, aHR* (95% CI)			<35 years	≥35 years	POC	2.02 (1.51-2.70)	1.33 (0.99-1.79)	No HC	Ref	Ref	Method	Risk of VTE/ATE				Cases	Events/1000 WY	aHR* (95% CI)	POP	26	14.5	3.69 (2.10-6.48)	DMPA	52	12.5	4.69 (2.51-8.77)	Implant	0	0	--	IUD	17	3.4	Ref	Strengths: Large sample size Limitations: Only commercially insured claims Claims as proxy for actual contraceptive use No information on some covariates (family history of thrombosis) Combined ATE and VTE as primary outcome Unknown timing of HC in relation to VTE incidence	II-2, fair
Method	Risk of VTE/ATE, aHR* (95% CI)																																											
	<35 years	≥35 years																																										
POC	2.02 (1.51-2.70)	1.33 (0.99-1.79)																																										
No HC	Ref	Ref																																										
Method	Risk of VTE/ATE																																											
	Cases	Events/1000 WY	aHR* (95% CI)																																									
POP	26	14.5	3.69 (2.10-6.48)																																									
DMPA	52	12.5	4.69 (2.51-8.77)																																									
Implant	0	0	--																																									
IUD	17	3.4	Ref																																									
Tepper, 2019 [17] USA None	Retrospective cohort Private insurance claims database	Women ages 15-44 with hospital delivery (n=3,113,170) Exclusions: abortion, ectopic pregnancy, molar pregnancy, other abnormal products of conception, prescribed anticoagulants during 6 months before hospital delivery	Postpartum ICD-9-CM and CPT codes	DMPA, immediate postpartum (given within first 7 days postpartum) (n=11,159) No DMPA (n=3,102,011) ICD-9-CM, CPT, and pharmacy claim codes	VTE (DVT or PE) ICD-9-CM codes Outpatient diagnosis required a filled anticoagulation prescription 12 week follow-up	<table><tr><th>Method</th><th colspan="3">Risk of VTE</th></tr><tr><td></td><th>Cases</th><th>VTE IR/10,000 Women-Days (95% CI)</th><th>VTE, IRR* (95% CI)</th></tr><tr><td>DMPA</td><td>34</td><td>0.42 (0.30-0.59)</td><td>1.94 (1.38-2.72)</td></tr><tr><td>No DMPA</td><td>3107</td><td>0.15 (0.15-0.16)</td><td>Ref</td></tr></table> *Adjusted for age, pregestational diabetes, chronic HTN, obesity, smoking, cesarean delivery, gestational HTN, preeclampsia, eclampsia, multiple birth, anemia, hemorrhage, postpartum infection, intrauterine fetal demise, other severe complications	Method	Risk of VTE				Cases	VTE IR/10,000 Women-Days (95% CI)	VTE, IRR* (95% CI)	DMPA	34	0.42 (0.30-0.59)	1.94 (1.38-2.72)	No DMPA	3107	0.15 (0.15-0.16)	Ref	Strengths: Large sample size Limitations: Only private insurance claims Possible misclassification bias given no inpatient drug codes VTE outcomes not verified in medical records	II-2, fair																				
Method	Risk of VTE																																											
	Cases	VTE IR/10,000 Women-Days (95% CI)	VTE, IRR* (95% CI)																																									
DMPA	34	0.42 (0.30-0.59)	1.94 (1.38-2.72)																																									
No DMPA	3107	0.15 (0.15-0.16)	Ref																																									
Floyd, 2020 [18] USA	Retrospective cohort	Women with a singleton delivery (n=3,387,120)	Postpartum within 30 days	Implant (ETG), immediate postpartum	VTE (DVT or PE)	<table><tr><th>Method</th><th>Cases</th><th>VTE aOR* (95% CI)</th></tr></table>	Method	Cases	VTE aOR* (95% CI)	Strengths:	II-2, fair																																	
Method	Cases	VTE aOR* (95% CI)																																										

Author, Published, Location, Support	Study Design, Years	Population	Medical condition	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading		
None	2016 National hospital readmissions database	Exclusions: history of VTE or anticoagulation ICD-10-CM and ICD-10 PCS codes	ICD-10-CM and ICD-10 PCS codes	(placed during delivery admission) (n=8369) No implant (n=3, 378,751) Implant identified with ICD-10-CM and ICD-10-PCS codes for both insertion of implant and delivery	Defined as readmission for VTE within 30 days of discharge	Implant	7	1.81 (0.44-7.45)	Large national sample size, good generalizability Limitations: Retrospective, claims data, only inpatient data Possible misclassification of cases No implant group may be using a different contraceptive method	
						No implant	1192	Ref		
						*Adjusted for age, insurance payer, hypertension, tobacco, infection, postpartum hemorrhage				
						Method	Absolute risk of VTE/ 1,000 deliveries (95% CI)			
						Implant	0.85 (0.22-1.45)			
No implant	0.35 (0.33-0.37)									
Maher, 2022 [19] USA None	Retrospective cohort 2010-2020 Single-institution electronic claims query	Patients ages 13-20 years (n=89) Exclusion: stroke, arterial thrombosis, SVT, on HRT, pregnancy	History of hormone-associated VTE New diagnosis of VTE while on estrogen or progestin containing medication	COC (n=4) POC (n=45) -POP (n=18) -LNG-IUD (n=19) -DMPA (n=5) -Implant (ETG) (n=3) No HC (n=37) Prescribed within 12 months of index VTE Identified by medical record review	Recurrent VTE Defined as VTE within 12 months of index VTE Manual chart review after initial claims query by ICD-9 for index VTE	Method	Recurrent VTE, n (%)		Strengths: Contraceptive use and outcomes confirmed with medical records Limitations: Limited documentation of contraceptive visits outside of health system No statistical testing performed Hormonal contraception not further defined by type for those on indefinite anticoagulation	II-2, poor
						COC	0 (0)			
						POP	1 (5.6)			
						LNG-IUD	1 (5.3)			
						DMPA	0 (0)			
						Implant	1 (33.3)			
						No HC	5 (13.5)			

Abbreviations: AMI, acute myocardial infarction; ATE, arterial thromboembolism; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; CHC, combined hormonal contraception; COC, combined oral contraception; CPT, Current Procedural Terminology; DSG, desogestrel; DVT, deep venous thromboembolism; EE, ethinyl estradiol; ETG, etonogestrel; DMPA, depot medroxyprogesterone acetate; HC, hormonal contraception; HRT, hormone replacement therapy; HTN, hypertension; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-PCS, International Classification of Diseases, Tenth Revision, Procedure Coding System; IR, incidence rate; IRR, incidence rate ratio; IUD, intrauterine device; LNG, levonorgestrel; MI, myocardial infarction; NET-EN, norethisterone enanthate; NIH, National Institutes of Health; NR, not reported; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; POC, progestin-only contraception; POI, progestin-only injectable; POP, progestin-only pill; PT, prothrombin; RCT, randomized controlled trial; SVT, superficial venous thrombosis; TIA, transient ischemic attack; VTE, venous thromboembolism; WY, women-years.

