EUROPEAN STROKE ORGANISATION

Guidelines on Stroke in Women:

Management of Menopause, Pregnancy, and Postpartum

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Background - Hormone replacement therapy

- Increased vulnerability for stroke in women during menopause
- Conflicting results regarding stroke risk [1, 2]
- Actual guidelines are lacking

1 Towfighi A, et al Neurology. 2007;69(20):1898-904.
2 Sohrabji F,et al Horm Behav. 2019;111:87-95.

Background - Stroke in pregnancy

- Widely varying estimates from 1.5 to 98 per 100,000 deliveries
- Rate of 30/100,000 pregnancies [1]
- Is generally increasing [2]
- Guidelines regarding acute treatment IVT/MT in pregnant women lacking

1 Leffert et al, Am J Obstet Gynecol. 2016;214(6):723.e1-.e11.
2 Karjalainen L Neurology. 2021;96(21):e2564-e75.

The European Stroke Organisation Guidelines: a standard operating procedure

- Grading of Recommendations and Assessment, Development and Evaluation (Grade approach)
- Formulation of 2 PICO questions (8 subheadings) (Patient, Intervention, Comparison, Outcome) questions
- Identify all main outcomes and rate their relative importance (15 critical outcomes)
- Systematic literature review for each PICO question
- Assessment of the risk of bias in each trial
- Summarize all relevant evidence in GRADE evidence profiles
- Meta-analyses
- Grade the quality of evidence for each question and outcome –very low, low, high
- Grade the strength of recommendation (weak- strong) Expert consensus statement (Delphi votes)
- Consensus among the module working group regarding Guidelines document

Steiner T, et al. Eur Stroke J. 2021 Sep;6(3):CXXII-CXXXIV.

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Critical Outcomes

PICO 1 (HRT)	Average
Stroke, all	9
Stroke, ischaemic	9
Stroke, haemorrhagic	9
CVT	8
Transient Ischaemic attack	8
Cardiovascular and MI	7
Systemic embolism	7
Mortality, all cause	9
Functional outcome mRS 3 months	8

PICO 2 (IVT/MT pregnancy)	Average
mRS at 90 days	9
Recanalization (MT)	7
Treatment complications (MT)	7
Mortality, all cause, overall	9
Intra-hospital mortality	9
Haemorrhage	9
Major bleeding	9
Intracerebral haemorrhage	9
Symptomatic cerebral haemorrhage	9
Intracranial bleeding	9
Gastrointestinal bleeding, major	9
Complication in pregnancy	9
Premature delivery	8
Abortion	9
Healthy baby	8

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Hormone Replacement Therapy (HRT)

PICO 1.1: In postmenopausal women, does HRT compared to non-prior HRT reduce the risk of ischaemic stroke in primary prevention?

Evidence-based Recommendation

In postmenopausal women, we suggest against the use of HRT to reduce the risk of ischaemic stroke

Quality of evidence: **Very low ⊕**

Strength of recommendation: **Weak against intervention ↓**

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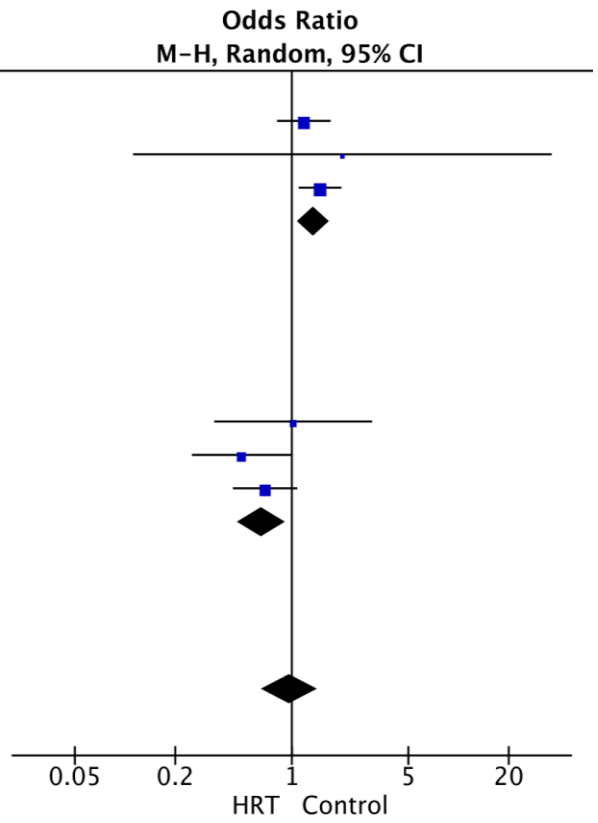
Grade Evidence Table for ischaemic stroke

