APPENDIX D4 – Additional forest plots and analyses 2nd stage

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1 Ambulatory ECG review– further analyses

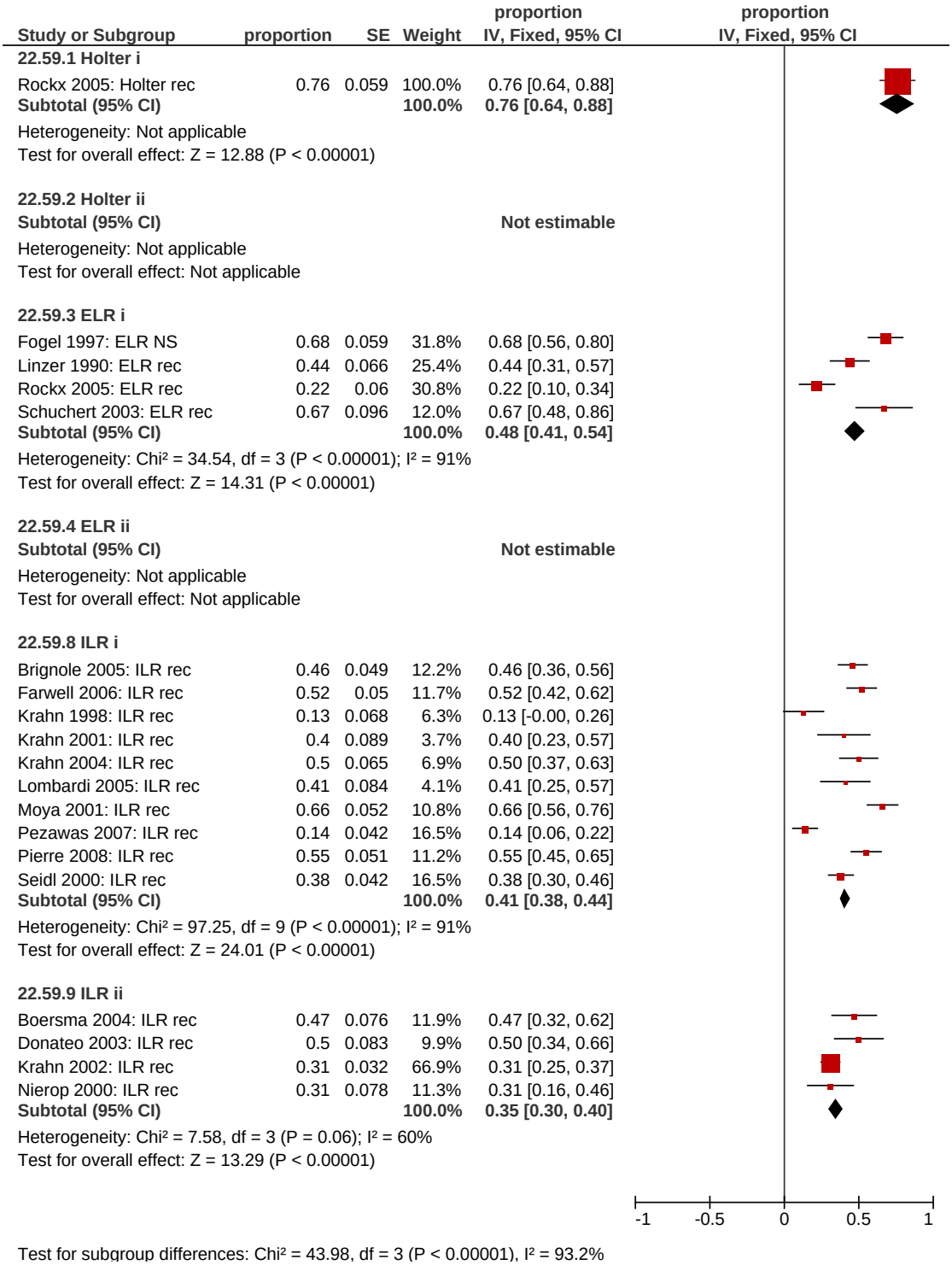
1.1 Subgroup analysis: studies for which patients were included or excluded following secondary tests

The following set of forest plots explores further the population group, unexplained following secondary tests and divides the population into two subgroups, depending on whether:

(i) patients were excluded if they had a positive result on a prior test

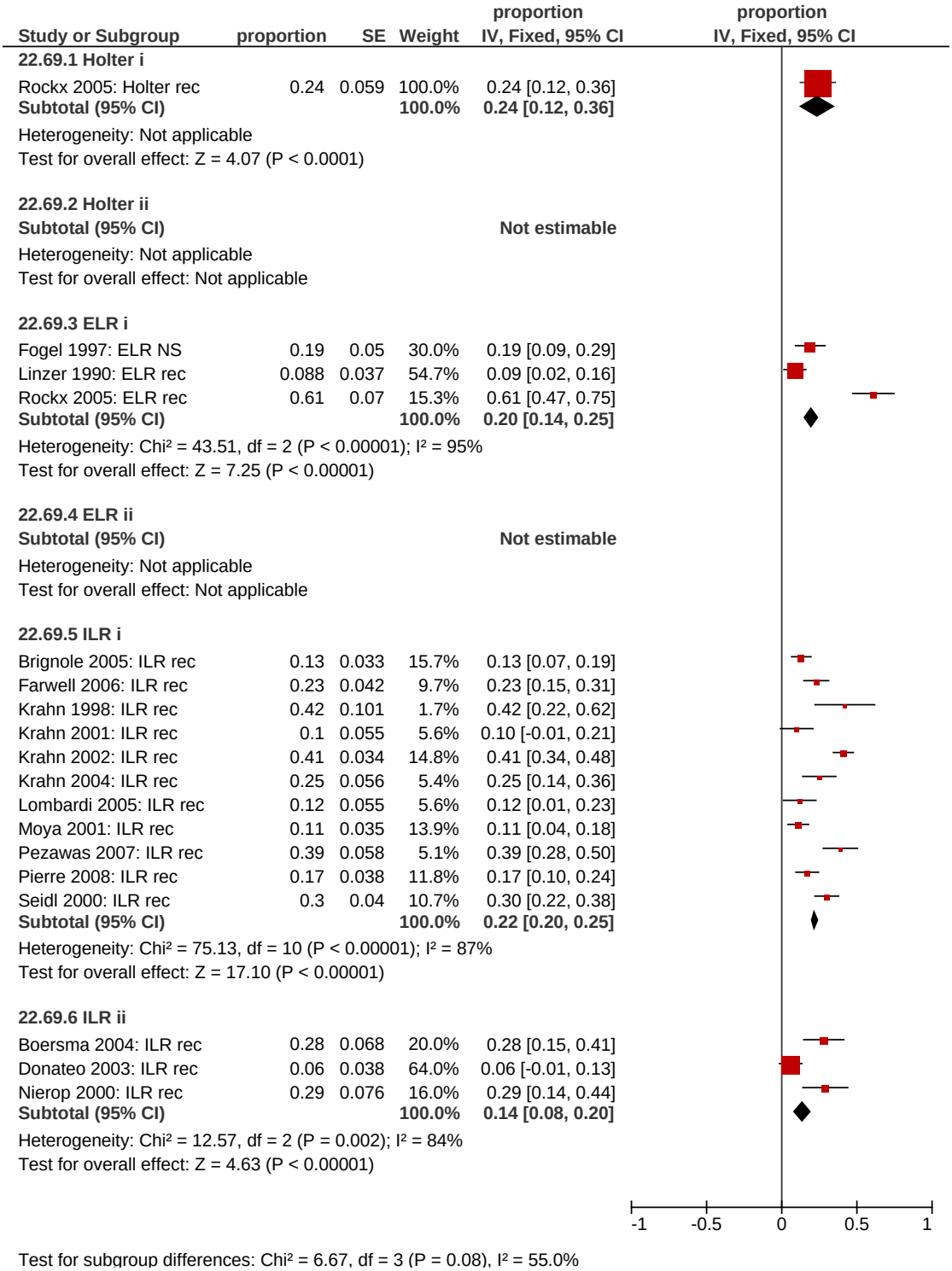
(ii) they were not excluded even if they had a positive test on a prior test

1.1.1 No TLoC during monitoring; unexplained TLoC following secondary tests



Test for subgroup differences: Chi² = 43.98, df = 3 (P < 0.00001), I² = 93.2%

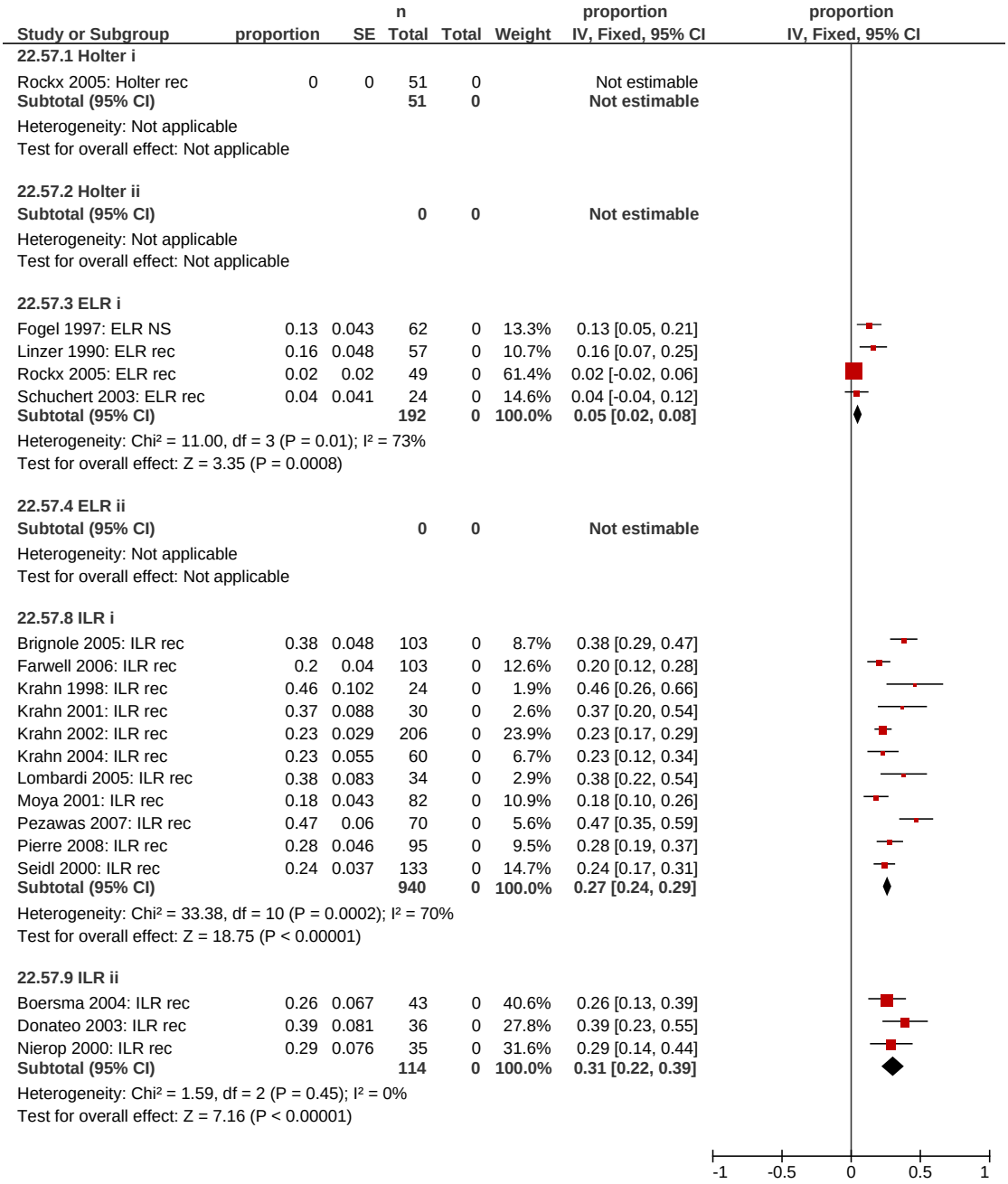
1.1.2 Normal Rhythm during TLoC; unexplained TLoC following secondary tests



Study or Subgroup	proportion	SE	Weight	proportion IV, Fixed, 95% CI
22.69.1 Holter i				
Rockx 2005: Holter rec	0.24	0.059	100.0%	0.24 [0.12, 0.36]
Subtotal (95% CI)			**100.0%**	**0.24 [0.12, 0.36]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.07 (P < 0.0001)				
22.69.2 Holter ii				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
22.69.3 ELR i				
Fogel 1997: ELR NS	0.19	0.05	30.0%	0.19 [0.09, 0.29]
Linzer 1990: ELR rec	0.088	0.037	54.7%	0.09 [0.02, 0.16]
Rockx 2005: ELR rec	0.61	0.07	15.3%	0.61 [0.47, 0.75]
Subtotal (95% CI)			**100.0%**	**0.20 [0.14, 0.25]**
Heterogeneity: Chi^2 = 43.51, df = 2 (P < 0.00001); I^2 = 95%				
Test for overall effect: Z = 7.25 (P < 0.00001)				
22.69.4 ELR ii				
Subtotal (95% CI)				**Not estimable**
Heterogeneity: Not applicable				
Test for overall effect: Not applicable				
22.69.5 ILR i				
Brignole 2005: ILR rec	0.13	0.033	15.7%	0.13 [0.07, 0.19]
Farwell 2006: ILR rec	0.23	0.042	9.7%	0.23 [0.15, 0.31]
Krahn 1998: ILR rec	0.42	0.101	1.7%	0.42 [0.22, 0.62]
Krahn 2001: ILR rec	0.1	0.055	5.6%	0.10 [-0.01, 0.21]
Krahn 2002: ILR rec	0.41	0.034	14.8%	0.41 [0.34, 0.48]
Krahn 2004: ILR rec	0.25	0.056	5.4%	0.25 [0.14, 0.36]
Lombardi 2005: ILR rec	0.12	0.055	5.6%	0.12 [0.01, 0.23]
Moya 2001: ILR rec	0.11	0.035	13.9%	0.11 [0.04, 0.18]
Pezawas 2007: ILR rec	0.39	0.058	5.1%	0.39 [0.28, 0.50]
Pierre 2008: ILR rec	0.17	0.038	11.8%	0.17 [0.10, 0.24]
Seidl 2000: ILR rec	0.3	0.04	10.7%	0.30 [0.22, 0.38]
Subtotal (95% CI)			**100.0%**	**0.22 [0.20, 0.25]**
Heterogeneity: Chi^2 = 75.13, df = 10 (P < 0.00001); I^2 = 87%				
Test for overall effect: Z = 17.10 (P < 0.00001)				
22.69.6 ILR ii				
Boersma 2004: ILR rec	0.28	0.068	20.0%	0.28 [0.15, 0.41]
Donateo 2003: ILR rec	0.06	0.038	64.0%	0.06 [-0.01, 0.13]
Nierop 2000: ILR rec	0.29	0.076	16.0%	0.29 [0.14, 0.44]
Subtotal (95% CI)			**100.0%**	**0.14 [0.08, 0.20]**
Heterogeneity: Chi^2 = 12.57, df = 2 (P = 0.002); I^2 = 84%				
Test for overall effect: Z = 4.63 (P < 0.00001)				

Test for subgroup differences: Chi^2 = 6.67, df = 3 (P = 0.08), I^2 = 55.0%

1.1.3 Arrhythmia during TLoC; unexplained TLoC following secondary tests



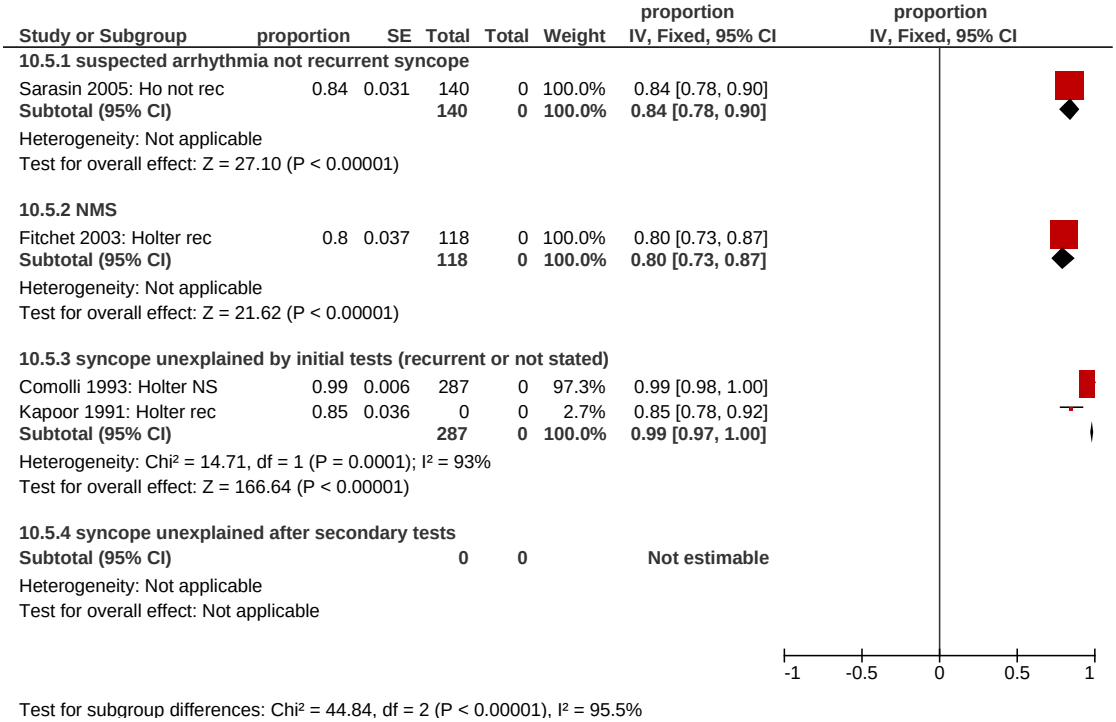
Test for subgroup differences: Chi² = 111.54, df = 2 (P < 0.00001), I² = 98.2%

1.2 Ambulatory ECG – results for each type of test, by population

The following set of forest plots show the results for each test and each outcome, by population group.

