Summary of Findings

1. Studies with follow-up ≤ 1 year

Table 3. Summary of Findings – Comparison of thromboprophylaxis A versus thromboprophylaxis B with outcomes thrombosis, hemorrhage, mortality, ischemic stroke, quality of life (QOL) and adverse events

Population: Children with an indication for the Fontan procedure
Intervention: Thromboprophylaxis A (specified in table)
Comparator: Thromboprophylaxis B (specified in table)

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Summary
Aspirin versus warfarin					
		Aspirin	Warfarin		
Thrombotic complications (critical)	Relative risk: **1.26** (95% CI 0.25 to 6.29) Based on data from 155 participants in 1 study Follow-up: 30 days	**5** per 100	**4** per 100	**Very low** Due to risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of aspirin on thrombotic complications, when compared with warfarin in children with an indication for the Fontan procedure (Ankola, 2021)
		Difference: **1 more per 100** (95% CI 6 fewer to 8 more)			
• Hemorrhage (important) • Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)	-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of aspirin on hemorrhage, mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with warfarin in children with an indication for the Fontan procedure
Aspirin versus enoxaparin					
		Aspirin	Enoxaparin		
Thrombotic complications (critical)	Relative risk: **0.63** (95% CI 0.08 to 4.99)	**5** per 100	**8** per 100		

	Based on data from 116 participants in 1 study Follow-up: 30 days	Difference: **3 fewer per 100** (95% CI 18 fewer to 12 more)		**Very low** Due to risk of bias, due to very serious imprecision[2]	The evidence is very uncertain about the effect of aspirin on thrombotic complications, when compared with enoxaparin in children with an indication for the Fontan procedure (Ankola, 2021)
• Hemorrhage (important) • Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)	-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of aspirin on hemorrhage, mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with enoxaparin in children with an indication for the Fontan procedure
Warfarin versus enoxaparin					
		Warfarin	Enoxaparin		
Thrombotic complications (critical)	Relative risk: **0.50** (95% CI 0.05 to 5.10) Based on data from 65 participants in 1 study Follow-up: 30 days	**4** per 100	**8** per 100	**Very low** Due to risk of bias, due to very serious imprecision[3]	The evidence is very uncertain about the effect of warfarin on thrombotic complications, when compared with enoxaparin in children with an indication for the Fontan procedure (Ankola, 2021)
		Difference: **4 fewer per 100** (95% CI 19 fewer to 12 more)			
• Hemorrhage (important) • Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)	-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of warfarin on hemorrhage, mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with enoxaparin in children with an indication for the Fontan procedure

Aspirin versus rivaroxaban						
			Aspirin	Rivaroxaban		
Thrombotic complications (critical)		Relative risk: **3.76** (95% CI 0.35 to 40.04) Based on data from 98 participants in 1 study Follow-up: 12 months	**6** per 100	**2** per 100	**Very low** Due to risk of bias, due to very serious imprecision[4]	The evidence is very uncertain about the effect of aspirin on thrombotic complications, when compared with rivaroxaban in children with an indication for the Fontan procedure (McCrindle, 2021)
			Difference: **4 more per 100** (95% CI 4 fewer to 13 more)			
Hemorrhage (important)	Major bleeding	Relative risk: **0.62** (95% CI 0.03 to 14.80) Based on data from 98 participants in 1 study Follow-up: 12 months	**0** per 100	**2** per 100	**Very low** Due to risk of bias, due to very serious imprecision[5]	The evidence is very uncertain about the effect of aspirin on major bleeding, when compared with rivaroxaban in children with an indication for the Fontan procedure (McCrindle, 2021)
			Difference: **2 fewer per 100** (95% CI 7 fewer to 4 more)			
	Clinically relevant nonmajor bleeding	Relative risk: **1.41** (95% CI 0.34 to 5.95) Based on data from 98 participants in 1 study Follow-up: 12 months	**9** per 100	**6** per 100	**Very low** Due to risk of bias, due to very serious imprecision[6]	The evidence is very uncertain about the effect of aspirin on clinically relevant nonmajor bleeding, when compared with rivaroxaban in children with an indication for the Fontan procedure (McCrindle, 2021)
			Difference: **3 fewer per 100** (95% CI 9 fewer to 14 more)			
	Trivial bleeding	Relative risk: **1.08** (95% CI 0.61 to 1.91) Based on data from 98 participants in 1 study Follow-up: 12 months	**35** per 100	**33** per 100	**Very low** Due to risk of bias, due to very serious imprecision[7]	The evidence is very uncertain about the effect of aspirin on trivial bleeding, when compared with rivaroxaban in children with an indication for the Fontan procedure (McCrindle, 2021)
			Difference: **2 more per 100** (95% CI 17 fewer to 22 more)			