Appendix B.2: Evidence for risk of venous or arterial thrombosis among women with no or unspecified medical conditions using progestin-only contraception

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading												
Thorogood, 1991 [20] England and Wales British Heart Foundation, Committee on Safety of Medicines, Family Health International	Case control 1986-1988	Ages <40 Cases: death certificates Controls (community): living controls from same general practitioner, matched on age (5-year age groups) and marital status Exclusions: resident of institution for 1 month, pregnant within 2 months, another life threatening illness such as cancer	POP Use within 1 month Physician questionnaire	Death due to AMI Diagnosis codes from death certificates, confirmed by post-mortem reports and medical records	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>AMI (%)</th></tr><tr><td>POP</td><td>3</td><td>12</td><td>20.0</td></tr><tr><td>Never or no use within 10 years</td><td>66</td><td>143</td><td>31.6</td></tr></table>	Method	Cases	Controls	AMI (%)	POP	3	12	20.0	Never or no use within 10 years	66	143	31.6	Strengths: AMI diagnoses confirmed by medical records Limitations: Use of deceased cases and living controls <10 cases using POPs OR not reported for comparison of interest	II-2, poor
Method	Cases	Controls	AMI (%)																
POP	3	12	20.0																
Never or no use within 10 years	66	143	31.6																
Lidegaard, 1993 [21] Denmark Support not stated	Case control 1985-1989	Ages 15-44 Cases: first episode identified from national registry using discharge diagnosis codes Controls (community): randomly selected from national registry, matched on age Exclusions: history thromboembolism, current pregnancy, HTN; controls also excluded if they had migraine or other pre-disposing medical factor	POP Use at time of event Participant questionnaire	Ischemic stroke Identified by diagnosis codes Confirmed by physician or subject confirmation or CT scan	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>Stroke aOR* (95% CI)</th></tr><tr><td>POP</td><td>7</td><td>18</td><td>0.9 (0.4-2.4)</td></tr><tr><td>Never users</td><td>56</td><td>181</td><td>Ref</td></tr></table> *Adjusted for age, smoking, education	Method	Cases	Controls	Stroke aOR* (95% CI)	POP	7	18	0.9 (0.4-2.4)	Never users	56	181	Ref	Strengths: National dataset Stroke diagnoses confirmed physician or subject or radiology results Limitations: <10 cases using POPs POP use not confirmed Included TIA Did not account for recent pregnancy	II-2, fair
Method	Cases	Controls	Stroke aOR* (95% CI)																
POP	7	18	0.9 (0.4-2.4)																
Never users	56	181	Ref																
Tzourio, 1995 [22]	Case control	Ages 18-44	POP	Ischemic stroke		Strengths:	II-2, poor												

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																								
France GLAXO France	1990-1993	Cases (N=41): hospitalized with first episode, diagnosis codes Controls (hospital) (N=62): randomly selected from same hospitals, orthopedic or benign rheumatologic illnesses Exclusions: not stated (no participants had history of stroke)	Use within 1 month Participant questionnaire	Identified by diagnosis codes Confirmed by radiology results	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>Stroke OR</th></tr><tr><td>POP</td><td>1</td><td>4</td><td>1.0</td></tr><tr><td>Reference group</td><td>40</td><td>58</td><td>Ref</td></tr></table>	Method	Cases	Controls	Stroke OR	POP	1	4	1.0	Reference group	40	58	Ref	Stroke diagnoses confirmed by radiology results Limitations: <10 cases and controls using POPs POP use not confirmed Did not account for recent pregnancy or other confounding factors Did not report confidence interval													
Method	Cases	Controls	Stroke OR																												
POP	1	4	1.0																												
Reference group	40	58	Ref																												
Lidegaard, 1998 [23] Denmark Organon, Wyeth-Ayerst, Schering AG	Case control 1994-1995	Ages 15-44 Cases: identified from national registry using discharge diagnostic codes Controls (community): randomly selected from national registry Exclusions: history VTE or AMI, pregnancy at time of thrombosis	POP Current use (at time of admission for cases and time of interview for controls) Participant questionnaire	VTE Identified by diagnosis codes and physician confirmation Classified as uncertain, probable, or certain (based on radiologic results and/or anticoagulation); all analyzed together	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>POP</td><td>4</td><td>6</td><td>2.6 (0.7-9.8)</td></tr><tr><td>Former users</td><td>130</td><td>618</td><td>Ref</td></tr></table> *Adjusted for age, age at first birth, smoking	Method	Cases	Controls	VTE aOR* (95% CI)	POP	4	6	2.6 (0.7-9.8)	Former users	130	618	Ref	Strengths: High response rate for cases and controls (approximately 90%) High percent (>95%) VTE diagnoses confirmed by radiologic results and/or anticoagulation Limitations: <10 cases and controls using POPs POP use not confirmed Did not account for recent pregnancy	II-2, fair												
Method	Cases	Controls	VTE aOR* (95% CI)																												
POP	4	6	2.6 (0.7-9.8)																												
Former users	130	618	Ref																												
Petitti 1998 [24] United States NIH	Pooled case control 1991-1995 (stroke) [25, 26] 1991-1994 (AMI) [27]	Ages 18-44 Stroke [25, 26]: Cases: discharge diagnoses from hospitals, death registers Controls (community): random-digit dialing of residents of same counties as cases, or randomly selected from insurance plan and	Implant (LNG) Use within 1 month [25-27] Participant questionnaire	Ischemic stroke AMI Diagnosis codes, confirmed by physician review of records	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>Stroke aOR* (95% CI)</th></tr><tr><td>Implant</td><td>1</td><td>3</td><td>1.0 (0.1-9.2)</td></tr><tr><td>Noncurrent users</td><td>517</td><td>1544</td><td>Ref</td></tr></table> *Adjusted for age <table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>AMI aOR* (95% CI)</th></tr><tr><td>Implant</td><td>1</td><td>1</td><td>3.5 (0.2-56.5)</td></tr><tr><td>Noncurrent users</td><td>306</td><td>1048</td><td>Ref</td></tr></table> *Adjusted for age	Method	Cases	Controls	Stroke aOR* (95% CI)	Implant	1	3	1.0 (0.1-9.2)	Noncurrent users	517	1544	Ref	Method	Cases	Controls	AMI aOR* (95% CI)	Implant	1	1	3.5 (0.2-56.5)	Noncurrent users	306	1048	Ref	Strengths: Stroke and AMI diagnoses confirmed by medical records Limitations: Implant use obtained from proxys for deceased cases, and not confirmed <5 cases and controls using implants Did not account for pregnancy/postpartum	II-2, fair
Method	Cases	Controls	Stroke aOR* (95% CI)																												
Implant	1	3	1.0 (0.1-9.2)																												
Noncurrent users	517	1544	Ref																												
Method	Cases	Controls	AMI aOR* (95% CI)																												
Implant	1	1	3.5 (0.2-56.5)																												
Noncurrent users	306	1048	Ref																												