1.2.1 Holter 24-hour monitoring

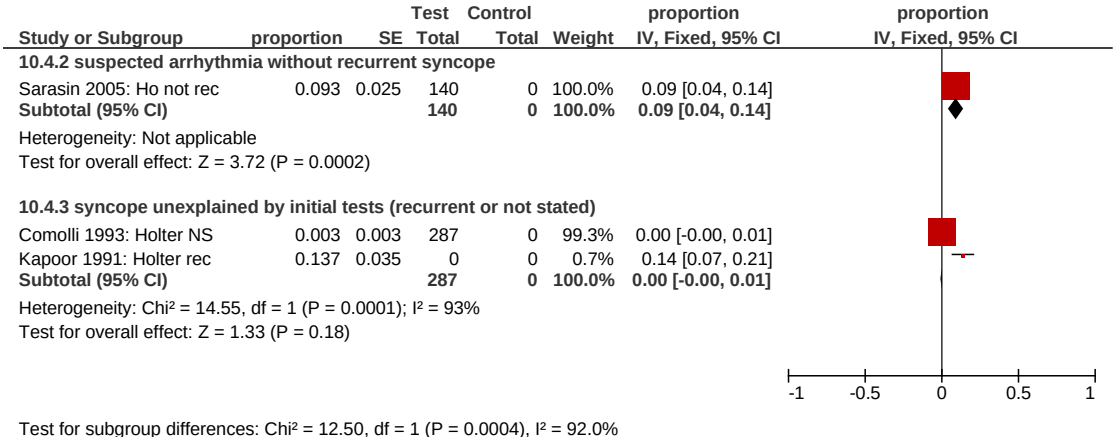
1.2.1.1 No TLoC during monitoring



Test for subgroup differences: Chi² = 44.84, df = 2 (P < 0.00001), I² = 95.5%

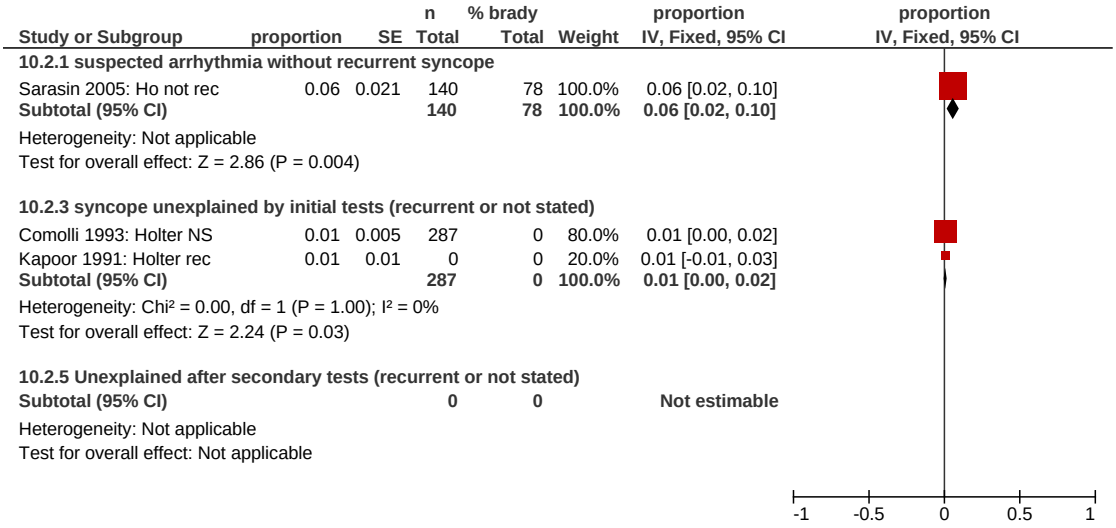
1.2.1.2 Normal rhythm during TLoC

No NM syncope patients had Holter monitoring and reported this outcome



Test for subgroup differences: Chi² = 12.50, df = 1 (P = 0.0004), I² = 92.0%

1.2.1.3 Arrhythmia during TLoC

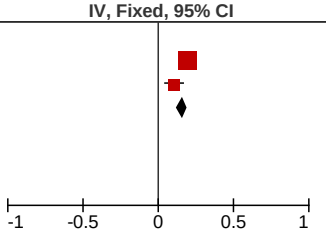


Test for subgroup differences: Chi² = 5.42, df = 1 (P = 0.02), I² = 81.6%

1.2.1.4 Arrhythmia not during TLoC

Study or Subgroup	proportion	SE	n Total	% brady Total	Weight	proportion IV, Fixed, 95% CI
10.3.3 patients with syncope unexplained by initial tests (recurrent or not stated)						
Comolli 1993: Holter NS	0.192	0.023	287	58	64.5%	0.19 [0.15, 0.24]
Kapoor 1991: Holter rec	0.105	0.031	95	0	35.5%	0.10 [0.04, 0.17]
Subtotal (95% CI)			**382**	**58**	**100.0%**	**0.16 [0.12, 0.20]**

Heterogeneity: Chi² = 5.08, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 8.72 (P < 0.00001)

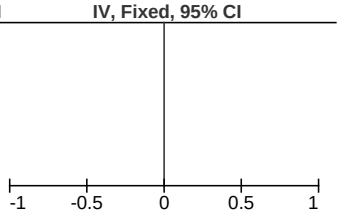


Test for subgroup differences: Not applicable

1.2.1.5 No ECG during TLoC

Study or Subgroup	proportion	SE	Test Total	Control Total	Weight	proportion IV, Fixed, 95% CI
10.6.3 syncope unexplained by initial tests (recurrent or not stated)						
Comolli 1993: Holter NS	0	0	287	0		Not estimable
Subtotal (95% CI)			**287**	**0**		**Not estimable**

Heterogeneity: Not applicable
Test for overall effect: Not applicable



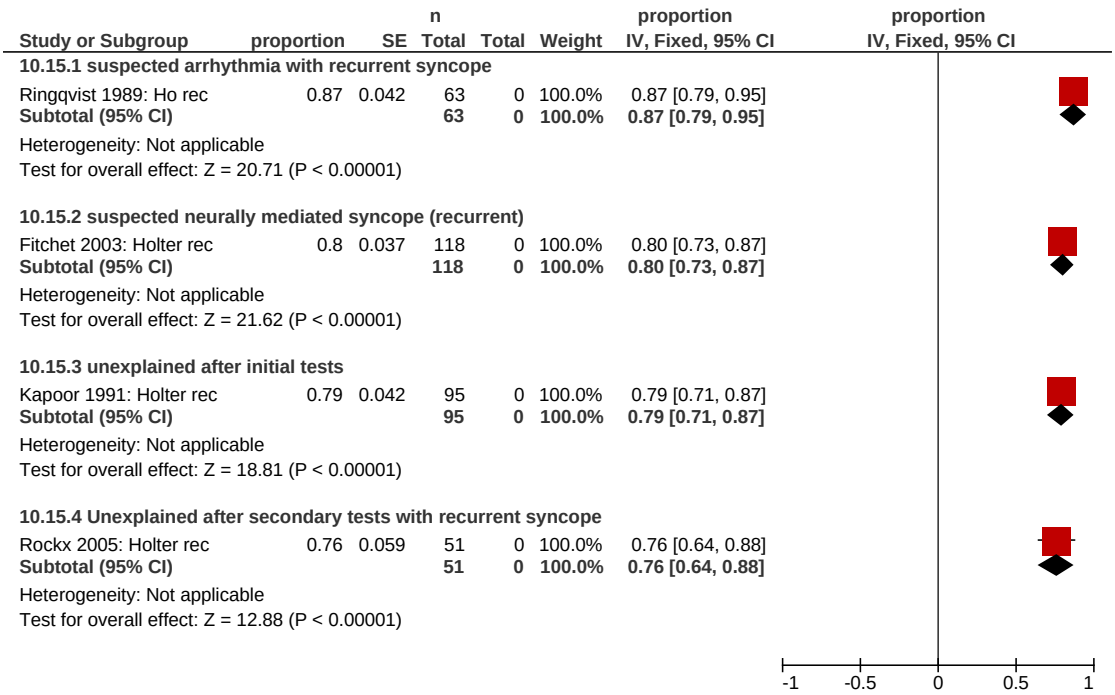
Test for subgroup differences: Not applicable

1.2.1.6 Adverse events

No studies reported this outcome

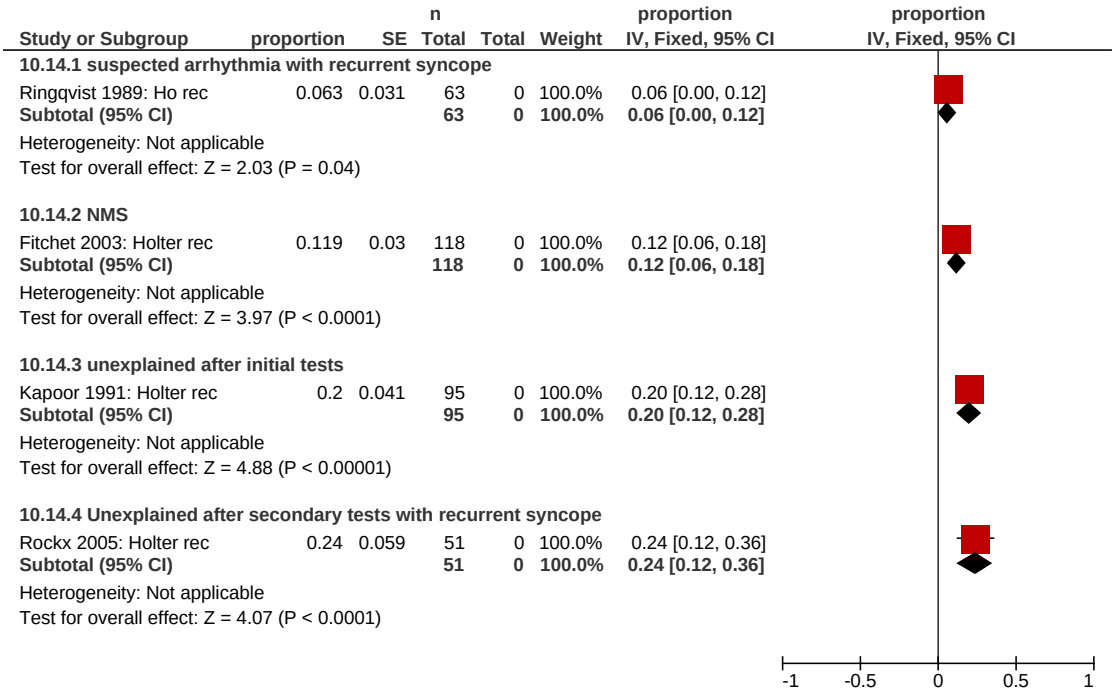
1.2.2 48-hour Holter monitoring or longer

1.2.2.1 No TLoC during recording period



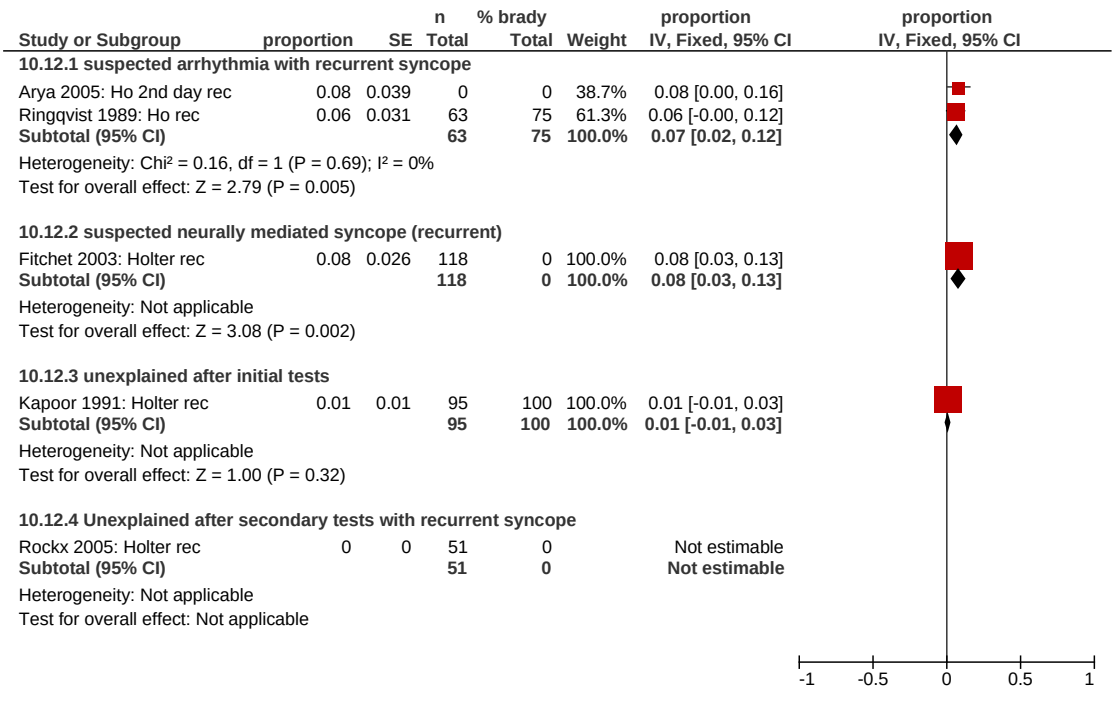
Test for subgroup differences: Chi² = 3.06, df = 3 (P = 0.38), I² = 1.9%

1.2.2.2 Normal rhythm during TLoC



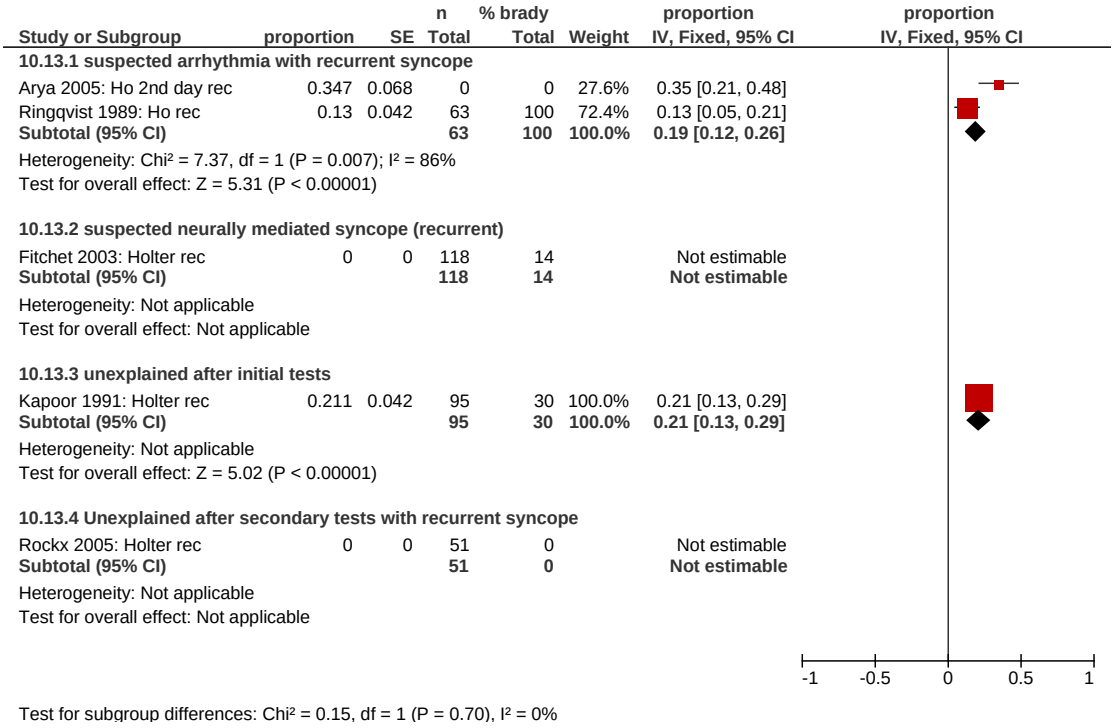
Test for subgroup differences: Chi² = 11.17, df = 3 (P = 0.01), I² = 73.1%

1.2.2.3 Arrhythmia during TLoC



Test for subgroup differences: Chi² = 9.83, df = 2 (P = 0.007), I² = 79.6%

1.2.2.4 Arrhythmia not during TLoC



1.2.2.5 No ECG during TLoC

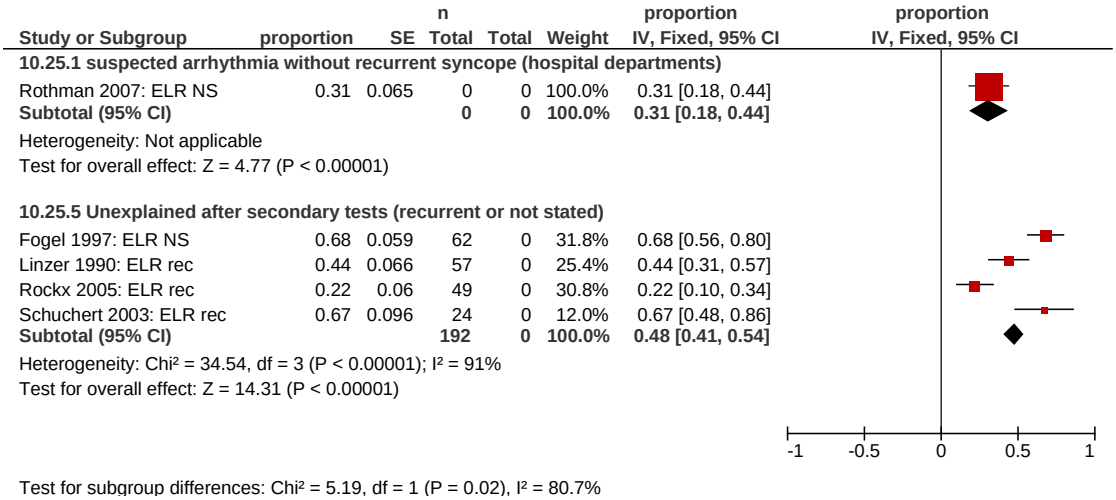
No studies reported this outcome.

1.2.2.6 Adverse events

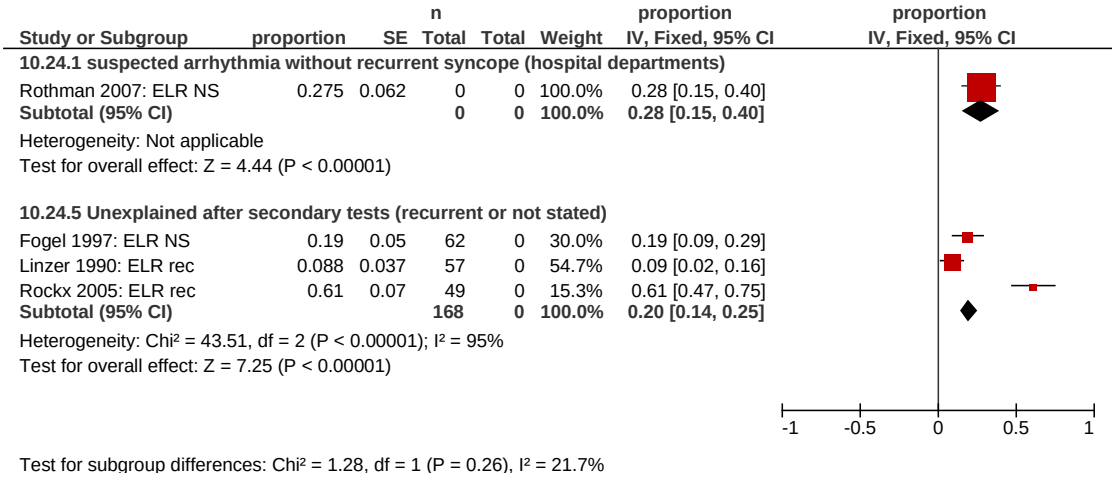
No studies reported this outcome.

