# Effects of ischaemic conditioning on major clinical outcomes in people undergoing invasive procedures: A systematic review and meta-analysis

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# **Objective:**

To summarise the benefits and harms of ischaemic conditioning on major clinical outcomes.

## Design:

Systematic review and meta-analysis. Two authors independently extracted data from individual studies. Random effects models were used to calculate summary estimates for all-cause mortality and other pre-specified clinical outcomes. All-cause mortality and secondary outcomes with a p-value<0.1 were examined for study quality using the GRADE assessment tool, the impact of pre-specified characteristics using meta-regression and Cochran C test, and trial sequential analysis using the Copenhagen Trial Unit Method.

secondary outcomes including stroke (18 trials, 5,995 participants, 149 events, RR 0.72, 95%Cl 0.52 to 0.997, p=0.048, GRADE: very low quality evidence) and acute kidney injury (36 trials, 8,613 participants, 1,450 events, RR 0.84, 95%Cl 0.72 to 0.98, p=0.02, GRADE: low quality evidence) although the benefits appear to be confined to non-surgical settings and to mild episodes of acute kidney injury only. To confirm the observed effect size reflects true benefit would require future trials to increase the number of studied participants by 4420% for mortality, 520% for stroke and 170% for acute kidney injury.

Figure 3: Effect of ischaemic conditioning on secondary outcomes \*

Figure 1: PRISMA flow diagram of identification process for eligible studies



\*4 reports studied two eligible interventions which have been analysed as separate reports.

Secondary outcome					RR (95% CI)	Events Ischaemic conditioning	Events Control	P-value
Cardiovascular event composite <sup>†</sup>			$\diamond$		0.88 (0.73 to 1.05)	658/3049	706/3060	0.16
Myocardial Infarction <sup>‡</sup>			$\bigcirc$		0.84 (0.69 to 1.03)	328/4200	386/4211	0.10
Defined by a single biochemical or ECG m	arker			>	0.86 (0.39 to 1.88)	21/667	25/659	0.71
Diagnostic criteria not specified		$\langle$			0.79 (0.46 to 1.37)	24/695	31/703	0.41
Defined by biomarker and clinical criteria		<			0.84 (0.64 to 1.12)	283/2838	330/2849	0.23
Stroke		<	>		0.72 (0.52 to 1.00)	62/3017	87/3009	0.05
Arrhythmia			$\diamond$		0.90 (0.76 to 1.06)	659/3314	721/3331	0.19
Acute kidney injury			$\diamond$		0.84 (0.72 to 0.98)	682/4234	768/4239	0.02
AKIN 1§		<	$\bigcirc$		0.81 (0.63 to 1.04)	353/1538	392/1567	0.12
AKIN 2 <sup>II</sup>		<			0.90 (0.67 to 1.21)	84/1448	94/1473	0.49
AKIN 3¶		c		>	1.15 (0.66 to 1.98)	84/2443	75/2460	0.63
Primary graft non-function	<				0.69 (0.33 to 1.43)	8/162	14/163	0.31
Delayed graft function					0.45 (0.10 to 2.04)	2/133	8/133	0.30
	.25	.5	1	2.5	5			
Favours ischa	aemic cor	nditioning		Favours	control			

Composite of major deverse calculovased are events as defined by study authors
As defined by study authors
Acute kidney injury network criterion 1 derived where available from study author definition as per Appendix table 2
Acute kidney injury network criterion 2 derived where available from study author definition as per Appendix table 2
Acute kidney injury network criterion 3 derived where available from study author definition as per Appendix table 2

#### Data Sources

MEDLINE, EMBASE, the Cochrane Databases and the International Clinical

#### Conclusions

Ischaemic conditioning has no overall effect on the risk of death. Possible effects on stroke and AKI are uncertain given methodological concerns and low event rates. Adoption of ischaemic conditioning cannot be recommended for routine use unless further, sufficient high quality evidence demonstrates benefit.

Trials Registry platform (ICTRP) from inception through October 2015.

#### **Eligibility criteria for selecting studies** All randomised controlled trials assessing the effects of ischaemic

conditioning compared with control on clinical outcomes.