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																																
		matched on age and location Exclusions: history heart disease, stroke AMI [27]: Cases: discharge diagnoses from hospital, emergency rooms Controls (community): randomly selected from insurance plan, matched on age and location Exclusions: history heart disease				or other important confounders																																																	
WHO, 1998 [2] Multiple countries in Africa, Asia, Europe and Latin America World Bank, NIH	Case control 1989-1993	Ages 20-44 Cases: admitted to hospital, identified by physicians Controls (hospital): hospitalized at same hospitals, matched by 5-year age band Exclusions: TIA, death within 24 hours of admission, history of VTE, stroke or AMI, menopause, pregnancy, bedrest or surgery	POP POI (most DMPA) Use within 3 months [3] Participant questionnaire	VTE Stroke AMI Ascertained by recruitment system at hospitals [3] Diagnosis verified by medical records and imaging	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>POP</td><td>21</td><td>63</td><td>1.8 (0.8-4.2)</td></tr><tr><td>POI</td><td>11</td><td>34</td><td>2.2 (0.7-7.3)</td></tr><tr><td>Nonusers</td><td>635</td><td>2288</td><td>Ref</td></tr></table> *Adjusted for BMI <table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>Stroke aOR* (95% CI)</th></tr><tr><td>POP</td><td>27</td><td>60</td><td>1.1 (0.6-1.9)</td></tr><tr><td>POI</td><td>25</td><td>81</td><td>0.9 (0.5-1.5)</td></tr><tr><td>Nonusers</td><td>1774</td><td>5183</td><td>Ref</td></tr></table> *Adjusted for HTN, marital status, smoking <table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>AMI aOR* (95% CI)</th></tr><tr><td>POP</td><td>3</td><td>6</td><td>0.98 (0.2-6.0)</td></tr><tr><td>POI</td><td>1</td><td>7</td><td>0.7 (0.1-6.0)</td></tr><tr><td>Nonusers</td><td>259</td><td>795</td><td>Ref</td></tr></table> *Adjusted for HTN, diabetes, smoking All results similar when reported separately for Europe and developing countries	Method	Cases	Controls	VTE aOR* (95% CI)	POP	21	63	1.8 (0.8-4.2)	POI	11	34	2.2 (0.7-7.3)	Nonusers	635	2288	Ref	Method	Cases	Controls	Stroke aOR* (95% CI)	POP	27	60	1.1 (0.6-1.9)	POI	25	81	0.9 (0.5-1.5)	Nonusers	1774	5183	Ref	Method	Cases	Controls	AMI aOR* (95% CI)	POP	3	6	0.98 (0.2-6.0)	POI	1	7	0.7 (0.1-6.0)	Nonusers	259	795	Ref	Strengths: Multiple countries Proxy interviews for deceased cases [3] VTE, stroke, and AMI diagnoses confirmed with medical records Matched on age and adjusted for confounding; excluded women with recent pregnancy Limitations: Hospital controls Participation rate of controls not reported (97% participation rate of cases) [3] Contraceptive use and medical conditions not verified Contraceptive formulations not specified	II-2, fair
Method	Cases	Controls	VTE aOR* (95% CI)																																																				
POP	21	63	1.8 (0.8-4.2)																																																				
POI	11	34	2.2 (0.7-7.3)																																																				
Nonusers	635	2288	Ref																																																				
Method	Cases	Controls	Stroke aOR* (95% CI)																																																				
POP	27	60	1.1 (0.6-1.9)																																																				
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Nonusers	1774	5183	Ref																																																				
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POP	3	6	0.98 (0.2-6.0)																																																				
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Nonusers	259	795	Ref																																																				