1.2.3 External event recorder

1.2.3.1 No TLoC during recording period

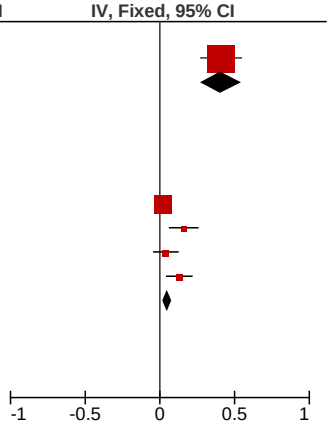


1.2.3.2 Normal rhythm during TLoC



1.2.3.3 Arrhythmia during TLoC

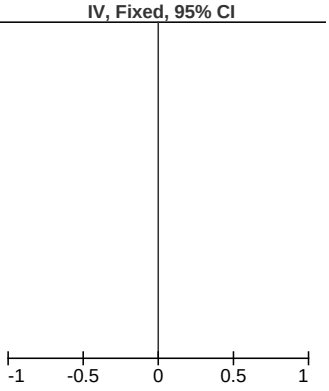
Study or Subgroup	proportion	SE	n Total	% brady Total	Weight	proportion IV, Fixed, 95% CI
10.22.1 suspected arrhythmia without recurrent syncope (hospital departments)						
Rothman 2007: ELR NS	0.41	0.069	0	0	100.0%	0.41 [0.27, 0.55]
Subtotal (95% CI)			**0**	**0**	**100.0%**	**0.41 [0.27, 0.55]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 5.94 (P < 0.00001)						
10.22.5 Unexplained after secondary tests (recurrent or not stated)						
Rockx 2005: ELR rec	0.02	0.02	49	100	61.4%	0.02 [-0.02, 0.06]
Linzer 1990: ELR rec	0.16	0.048	57	71	10.7%	0.16 [0.07, 0.25]
Schuchert 2003: ELR rec	0.04	0.041	24	69	14.6%	0.04 [-0.04, 0.12]
Fogel 1997: ELR NS	0.13	0.043	62	0	13.3%	0.13 [0.05, 0.21]
Subtotal (95% CI)			**192**	**240**	**100.0%**	**0.05 [0.02, 0.08]**
Heterogeneity: Chi² = 11.00, df = 3 (P = 0.01); I² = 73%						
Test for overall effect: Z = 3.35 (P = 0.0008)						



Test for subgroup differences: Chi² = 25.53, df = 1 (P < 0.00001), I² = 96.1%

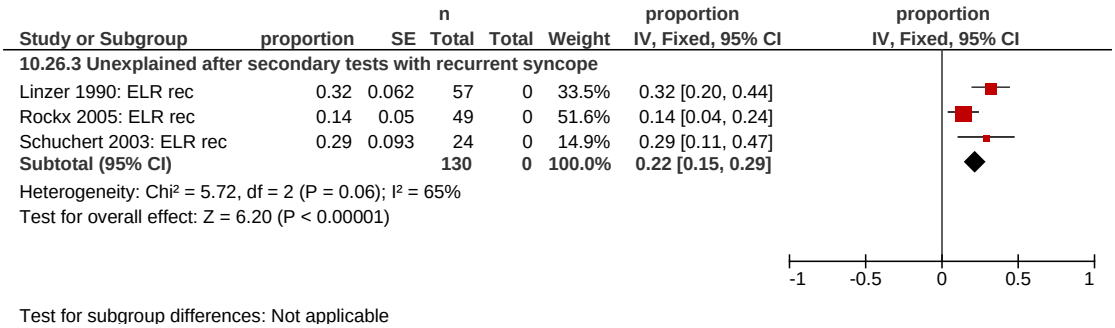
1.2.3.4 Arrhythmia not during TLoC

Study or Subgroup	proportion	SE	n Total	% brady Total	Weight	proportion IV, Fixed, 95% CI
10.23.1 suspected arrhythmia without recurrent syncope (hospital departments)						
Rothman 2007: ELR NS	0	0	52	0		Not estimable
Subtotal (95% CI)			**52**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.23.3 Unexplained after secondary tests with recurrent syncope						
Rockx 2005: ELR rec	0	0	49	0		Not estimable
Schuchert 2003: ELR rec	0	0	24	0		Not estimable
Subtotal (95% CI)			**73**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Test for subgroup differences: Not applicable

1.2.3.5 No ECG during TLoC

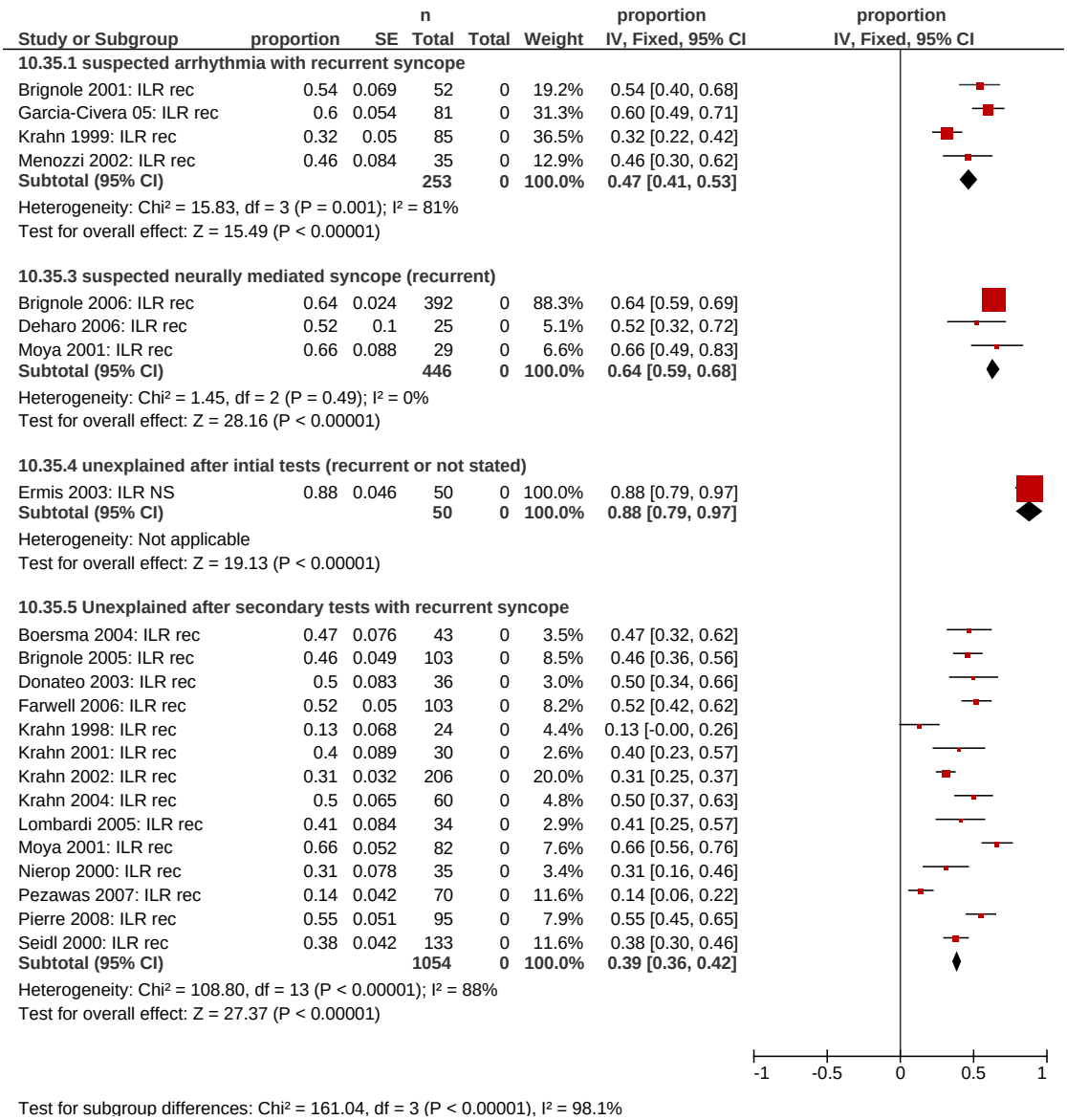


1.2.3.6 Adverse events

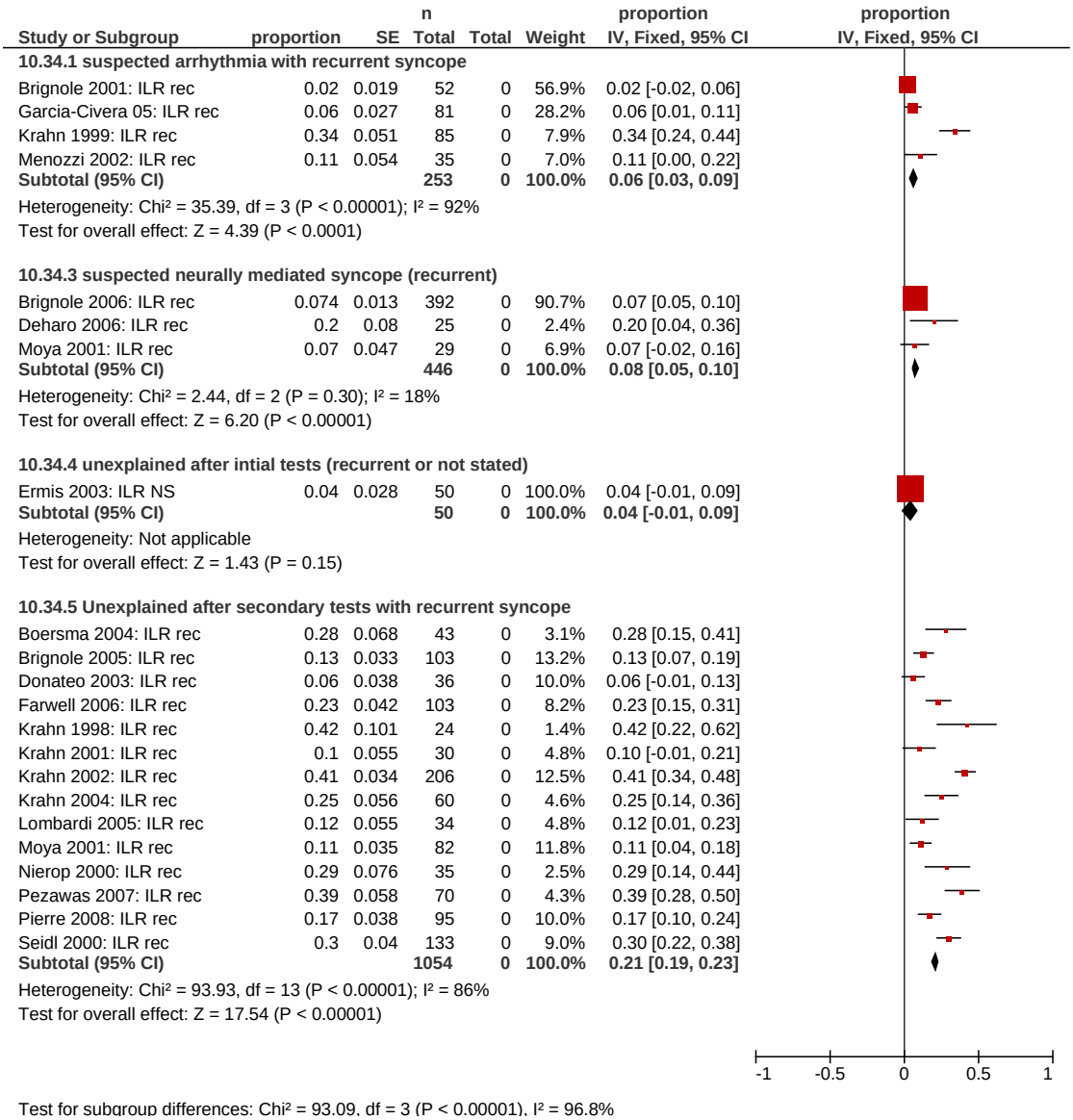
No studies reported this outcome.

1.2.4 Implantable Event Recorder

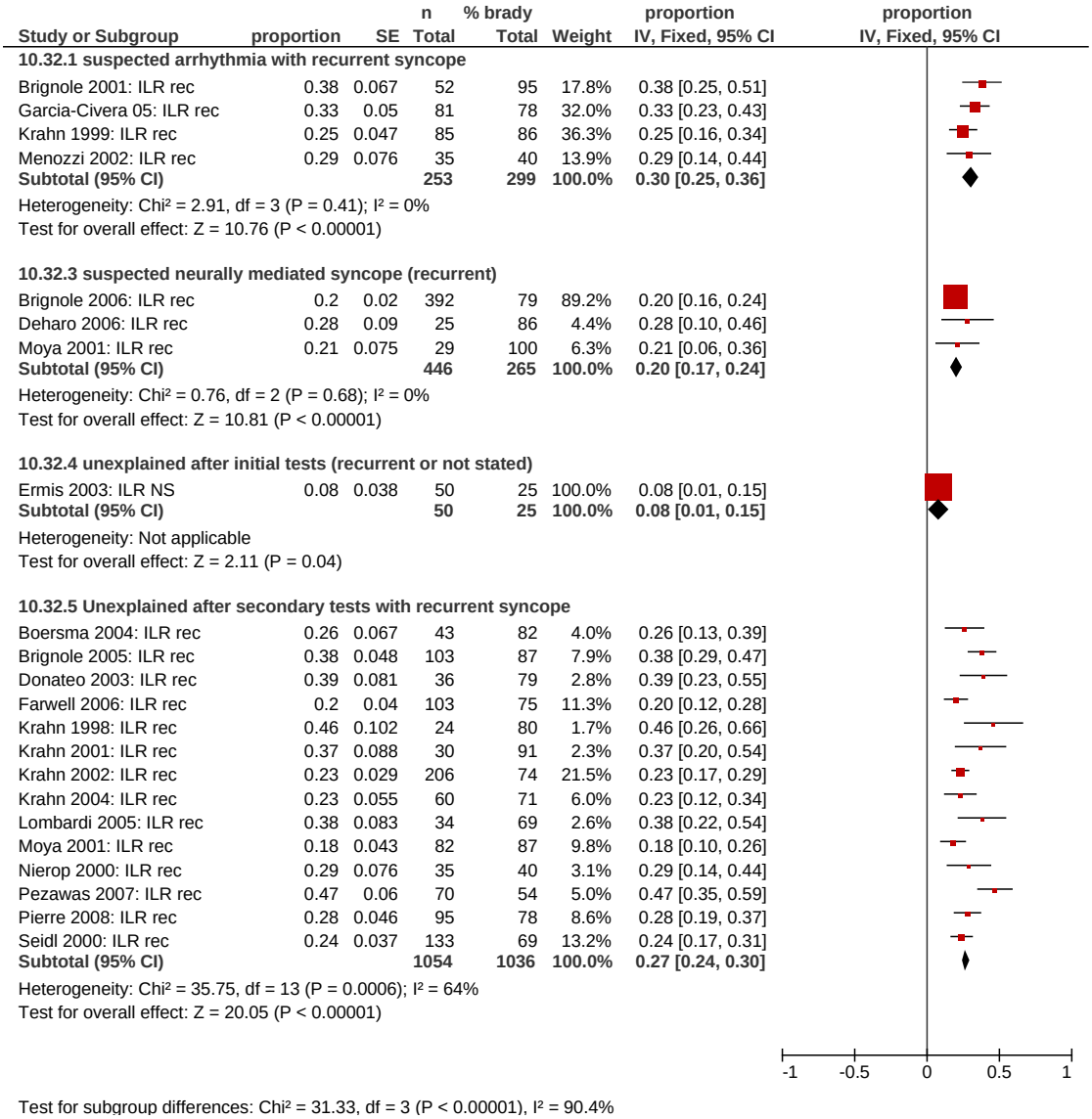
1.2.4.1 No TLoC during recording period



1.2.4.2 Normal rhythm during TLoC



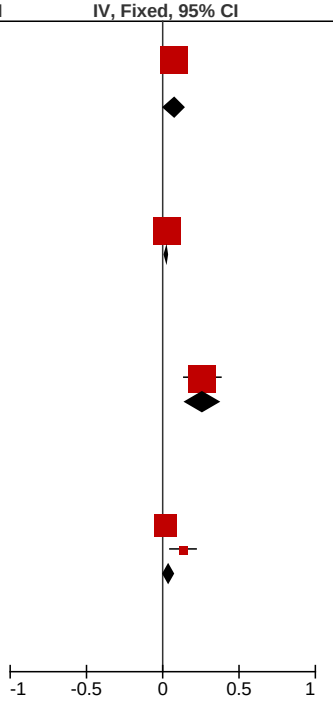
1.2.4.3 Arrhythmia during TLoC



Test for subgroup differences: Chi² = 31.33, df = 3 (P < 0.00001), I² = 90.4%

1.2.4.4 Arrhythmia not during TLoC

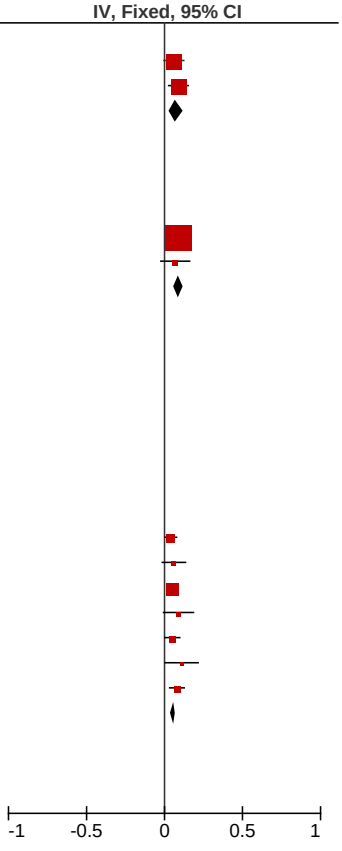
Study or Subgroup	proportion	SE	n Total	% brady Total	Weight	proportion IV, Fixed, 95% CI
10.33.1 suspected arrhythmia with recurrent syncope						
Brignole 2001: ILR rec	0.077	0.037	52	100	100.0%	0.08 [0.00, 0.15]
Menozzi 2002: ILR rec	0	0	35	40		Not estimable
Subtotal (95% CI)			**87**	**140**	**100.0%**	**0.08 [0.00, 0.15]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.08 (P = 0.04)						
10.33.2 suspected neurally mediated syncope (recurrent)						
Brignole 2006: ILR rec	0.028	0.008	392	100	100.0%	0.03 [0.01, 0.04]
Subtotal (95% CI)			**392**	**100**	**100.0%**	**0.03 [0.01, 0.04]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.50 (P = 0.0005)						
10.33.3 unexplained after intial tests (recurrent or not stated)						
Ermis 2003: ILR NS	0.26	0.062	50	0	100.0%	0.26 [0.14, 0.38]
Subtotal (95% CI)			**50**	**0**	**100.0%**	**0.26 [0.14, 0.38]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.19 (P < 0.0001)						
10.33.4 Unexplained after secondary tests with recurrent syncope						
Boersma 2004: ILR rec	0.02	0.023	43	100	78.5%	0.02 [-0.03, 0.07]
Krahn 2004: ILR rec	0.133	0.044	60	88	21.5%	0.13 [0.05, 0.22]
Subtotal (95% CI)			**103**	**188**	**100.0%**	**0.04 [0.00, 0.08]**
Heterogeneity: Chi² = 5.18, df = 1 (P = 0.02); I² = 81%						
Test for overall effect: Z = 2.17 (P = 0.03)						