Figure 2: Effect of ischaemic conditioning on all-cause mortality\*

Author (year)	RR (95% CI)	Events, ischaemic conditioning	Events, control	% Weight
Ischaemic pre-conditioning				
Amr (2010)	0.33 (0.01, 7.58)	0/15	1/15	0.36
Walsh (2009)	3.63 (0.16, 84.11)	1/18	0/22	0.36
Walsh (2010)	5.78 (0.32, 105.12)	3/22	0/18	0.42
Cescon (2006)	0.21 (0.01, 4.12)	0/23	2/24	0.39
Hou (2009)	3.00 (0.13, 70.16)	1/24	0/24	0.35
Lucchinetti (2012)	0.35 (0.01, 8.12)	0/27	1/28	0.35
Amador (2007)	0.33 (0.01, 7.87)	0/30	1/30	0.35
Azoulay (2006)	5.00 (0.25, 99.95)	2/30	0/30	0.39
Lin (2014)	1.17 (0.44, 3.06)	7/30	6/30	3.76
Luo (2001)	0.33 (0.01, 7.87)	0/30	1/30	0.35
Heizmann (2008)	5.16 (0.26, 103.25)	2/30	0/31	0.39
Murphy (2014)	3.00 (0.33, 27.29)	3/31	1/31	0.72
Mouton (2015)	0.15 (0.01, 2.74)	0/34	3/35	0.41
Petrowsky (2006)	2.92 (0.12, 69.43)	1/37	0/36	0.35
Aenting (2015)	0.20 (0.01, 4.03)	0/36	2/36	0.39
Ni (2007)	0.67 (0.12, 3.78)	2/41	3/41	1.16
(1998)	0.35 (0.01, 8.36)	0/34	1/36	0.35
Scatton (2011)	0.95 (0.14, 6.46)	2/43	2/41	0.96
Gallagher (2015)	1.00 (0.15, 6.78)	2/43	2/43	0.96
'oung (2012)	1.00 (0.06, 15.53)	1/48	1/48	0.47
r (2012)	0.20 (0.01, 4.06)	0/50	2/50	0.39
e (2014)	0.33 (0.01, 7.99)	0/50	1/50	0.35
oneru (2007)	0.64 (0.32, 1.27)	10/50	16/51	7.43
'edersen (2012)	0.47 (0.04, 5.05)	1/54	2/51	0.62
Cimmerman (2011)	0.20 (0.01, 4.08)	0/60	2/60	0.39
andilio (2015)	0.09 (0.01, 1.62)	0/90	5/90	0.42
loole (2009)	0.20 (0.02, 1.72)	1/95	5/97	0.77
arbock (2015)	1.40 (0.46, 4.29)	7/120	5/120	2.80
Valsh (2015)	1.47 (0.65, 3.31)	13/128	9/130	5.29
lougaard (2014)	0.76 (0.29, 2.03)	6/22	5/14	3.65
hielmann (2013)	0.28 (0.08, 0.99)	3/162	11/167	2.22
otker (2010)	0.53 (0.26, 1.06)	11/166	21/167	7.22
leybohm (2015)	1.08 (0.51, 2.28)	14/692	13/693	6.28
lausenloy (2015)	1.29 (0.92, 1.82)	69/801	54/811	29.90
ubtotal (I-squared = 0.0%, p = 0.482)	0.94 (0.77, 1.16)	162/3896	178/3916	80.96
schaemic post-conditioning				
arcia (2011)	3.00 (0.13, 69.31)	1/19	0/19	0.36
raszkiewicz (2015)	1.03 (0.15, 6.91)	2/36	2/37	0.97
im (2014)	1.00 (0.15, 6.75)	2/39	2/39	0.96
urdu (2012)	0.20 (0.01, 4.14)	0/39	2/40	0.39
rimi (2013)	0.33 (0.01, 7.98)	0/48	1/48	0.35
(2009)	0.53 (0.05, 5.67)	1/48	2/51	0.63
Donborg (2010)	3.05 (0.33, 28.47)	3/55	1/56	0.70
ettereos (2013)	0.50 (0.05, 5.39)	1/113	2/112	0.62
arrasco-Chinchilla (2013)	4.83 (0.23, 99.56)	2/118	0/114	0.38
imalanathan (2014)	2.00 (0.37, 10.74)	4/136	2/136	1.24
	1.31 (0.65, 2.66)	17/347	13/348	7.02
long (2014)	0.71 (0.32, 1.58)	10/644	14/636	5.42
ubtotal (I-squared = 0.0%, p = 0.837)	1.05 (0.68, 1.61)	43/1757	41/1750	19.04
		005/5050	0.4045000	100.00

Figure 4: Subgroup analyses of the effect of ischaemic conditioning on all-cause mortality (A), myocardial infarction (B), stroke (C) and acute kidney injury (D)\*