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																				
						<10 events for some comparisons of interest																																					
Dunn, 1999 [28] England, Scotland, Wales NV Organon, Schering AG	Case control 1993-1995	Ages 16-44 Cases: hospitals or death register Controls (community): same general practice as cases, matched on age Exclusions: History AMI, pregnancy within 6 wks, menopause, hysterectomy, oophorectomy, breast or ovarian cancer	POP Use within 3 months Participant or proxy (for deceased cases) questionnaire; validated with records from general practitioner or family planning clinic	AMI Diagnosis codes from hospital records or death records, confirmed by physician review of medical records	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>AMI aOR* (95% CI)</th></tr><tr><td>POP</td><td>9</td><td>49</td><td>1.5 (0.6-3.7)</td></tr><tr><td>No oral contraception</td><td>386</td><td>1467</td><td>Ref</td></tr></table> *Adjusted for smoking, BMI, blood pressure measurement in past year, diabetes, angina, hypertension, family history of ischemic heart disease, use of other drugs, additional variables from univariate analysis; interview and medical record data	Method	Cases	Controls	AMI aOR* (95% CI)	POP	9	49	1.5 (0.6-3.7)	No oral contraception	386	1467	Ref	Strengths: Contraceptive use verified AMI diagnosis confirmed by medical records ORs adjusted for important confounders Limitations: Among cases, differential participation between living (73%) and deceased (20%) <10 cases using POPs	II-2, fair																								
Method	Cases	Controls	AMI aOR* (95% CI)																																								
POP	9	49	1.5 (0.6-3.7)																																								
No oral contraception	386	1467	Ref																																								
Heinemann, 1999 [4] Europe Schering AG	Case control 1993-1996	Ages 16-44 Cases: hospitalized and death reports [5] Controls (hospital and community): hospital controls and community controls (from general practice or neighborhood) [6], matched on age Exclusions: history thrombosis, hysterectomy, pregnancy, surgery, severe trauma	POP Use within 3 months Participant questionnaire [5], confirmed by examining pill packs	VTE Ischemic stroke AMI Obtained from hospitals and death reports, confirmed by radiology results and necropsy reports [5]	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>POP</td><td>7</td><td>54</td><td>0.7 (0.3-1.7)</td></tr><tr><td>Nonusers</td><td>174</td><td>1346</td><td>Ref</td></tr></table> *Adjusted for BMI <table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>Stroke aOR* (95% CI)</th></tr><tr><td>POP</td><td>3</td><td>10</td><td>1.6 (0.2-10.7)</td></tr><tr><td>Nonusers</td><td>87</td><td>482</td><td>Ref</td></tr></table> *Adjusted for HTN, alcohol, smoking <table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>AMI aOR* (95% CI)</th></tr><tr><td>POP</td><td>7</td><td>17</td><td>0.9 (0.3-2.9)</td></tr><tr><td>Nonusers</td><td>126</td><td>457</td><td>Ref</td></tr></table> *Adjusted for HTN, diabetes, education, smoking	Method	Cases	Controls	VTE aOR* (95% CI)	POP	7	54	0.7 (0.3-1.7)	Nonusers	174	1346	Ref	Method	Cases	Controls	Stroke aOR* (95% CI)	POP	3	10	1.6 (0.2-10.7)	Nonusers	87	482	Ref	Method	Cases	Controls	AMI aOR* (95% CI)	POP	7	17	0.9 (0.3-2.9)	Nonusers	126	457	Ref	Strengths: Multinational Use of both hospital and community controls (combined, but results similar when examined separately) Proxy interviews for deceased cases [6] POP use verified VTE, stroke, and AMI diagnoses confirmed by radiology and necropsy Matched on age and adjusted for confounders; excluded women with recent pregnancy Limitations: <10 POP users for some comparisons of interest	II-2, good
Method	Cases	Controls	VTE aOR* (95% CI)																																								
POP	7	54	0.7 (0.3-1.7)																																								
Nonusers	174	1346	Ref																																								
Method	Cases	Controls	Stroke aOR* (95% CI)																																								
POP	3	10	1.6 (0.2-10.7)																																								
Nonusers	87	482	Ref																																								
Method	Cases	Controls	AMI aOR* (95% CI)																																								
POP	7	17	0.9 (0.3-2.9)																																								
Nonusers	126	457	Ref																																								
Poulter, 1999 [29]	Case control 1989-1995	Ages 20-49	Oral progestins for therapeutic reasons	VTE Stroke AMI	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE</th></tr></table>	Method	Cases	Controls	VTE	Strengths:	II-2, poor																																
Method	Cases	Controls	VTE																																								

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																				
(Same study as WHO, 1998 [2]) Multiple countries in Africa, Asia, Europe and Latin America World Bank, NIH		Cases: admitted to collaborating hospitals Controls (hospitalized): hospitalized, matched by 5-year age band Exclusions: TIA, history thrombosis, natural or surgical menopause, pregnant or postpartum, prolonged bed rest, surgery	(formulation and dose not specified) Use within 3 months [3] Participant questionnaire [3]	Ascertained by recruitment system at hospitals [3] Diagnosis confirmed by medical records and imaging	<table><tr><td></td><td></td><td></td><td>aOR* (95% CI)</td></tr><tr><td>POC</td><td>3</td><td>3</td><td>5.9 (1.2-30.1)</td></tr><tr><td>Past or never users</td><td>NR</td><td>NR</td><td>Ref</td></tr></table> *Adjusted for BMI <table><tr><td>Method</td><td>Cases</td><td>Controls</td><td>Stroke aOR* (95% CI)</td></tr><tr><td>POC</td><td>2</td><td>6</td><td>1.1 (0.2-7.1)</td></tr><tr><td>Past or never users</td><td>NR</td><td>NR</td><td>Ref</td></tr></table> *Adjusted for hypertension, marital status, smoking <table><tr><td>Method</td><td>Cases</td><td>Controls</td><td>AMI aOR* (95% CI)</td></tr><tr><td>POC</td><td>2</td><td>3</td><td>0.9 (0.1-15.3)</td></tr><tr><td>Past or never users</td><td>NR</td><td>NR</td><td>Ref</td></tr></table> *Adjusted for hypertension, diabetes, smoking				aOR* (95% CI)	POC	3	3	5.9 (1.2-30.1)	Past or never users	NR	NR	Ref	Method	Cases	Controls	Stroke aOR* (95% CI)	POC	2	6	1.1 (0.2-7.1)	Past or never users	NR	NR	Ref	Method	Cases	Controls	AMI aOR* (95% CI)	POC	2	3	0.9 (0.1-15.3)	Past or never users	NR	NR	Ref	VTE, stroke and AMI diagnoses confirmed by medical records Limitations: Formulation and dose of POC not stated Conditions being treated not reported <10 cases using POC	
			aOR* (95% CI)																																								
POC	3	3	5.9 (1.2-30.1)																																								
Past or never users	NR	NR	Ref																																								
Method	Cases	Controls	Stroke aOR* (95% CI)																																								
POC	2	6	1.1 (0.2-7.1)																																								
Past or never users	NR	NR	Ref																																								
Method	Cases	Controls	AMI aOR* (95% CI)																																								
POC	2	3	0.9 (0.1-15.3)																																								
Past or never users	NR	NR	Ref																																								
Vasilakis, 1999 [30] United Kingdom WHO	Nested case control 1993-1997	Ages <50 Cases: computer records from hospital admissions Controls (community): matched on age and general practice Exclusions [31]: history VTE, stroke, AMI, cancer, epilepsy, diabetes, hypertension, hyperlipidemia, cystic fibrosis	POC (not specified) “Current” use, not further defined Computer record	VTE Computer hospital records, some validated by physician	<table><tr><td>Method</td><td>Cases</td><td>Controls</td><td>VTE aRR* (95% CI)</td></tr><tr><td>POC all</td><td>7</td><td>36</td><td>2.4 (0.8-6.5)</td></tr><tr><td>POC for contraception</td><td>2</td><td>26</td><td>1.3 (0.3-6.8)</td></tr><tr><td>POC for menstrual disorders</td><td>5</td><td>10</td><td>5.3 (1.5-18.7)</td></tr><tr><td>No current use</td><td>13</td><td>161</td><td>Ref</td></tr></table> * Adjusted for BMI and smoking	Method	Cases	Controls	VTE aRR* (95% CI)	POC all	7	36	2.4 (0.8-6.5)	POC for contraception	2	26	1.3 (0.3-6.8)	POC for menstrual disorders	5	10	5.3 (1.5-18.7)	No current use	13	161	Ref	Strengths: VTE diagnoses confirmed with medical records Limitations: Formulation and dose of POC not specified All POC methods analyzed together	II-2, poor																
Method	Cases	Controls	VTE aRR* (95% CI)																																								
POC all	7	36	2.4 (0.8-6.5)																																								
POC for contraception	2	26	1.3 (0.3-6.8)																																								
POC for menstrual disorders	5	10	5.3 (1.5-18.7)																																								
No current use	13	161	Ref																																								
Lidegaard, 2002 [32, 33] Denmark Organon, Wyeth-Ayerst, Schering AG	Case control 1994-1998	Ages 15-44 Cases: diagnosis codes from national registry of hospital discharges Controls (community): randomly selected from national registry, matched on age	POP Current use (at time of admission for cases and time of interview for controls) Participant questionnaire	VTE Ischemic stroke + TIA Discharge diagnosis codes, confirmed by physician and patient	<table><tr><td>Method</td><td>Cases</td><td>Controls</td><td>VTE aOR* (95% CI)</td></tr><tr><td>POP</td><td>8</td><td>28</td><td>2.0 (0.8-5.1)</td></tr><tr><td>Past or never users</td><td>458</td><td>2738</td><td>Ref</td></tr></table> *Adjusted for age, year, BMI, education, coagulation disturbances, family VTE, previous birth, diabetes, smoking <table><tr><td>Method</td><td>Cases</td><td>Controls</td><td>Stroke/TIA aOR* (95% CI)</td></tr><tr><td>POP</td><td>4</td><td>28</td><td>1.0 (0.3-3.0)</td></tr><tr><td>Past or never users</td><td>397</td><td>2738</td><td>Ref</td></tr></table> *Adjusted for age, year, smoking, migraine, education	Method	Cases	Controls	VTE aOR* (95% CI)	POP	8	28	2.0 (0.8-5.1)	Past or never users	458	2738	Ref	Method	Cases	Controls	Stroke/TIA aOR* (95% CI)	POP	4	28	1.0 (0.3-3.0)	Past or never users	397	2738	Ref	Strengths: Contraceptive type prompted by list of available OC VTE and stroke diagnoses confirmed by physician and patient High response rate (approx. 90%) Limitations: Did not account for recent pregnancy	II-2, fair												
Method	Cases	Controls	VTE aOR* (95% CI)																																								
POP	8	28	2.0 (0.8-5.1)																																								
Past or never users	458	2738	Ref																																								
Method	Cases	Controls	Stroke/TIA aOR* (95% CI)																																								
POP	4	28	1.0 (0.3-3.0)																																								
Past or never users	397	2738	Ref																																								