Test for subgroup differences: Chi² = 15.43, df = 3 (P = 0.001), I² = 80.6%

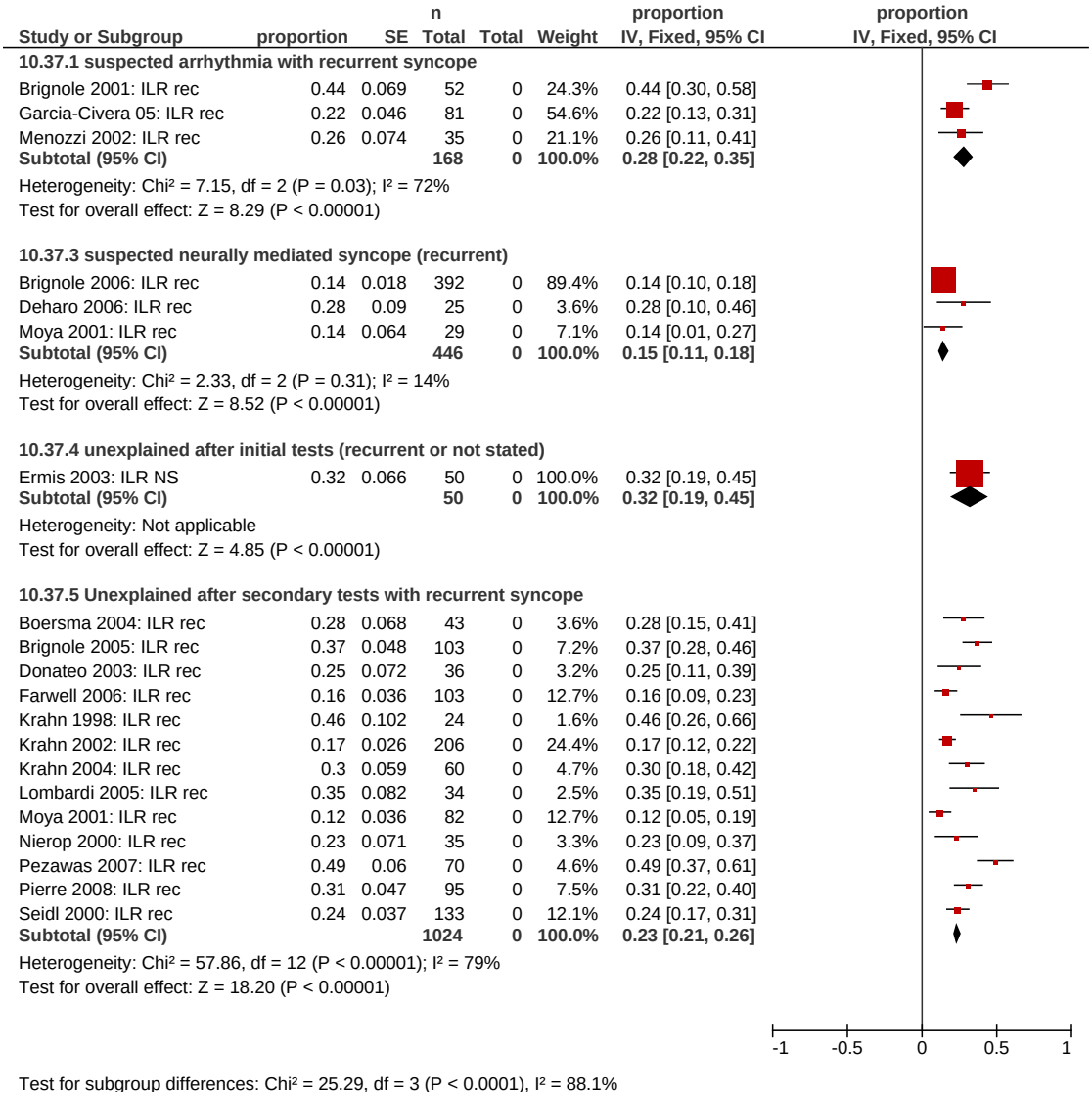
1.2.4.5 No ECG during TLoC

Study or Subgroup	proportion	SE	n Total	Total	Weight	proportion IV, Fixed, 95% CI
10.36.1 suspected arrhythmia with recurrent syncope						
Brignole 2001: ILR rec	0.06	0.032	52	0	50.0%	0.06 [-0.00, 0.12]
Krahn 1999: ILR rec	0.09	0.032	85	0	50.0%	0.09 [0.03, 0.15]
Subtotal (95% CI)			**137**	**0**	**100.0%**	**0.07 [0.03, 0.12]**
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
10.36.2 suspected neurally mediated syncope (recurrent)						
Brignole 2006: ILR rec	0.09	0.015	392	0	90.8%	0.09 [0.06, 0.12]
Moya 2001: ILR rec	0.069	0.047	29	0	9.2%	0.07 [-0.02, 0.16]
Subtotal (95% CI)			**421**	**0**	**100.0%**	**0.09 [0.06, 0.12]**
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%						
Test for overall effect: Z = 6.16 (P < 0.00001)						
10.36.3 unexplained after intial tests (recurrent or not stated)						
Subtotal (95% CI)			**0**	**0**		**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.36.4 Unexplained after secondary tests with recurrent syncope						
Brignole 2005: ILR rec	0.04	0.019	103	0	22.8%	0.04 [0.00, 0.08]
Donateo 2003: ILR rec	0.06	0.038	36	0	5.7%	0.06 [-0.01, 0.13]
Krahn 2002: ILR rec	0.05	0.015	206	0	36.6%	0.05 [0.02, 0.08]
Lombardi 2005: ILR rec	0.09	0.049	34	0	3.4%	0.09 [-0.01, 0.19]
Moya 2001: ILR rec	0.05	0.024	82	0	14.3%	0.05 [0.00, 0.10]
Nierop 2000: ILR rec	0.11	0.054	35	0	2.8%	0.11 [0.00, 0.22]
Seidl 2000: ILR rec	0.08	0.024	133	0	14.3%	0.08 [0.03, 0.13]
Subtotal (95% CI)			**629**	**0**	**100.0%**	**0.06 [0.04, 0.07]**
Heterogeneity: Chi² = 3.42, df = 6 (P = 0.75); I² = 0%						
Test for overall effect: Z = 6.13 (P < 0.00001)						



Test for subgroup differences: Chi² = 3.84, df = 2 (P = 0.15), I² = 47.9%

1.2.4.6 Number of patients started on therapy

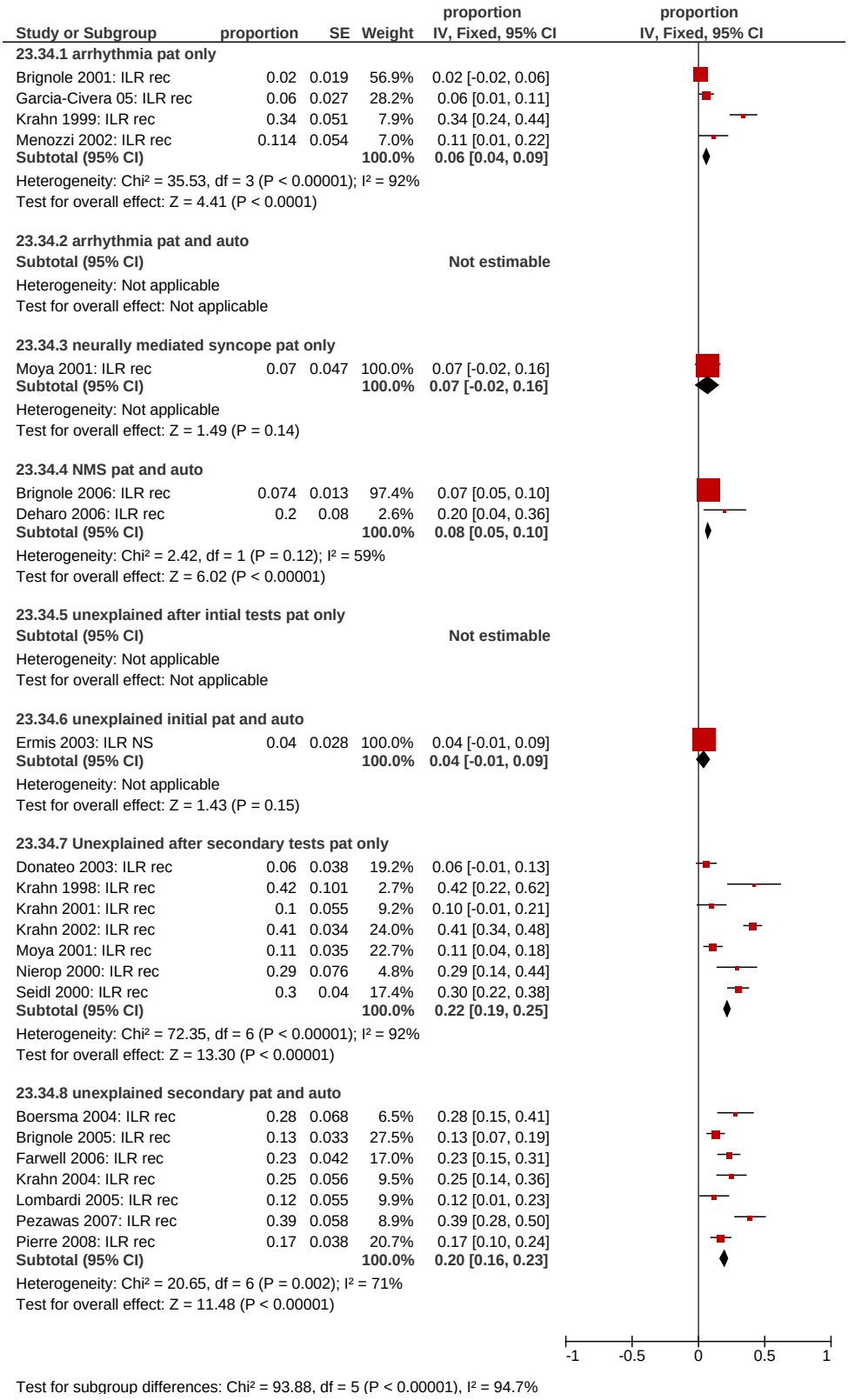


1.2.4.7 Adverse events

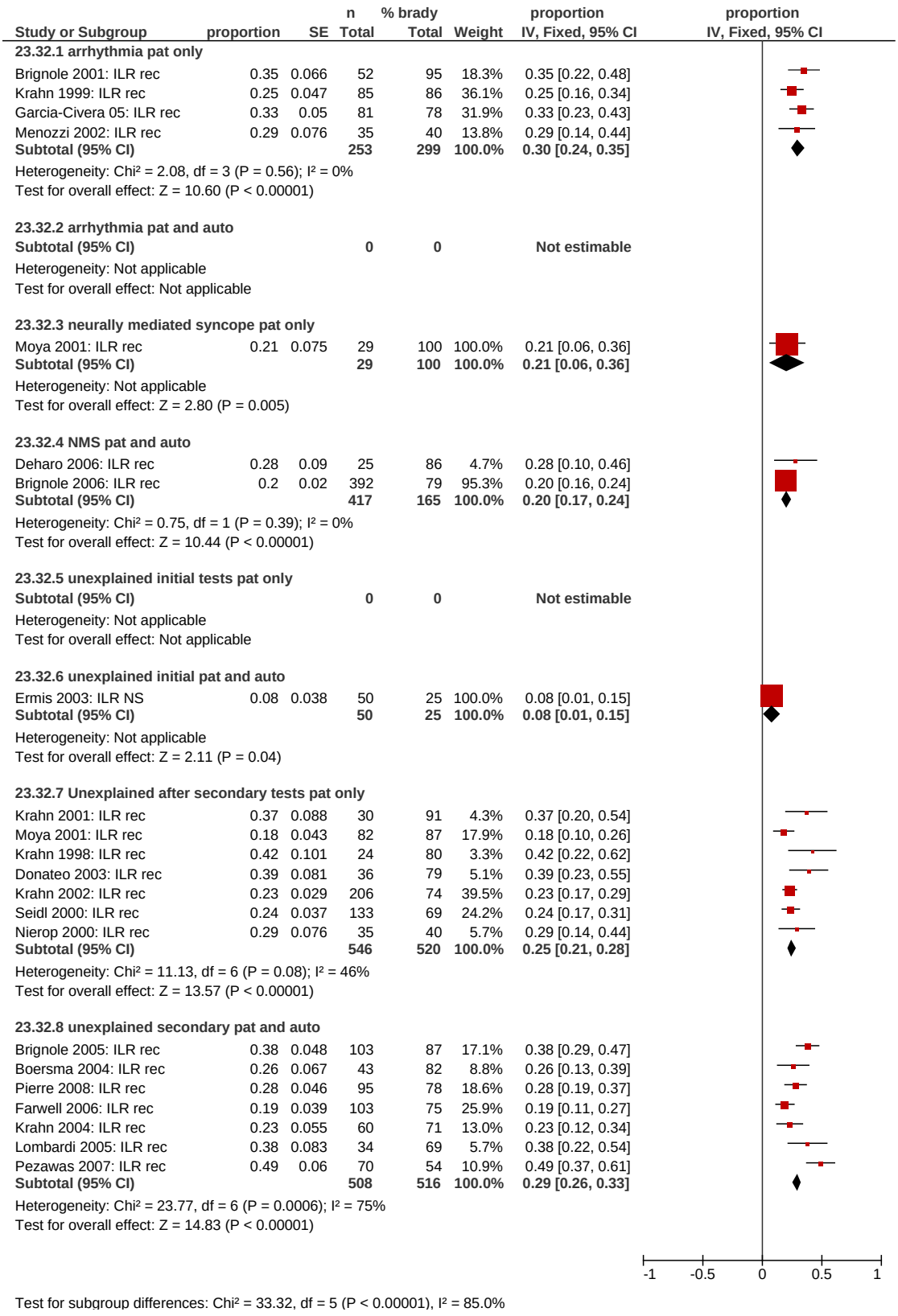
No studies reported this outcome.

1.3 Implantable Event Recorder only: subgroup analyses by patient or patient + automatic activation

1.3.1 Normal rhythm during TLoC

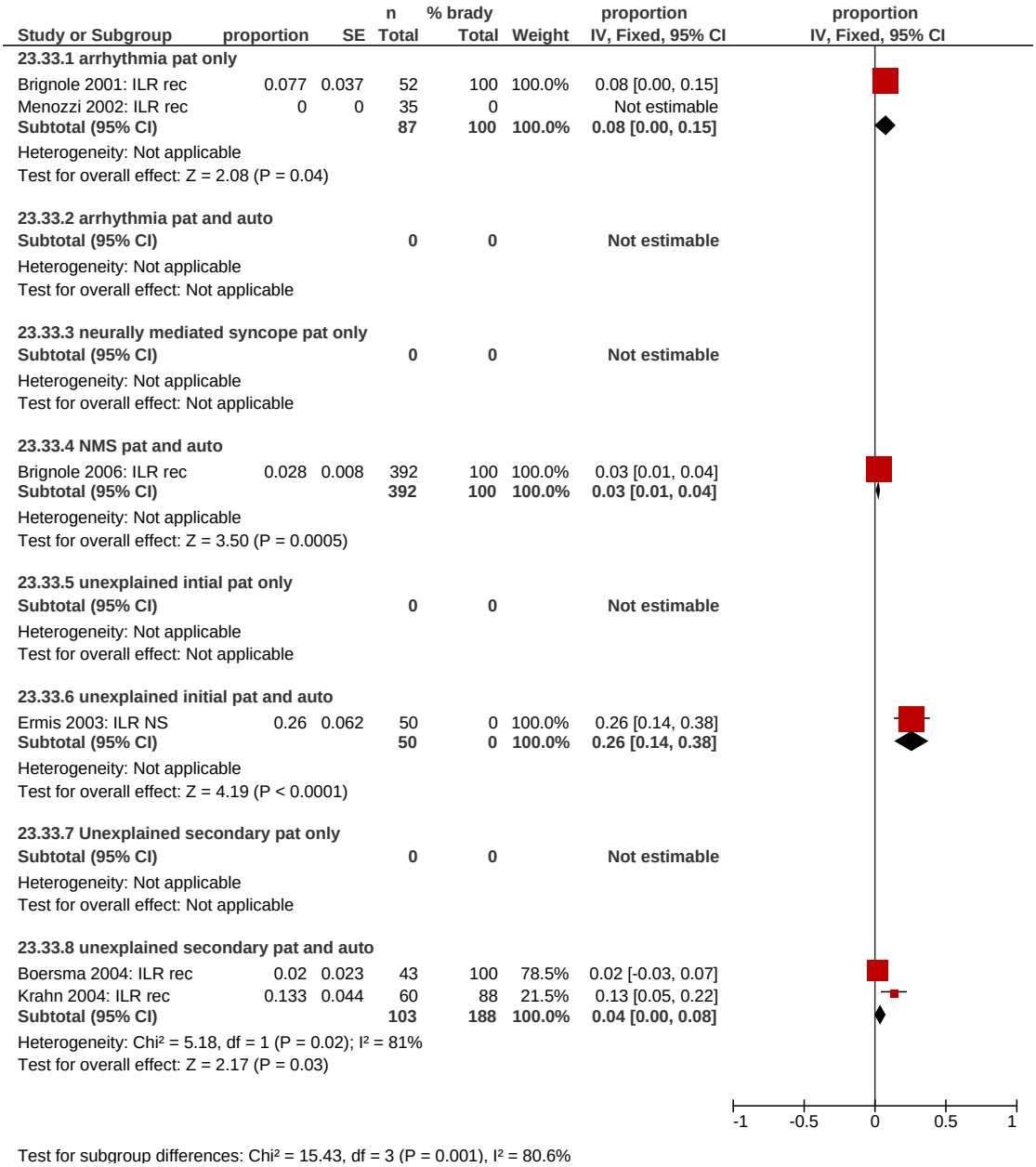


1.3.2 Arrhythmia during TLoC



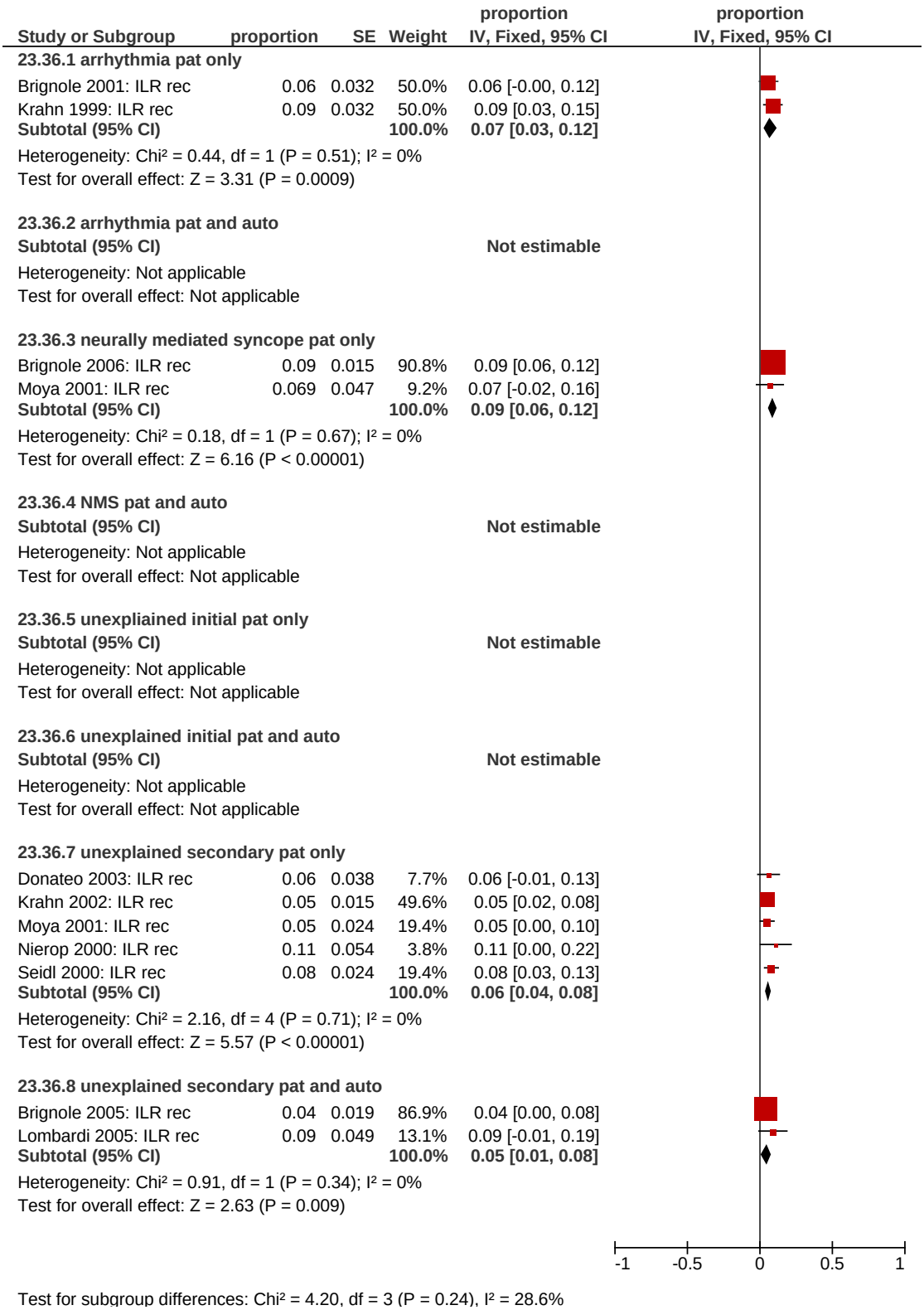
Test for subgroup differences: Chi² = 33.32, df = 5 (P < 0.00001), I² = 85.0%