Ischemic stroke (important)	Relative risk: **5.57** (95% CI 0.23 to 133.19) Based on data from 98 participants in 1 study Follow-up: 12 months	**3** per 100	**0** per 100	**Very low** Due to risk of bias, due to very serious imprecision[8]	The evidence is very uncertain about the effect of aspirin on ischemic stroke, when compared with rivaroxaban in children with an indication for the Fontan procedure (McCrindle, 2021)
		Difference: **3 more per 100** (95% CI 4 fewer to 10 more)			
Adverse events (important)	Relative risk: **0.99** (95% CI 0.84 to 1.18) Based on data from 98 participants in 1 study Follow-up: 12 months	**85** per 100	**86** per 100	**Moderate** Due to risk of bias[9]	There is likely little to no effect of aspirin on adverse events, when compared with rivaroxaban in children with an indication for the Fontan procedure (McCrindle, 2021)
		Difference: **1 fewer per 100** (95% CI 15 fewer to 14 more)			
• Mortality (important) • Quality of life (QOL)	-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of aspirin on mortality, and quality of life (QOL), when compared with rivaroxaban in children with an indication for the Fontan procedure

1. **Risk of bias: some concerns (-1 level).** No exclusion criteria were defined, and it is unclear whether the outcomes of interest were not present at the start of the study. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
2. **Risk of bias: some concerns (-1 level).** No exclusion criteria were defined, and it is unclear whether the outcomes of interest were not present at the start of the study. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
3. **Risk of bias: some concerns (-1 level).** No exclusion criteria were defined, and it is unclear whether the outcomes of interest were not present at the start of the study. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
4. **Risk of bias: some concerns (-1 level).** Method of randomization is unclear, no reporting on allocation concealment, and the study was not blinded. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
5. **Risk of bias: some concerns (-1 level).** Method of randomization is unclear, no reporting on allocation concealment, and the study was not blinded. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
6. **Risk of bias: some concerns (-1 level).** Method of randomization is unclear, no reporting on allocation concealment, and the study was not blinded. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
7. **Risk of bias: some concerns (-1 level).** Method of randomization is unclear, no reporting on allocation concealment, and the study was not blinded. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
8. **Risk of bias: some concerns (-1 level).** Method of randomization is unclear, no reporting on allocation concealment, and the study was not blinded. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
9. **Risk of bias: some concerns (-1 level).** Method of randomization is unclear, no reporting on allocation concealment, and the study was not blinded.

2. Studies with follow-up > 1 year

Table 4. Summary of Findings – Comparison of thromboprophylaxis A versus thromboprophylaxis B with outcomes thrombosis, hemorrhage, mortality, ischemic stroke, quality of life (QOL) and adverse events

Population: Children with an indication for the Fontan procedure
Intervention: Thromboprophylaxis A (specified in table)
Comparator: Thromboprophylaxis B (specified in table)

Outcome		Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Summary
Aspirin versus warfarin						
			Aspirin	Warfarin		
Thrombotic complications (critical)		Relative risk: **1.42** (95% CI 0.35 to 40.04) Based on data from 1533 participants in 7 studies Follow-up: ≥ 24 months	**19** per 100	**9** per 100	**Very low** Due to risk of bias, due to very serious imprecision[1]	The evidence is very uncertain about the effect of aspirin on thrombotic complications, when compared with warfarin in children with an indication for the Fontan procedure (Al-Jazairi, 2019; Egbe, 2017; Iyengar, 2016; McCrindle, 2013; Pessotti, 2014; Potter, 2013; Seipelt, 2002)
			Difference: **5 more per 100** (95% CI 9 fewer to 19 more)			
Hemorrhage (important)	Major bleeding	Relative risk: **0.89** (95% CI 0.74 to 1.08) Based on data from 147 participants in 2 studies Follow-up: 2.5 years-13.6 years	**12** per 100	**14** per 100	**Very low** Due to risk of bias, due to serious imprecision[2]	The evidence is very uncertain about the effect of aspirin on major bleeding, when compared with warfarin in children with an indication for the Fontan procedure (Al-Jazairi, 2019; McCrindle, 2013)
			Difference: **0 fewer per 100** (95% CI 11 fewer to 10 more)			
	Clinically relevant nonmajor bleeding	Relative risk: **0.45** (95% CI 0.20 to 1.01) Based on data from 32 participants in 1 study	**31** per 100	**69** per 100	**Very low** Due to risk of bias, due to serious imprecision[3]	The evidence is very uncertain about the effect of aspirin on clinically relevant nonmajor bleeding, when compared with warfarin in children with an indication for the Fontan procedure
			Difference: **38 fewer per 100**			