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																				
		Exclusions: history thrombosis, pregnant at time of diagnosis				<10 VTE and stroke cases using POPs Included TIA (36% of cases), analysed together with cerebral infarction																					
Lidegaard, 2009 [34] Denmark Gyn Clinic, Rigshospitalet	Retrospective cohort 1995-2005	Ages 15-49 Cohort (>10 million WY): national registry Exclusions: cancer, history cardiovascular event, pregnant or postpartum	POP LNG-IUD Current use (valid prescription at hospital admission) Obtained from filled prescriptions	VTE Diagnosis codes (validated in previous study, 10% uncertain)	<table><tr><th>Method</th><th>VTE N</th><th>IR (per 10,000 WY)</th><th>VTE Adjusted rate ratio* (95% CI)</th></tr><tr><td>POP (LNG or NOR)</td><td>12</td><td>1.8</td><td>0.6 (0.3-1.04)</td></tr><tr><td>POP (DSG)</td><td>3</td><td>3.3</td><td>1.1 (0.4-3.4)</td></tr><tr><td>LNG-IUD</td><td>34</td><td>3.4</td><td>0.9 (0.6-1.3)</td></tr><tr><td>Past or never users</td><td>2168</td><td>3.0</td><td>Ref</td></tr></table> *Adjusted for age, calendar year, education	Method	VTE N	IR (per 10,000 WY)	VTE Adjusted rate ratio* (95% CI)	POP (LNG or NOR)	12	1.8	0.6 (0.3-1.04)	POP (DSG)	3	3.3	1.1 (0.4-3.4)	LNG-IUD	34	3.4	0.9 (0.6-1.3)	Past or never users	2168	3.0	Ref	Strengths: Large national cohort Limitations: VTE diagnoses not confirmed <10 VTEs among users of some POPs No information on BMI	II-2, fair
Method	VTE N	IR (per 10,000 WY)	VTE Adjusted rate ratio* (95% CI)																								
POP (LNG or NOR)	12	1.8	0.6 (0.3-1.04)																								
POP (DSG)	3	3.3	1.1 (0.4-3.4)																								
LNG-IUD	34	3.4	0.9 (0.6-1.3)																								
Past or never users	2168	3.0	Ref																								
Barsoum, 2010 [35] United States NIH, US Public Health Service, Mayo Foundation	Case control 1998-2000	All ages Cases: inpatient, outpatient, emergency, nursing home, autopsy, death certificate Controls (community): from population, matched on age, medical care within 1 year of case event date, medical record number close to case's number	POC (not specified, some receiving non-contraceptive doses and formulations) Use within 3 months Obtained from medical record	VTE Diagnosis confirmed by medical records and imaging	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>POC</td><td>23</td><td>7</td><td>1.2 (0.4-3.6)</td></tr><tr><td>Nonusers</td><td>703</td><td>823</td><td>Ref</td></tr></table> *Adjusted for BMI, hospitalization, nursing home, trauma/fracture, cancer, leg paresis, varicose veins, pregnancy	Method	Cases	Controls	VTE aOR* (95% CI)	POC	23	7	1.2 (0.4-3.6)	Nonusers	703	823	Ref	Strengths: VTE diagnoses confirmed with medical records Limitations: Contraceptive types not specified Analysis may have included postmenopausal women <10 POC users among controls Did not account for history of VTE All POC methods analyzed together	II-2, poor								
Method	Cases	Controls	VTE aOR* (95% CI)																								
POC	23	7	1.2 (0.4-3.6)																								
Nonusers	703	823	Ref																								
Vlieg, 2010 [36] Netherlands Netherlands Heart Association, Dutch Cancer Foundation, Netherlands	Case control 1999-2004	Ages 18-50 Cases: anticoagulant clinics Controls (community): partners of patients.	DMPA LNG-IUD “Current use” not further defined [37]	VTE Diagnosis from anticoagulation clinic	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>DMPA</td><td>20</td><td>15</td><td>3.0 (1.2-7.5)</td></tr><tr><td>LNG-IUD</td><td>3</td><td>26</td><td>0.3 (0.1-1.3)</td></tr><tr><td>Nonhormonal</td><td>421</td><td>1102</td><td>Ref</td></tr></table> * Adjusted for age, BMI, family history DVT, smoking	Method	Cases	Controls	VTE aOR* (95% CI)	DMPA	20	15	3.0 (1.2-7.5)	LNG-IUD	3	26	0.3 (0.1-1.3)	Nonhormonal	421	1102	Ref	Strengths: Accounted for important confounders VTE diagnoses confirmed by clinics Limitations:	II-2, fair				
Method	Cases	Controls	VTE aOR* (95% CI)																								
DMPA	20	15	3.0 (1.2-7.5)																								
LNG-IUD	3	26	0.3 (0.1-1.3)																								
Nonhormonal	421	1102	Ref																								