1.3.3 Arrhythmia not during TLoC



Test for subgroup differences: Chi² = 15.43, df = 3 (P = 0.001), I² = 80.6%

1.3.4 No ECG during TLoC



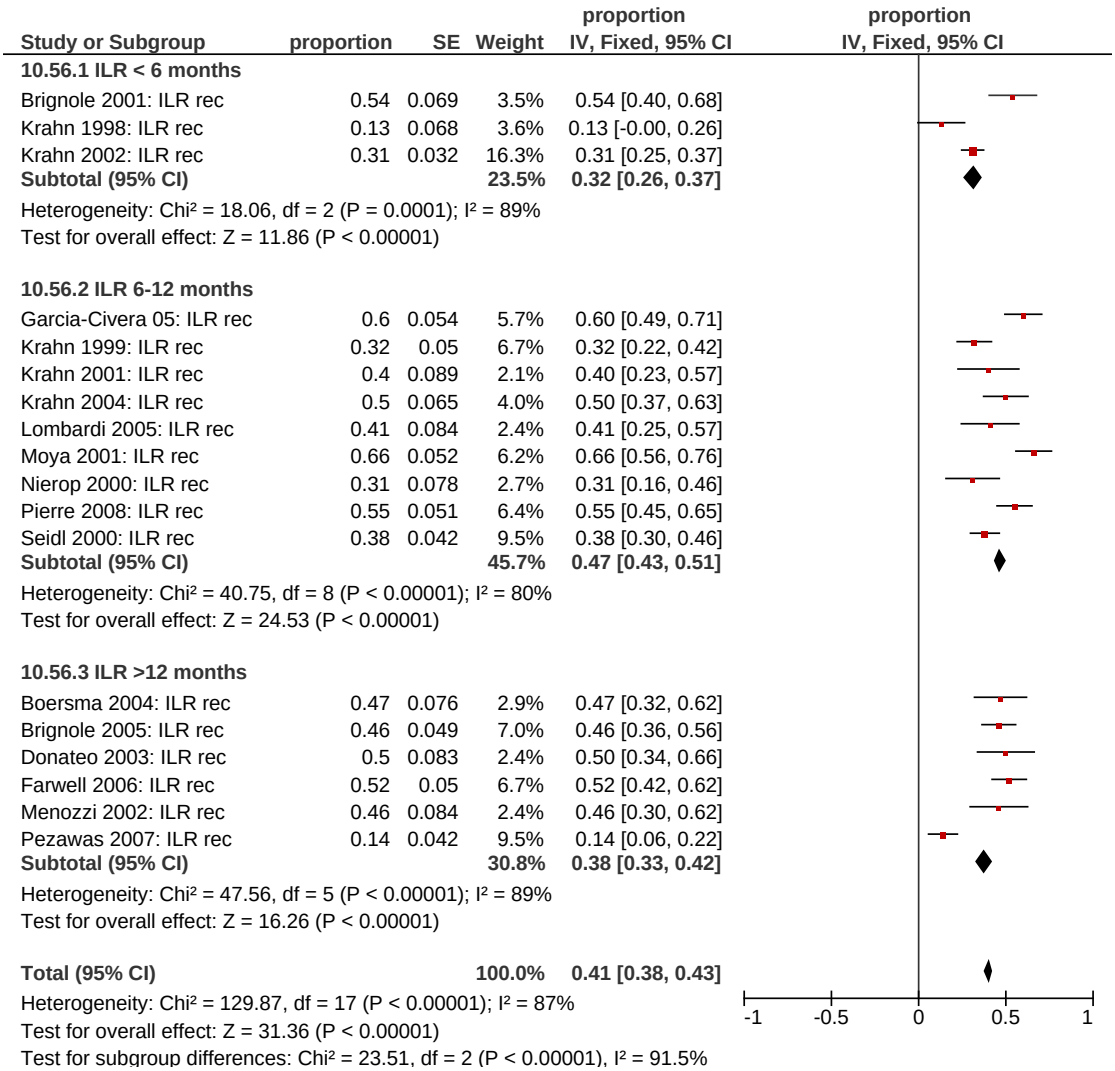
Test for subgroup differences: Chi² = 4.20, df = 3 (P = 0.24), I² = 28.6%

1.4 Implantable Event Recorder results only: subgroup analyses by duration, frequency and their product

For these subgroup analyses, the populations, suspected arrhythmic syncope and unexplained after secondary tests, were combined. This is reported for the outcome, no TLoC during monitoring.

1.4.1 Subgroup analysis by duration for IER: populations combined

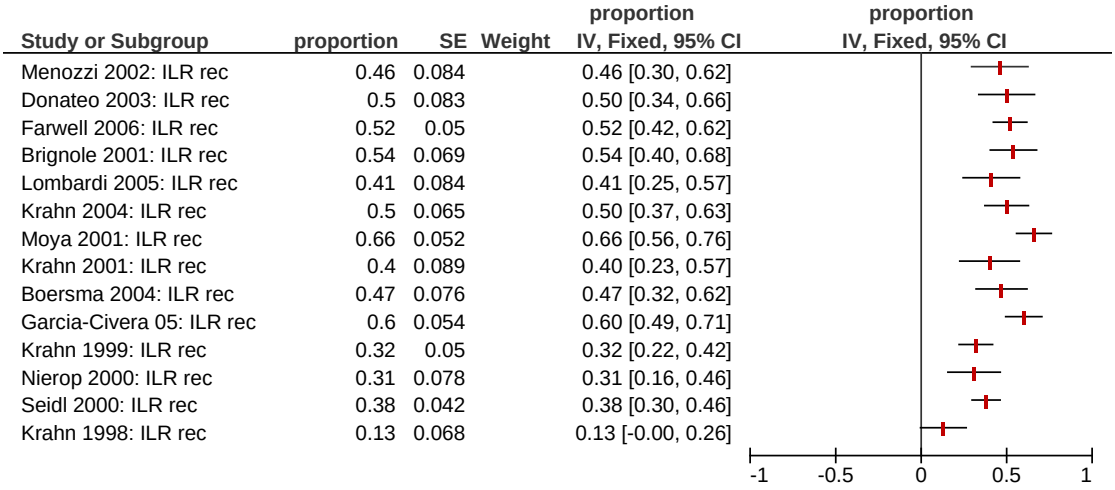
Subgroup analysis was carried out for the pre-specified durations, but this did not explain the heterogeneity.



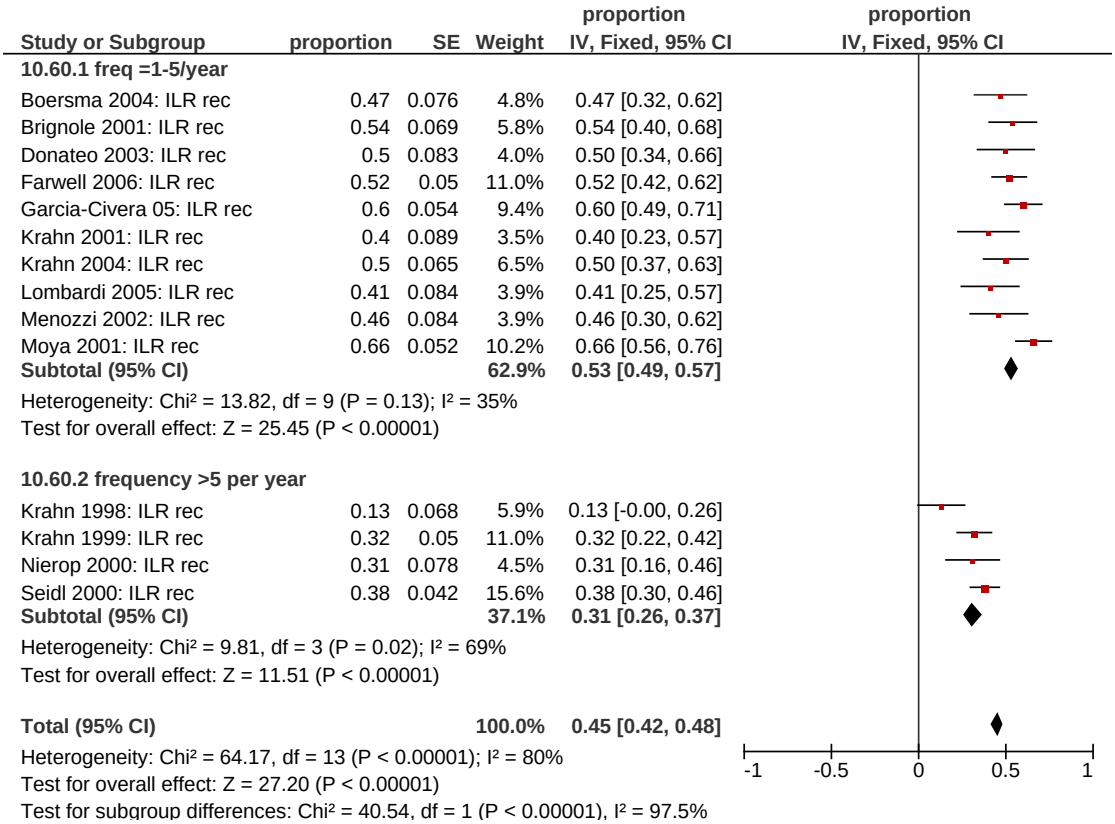
1.4.2 Subgroup analysis by frequency for IER: populations combined

The GDG had pre-specified separating the studies into highly frequent, frequent and infrequent, but all the studies for IER fell into the infrequent category. Firstly, we carried out an analysis, ordering the studies by frequency of previous TLoC and then carried out a post-hoc subgroup analysis, splitting the studies into three categories, 1 to 5 events per year, 5 to 10 and more than 10 events per year. There is some indication that the frequency is important and reduces the heterogeneity.

1.4.2.1 No TLoC during monitoring, IER, studies ordered by frequency



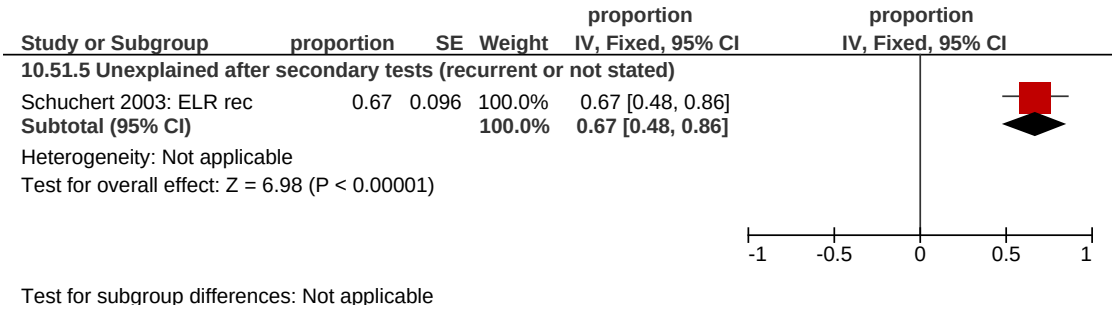
1.4.2.2 Post hoc subgroup analysis by frequency of TLoC



1.4.3 Sensitivity analysis taking into consideration frequency of previous TLoC – IER and EER

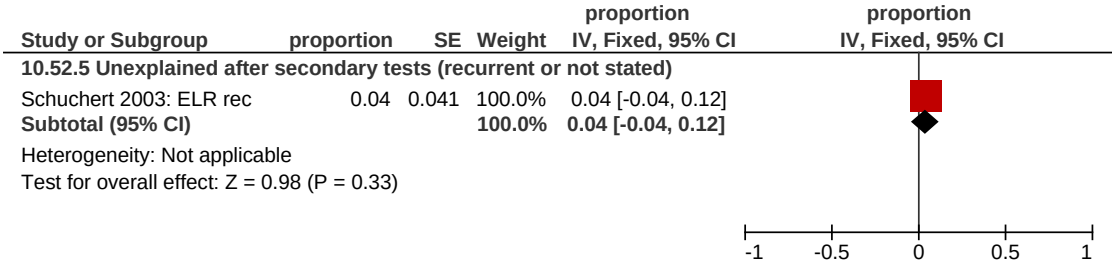
All the studies that reported the frequency of previous TLoC fall into the 'infrequent' category (i.e. less than 24 events per year). We carried out a sensitivity analysis, including only the studies that reported more than 5 events per year, this restricts the analyses to the following studies: Boersma (2004), Deharo (2006), Krahn (1999), Nierop (2000), Schuchert (2003) and Seidl (2000).

1.4.3.1 External event recorder: no TLoC during monitoring



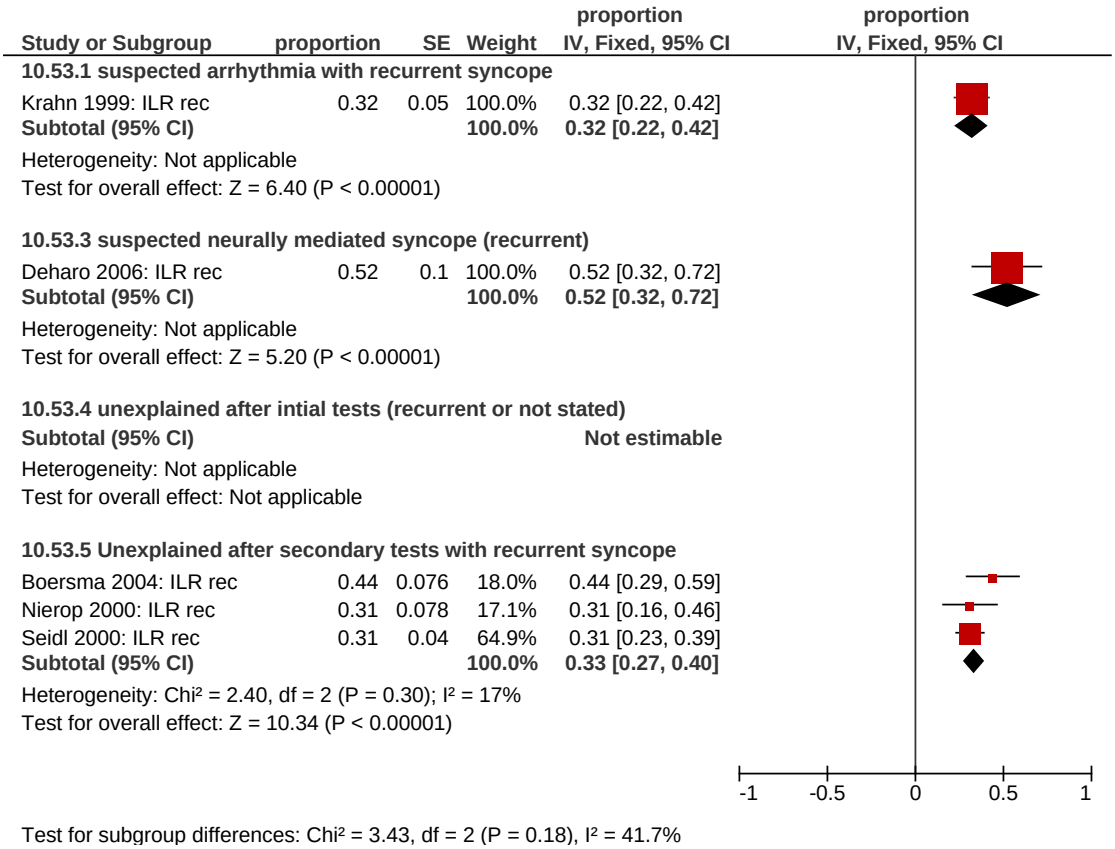
Test for subgroup differences: Not applicable

1.4.3.2 External event recorder: arrhythmia during TLoC



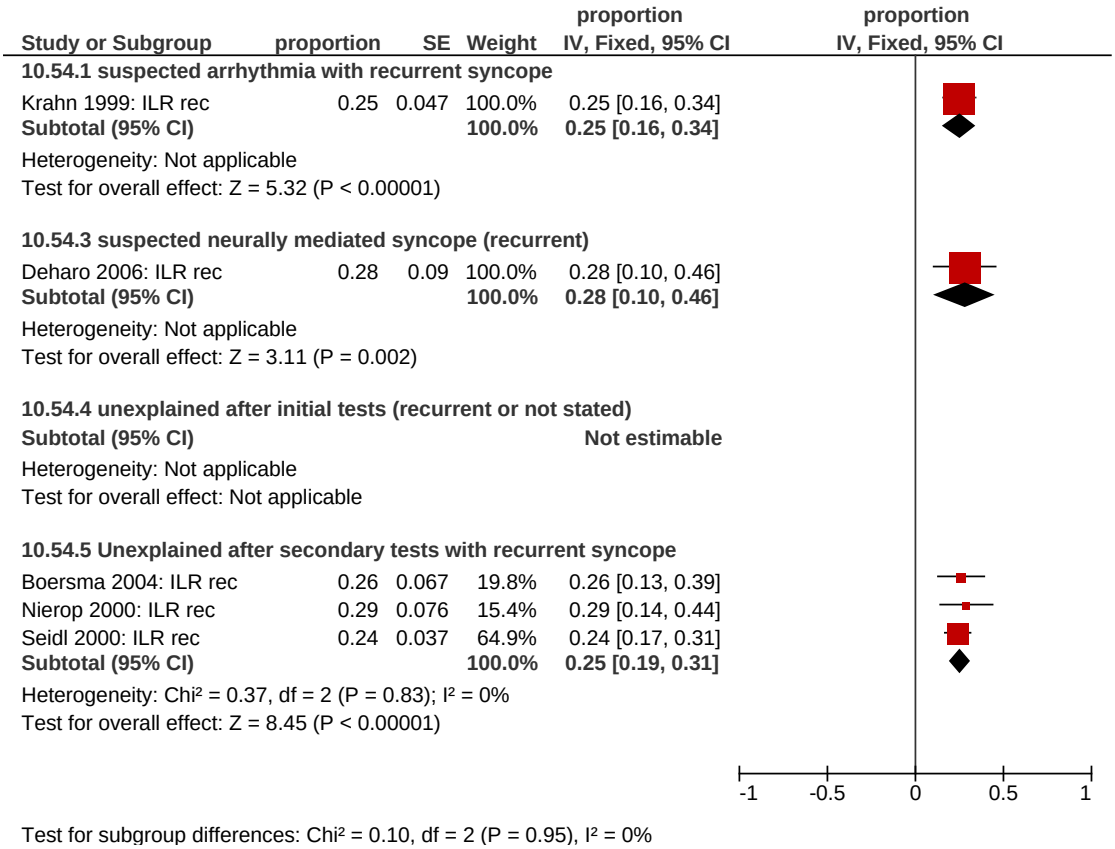
Test for subgroup differences: Not applicable