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectn	Imprecision	Other	HRT	Control	Relative (95% CI)	Absolute (95% CI)		
Ischaemic Stroke												
6	RCTs	not serious	serious	serious	serious	publication bias strongly suspected	286/29233 (1.0%)	194/15463 (1.3%)	OR 0.97 (0.66 to 1.41)	0 fewer per 1,000 (from 4 fewer to 5 more)	⨁◯◯◯ VERY LOW	CRITICAL
Ischaemic Stroke - HRT												
3	RCTs	not serious	not serious	not serious	not serious	publication bias strongly suspected	200/17922 (1.1%)	140/10726 (1.3%)	OR 1.36 (1.09 to 1.69)	5 more per 1,000 (from 1 more to 9 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Ischaemic Stroke - Receptor modulator												
3	RCTs	not serious	not serious	not serious	not serious	publication bias strongly suspected	86/11311 (0.8%)	54/4737 (1.1%)	OR 0.66 (0.47 to 0.93)	4 fewer per 1,000 (from 6 fewer to 1 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Pooled odds ratio for ischaemic stroke in postmenopausal women treated with HRT vs non-prior HRT

Study or Subgroup	HRT Events	HRT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.4.1 HRT						
HERS 2002	69	1380	59	1383	24.5%	1.18 [0.83, 1.69]
SMART 2015	6	8036	0	1241	1.7%	2.01 [0.11, 35.70]
WHI 2003	125	8506	81	8102	26.7%	1.48 [1.11, 1.96]
Subtotal (95% CI)		**17922**		**10726**	**52.9%**	**1.36 [1.09, 1.69]**
Total events	200		140			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.00$, df = 2 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 2.73 (P = 0.006)						
1.4.2 Receptor modulator						
Christiansen 2010 R-Modu	10	1849	5	942	8.9%	1.02 [0.35, 2.99]
de Villiers 2011 R-Modul	26	3758	13	943	15.9%	0.50 [0.26, 0.97]
PEARL 2010 R-Modul	50	5704	36	2852	22.3%	0.69 [0.45, 1.06]
Subtotal (95% CI)		**11311**		**4737**	**47.1%**	**0.66 [0.47, 0.93]**
Total events	86		54			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.35$, df = 2 (P = 0.51); $I^2 = 0\%$						
Test for overall effect: Z = 2.37 (P = 0.02)						
Total (95% CI)		**29233**		**15463**	**100.0%**	**0.97 [0.66, 1.41]**
Total events	286		194			
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 14.41$, df = 5 (P = 0.01); $I^2 = 65\%$						
Test for overall effect: Z = 0.18 (P = 0.86)						
Test for subgroup differences: $Chi^2 = 12.03$, df = 1 (P = 0.0005), $I^2 = 91.7\%$						



Quality of evidence: **Very low ⊕**

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Hormone Replacement Therapy (HRT)

PICO 1.2: In postmenopausal women, does HRT compared to non-prior HRT reduce the risk of haemorrhagic stroke in primary prevention?

Evidence-based Recommendation

In postmenopausal women, we suggest against the use of HRT to reduce the risk of haemorrhagic stroke