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																				
Organisation for Scientific Research		or random-digit dialling and matched on age Exclusions: history DVT, OC users, postmenopausal, pregnant or postpartum, severe psychiatric problems, non-Dutch speaking	Participant questionnaire			DMPA and LNG-IUD use not confirmed <10 cases using LNG-IUD																					
Lidegaard, 2011 [38] Denmark Bayer Schering	Retrospective cohort 2001-2009	Ages 15-49 Cohort (>8 million WY): national registry Exclusions: history thrombosis, cancer, hysterectomy, oophorectomy, sterilization, pregnant or postpartum, coagulation disorder	POP (NOR or DSG) LNG-IUD Use within 4 weeks Obtained from filled prescriptions	VTE Discharge diagnosis codes from national registry, confirmed with prescription for anticoagulant 200 randomly selected women validated by medical records	<table><tr><th>Method</th><th>VTE N</th><th>IR (per 10,000 WY)</th><th>VTE aRR* (95% CI)</th></tr><tr><td>POP (NOR)</td><td>9</td><td>2.0</td><td>0.6 (0.3-1.1)</td></tr><tr><td>POP (DSG)</td><td>6</td><td>2.1</td><td>0.6 (0.3-1.4)</td></tr><tr><td>LNG-IUD</td><td>55</td><td>3.5</td><td>0.8 (0.6-1.1)</td></tr><tr><td>Past or never users</td><td>1812</td><td>3.7</td><td>Ref</td></tr></table> * Adjusted for age, year, and education No significant differences when stratified by whether anticoagulation was used (confirmed VTEs) or not recorded	Method	VTE N	IR (per 10,000 WY)	VTE aRR* (95% CI)	POP (NOR)	9	2.0	0.6 (0.3-1.1)	POP (DSG)	6	2.1	0.6 (0.3-1.4)	LNG-IUD	55	3.5	0.8 (0.6-1.1)	Past or never users	1812	3.7	Ref	Strengths: Large national cohort VTE diagnoses confirmed by anticoagulant prescription, subset validated by medical records Limitations: <10 VTEs among users of each POP Contraceptive use from prescriptions only, not verified ~1/4 VTE diagnoses not able to be confirmed by medical records No information on BMI	II-2, fair
Method	VTE N	IR (per 10,000 WY)	VTE aRR* (95% CI)																								
POP (NOR)	9	2.0	0.6 (0.3-1.1)																								
POP (DSG)	6	2.1	0.6 (0.3-1.4)																								
LNG-IUD	55	3.5	0.8 (0.6-1.1)																								
Past or never users	1812	3.7	Ref																								
Bergendal, 2012 [13] Sweden Janssen-Cilag, Novartis, Organon, Schering, Wyeth, AFA, Center for Gender Medicine	Case control 2003-2009	Premenopausal Cases: hospitals Controls (community): randomly selected from population register, matched on age Exclusions: history thrombosis, pregnant or postpartum, current cancer	POC (LNG-IUD, ETG or LNG implants [12], DMPA) Use within 3 months Telephone interview	VTE Identified from study coordinator at hospitals, confirmed with radiology results	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr><tr><td>POC</td><td>54</td><td>85</td><td>0.98 (0.6-1.6)</td></tr><tr><td>Nonusers</td><td>389</td><td>480</td><td>Ref</td></tr></table> *Adjusted for age, BMI, smoking, use of hormones, bedrest/minor trauma, surgery, cast, surgery and cast, prothrombin mutation, factor V Leiden	Method	Cases	Controls	VTE aOR* (95% CI)	POC	54	85	0.98 (0.6-1.6)	Nonusers	389	480	Ref	Strengths: Contraceptive information prompted by pictures VTE diagnoses confirmed by radiology results Limitations: Differential participation rate between cases (90%) and controls (69%) Contraceptive type self-reported, not verified	II-2, poor								
Method	Cases	Controls	VTE aOR* (95% CI)																								
POC	54	85	0.98 (0.6-1.6)																								
Nonusers	389	480	Ref																								