1.4.3.3 Implantable event recorder: no TLoC during monitoring



Test for subgroup differences: Chi² = 3.43, df = 2 (P = 0.18), I² = 41.7%

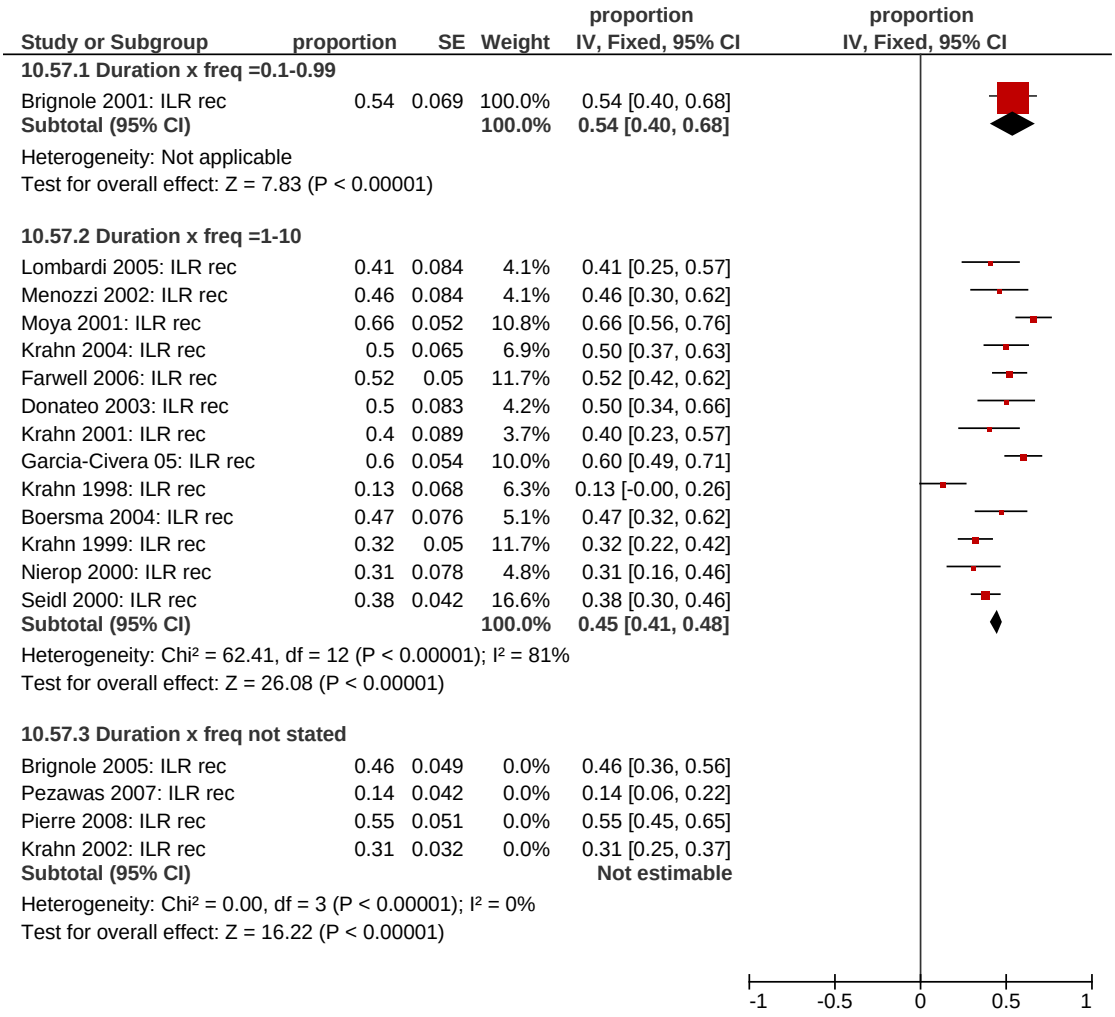
1.4.3.4 Implantable event recorder: Arrhythmia during TLoC



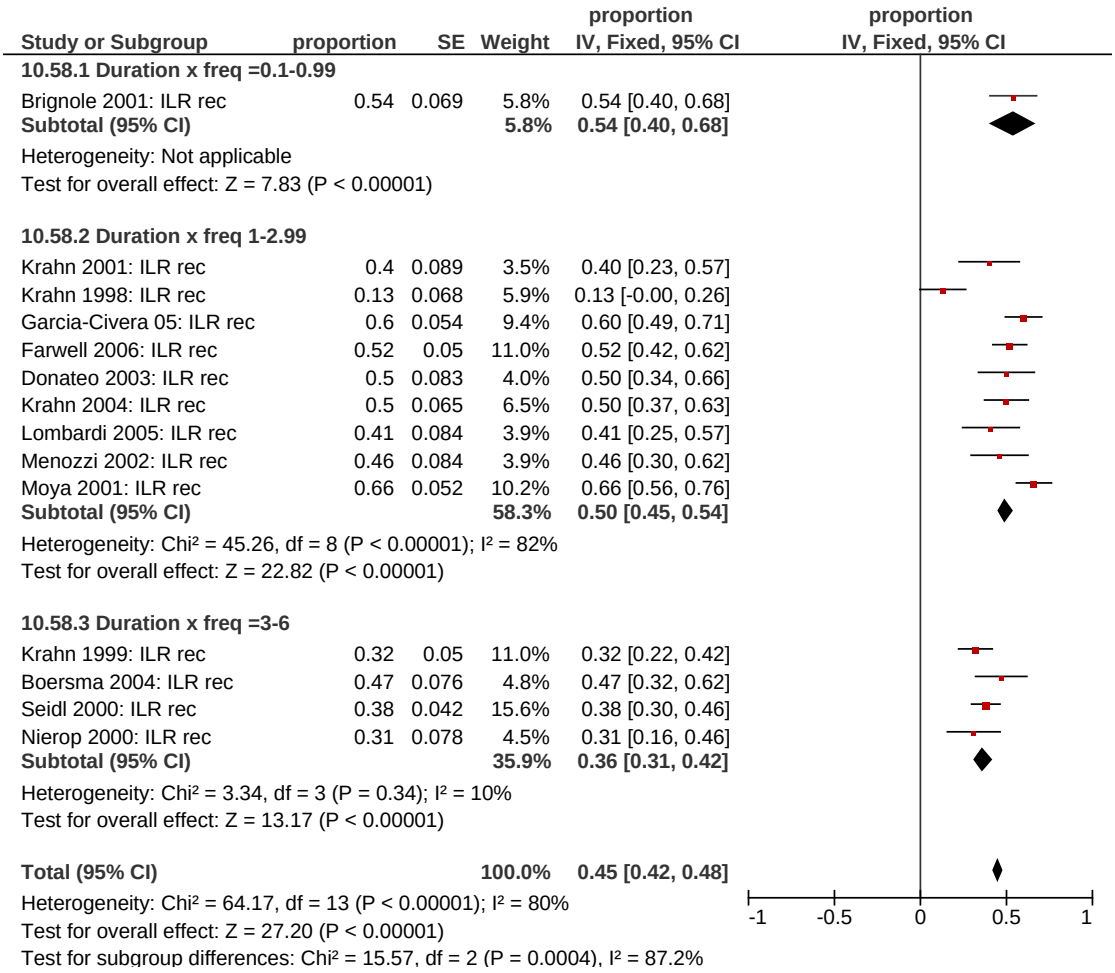
1.4.4 Subgroup analysis by the product of duration x frequency for the outcome, no TLoC during monitoring

Within the subgroup, studies are ordered by increasing duration x frequency product in the following pre-specified subgroups: below 0.1, 0.1 to 0.99, 1 to 10 and over 10 (not shown). However, all but one of the studies were in the 1 to 10 category. We then divided the 1-10 group studies post-hoc into three subgroups: 1 to 2.99; 3 to 5.99 and 6 and over. The product does not seem to be particularly important for explaining heterogeneity.

1.4.4.1 Pre-specificied subgroup analysis



1.4.4.2 Post-hoc subgroup analysis



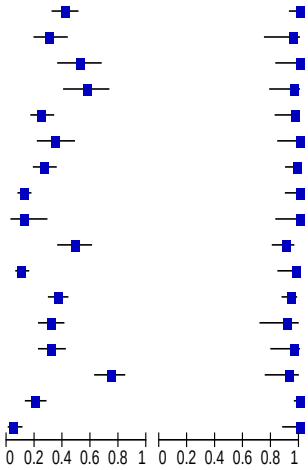
2 Tilt test additional analyses

2.1 HUT-passive

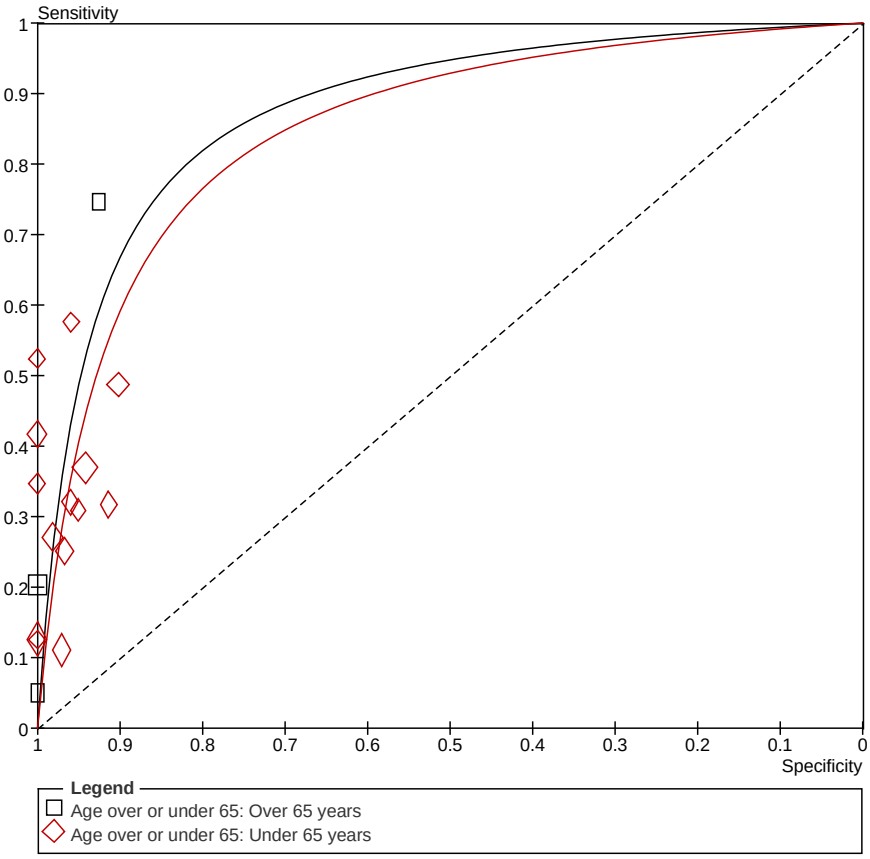
2.1.1 Age over or under 65 years (sorted by mean age in studies ('age continuous'); youngest to oldest)

2.1.1.1 Forest plot of sensitivity and specificity (ordered by age)

Study	TP	FP	FN	TN	Age over or under 65	age continuous	Sensitivity	Specificity
Hermosillo 2000	50	0	70	50	Under 65 years	33.0	0.42 [0.33, 0.51]	1.00 [0.93, 1.00]
Oraii 1999	20	1	45	19	Under 65 years	34.0	0.31 [0.20, 0.43]	0.95 [0.75, 1.00]
Lazzeri 2000	23	0	21	20	Under 65 years	35.0	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Gielerak 2002	23	1	17	23	Under 65 years	35.0	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Morillo 1995	30	1	90	29	Under 65 years	40.0	0.25 [0.18, 0.34]	0.97 [0.83, 1.00]
Theodorakis 2000	19	0	36	22	Under 65 years	40.0	0.35 [0.22, 0.49]	1.00 [0.85, 1.00]
Theodorakis 2003	34	1	92	53	Under 65 years	41.0	0.27 [0.19, 0.36]	0.98 [0.90, 1.00]
Del Rosso 2002 under 65s	28	0	196	35	Under 65 years	41.0	0.13 [0.08, 0.18]	1.00 [0.90, 1.00]
Aerts 1997	4	0	28	20	Under 65 years	43.0	0.13 [0.04, 0.29]	1.00 [0.83, 1.00]
Lagi 1992	35	7	37	64	Under 65 years	47.0	0.49 [0.37, 0.61]	0.90 [0.81, 0.96]
Del Rosso 1998	22	1	180	33	Under 65 years	49.0	0.11 [0.07, 0.16]	0.97 [0.85, 1.00]
Oribe 1997	74	6	127	96	Under 65 years	51.0	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Shen 1999	35	2	76	21	Under 65 years	55.0	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Brignole 1991	32	1	68	24	Under 65 years	60.0	0.32 [0.23, 0.42]	0.96 [0.80, 1.00]
Fitzpatrick 1991	53	2	18	25	Over 65 years	69.0	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Mussi 2001	26	0	102	101	Over 65 years	72.0	0.20 [0.14, 0.28]	1.00 [0.96, 1.00]
Del Rosso 2002 over 65s	5	0	95	29	Over 65 years	73.0	0.05 [0.02, 0.11]	1.00 [0.88, 1.00]



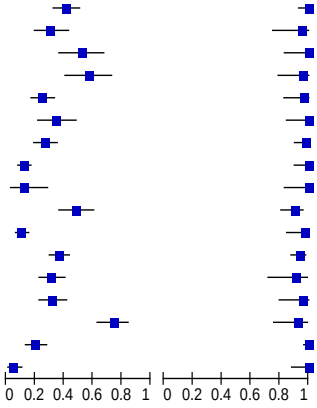
2.1.1.2 ROC curve (over versus under 65 years)



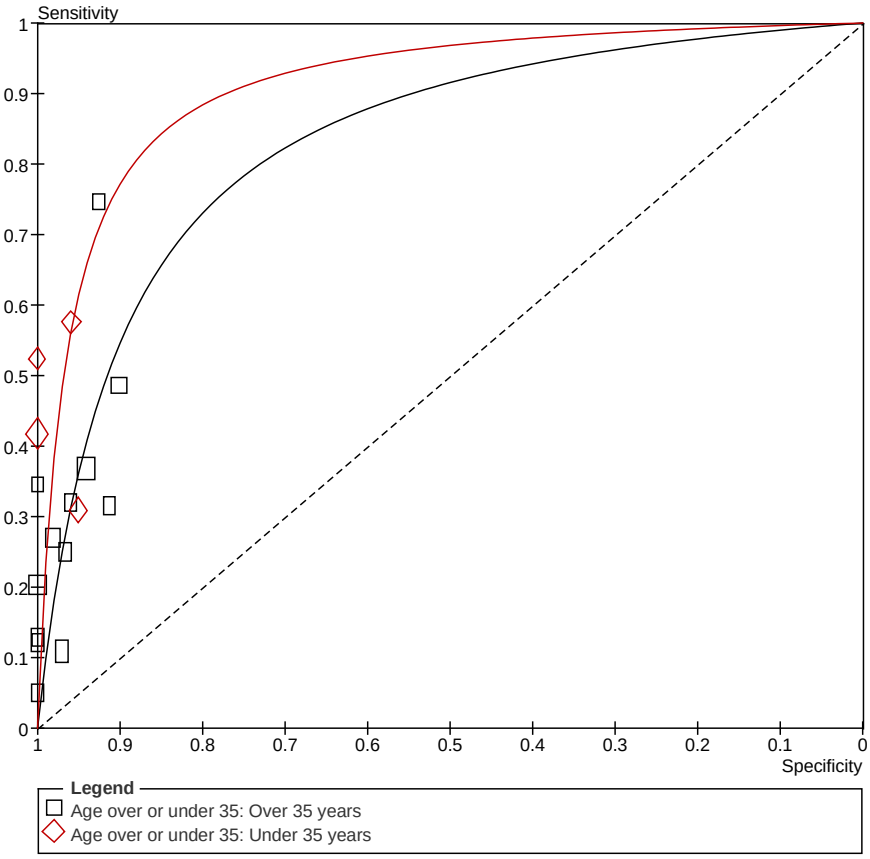
2.1.2 Age over or under 35 years

2.1.2.1 Forest plot (ordered by mean age)

Study	TP	FP	FN	TN	age continuous	Age over or under 35	Sensitivity	Specificity
Hermosillo 2000	50	0	70	50	33.0	Under 35 years	0.42 [0.33, 0.51]	1.00 [0.93, 1.00]
Oraii 1999	20	1	45	19	34.0	Under 35 years	0.31 [0.20, 0.43]	0.95 [0.75, 1.00]
Lazzeri 2000	23	0	21	20	35.0	Under 35 years	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Gielerak 2002	23	1	17	23	35.0	Under 35 years	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Morillo 1995	30	1	90	29	40.0	Over 35 years	0.25 [0.18, 0.34]	0.97 [0.83, 1.00]
Theodorakis 2000	19	0	36	22	40.0	Over 35 years	0.35 [0.22, 0.49]	1.00 [0.85, 1.00]
Theodorakis 2003	34	1	92	53	41.0	Over 35 years	0.27 [0.19, 0.36]	0.98 [0.90, 1.00]
Del Rosso 2002 under 65s	28	0	196	35	41.0	Over 35 years	0.13 [0.08, 0.18]	1.00 [0.90, 1.00]
Aerts 1997	4	0	28	20	43.0	Over 35 years	0.13 [0.04, 0.29]	1.00 [0.83, 1.00]
Lagi 1992	35	7	37	64	47.0	Over 35 years	0.49 [0.37, 0.61]	0.90 [0.81, 0.96]
Del Rosso 1998	22	1	180	33	49.0	Over 35 years	0.11 [0.07, 0.16]	0.97 [0.85, 1.00]
Oribe 1997	74	6	127	96	51.0	Over 35 years	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Shen 1999	35	2	76	21	55.0	Over 35 years	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Brignole 1991	32	1	68	24	60.0	Over 35 years	0.32 [0.23, 0.42]	0.96 [0.80, 1.00]
Fitzpatrick 1991	53	2	18	25	69.0	Over 35 years	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Mussi 2001	26	0	102	101	72.0	Over 35 years	0.20 [0.14, 0.28]	1.00 [0.96, 1.00]
Del Rosso 2002 over 65s	5	0	95	29	73.0	Over 35 years	0.05 [0.02, 0.11]	1.00 [0.88, 1.00]



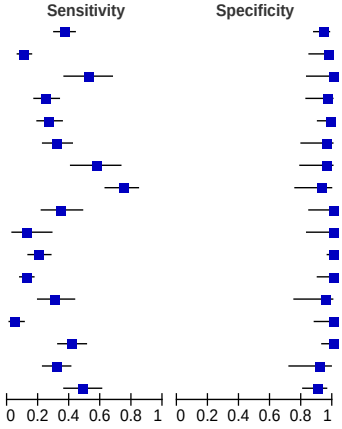
2.1.2.2 ROC curve (over versus under 35 years)



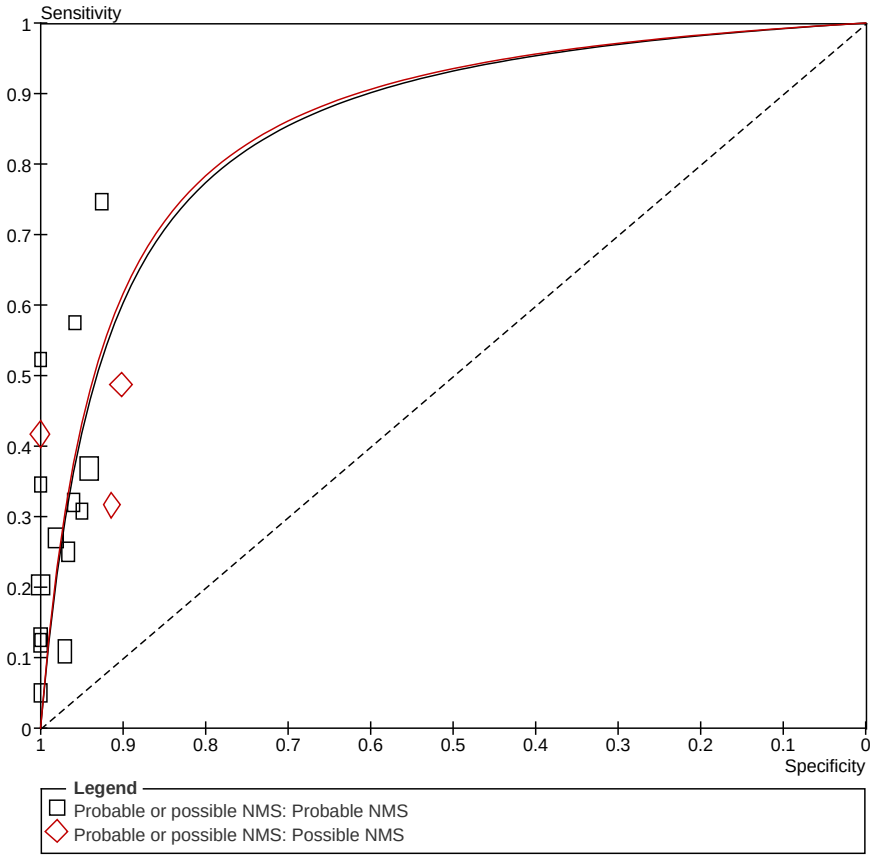
2.1.3 Subgroups for possible/probable NMS