Quality of evidence: **Low ⊕**

Strength of recommendation: **Weak against intervention ↓**

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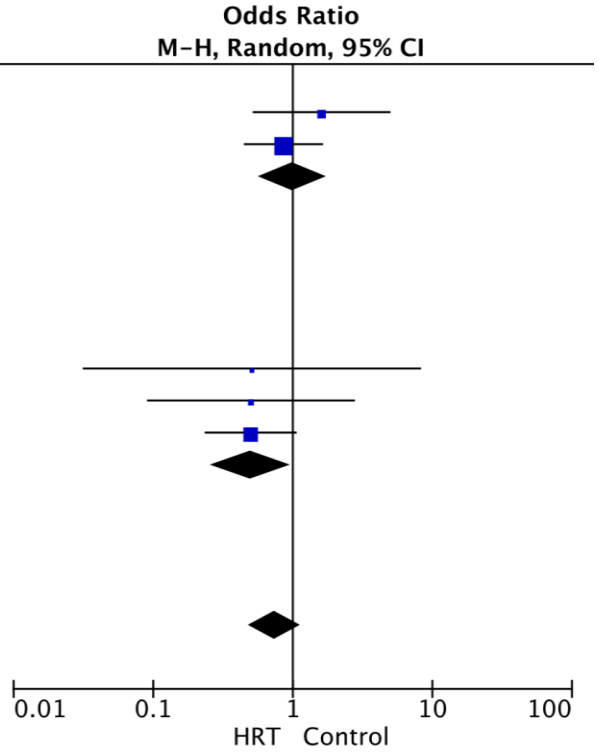
Grade Evidence Table for haemorrhagic stroke

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Hormonal replacement therapy	Control	Relative (95% CI)	Absolute (95% CI)		
Haemorrhagic Stroke												
5	RCTs	not serious	not serious	not serious	serious	publication bias strongly suspected	45/21197 (0.2%)	42/14222 (0.3%)	OR 0.75 (0.49 to 1.15)	1 fewer per 1,000 (from 2 fewer to 0 fewer)	⨁⨁◯◯ LOW	CRITICAL
Haemorrhagic Stroke - HRT												
2	RCTs	not serious	not serious	not serious	serious	publication bias strongly suspected	26/9886 (0.3%)	25/9485 (0.3%)	OR 1.00 (0.57 to 1.74)	0 fewer per 1,000 (from 1 fewer to 2 more)	⨁⨁◯◯ LOW	CRITICAL
Haemorrhagic Stroke - Receptor modulator												
3	RCTs	not serious	not serious	not serious	not serious	publication bias strongly suspected	19/11311 (0.2%)	17/4737 (0.4%)	OR 0.50 (0.26 to 0.97)	2 fewer per 1,000 (from 3 fewer to 0 fewer)	⨁⨁⨁◯ MODERATE	CRITICAL

Pooled odds ratio for haemorrhagic stroke in postmenopausal women treated with HRT vs non-prior HRT

Study or Subgroup	HRT Events	HRT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.5.1 HRT						
HERS 2002	8	1380	5	1383	14.4%	1.61 [0.52, 4.92]
WHI 2003	18	8506	20	8102	44.3%	0.86 [0.45, 1.62]
Subtotal (95% CI)		**9886**		**9485**	**58.7%**	**1.00 [0.57, 1.74]**
Total events	26		25			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.91$, df = 1 (P = 0.34); $I^2 = 0\%$						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.5.2 Receptor modulator						
Christiansen 2010 R-Modu	1	1849	1	942	2.3%	0.51 [0.03, 8.15]
de Villiers 2011 R-Modul	4	3758	2	943	6.2%	0.50 [0.09, 2.74]
PEARL 2010 R-Modul	14	5704	14	2852	32.7%	0.50 [0.24, 1.05]
Subtotal (95% CI)		**11311**		**4737**	**41.3%**	**0.50 [0.26, 0.97]**
Total events	19		17			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.00$, df = 2 (P = 1.00); $I^2 = 0\%$						
Test for overall effect: Z = 2.06 (P = 0.04)						
Total (95% CI)		**21197**		**14222**	**100.0%**	**0.75 [0.49, 1.15]**
Total events	45		42			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.40$, df = 4 (P = 0.49); $I^2 = 0\%$						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: $Chi^2 = 2.48$, df = 1 (P = 0.12), $I^2 = 59.7\%$						



Quality of evidence: **Low** ⊕

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Hormone Replacement Therapy (HRT)

PICO 1.3: In postmenopausal women with ischaemic stroke, does HRT compared to non-prior HRT impact functional outcome and mortality ?

PICO 1.4; In postmenopausal women with haemorrhagic stroke, does HRT compared to non-prior HRT impact functional outcome and mortality?