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																																								
						All POC methods analyzed together																																																									
Lidegaard, 2012 [39] Denmark Danish Heart Association	Retrospective cohort 1995-2009	Ages 15-49 Cohort (>14 million WY): national registry Exclusions: history thrombosis, cancer, hysterectomy, oophorectomy, sterilization, pregnant or postpartum, coagulation disorder	POP (NOR, LNG or DSG) LNG-IUD Implant (type unspecified) Use within 4 weeks [38] Obtained from filled prescriptions	Ischemic stroke AMI Discharge diagnosis codes from national registry	<table><thead><tr><th>Method</th><th>Stroke N</th><th>IR (per 100,000 WY)</th><th>Stroke aRR* (95% CI)</th></tr></thead><tbody><tr><td>POP (NOR)</td><td>28</td><td>32.6</td><td>1.4 (0.9-2.0)</td></tr><tr><td>POP (LNG)</td><td>1</td><td>11.7</td><td>0.4 (0.1-3.1)</td></tr><tr><td>POP (DSG)</td><td>9</td><td>30.8</td><td>1.4 (0.7-2.6)</td></tr><tr><td>LNG-IUD</td><td>45</td><td>24.3</td><td>0.7 (0.5-0.98)</td></tr><tr><td>Implant</td><td>3</td><td>12.0</td><td>0.9 (0.3-2.7)</td></tr><tr><td>Past or never users</td><td>2260</td><td>24.2</td><td>Ref</td></tr></tbody></table> *Adjusted for age, calendar year, education, HTN, heart disease, diabetes, hyperlipidemia <table><thead><tr><th>Method</th><th>AMI N</th><th>IR (per 100,000 WY)</th><th>AMI aRR* (95% CI)</th></tr></thead><tbody><tr><td>POP (NOR)</td><td>9</td><td>10.5</td><td>0.8 (0.4-1.6)</td></tr><tr><td>POP (LNG)</td><td>0</td><td>0</td><td>0 (0.0-35.0)</td></tr><tr><td>POP (DSG)</td><td>4</td><td>13.7</td><td>1.5 (0.6-3.9)</td></tr><tr><td>LNG-IUD</td><td>31</td><td>16.8</td><td>1.0 (0.7-1.5)</td></tr><tr><td>Implant</td><td>3</td><td>12.0</td><td>2.1 (0.7-6.7)</td></tr><tr><td>Past or never users</td><td>1228</td><td>13.2</td><td>Ref</td></tr></tbody></table> *Adjusted for age, calendar year, education, HTN, heart disease, diabetes, hyperlipidemia	Method	Stroke N	IR (per 100,000 WY)	Stroke aRR* (95% CI)	POP (NOR)	28	32.6	1.4 (0.9-2.0)	POP (LNG)	1	11.7	0.4 (0.1-3.1)	POP (DSG)	9	30.8	1.4 (0.7-2.6)	LNG-IUD	45	24.3	0.7 (0.5-0.98)	Implant	3	12.0	0.9 (0.3-2.7)	Past or never users	2260	24.2	Ref	Method	AMI N	IR (per 100,000 WY)	AMI aRR* (95% CI)	POP (NOR)	9	10.5	0.8 (0.4-1.6)	POP (LNG)	0	0	0 (0.0-35.0)	POP (DSG)	4	13.7	1.5 (0.6-3.9)	LNG-IUD	31	16.8	1.0 (0.7-1.5)	Implant	3	12.0	2.1 (0.7-6.7)	Past or never users	1228	13.2	Ref	Strengths: Large national cohort Limitations: Stroke and AMI diagnoses not confirmed <10 strokes and AMI among users of most POCs No information on BMI	II-2, fair
Method	Stroke N	IR (per 100,000 WY)	Stroke aRR* (95% CI)																																																												
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Lidegaard, 2012 [40] Denmark Gyn Clinic, Rigshospitalet	Retrospective cohort 2001-2010	Ages 15-49 Cohort (>9 million WY): National registry Exclusions: history thrombosis, cancer, hysterectomy, oophorectomy, sterilization, pregnant or postpartum, coagulation disorder	LNG-IUD Implant (ETG) Use within 4 weeks Obtained from filled prescriptions	VTE Discharge diagnosis codes from national registry, confirmed with prescription for anticoagulant	<table><thead><tr><th></th><th colspan="3">All VTE</th><th colspan="3">Confirmed VTE†</th></tr><tr><th>Method</th><th>N</th><th>IR (per 100,000 WY)</th><th>aRR* (95% CI)</th><th>N</th><th>IR (per 100,000 WY)</th><th>VTE aRR* (95% CI)</th></tr></thead><tbody><tr><td>LNG-IUD</td><td>88</td><td>3.7</td><td>0.8 (0.7-0.99)</td><td>33</td><td>1.4</td><td>0.6 (0.4-0.8)</td></tr><tr><td>Implant</td><td>15</td><td>5.1</td><td>2.1 (1.3-3.5)</td><td>5</td><td>1.7</td><td>1.4 (0.6-3.4)</td></tr><tr><td>Past or never users</td><td>2262</td><td>3.8</td><td>Ref</td><td>1209</td><td>2.1</td><td>Ref</td></tr></tbody></table> *Adjusted for age, calendar year, education †Confirmed by prescription for anticoagulant		All VTE			Confirmed VTE†			Method	N	IR (per 100,000 WY)	aRR* (95% CI)	N	IR (per 100,000 WY)	VTE aRR* (95% CI)	LNG-IUD	88	3.7	0.8 (0.7-0.99)	33	1.4	0.6 (0.4-0.8)	Implant	15	5.1	2.1 (1.3-3.5)	5	1.7	1.4 (0.6-3.4)	Past or never users	2262	3.8	Ref	1209	2.1	Ref	Strengths: Large national cohort VTE diagnoses confirmed by anticoagulant prescription Limitations: <10 VTEs among implant users Contraceptive use from prescriptions only, not verified No information on BMI	II-2, fair																					
	All VTE			Confirmed VTE†																																																											
Method	N	IR (per 100,000 WY)	aRR* (95% CI)	N	IR (per 100,000 WY)	VTE aRR* (95% CI)																																																									
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Bergendal, 2014 [11] (same study as Bergendal, 2012 [13])	Case control 2003-2009	Ages 18-54 Cases: inpatient and outpatient	High dose: DMPA Medium dose: implants (ETG)	VTE Diagnosis confirmed by medical records and imaging	<table><thead><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (95% CI)</th></tr></thead><tbody><tr><td>High dose</td><td>47</td><td>23</td><td>2.2 (1.3-4.0)</td></tr></tbody></table>	Method	Cases	Controls	VTE aOR* (95% CI)	High dose	47	23	2.2 (1.3-4.0)	Strengths: Population-based VTE diagnoses confirmed with medical records	II-2, fair																																																
Method	Cases	Controls	VTE aOR* (95% CI)																																																												
High dose	47	23	2.2 (1.3-4.0)																																																												