A Category	Characteristics		Relative Risk (95% CI)	Weight (%)	p for between-subg heterogeneity	roup	5	Category	Characteristic		Relative Risk 95%Cl	Weight %	p for between-subgroup heterogeneity
Population	Adult	<i>\</i>	1.00 (0.82 to 1.22)	98.64	0.420			Intervention site	Peripheral	$\diamond$	0.89 (0.77 to 1.02)	96.10	0.530
	Paediatric		0.50 (0.09 to 2.67)	1.36					Central		0.71 (0.35 to 1.42)	3.90	
Intervention site	Peripheral		1.01 (0.81 to 1.26)	77.41	0.799			Type of peripheral	Upper limb	$\diamond$	0.85 (0.73 to 0.98)	86.41	0.107
Type of peripheral	Central		0.95 (0.85 to 1.43)	22.59	0 731			Intervention	Not a peripheral intervention		>> 0.71 (0.35 to 1.42)	3.90	
intervention			0.95 (0.63 to 1.24)	22 59	0.751				Lower limb		1.37 (0.88 to 2.12)	9 69	
	Lower limb		1.25 (0.68 to 2.28)	10.54							, , , , , , , , , , , , , , , , , , ,	0100	
								Cardiac condition or not	Cardiac condition		0.88 (0.76 to 1.01)	96.51	0.782
Cardiac condition or not	Cardiac condition	$\diamond$	1.04 (0.84 to 1.29)	79.68	0.362				Non-cardiac condition	$\leq$	0.98 (0.47 to 2.03)	3.49	
	Non-cardiac condition	$\langle \rangle$	0.83 (0.54 to 1.28)	20.32				Pre- or post-ischaemic conditioning	Pre	$\bigcirc$	0.87 (0.75 to 1.00)	95.92	0.304
									Post		1.25 (0.63 to 2.47)	4.08	
Pre or post ischaemic conditioning	Pre	$\diamond$	0.98 (0.79 to 1.22)	80.86	0.787			Surgical or non-surgical	Non-surgical setting	$\sim$	> 0.76 (0.45 to 1.27)	7.02	0.548
conditioning	Post		1.05 (0.67 to 1.64)	19.14				setting	Surgical setting	$\diamond$	0.89 (0.77 to 1.03)	92.98	
Surgical or non-surgical	Non-surgical setting	$\diamond$	0.85 (0.57 to 1.26)	24.19	0.366			Specific setting	Surgery for cardiac conditions		0.89 (0.77 to 1.03)	89.49	0.936
setting	Surgical setting	$\diamond$	1.05 (0.84 to 1.31)	75.81					PCI and other intravascular	$\sim$	> 0.76 (0.45 to 1.27)	7.02	
Specific setting	PCI and other intravascular	$\langle \rangle$	0.86 (0.56 to 1.33)	20.20	0.836				Vascular surgery		0.97 (0.45 to 2.09)	3.24	
	Vascular surgery		1.18 (0.30 to 4.64)	2.05					Transplantation		1 00 /0 06 to 15 44	0.05	
	Transplantation	$\langle \rangle$	0.80 (0.47 to 1.36)	13.24				Time of an early all				0.25	0.701
	Cardiac surgery	$\diamond$	1.11 (0.86 to 1.43)	59.48				l ype of anaesthetic	Volatile anaesthetic	Y	0.91 (0.77 to 1.06)	74.85	0.781
	Liver resection		0.95 (0.14 to 6.46)	1.04					Anaesthetic type not reported		1.28 (0.36 to 4.57)	1.16	
	Secondary stroke prevention		0.76 (0.29 to 2.03)	3.98					Non-volatile anaesthetic	$\sim$	> 0.80 (0.58 to 1.12)	16.98	
Type of anaesthetic	Anaesthetic not required	$\langle \rangle$	0.85 (0.57 to 1.26)	24.19	0.294				Anaesthetic not required		> 0.76 (0.45 to 1.27)	7.02	
	Volatile anaesthetic	$\diamond$	1.16 (0.88 to 1.54)	49.41				Use of sham procedure in	Yes	$\diamond$	0.90 (0.78 to 1.04)	92.50	0.179
	Anaesthetic not reported	$\langle \rangle$	0.63 (0.32 to 1.22)	8.78				control arm	No	$\langle \rangle$	0.63 (0.38 to 1.05)	7.50	
	Non-volatile anaesthetic	$\Leftrightarrow$	1.00 (0.63 to 1.59)	17.63				Diagnostic criteria	Single marker of ischaemia †		> 0.74 (0.40 to 1.37)	5.07	0.855
Use of sham procedure in	Yes	$\diamond$	1.11 (0.87 to 1.41)	67.01	0.110				Biomarker and clinical criteria <sup>‡</sup>	$\diamond$	0.89 (0.77 to 1.03)	89.11	