2.1.3.1 Forest plot (probable versus possible NMS)

Study	TP	FP	FN	TN	Probable or possible NMS	Sensitivity	Specificity
Oribe 1997	74	6	127	96	Probable NMS	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Del Rosso 1998	22	1	180	33	Probable NMS	0.11 [0.07, 0.16]	0.97 [0.85, 1.00]
Lazzeri 2000	23	0	21	20	Probable NMS	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Morillo 1995	30	1	90	29	Probable NMS	0.25 [0.18, 0.34]	0.97 [0.83, 1.00]
Theodorakis 2003	34	1	92	53	Probable NMS	0.27 [0.19, 0.36]	0.98 [0.90, 1.00]
Brignole 1991	32	1	68	24	Probable NMS	0.32 [0.23, 0.42]	0.96 [0.80, 1.00]
Gielerak 2002	23	1	17	23	Probable NMS	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Fitzpatrick 1991	53	2	18	25	Probable NMS	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Theodorakis 2000	19	0	36	22	Probable NMS	0.35 [0.22, 0.49]	1.00 [0.85, 1.00]
Aerts 1997	4	0	28	20	Probable NMS	0.13 [0.04, 0.29]	1.00 [0.83, 1.00]
Mussi 2001	26	0	102	101	Probable NMS	0.20 [0.14, 0.28]	1.00 [0.96, 1.00]
Del Rosso 2002 under 65s	28	0	196	35	Probable NMS	0.13 [0.08, 0.18]	1.00 [0.90, 1.00]
Oraii 1999	20	1	45	19	Probable NMS	0.31 [0.20, 0.43]	0.95 [0.75, 1.00]
Del Rosso 2002 over 65s	5	0	95	29	Probable NMS	0.05 [0.02, 0.11]	1.00 [0.88, 1.00]
Hermosillo 2000	50	0	70	50	Possible NMS	0.42 [0.33, 0.51]	1.00 [0.93, 1.00]
Shen 1999	35	2	76	21	Possible NMS	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Lagi 1992	35	7	37	64	Possible NMS	0.49 [0.37, 0.61]	0.90 [0.81, 0.96]



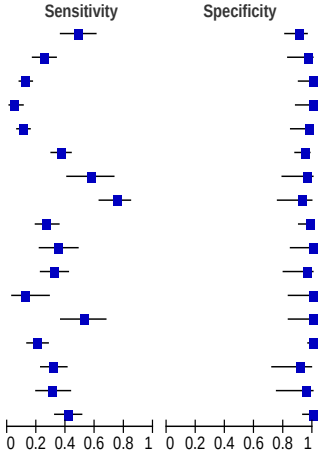
2.1.3.2 ROC curve (probable versus possible NMS)



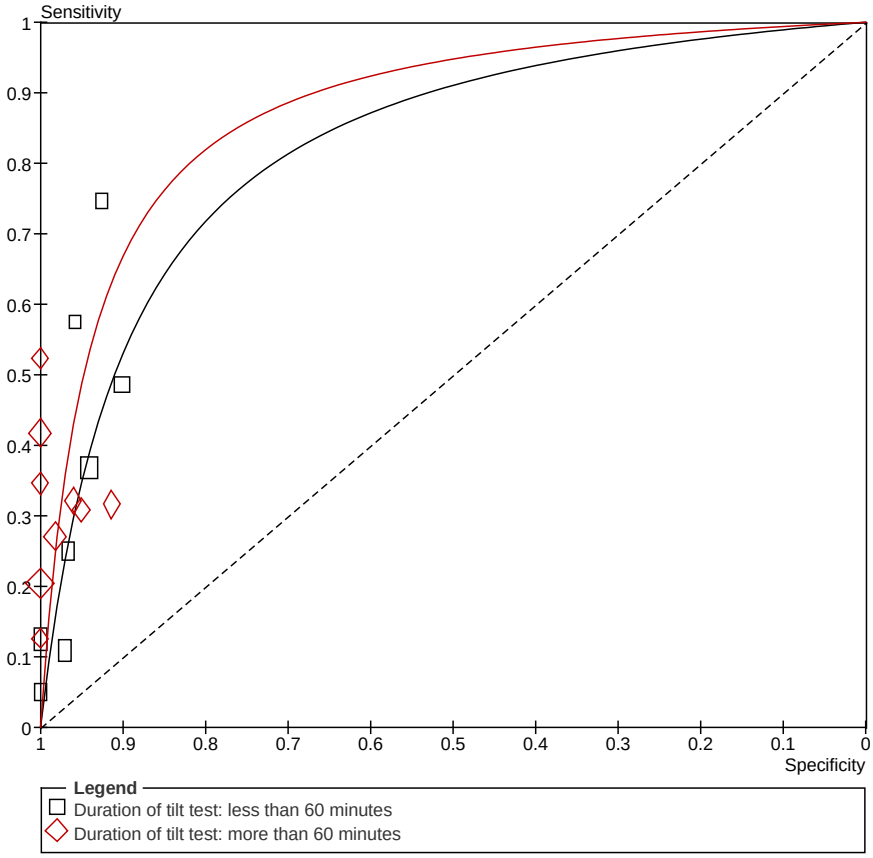
2.1.4 Subgroup analysis by duration of tilt test (more or less than 60 minutes – median value)

2.1.4.1 Forest plot (ordered by duration of tilt)

Study	TP	FP	FN	TN	Duration of tilt test	Duration of test continuous	Sensitivity	Specificity
Lagi 1992	35	7	37	64	less than 60 minutes		0.49 [0.37, 0.61]	0.90 [0.81, 0.96]
Morillo 1995	30	1	90	29	less than 60 minutes	45.0	0.25 [0.18, 0.34]	0.97 [0.83, 1.00]
Del Rosso 2002 under 65s	28	0	196	35	less than 60 minutes	45.0	0.13 [0.08, 0.18]	1.00 [0.90, 1.00]
Del Rosso 2002 over 65s	5	0	95	29	less than 60 minutes	45.0	0.05 [0.02, 0.11]	1.00 [0.88, 1.00]
Del Rosso 1998	22	1	180	33	less than 60 minutes	55.0	0.11 [0.07, 0.16]	0.97 [0.85, 1.00]
Oribe 1997	74	6	127	96	less than 60 minutes	60.0	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Gielerak 2002	23	1	17	23	less than 60 minutes	60.0	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Fitzpatrick 1991	53	2	18	25	less than 60 minutes	60.0	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Theodorakis 2003	34	1	92	53	more than 60 minutes	65.0	0.27 [0.19, 0.36]	0.98 [0.90, 1.00]
Theodorakis 2000	19	0	36	22	more than 60 minutes	65.0	0.35 [0.22, 0.49]	1.00 [0.85, 1.00]
Brignole 1991	32	1	68	24	more than 60 minutes	70.0	0.32 [0.23, 0.42]	0.96 [0.80, 1.00]
Aerts 1997	4	0	28	20	more than 60 minutes	70.0	0.13 [0.04, 0.29]	1.00 [0.83, 1.00]
Lazzeri 2000	23	0	21	20	more than 60 minutes	75.0	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Mussi 2001	26	0	102	101	more than 60 minutes	75.0	0.20 [0.14, 0.28]	1.00 [0.96, 1.00]
Shen 1999	35	2	76	21	more than 60 minutes	90.0	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Oraii 1999	20	1	45	19	more than 60 minutes	100.0	0.31 [0.20, 0.43]	0.95 [0.75, 1.00]
Hermosillo 2000	50	0	70	50	more than 60 minutes	122.0	0.42 [0.33, 0.51]	1.00 [0.93, 1.00]



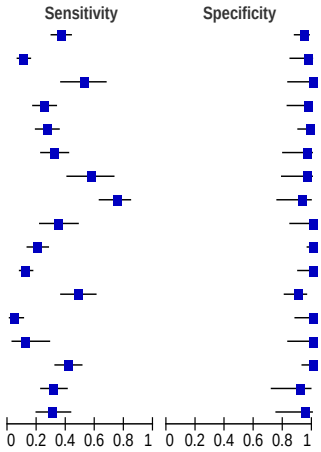
2.1.4.2 ROC curve (over versus under 60 minutes duration)



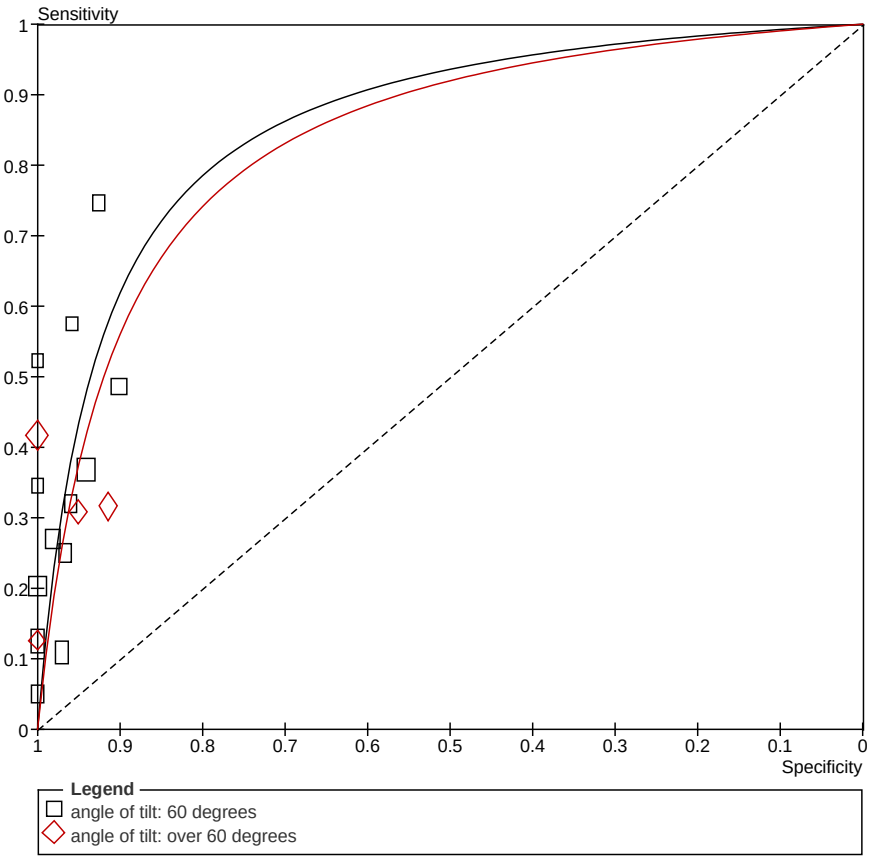
2.1.5 Subgroup analysis by angle of tilt (above and below 60 degrees – median value)

2.1.5.1 Forest plot

Study	TP	FP	FN	TN	angle of tilt	Angle of tilt continuous	Sensitivity	Specificity
Oribe 1997	74	6	127	96	60 degrees	60.0	0.37 [0.30, 0.44]	0.94 [0.88, 0.98]
Del Rosso 1998	22	1	180	33	60 degrees	60.0	0.11 [0.07, 0.16]	0.97 [0.85, 1.00]
Lazzeri 2000	23	0	21	20	60 degrees	60.0	0.52 [0.37, 0.68]	1.00 [0.83, 1.00]
Morillo 1995	30	1	90	29	60 degrees	60.0	0.25 [0.18, 0.34]	0.97 [0.83, 1.00]
Theodorakis 2003	34	1	92	53	60 degrees	60.0	0.27 [0.19, 0.36]	0.98 [0.90, 1.00]
Brignole 1991	32	1	68	24	60 degrees	60.0	0.32 [0.23, 0.42]	0.96 [0.80, 1.00]
Gielerak 2002	23	1	17	23	60 degrees	60.0	0.57 [0.41, 0.73]	0.96 [0.79, 1.00]
Fitzpatrick 1991	53	2	18	25	60 degrees	60.0	0.75 [0.63, 0.84]	0.93 [0.76, 0.99]
Theodorakis 2000	19	0	36	22	60 degrees	60.0	0.35 [0.22, 0.49]	1.00 [0.85, 1.00]
Mussi 2001	26	0	102	101	60 degrees	60.0	0.20 [0.14, 0.28]	1.00 [0.96, 1.00]
Del Rosso 2002 under 65s	28	0	196	35	60 degrees	60.0	0.13 [0.08, 0.18]	1.00 [0.90, 1.00]
Lagi 1992	35	7	37	64	60 degrees	60.0	0.49 [0.37, 0.61]	0.90 [0.81, 0.96]
Del Rosso 2002 over 65s	5	0	95	29	60 degrees	60.0	0.05 [0.02, 0.11]	1.00 [0.88, 1.00]
Aerts 1997	4	0	28	20	over 60 degrees	70.0	0.13 [0.04, 0.29]	1.00 [0.83, 1.00]
Hermosillo 2000	50	0	70	50	over 60 degrees	70.0	0.42 [0.33, 0.51]	1.00 [0.93, 1.00]
Shen 1999	35	2	76	21	over 60 degrees	70.0	0.32 [0.23, 0.41]	0.91 [0.72, 0.99]
Oraii 1999	20	1	45	19	over 60 degrees	70.0	0.31 [0.20, 0.43]	0.95 [0.75, 1.00]



2.1.5.2 ROC curve

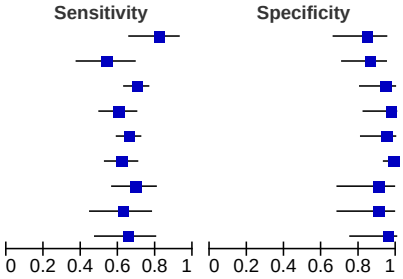


2.2 HUT-GTN

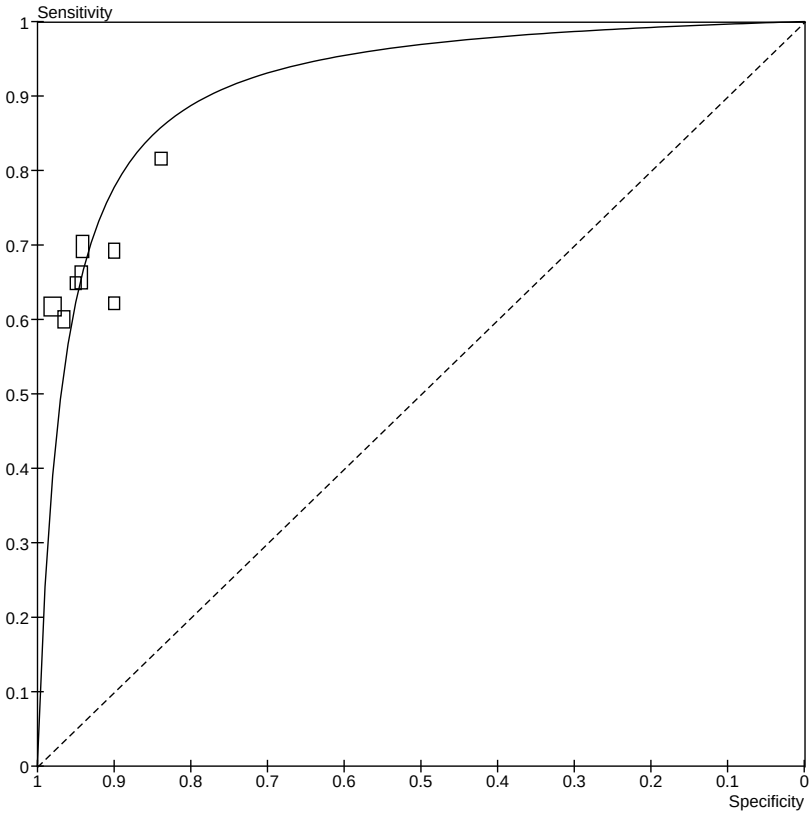
Nine studies used GTN stimulated HUT. There was high specificity for each study, and the studies were generally fairly homogeneous.

2.2.1.1 Forest plot of all HUT-GTN studies

Study	TP	FP	FN	TN	Sensitivity	Specificity
Aerts 2005b GTN	31	5	7	26	0.82 [0.66, 0.92]	0.84 [0.66, 0.95]
Bartoletti 1999 GTN	23	6	20	35	0.53 [0.38, 0.69]	0.85 [0.71, 0.94]
Del Rosso 1998	141	2	61	32	0.70 [0.63, 0.76]	0.94 [0.80, 0.99]
Del Rosso 2002 over 65s	60	1	40	28	0.60 [0.50, 0.70]	0.97 [0.82, 1.00]
Del Rosso 2002 under 65s	147	2	77	33	0.66 [0.59, 0.72]	0.94 [0.81, 0.99]
Mussi 2001	79	2	49	99	0.62 [0.53, 0.70]	0.98 [0.93, 1.00]
Oraii 1999	45	2	20	18	0.69 [0.57, 0.80]	0.90 [0.68, 0.99]
Zeng 2001	23	2	14	18	0.62 [0.45, 0.78]	0.90 [0.68, 0.99]
Zeng 2001b	24	1	13	19	0.65 [0.47, 0.80]	0.95 [0.75, 1.00]



2.2.1.2 ROC curve for all studies of HUT-GTN



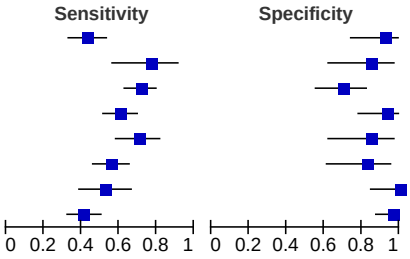
2.3 HUT-IPN

Eight studies used HUT-IPN; there was some heterogeneity. Subgroup analyses were conducted for age above and below 35 years (there were no studies with a mean age above 65 years); and probable or possible NMS.