Evidence-based Recommendation

In postmenopausal women, we suggest against the use of HRT to reduce mortality

Quality of evidence: **Very low ⊕**

Strength of recommendation: **Weak against intervention ↓**

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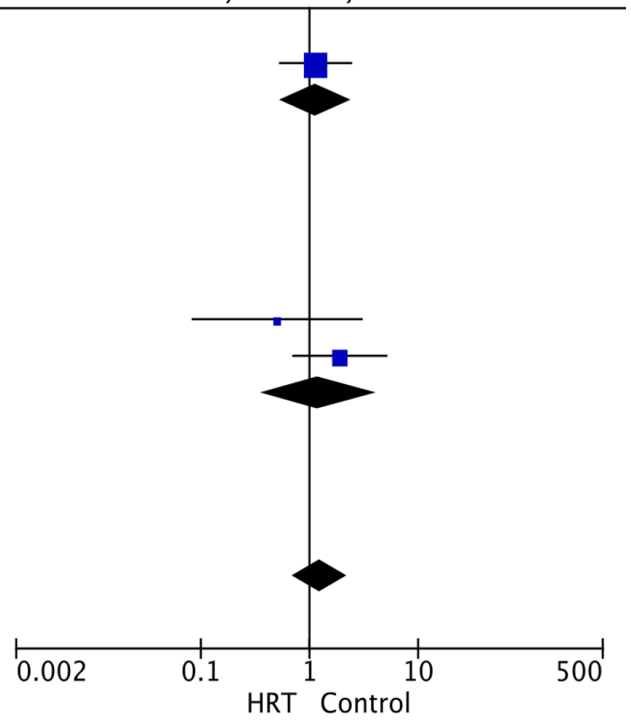
Pooled Odds Ratio for Fatal stroke stroke in postmenopausal women treated with HRT vs non-prior HRT

Study or Subgroup	HRT Events	HRT Total	Control Events	Control Total	Weight	Odds Ratio M-H, Random, 95% CI
1.14.1 HRT						
ESPRIT-UK 2014	15	513	13	504	56.8%	1.14 [0.54, 2.42]
Subtotal (95% CI)		**513**		**504**	**56.8%**	**1.14 [0.54, 2.42]**
Total events	15		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.34 (P = 0.74)						
1.14.2 Receptor modulator						
Christiansen 2010 R-Modu	3	5607	2	1885	10.1%	0.50 [0.08, 3.02]
PEARL 2010 R-Modul	19	5704	5	2852	33.1%	1.90 [0.71, 5.10]
Subtotal (95% CI)		**11311**		**4737**	**43.2%**	**1.22 [0.35, 4.19]**
Total events	22		7			
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 1.64$, df = 1 (P = 0.20); $I^2 = 39\%$						
Test for overall effect: Z = 0.31 (P = 0.76)						
Total (95% CI)		**11824**		**5241**	**100.0%**	**1.24 [0.70, 2.19]**
Total events	37		20			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.76$, df = 2 (P = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 0.75 (P = 0.45)						
Test for subgroup differences: $Chi^2 = 0.01$, df = 1 (P = 0.93), $I^2 = 0\%$						



Quality of evidence: Very low ⊕

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Help - she´s pregnant !

IVT during pregnancy

PICO 2.1. In pregnant women with acute ischaemic stroke, does IVT improve outcome as compared to no IVT?

Evidence-based recommendation

Available data do not allow a specific recommendation on IVT in pregnant women with acute ischaemic stroke.

Expert consensus statement (Delphi vote)

A majority of members (12/13) suggests that pregnant women with acute disabling ischaemic stroke, who otherwise meet eligibility criteria, can be treated with IVT after appropriately assessing the benefit/risk profile on an individual basis.

Grade Evidence Table for IVT in pregnancy

Certainty assessment							Impact	Certainty	Importance
№ of cases	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Maternal recovery									
33	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Patients improved or had good recovery, 32 out of 33 cases (97%)	⊕◯◯◯ VERY LOW	CRITICAL
Healthy baby									
32	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Healthy baby 28 out of 32 cases, (87.5%)	⊕◯◯◯ VERY LOW	CRITICAL
Abortion or Medical termination of pregnancy									
32	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Abortion or MTP, 4 out of 32 cases (13%)	⊕◯◯◯ VERY LOW	CRITICAL
Intracranial haemorrhage									
33	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Intracerebral haemorrhage 3 out of 33 cases (9%)	⊕◯◯◯ VERY LOW	CRITICAL
Intrauterine bleeding									
33	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Intrauterine bleeding,1 out of 33 cases, (3%)	⊕◯◯◯ VERY LOW	IMPORTANT

Mechanical thrombectomy during pregnancy

PICO 2.1. In pregnant women with acute ischaemic stroke, does MT/IAT improve outcome as compared to no MT/IAT?