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results	Strengths/Limitations	Quality Grading																																										
Sweden Janssen-Cilag, Novartis, Organon, Schering, Wyeth, AFA Insurance, Karolinska Institutet, Medical Products Agency		Controls (community): from population register, matched on age Exclusions: history thrombosis, pregnancy within 3 months, current cancer	or LNG) [12], oral DSG Low dose: Oral LNG, LYN, NET Very low dose: LNG-IUD Use within 3 months Participant questionnaire	Included only if initiated anticoagulation	<table><tr><td>Medium dose</td><td>25</td><td>35</td><td>0.9 (0.5-1.6)</td></tr><tr><td>Low dose</td><td>12</td><td>20</td><td>0.8 (0.4-1.9)</td></tr><tr><td>Very low dose</td><td>61</td><td>99</td><td>0.6 (0.4-1.0)</td></tr><tr><td>Nonhormonal</td><td>492</td><td>618</td><td>Ref</td></tr></table> *Matched on age, adjusted for smoking, BMI, immobilization	Medium dose	25	35	0.9 (0.5-1.6)	Low dose	12	20	0.8 (0.4-1.9)	Very low dose	61	99	0.6 (0.4-1.0)	Nonhormonal	492	618	Ref	Adjusted for confounders, excluded women with recent pregnancy Limitations: Differential participation rate between cases (90%) and controls (69%) [13] Contraceptive type self-reported, not verified																											
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Cockrum, 2022 [41] USA NIH	Nested case control 2010-2018 Private insurance claims database	Women ages 15-49 Cases: incident acute VTE Controls: no prior VTE, matched 1:5 by year of birth and index date through risk sampling Exclusions: chronic or pregnancy-related VTE, earlier anticoagulation prescription that could indicate recurrent VTE, diagnoses that could be treated with high-dose progestins, had megestrol acetate prescription within 1 year or estrogen-containing medication 84 days before index date	POC, current use -LNG-IUD -POP (NET) -Implant (ETG) -DMPA Non-use, no current use of any progestin Current use, defined as within 28 days before index date Filled outpatient prescriptions from pharmacy claims	VTE (DVT, PE, or both) ICD-9 or ICD-10 codes from inpatient and outpatient claims Outpatient diagnosis required a new anticoagulation prescription within 42 days of index date	<table><tr><th>Method</th><th>Cases</th><th>Controls</th><th>VTE aOR* (99% CI)</th></tr><tr><td>LNG-IUD</td><td>77</td><td>446</td><td>0.72 (0.50-1.05)</td></tr><tr><td>POP (NET)</td><td>131</td><td>724</td><td>0.57 (0.43-0.76)</td></tr><tr><td>Implant</td><td>39</td><td>177</td><td>1.09 (0.66-1.82)</td></tr><tr><td>Oral progesterone</td><td>51</td><td>202</td><td>1.07 (0.75-1.54)</td></tr><tr><td>Oral MPA</td><td>111</td><td>232</td><td>1.98 (1.41-2.80)</td></tr><tr><td>POP (NETA)</td><td>87</td><td>114</td><td>3.00 (1.96-4.59)</td></tr><tr><td>DMPA</td><td>355</td><td>657</td><td>2.37 (1.95-2.88)</td></tr><tr><td>Noncurrent users</td><td>20554</td><td>104473</td><td>Ref</td></tr></table> *Adjusted for obesity (BMI 30 or higher), smoking, atherosclerotic cardiovascular disease, HTN, congestive heart failure, chronic kidney disease, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, cancer (with exclusions), hemiplegia or paraplegia, hypercoagulable state, superficial venous thrombosis, varicose veins, history of surgery or lower extremity fracture within 180 days before index date, and history of hospitalization within 180 days of index date <table><tr><th>Method</th><th>Absolute risk of excess VTE/10,000 exposed women (99% CI)</th></tr><tr><td>DMPA, ages 20-24</td><td>5 (3-7)</td></tr><tr><td>DMPA, ages 45-49</td><td>8 (6-11)</td></tr></table>	Method	Cases	Controls	VTE aOR* (99% CI)	LNG-IUD	77	446	0.72 (0.50-1.05)	POP (NET)	131	724	0.57 (0.43-0.76)	Implant	39	177	1.09 (0.66-1.82)	Oral progesterone	51	202	1.07 (0.75-1.54)	Oral MPA	111	232	1.98 (1.41-2.80)	POP (NETA)	87	114	3.00 (1.96-4.59)	DMPA	355	657	2.37 (1.95-2.88)	Noncurrent users	20554	104473	Ref	Method	Absolute risk of excess VTE/10,000 exposed women (99% CI)	DMPA, ages 20-24	5 (3-7)	DMPA, ages 45-49	8 (6-11)	Strengths: Large sample size Current use well-defined Good generalizability Limitations: Only private insurance claims Prescription dispensed as a proxy for actual oral contraceptive use Possible misclassification bias as 35% of inpatient VTE diagnoses did not have an anticoagulation prescription	II-2, fair
Method	Cases	Controls	VTE aOR* (99% CI)																																														
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Heikinheimo, 2022 [42]	Nested case control	Women ages 15-49	POP, current use, at least 2 prescriptions	VTE (DVT, PE, or cerebral		Strengths: Population-based study, large sample size, high-	II-2, fair																																										

Author, Publication, Location, Support	Study Design, Years	Population	Exposure	Outcome	Results				Strengths/Limitations	Quality Grading
Finland Foundation for Primary Care Research	2017-2019	Cases: incident VTE	filled in 180-day period	infarction due to CVT)	Method	Cases	Controls	VTE aOR* (95% CI)	quality Finnish register data, study design Limitations: Contraceptive use from prescriptions only, not verified No information on some covariates (BMI, smoking)	
	Larger register-based prospective cohort study	Controls: no prior VTE, matched 4:1 by age	No HC use	ICD-10 codes	All POP	71	343	0.90 (0.68-1.18)		
					NET	<5	26	0.53 (0.16-1.75)		
					DSG	69	317	0.72 (0.53-0.99)		
					No HC use	990	4327	Ref		
					*Adjusted for marital status, socioeconomic status, education, cancer, chronic diseases					

Abbreviations: AMI, acute myocardial infarction; aOR, adjusted odds ratio; aRR, adjusted relative risk; BMI, body mass index; CI, confidence interval; CT, computed tomography; CVT, cerebral venous thrombosis; DMPA, depot medroxyprogesterone acetate; DSG, desogestrel; DVT, deep venous thrombosis; ETG, etonogestrel; HC, hormonal contraception; HTN, hypertension; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-PCS, International Classification of Diseases, Tenth Revision, Procedure Coding; IR, incidence rate; IUD, intrauterine device; LNG, levonorgestrel; LYN, lynestrenol; MPA, medroxyprogesterone acetate; NIH, National Institutes of Health; NET, norethisterone; NETA, norethindrone acetate; NOR, norethindrone; NR, not reported; OC, oral contraception; OR, odds ratio; PE, pulmonary embolism; POC, progestin-only contraception; POI, progestin-only injectable; POP, progestin-only pill; TIA, transient ischemic attack; VTE, venous thromboembolism; WHO, World Health Organization; WY, women-years.

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