		Follow-up: 13.6 years (median)	(95% CI 70 fewer to 5 more)			(Al-Jazairi, 2019)
	Minor bleeding	Relative risk: **0.57** (95% CI 0.09 to 3.61) Based on data from 243 participants in 2 studies Follow-up: 2.5 years-13.6 years	**27** per 100 Difference: **22 fewer per 100** (95% CI 53 fewer to 10 more)	**49** per 100	**Very low** Due to risk of bias, due to very serious imprecision[4]	The evidence is very uncertain about the effect of aspirin on minor bleeding, when compared with warfarin in children with an indication for the Fontan procedure (Al-Jazairi, 2019; McCrindle, 2013)
Mortality (important)		Relative risk: **2.84** (95% CI 0.12 to 68.36) Based on data from 111 participants in 1 study Follow-up: 2.5 years	**2** per 100 Difference: **2 more per 100** (95% CI 3 fewer to 7 more)	**0** per 100	**Very low** Due to risk of bias, due to very serious imprecision[5]	The evidence is very uncertain about the effect of aspirin on mortality, when compared with warfarin in children with an indication for the Fontan procedure (McCrindle, 2013; Pessotti, 2014)
		Relative risk: **0.20** (95% CI 0.01 to 3.85) Based on data from 30 participants in 1 study Follow-up: 2 years	**0** per 100 Difference: **13 fewer per 100** (95% CI 33 fewer to 6 more)	**13** per 100		
• Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of aspirin on ischemic stroke, quality of life (QOL), and adverse events, when compared with warfarin in children with an indication for the Fontan procedure
DOACs versus antiplatelets						
			DOACs	Antiplatelets		
Thrombotic complications (critical)		Relative risk: **0.17** (95% CI 0.01 to 3.18)	**0** per 100	**7** per 100		

		Based on data from 79 participants in 1 study Follow-up: 95 months (mean)	Difference: **7 fewer per 100** (95% CI 16 fewer to 2 more)		**Very low** Due to risk of bias, due to very serious imprecision[6]	The evidence is very uncertain about the effect of DOACs on thrombotic complications, when compared with antiplatelets in children with an indication for the Fontan procedure (Kawamatsu, 2021)
Hemorrhage (important)	Major bleeding	Relative risk: **0.40** (95% CI 0.04 to 3.66) Based on data from 79 participants in 1 study Follow-up: 95 months (mean)	**3** per 100	**7** per 100 Difference: **4 fewer per 100** (95% CI 14 fewer to 5 more)	**Very low** Due to risk of bias, due to very serious imprecision[7]	The evidence is very uncertain about the effect of DOACs on major bleeding, when compared with antiplatelets in children with an indication for the Fontan procedure (Kawamatsu, 2021)
	Minor bleeding	Relative risk: **1.19** (95% CI 0.08 to 18.43) Based on data from 79 participants in 1 study Follow-up: 95 months (mean)	**3** per 100	**2** per 100 Difference: **0 per 100** (95% CI 7 fewer to 7 more)	**Very low** Due to risk of bias, due to very serious imprecision[8]	The evidence is very uncertain about the effect of DOACs on minor bleeding, when compared with antiplatelets in children with an indication for the Fontan procedure (Kawamatsu, 2021)
• Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of DOACs on mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with antiplatelets in children with an indication for the Fontan procedure
DOACs versus VKAs						
			DOACs	VKAs		
Thrombotic complications (critical)		Relative risk: **0.10** (95% CI 0.01 to 1.80)	**0** per 100	**12** per 100		