Evidence-based recommendation
Available data do not allow a specific recommendation on MT/IAT in pregnant women with acute ischaemic stroke.

Expert consensus statement (Delphi vote)
All members (13/13) suggest that pregnant women with acute disabling ischaemic stroke, who otherwise meet eligibility criteria, can be treated with MT after appropriately assessing the benefit/risk profile on an individual basis.

A majority of members (12/13) suggests that in pregnant women with acute ischaemic stroke related to large vessel occlusion, if MT is available, MT alone should be preferred over IVT or bridging therapy (IVT+MT).

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Grade Evidence Table for MT/IAT in pregnancy

Certainty assessment							Impact	Certainty	Importance
№ of cases	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Maternal recovery									
23	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Maternal recovery was good to excellent in 23 out of 23 cases	⊕◯◯◯ VERY LOW	CRITICAL
Healthy baby									
19	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Healthy baby was delivered in 18 out of 19 cases , 95%	⊕◯◯◯ VERY LOW	CRITICAL
Abortion or Medical termination of pregnancy									
19	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Abortion or MTP occurred in 1 out of 19 cases , 5%	⊕◯◯◯ VERY LOW	CRITICAL
Intracranial haemorrhage									
23	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	Intracerebral haemorrhage occurred in 2 out of 23 cases ,9%	⊕◯◯◯ VERY LOW	IMPORTANT
Intrauterine bleeding									
23	Case report	serious	not serious	not serious	not assessed	publication bias strongly suspected	No case reported intrauterine bleeding	⊕◯◯◯ VERY LOW	IMPORTANT

IVT during postpartum

PICO 2.3. In women with acute ischaemic stroke during the postpartum period, does IVT improve outcome compared to no IVT?

Evidence-based recommendation

Available data do not allow a specific recommendation on IVT in women with acute ischaemic stroke during the postpartum period (defined as ≥ 10 days < 3 months).

Expert consensus statement (Delphi vote)

All members (13/13) suggest that postpartum women with disabling ischaemic stroke, occurring at least 10 days after delivery, who otherwise meet eligibility criteria, can be treated with IVT with alteplase after appropriate assessment of the benefit/risk profile on an individual basis.

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Mechanical thrombectomy during postpartum

PICO 2.4. In women with acute ischaemic stroke during the postpartum period, does MT/IAT improve outcome compared to no MT/IAT?

Evidence-based recommendation

Available data do not allow a specific recommendation on MT in women with acute ischaemic stroke during the postpartum period (defined as ≥ 10 days < 3 months).

Expert consensus statement (Delphi vote)

All members (13/13) suggest that postpartum women with disabling ischaemic stroke, occurring at least 10 days after delivery, who otherwise meet eligibility criteria, can be treated with MT after appropriate assessment of the benefit/risk profile on an individual basis.

A majority of members (12/13) suggests that in pregnant women with acute ischaemic stroke related to large vessel occlusion, if MT is available, MT alone should be preferred over IVT or bridging therapy (IVT+MT).

IVT during menstruation

PICO 2.5 In women with acute ischaemic stroke during menstruation, does IVT improve outcome compared to no IVT?

Evidence-based recommendation
Available data do not allow a specific recommendation on IVT in women with acute ischaemic stroke during menstruation.

Expert consensus statement (Delphi vote)
All members (13/13) suggest that women with acute ischaemic stroke during menstruation, who otherwise meet eligibility criteria, can be treated with IVT with alteplase after appropriate assessment of the benefit/risk profile on an individual basis.

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Areas of future research

Hormone replacement therapy – „neglected“ area of research

- More RCTs needed
- Actual dosage and application mode
- Sub-group analyses risk groups

IVT/MT during pregnancy, postpartum, and menstruation

- Include patients in registries globally (e.g. SiPP registry)
- Define risk profiles and prevention for ischaemic stroke under pregnancy, postpartum

Summary - Conclusions

- Low to very low evidence in all recommendations
- 5 Expert consensus statements in IVT/MT pregnancy,postpartum, menstruation
- The guidelines highlight the need to identify evidence for stroke prevention and acute treatment in women in more vulnerable periods of their lifetime to generate reliable data for future guidelines

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Thank you for your attention !

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- Luzia Balmer, Sabrina Mutter ESO Headquarters

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