Control arm	No	$\Leftrightarrow$	0.79 (0.56, to 1.11)	32.99					Not specified §	$\sim$	0.89 (0.51 to 1.58)	5.82	
Overall		♦	0.99 (0.82 to 1.21)	100.00				Overall		$\diamond$	0.88 (0.77 to 1.01)	100.00	
		.1 .25 .5 1 2.5 5	10						.1 .1	25 .5 <b>1</b>	2.5 5		
~	Favours ischaer	mic conditioning Favours co	ontrol				П		Favours ischaemic c	onditioning	Favours control		
Category	Characteristic		Rela	tive Risk	Weight	p for between-subgroup	U	Category	Characteristic		Relative risk (05%, Cl)	Weight (%)	P for between-subgroup beterpagneity
			95%	CI	%	heterogeneity			1 d. H.		,00.00,		
Type of peripheral	Lipper limb		0.60	(0.48 to 0.98)	2) 90.74	0.507		Population	Adult	0	0.92 (0.84, 1.01)	94.02	0.661
intervention			0.00	(0.40 10 0.30)	,) 30.74	0.507			Paediatric	~	> 0.85 (0.60, 1.21)	5.98	
	Lower limb		1.02	(0.34 to 3.07)	") 9.26			Intervention site	Peripheral	•	0.94 (0.86, 1.03)	96.97	0.001
Cardiac condition or not	Cordian condition		0.00	(0 57 to 1 17	N 07.00				Central	$\sim$	0.41 (0.25, 0.67)	3.03	
Cardiac condition of hot	Cardiac condition		0.82	(0.57 to 1.17)	7) 87.32	0.030		Type of peripheral intervention	Upper limb	•	0.98 (0.87, 1.05)	80.69	0.003
	Non-cardiac condition		0.27	(0.10 to 0.69)	9) 12.68				Lower limb	~	0.92 (0.74, 1.15)	14.92	
Bre- or post-ischaomia	Bro	$\langle \rangle$	0.67	(0.47 to 0.07)	7) <u>85.04</u>	0.400			Both upper and lower limb		0.47 (0.23, 0.99)	1.36	
conditioning	FIG		0.87	(0.47 10 0.97	65.04	0.423		Cardiac condition or not	Cardiac condition	0	0.90 (0.83, 0.99)	92.40	0.220
	Post		0.99	(0.41 to 2.36)	6) 14.96			Pre or post ischaemic conditioning	Pre		0.93 (0.85, 1.02)	68.80	0.514
Surgical or non-surgical	Non-surgical setting		0.28	(0.14 to 0.56)	6) 22.17	0.003		to a posterior and the second ling	Post	0	0.84 (0.85, 1.09)	11.20	AND AND A T
setting	Surgical setting		> 0.93	(0.64 to 1.36)	6) 77.83			Surgical or non surgical setting	Surgical setting	0	0.95 (0.88, 1.05)	92.72	0.000
			5.00		,			Specific setting	Cardiac surgery	~	0.51 (0.37, 0.70) 0.95 (0.87, 1.04)	85.39	0.002
Specific setting	Surgery for cardiac conditions	$\triangleleft$	> 0.93	(0.64 to 1.36)	6) 77.83	0.013			Percutaneous coronary & other intravasc.	$\sim$	0.51 (0.37, 0.70)	7.28	
	PCI and other intravascular		0.29	(0.10 to 0.86)	6) 9.49				Vascular surgery	<	> 1.11 (0.80, 1.53)	7.13	





\* Overall RR for the subgroup analysis are derived from the fixed effects model of eligible studies with at least one event in each arm and so may differ from the main analysis method.
† 6 trials defined myocardial infarction by a single biochemical or ECG marker of ischaemia
‡ 16 trials defined myocardial infarction by a biomarker and clinical criteria
§ 14 trials did not describe their diagnostic criteria

## Results

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Eighty-nine trials were identified with a median 79 participants (interquartile range (IQR) 55, 123) and median 1 month (IQR 0.5, 10) intended duration. Ischaemic conditioning had no impact on all-cause mortality (67 trials, 424 events, 11,614 participants, RR 0.96, 95% confidence interval 0.80 to 1.16, p=0.68, GRADE: moderate quality evidence) regardless of the clinical setting in which it was used or the particular intervention-related characteristics. Ischaemic conditioning may reduce the rates of some

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