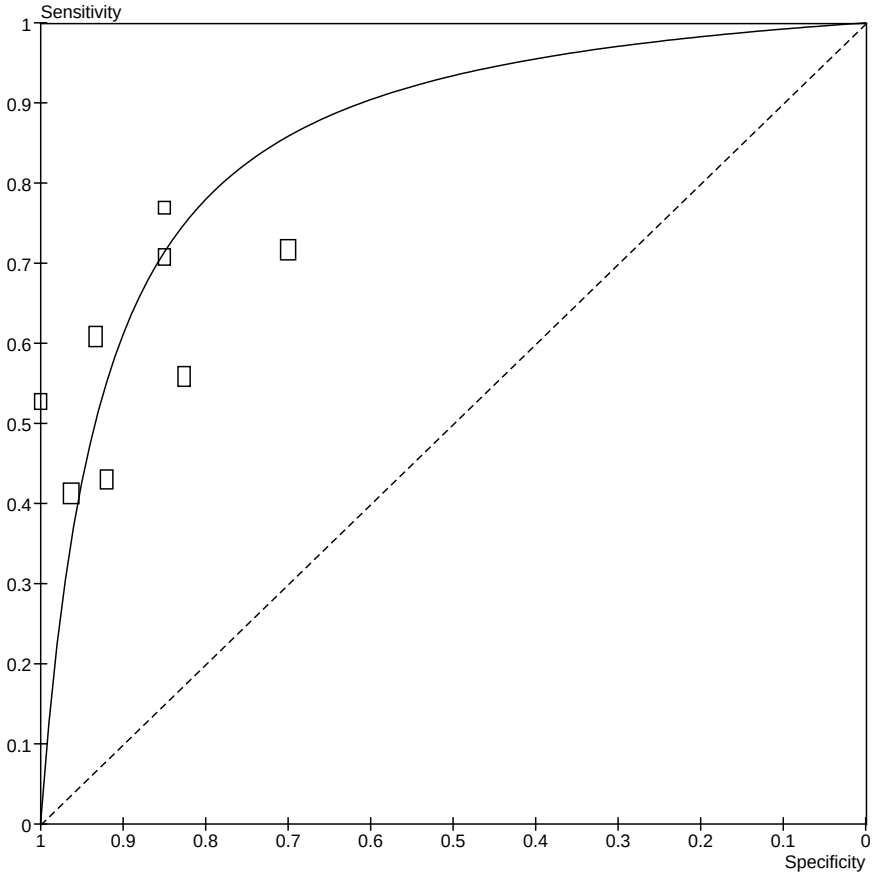
2.3.1 All IPN studies

2.3.1.1 Forest plot of all IPN studies

Study	TP	FP	FN	TN	Sensitivity	Specificity
Brignole 1991	43	2	57	23	0.43 [0.33, 0.53]	0.92 [0.74, 0.99]
Doi 2002exerciseunrelated	20	3	6	17	0.77 [0.56, 0.91]	0.85 [0.62, 0.97]
Hermosillo 2000	86	15	34	35	0.72 [0.63, 0.80]	0.70 [0.55, 0.82]
Morillo 1995	73	2	47	28	0.61 [0.52, 0.70]	0.93 [0.78, 0.99]
Oraii IPN 1999	46	3	19	17	0.71 [0.58, 0.81]	0.85 [0.62, 0.97]
Shen 1999	62	4	49	19	0.56 [0.46, 0.65]	0.83 [0.61, 0.95]
Theodorakis 2000	29	0	26	22	0.53 [0.39, 0.66]	1.00 [0.85, 1.00]
Theodorakis 2003	52	2	74	52	0.41 [0.33, 0.50]	0.96 [0.87, 1.00]



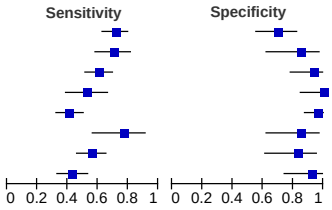
2.3.1.2 ROC curve for all HUT-IPN studies



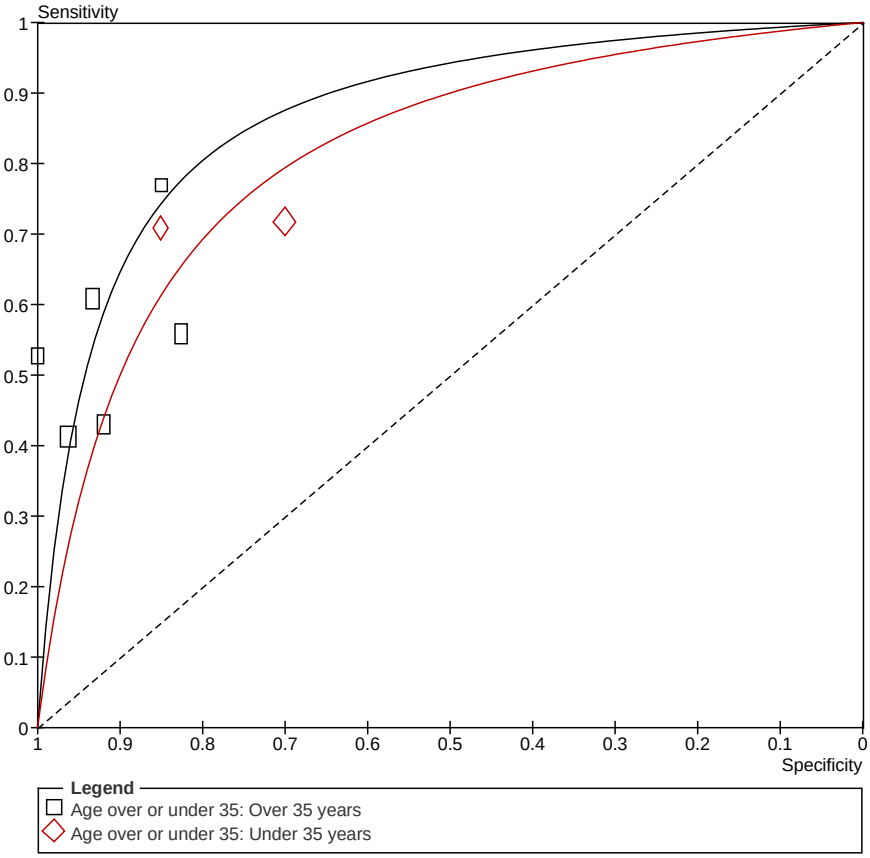
2.3.2 Subgroup analysis by age over or under 35 years

2.3.2.1 Forest plot (ordered by mean age)

Study	TP	FP	FN	TN	age continuous	Age over or under 35	Sensitivity	Specificity
Hermosillo 2000	86	15	34	35	33.0	Under 35 years	0.72 [0.63, 0.80]	0.70 [0.55, 0.82]
Oraii 1999	46	3	19	17	34.0	Under 35 years	0.71 [0.58, 0.81]	0.85 [0.62, 0.97]
Morillo 1995	73	2	47	28	40.0	Over 35 years	0.61 [0.52, 0.70]	0.93 [0.78, 0.99]
Theodorakis 2000	29	0	26	22	40.0	Over 35 years	0.53 [0.39, 0.66]	1.00 [0.85, 1.00]
Theodorakis 2003	52	2	74	52	41.0	Over 35 years	0.41 [0.33, 0.50]	0.96 [0.87, 1.00]
Doi 2002 ISO	20	3	6	17	46.0	Over 35 years	0.77 [0.56, 0.91]	0.85 [0.62, 0.97]
Shen 1999	62	4	49	19	55.0	Over 35 years	0.56 [0.46, 0.65]	0.83 [0.61, 0.95]
Brignole 1991	43	2	57	23	60.0	Over 35 years	0.43 [0.33, 0.53]	0.92 [0.74, 0.99]



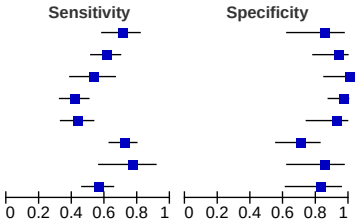
2.3.2.2 ROC curve (over versus under 35 years)



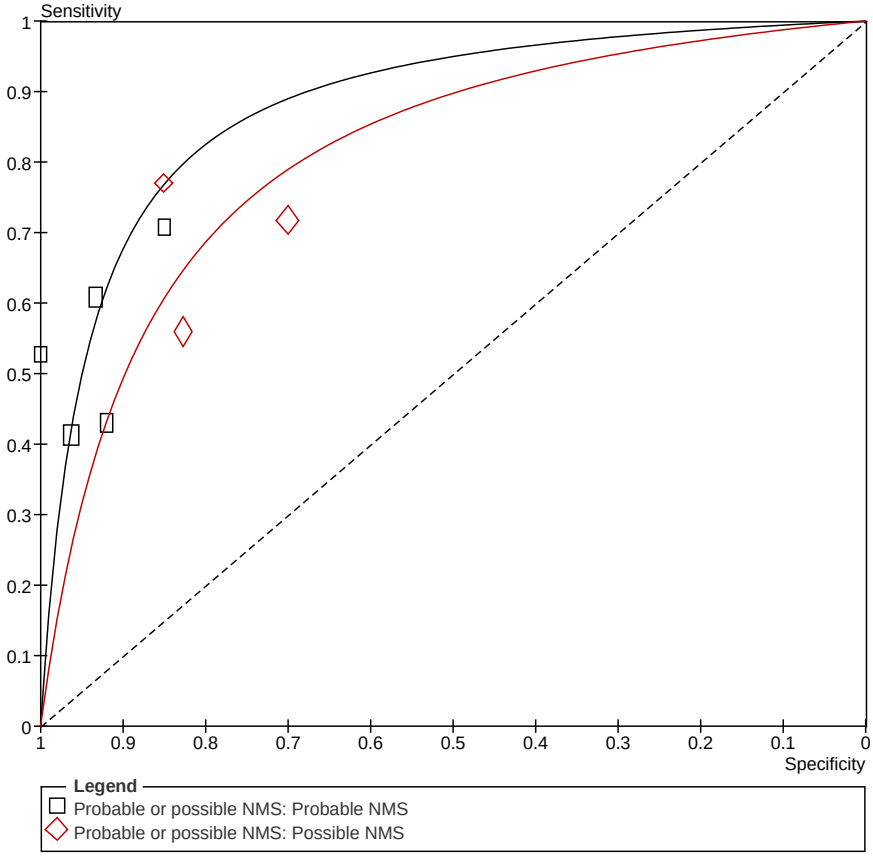
2.3.3 Subgroup analysis by probable or possible NM syncope

2.3.3.1 Forest plot (probable versus possible NMS)

Study	TP	FP	FN	TN	Probable or possible NMS	Sensitivity	Specificity
Oraii 1999	46	3	19	17	Probable NMS	0.71 [0.58, 0.81]	0.85 [0.62, 0.97]
Morillo 1995	73	2	47	28	Probable NMS	0.61 [0.52, 0.70]	0.93 [0.78, 0.99]
Theodorakis 2000	29	0	26	22	Probable NMS	0.53 [0.39, 0.66]	1.00 [0.85, 1.00]
Theodorakis 2003	52	2	74	52	Probable NMS	0.41 [0.33, 0.50]	0.96 [0.87, 1.00]
Brignole 1991	43	2	57	23	Probable NMS	0.43 [0.33, 0.53]	0.92 [0.74, 0.99]
Hermosillo 2000	86	15	34	35	Possible NMS	0.72 [0.63, 0.80]	0.70 [0.55, 0.82]
Doi 2002 ISO	20	3	6	17	Possible NMS	0.77 [0.56, 0.91]	0.85 [0.62, 0.97]
Shen 1999	62	4	49	19	Possible NMS	0.56 [0.46, 0.65]	0.83 [0.61, 0.95]



2.3.3.2 ROC curve (probable versus possible NMS)

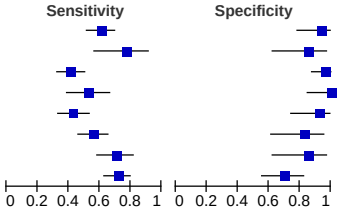


2.3.4 Subgroup analysis comparing duration of tilt over or under 60 minutes

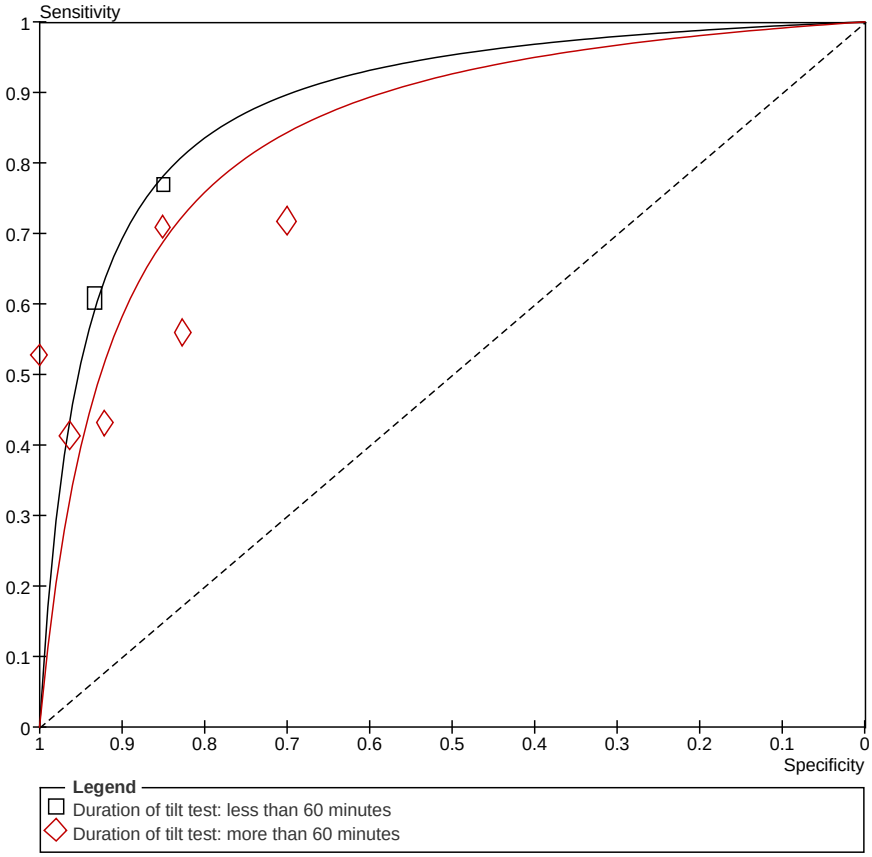
We note that there are only two studies with a duration of tilt below 60 minutes, so the subgroup analysis is not really meaningful.

2.3.4.1 Forest plot (ordered by duration of tilt)

Study	TP	FP	FN	TN	Duration of tilt test	Duration of test continuous	Sensitivity	Specificity
Morillo 1995	73	2	47	28	less than 60 minutes	45.0	0.61 [0.52, 0.70]	0.93 [0.78, 0.99]
Doi 2002 ISO	20	3	6	17	less than 60 minutes	45.0	0.77 [0.56, 0.91]	0.85 [0.62, 0.97]
Theodorakis 2003	52	2	74	52	more than 60 minutes	65.0	0.41 [0.33, 0.50]	0.96 [0.87, 1.00]
Theodorakis 2000	29	0	26	22	more than 60 minutes	65.0	0.53 [0.39, 0.66]	1.00 [0.85, 1.00]
Brignole 1991	43	2	57	23	more than 60 minutes	70.0	0.43 [0.33, 0.53]	0.92 [0.74, 0.99]
Shen 1999	62	4	49	19	more than 60 minutes	90.0	0.56 [0.46, 0.65]	0.83 [0.61, 0.95]
Oraii 1999	46	3	19	17	more than 60 minutes	100.0	0.71 [0.58, 0.81]	0.85 [0.62, 0.97]
Hermosillo 2000	86	15	34	35	more than 60 minutes	122.0	0.72 [0.63, 0.80]	0.70 [0.55, 0.82]



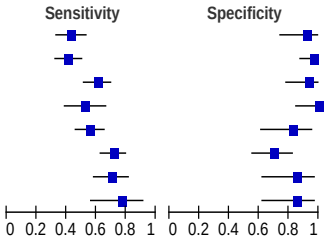
2.3.4.2 ROC curve (over versus under 60 min duration)



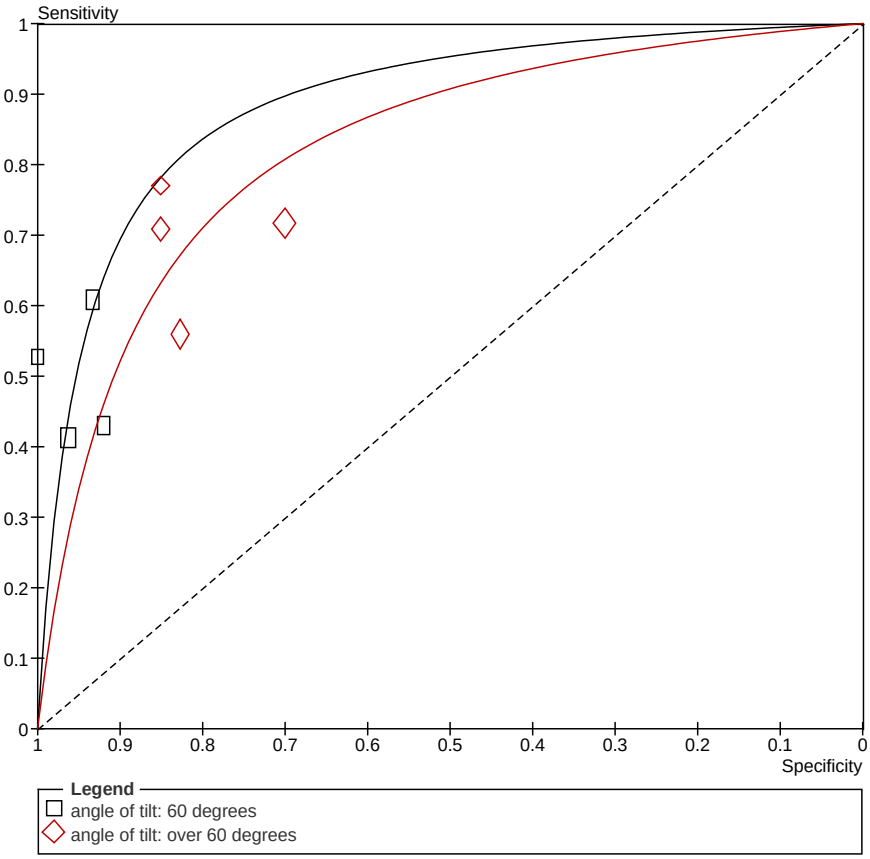
2.3.5 Subgroup analysis comparing angle of tilt over or under 60 degrees

2.3.5.1 Forest plot (ordered by angle)

Study	TP	FP	FN	TN	angle of tilt	Angle of tilt continuous	Sensitivity	Specificity
Brignole 1991	43	2	57	23	60 degrees	60.0	0.43 [0.33, 0.53]	0.92 [0.74, 0.99]
Theodorakis 2003	52	2	74	52	60 degrees	60.0	0.41 [0.33, 0.50]	0.96 [0.87, 1.00]
Morillo 1995	73	2	47	28	60 degrees	60.0	0.61 [0.52, 0.70]	0.93 [0.78, 0.99]
Theodorakis 2000	29	0	26	22	60 degrees	60.0	0.53 [0.39, 0.66]	1.00 [0.85, 1.00]
Shen 1999	62	4	49	19	over 60 degrees	70.0	0.56 [0.46, 0.65]	0.83 [0.61, 0.95]
Hermosillo 2000	86	15	34	35	over 60 degrees	70.0	0.72 [0.63, 0.80]	0.70 [0.55, 0.82]
Oraii 1999	46	3	19	17	over 60 degrees	70.0	0.71 [0.58, 0.81]	0.85 [0.62, 0.97]
Doi 2002 ISO	20	3	6	17	over 60 degrees	80.0	0.77 [0.56, 0.91]	0.85 [0.62, 0.97]



2.3.5.2 ROC curve (over versus under 60 degrees tilt)



Appendix D5: Other

1 Patient history for interactive diagnostic simulation

Name: Sheila Jones

Date of Birth: 08.11.1951

Married: 37 years with two chidren, both left home

Employment: PA to CEO of a non-governmental organisation

Medical history:

11 year history of **chest pain/light headed feeling**, with this I can get a feeling of pressure actually in my chest. Sometimes this is associated with pain in my teeth/jaw. Lots of visits to the GP and A and E, nothing ever really established, **something that does worry my husband and I**. **Three previous blackouts**, never explained, just told not to worry about them.

Previous cardiology referral about three years ago; I was told I do not have a cardiac problem, and not to worry about the blackouts. **Having experienced them for over ten years, I am not going to die from them!** It might be gall stones, but nothing showed on an ultrasound.

Quite a few ECGs, never showed anything. BP has been high, on medication. Had a treadmill test which only showed something right at the end, which I understand is normal. I was told I might have too much acid, and was started on Lansoprazole for 3 months, but this was continued. Loads of blood tests, all inconclusive, and I guess over time I have become dissatisfied that no one can tell me what is wrong. **I've lost count of how many doctors I have seen, it just keeps happening, and I suppose I have learnt to accept that this is just the way it is going to be.**

Medication:

Solifenacin	10mg morning (urinary condition)
Lansoprazole	15mg morning (heartburn)
Aspirin	75mg morning (high blood pressure)
Lisinopril	20mg morning and evening (high blood pressure)
Nicorandil	10mg morning and evening (smoking, 25 day for 34 years, gave up 5 years ago)
Simvastin	10mg morning (cholesterol)
Amitriptylene	1 – 3 before bed (help me sleep)

What happened today:

Whilst reading/babysitting, had a very sharp pain in my chest which lasted 15 – 20 minutes. Pain straight across chest, just a flicker in my jaw. Started at 8.35pm and stopped at 9pm. Ambulance arrived at 9.05pm, my BP was 120/90. I felt slightly sick and about to faint. It was similar to last time. I wanted to drink but didn't feel I had energy to lift the cup, asked for a straw. Bill my husband called for an ambulance because I wasn't with it for about 10 minutes, he said I was unconscious for about 4 minutes. I had an ECG with the ambulance crew, he thought it might show 'ischaemia' and that I should go to hospital.