		Based on data from 77 participants in 1 study Follow-up: 95 months (mean)	Difference: **12 fewer per 100** (95% CI 23 fewer to 1 fewer)		**Very low** Due to risk of bias, due to very serious imprecision[9]	The evidence is very uncertain about the effect of DOACs on thrombotic complications, when compared with VKAs in children with an indication for the Fontan procedure (Kawamatsu, 2021)
Hemorrhage (important)	Major bleeding	Relative risk: **0.19** (95% CI 0.02 to 1.50) Based on data from 77 participants in 1 study Follow-up: 95 months (mean)	**3** per 100 Difference: **12 fewer per 100** (95% CI 24 fewer to 0 more)	**15** per 100	**Very low** Due to risk of bias, due to very serious imprecision[10]	The evidence is very uncertain about the effect of DOACs on major bleeding, when compared with VKAs in children with an indication for the Fontan procedure (Kawamatsu, 2021)
	Minor bleeding	Relative risk: **0.38** (95% CI 0.04 to 3.49) Based on data from 77 participants in 1 study Follow-up: 95 months (mean)	**3** per 100 Difference: **5 fewer per 100** (95% CI 14 fewer to 5 more)	**7** per 100	**Very low** Due to risk of bias, due to very serious imprecision[11]	The evidence is very uncertain about the effect of DOACs on major bleeding, when compared with VKAs in children with an indication for the Fontan procedure (Kawamatsu, 2021)
• Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of DOACs on mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with VKAs in children with an indication for the Fontan procedure
DOACs versus combination of an antiplatelet and anticoagulant						
			DOACs	Combination of an antiplatelet and anticoagulant		
		Relative risk: **1**	**0**	**0**		

Thrombotic complications (critical)		Based on data from 50 participants in 1 study Follow-up: 95 months (mean)	per 100 Difference: **0 fewer per 100**	per 100	**Very low** Due to risk of bias[12]	The evidence is very uncertain about the effect of DOACs on thrombotic complications, when compared with a combination of an antiplatelet and anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
Hemorrhage (important)	Major bleeding	Relative risk: **0.05** (95% CI 0.01 to 0.35) Based on data from 50 participants in 1 study Follow-up: 95 months (mean)	**3** per 100 Difference: **54 fewer per 100** (95% CI 81 fewer to 28 fewer)	**57** per 100	**Very low** Due to risk of bias[13]	The evidence is very uncertain about the effect of DOACs on major bleeding, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
	Minor bleeding	Relative risk: **1.22** (95% CI 0.05 to 28.21) Based on data from 50 participants in 1 study Follow-up: 95 months (mean)	**3** per 100 Difference: **3 more per 100** (95% CI 8 fewer to 14 more)	**0** per 100	**Very low** Due to risk of bias, due to very serious imprecision[14]	The evidence is very uncertain about the effect of DOACs on major bleeding, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
• Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of DOACs on mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with a combination of an antiplatelet and anticoagulant in children with an indication for the Fontan procedure
Antiplatelets versus VKAs						
			Antiplatelets	VKAs		
Thrombotic complications (critical)		Relative risk: **0.57** (95% CI 0.15 to 2.24)	**7** per 100	**12** per 100		

		Based on data from 84 participants in 1 study Follow-up: 95 months (mean)	Difference: **5 fewer per 100** (95% CI 18 fewer to 7 more)		**Very low** Due to risk of bias, due to very serious imprecision[15]	The evidence is very uncertain about the effect of antiplatelets on thrombotic complications, when compared with VKAs in children with an indication for the Fontan procedure (Kawamatsu, 2021)
Hemorrhage (important)	Major bleeding	Relative risk: **0.48** (95% CI 0.13 to 1.78) Based on data from 84 participants in 1 study Follow-up: 95 months (mean)	**7** per 100 Difference: **8 fewer per 100** (95% CI 21 fewer to 7 more)	**15** per 100	**Very low** Due to risk of bias, due to very serious imprecision[16]	The evidence is very uncertain about the effect of antiplatelets on major bleeding, when compared with VKAs in children with an indication for the Fontan procedure (Kawamatsu, 2021)
	Minor bleeding	Relative risk: **0.32** (95% CI 0.03 to 2.93) Based on data from 84 participants in 1 study Follow-up: 95 months (mean)	**2** per 100 Difference: **5 fewer per 100** (95% CI 14 fewer to 4 more)	**7** per 100	**Very low** Due to risk of bias, due to very serious imprecision[17]	The evidence is very uncertain about the effect of antiplatelets on minor bleeding, when compared with VKAs in children with an indication for the Fontan procedure (Kawamatsu, 2021)
• Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of antiplatelets on mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with VKAs in children with an indication for the Fontan procedure
Antiplatelets versus combination of an antiplatelet and anticoagulant						
			Antiplatelets	Combination of an antiplatelet and anticoagulant		
		Relative risk: **2.39**	**7**	**0**		

Thrombotic complications (critical)		(95% CI 0.03 to 2.93) Based on data from 57 participants in 1 study Follow-up: 95 months (mean)	per 100 Difference: **7 more per 100** (95% CI 5 fewer to 19 more)	per 100	**Very low** Due to risk of bias, due to very serious imprecision[18]	The evidence is very uncertain about the effect of antiplatelets on thrombotic complications, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
Hemorrhage (important)	Major bleeding	Relative risk: **0.12** (95% CI 0.04 to 0.40) Based on data from 57 participants in 1 study Follow-up: 95 months (mean)	**7** per 100 Difference: **50 fewer per 100** (95% CI 77 fewer to 23 fewer)	**57** per 100	**Very low** Due to risk of bias[19]	The evidence is very uncertain about the effect of antiplatelets on major bleeding, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
	Minor bleeding	Relative risk: **1.02** (95% CI 0.04 to 23.78) Based on data from 57 participants in 1 study Follow-up: 95 months (mean)	**2** per 100 Difference: **2 fewer per 100** (95% CI 8 fewer to 13 more)	**0** per 100	**Very low** Due to risk of bias, due to very serious imprecision[20]	The evidence is very uncertain about the effect of antiplatelets on major bleeding, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
• Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of antiplatelets on mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with a combination of an antiplatelet and anticoagulant in children with an indication for the Fontan procedure
VKAs versus combination of an antiplatelet and anticoagulant						
			VKAs	Combination of an antiplatelet		

				and anticoagulant		
Thrombotic complications (critical)		Relative risk: **3.93** (95% CI 0.23 to 66.86) Based on data from 55 participants in 1 study Follow-up: 95 months (mean)	**12** per 100	**0** per 100	**Very low** Due to risk of bias, due to very serious imprecision[21]	The evidence is very uncertain about the effect of VKAs on thrombotic complications, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
			Difference: **12 more per 100** (95% CI 1 fewer to 26 more)			
Hemorrhage (important)	Major bleeding	Relative risk: **0.26** (95% CI 0.11 to 0.61) Based on data from 55 participants in 1 study Follow-up: 95 months (mean)	**15** per 100	**57** per 100	**Very low** Due to risk of bias[22]	The evidence is very uncertain about the effect of VKAs on major bleeding, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
			Difference: **43 fewer per 100** (95% CI 71 fewer to 14 fewer)			
	Minor bleeding	Relative risk: **2.50** (95% CI 0.14 to 45.62) Based on data from 55 participants in 1 study Follow-up: 95 months (mean)	**7** per 100	**0** per 100	**Very low** Due to risk of bias, due to very serious imprecision[23]	The evidence is very uncertain about the effect of VKAs on minor bleeding, when compared with a combination of an antiplatelet and an anticoagulant in children with an indication for the Fontan procedure (Kawamatsu, 2021)
			Difference: **7 fewer per 100** (95% CI 5 fewer to 20 more)			
• Mortality (important) • Ischemic stroke (important) • Quality of life (QOL) (important) • Adverse events (important)		-	-		**No GRADE** (No evidence was found)	No evidence was found regarding the effect of VKAs on mortality, ischemic stroke, quality of life (QOL), and adverse events, when compared with a combination of an antiplatelet and anticoagulant in children with an indication for the Fontan procedure

1. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcomes of interest were not present at the start of the study, confounder adjustment is not consistently conducted across all study, method of randomization is unclear, no blinding, and no reporting on allocation concealment. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
2. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, unclear reporting on multivariable statistical analyses, method of randomization unclear, and no blinding. **Imprecision: serious (-1 level).** The confidence interval crosses one border of clinical relevance.
3. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study and unclear reporting on multivariable statistical analyses. **Imprecision: serious (-1 level).** The confidence interval crosses one border of clinical relevance.
4. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, unclear reporting on multivariable statistical analyses, method of randomization is unclear, and no blinding. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
5. **Risk of bias: some concerns (-1 level).** Method of randomization is clear, no blinding, and no reporting on allocation concealment. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
6. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
7. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
8. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
9. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
10. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
11. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
12. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups.
13. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
14. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
15. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
16. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
17. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
18. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
19. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups.
20. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.

21. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.
22. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups.
23. **Risk of bias: some concerns (-1 level).** It is unclear whether the outcome of interest was not present at the start of the study, no proper confounder adjustment was conducted, co-interventions differed between the intervention groups. **Imprecision: very serious (-2 levels).** The confidence interval crosses both borders of clinical relevance.