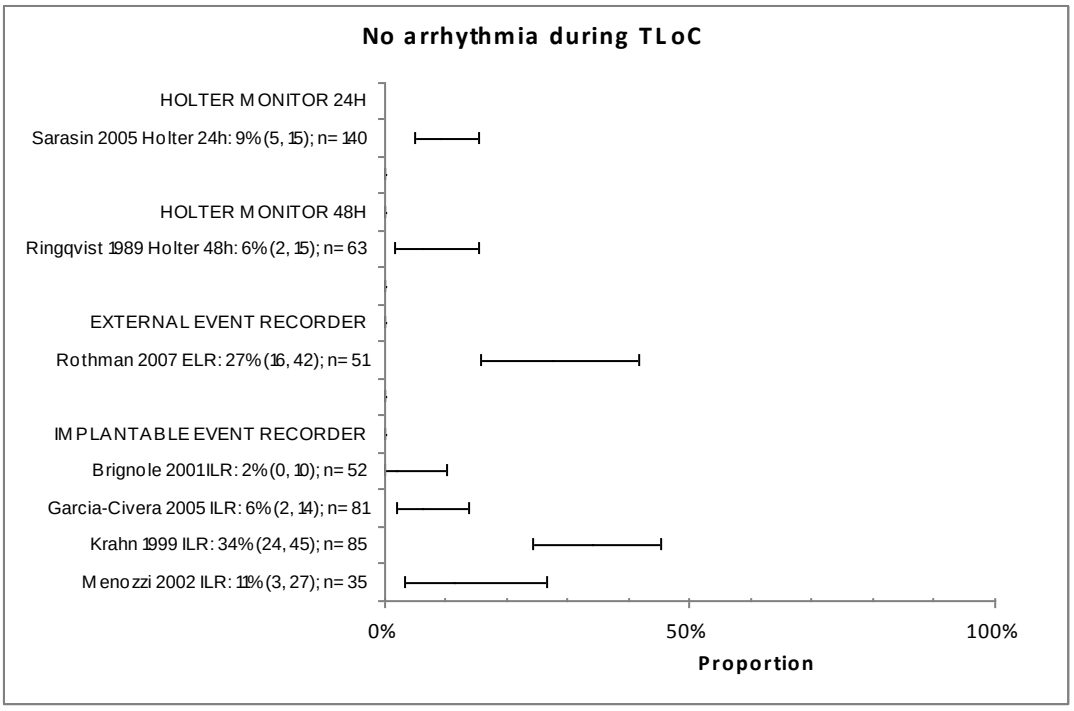
APPENDICES D4 and D5 - Additional forest plots 2nd stage and Interactive diagnostic simulation

APPENDIX D4 – Additional forest plots and analyses 2nd stage

1 Ambulatory ECG review – analyses by suspected cause

1.1 Suspected cardiac cause

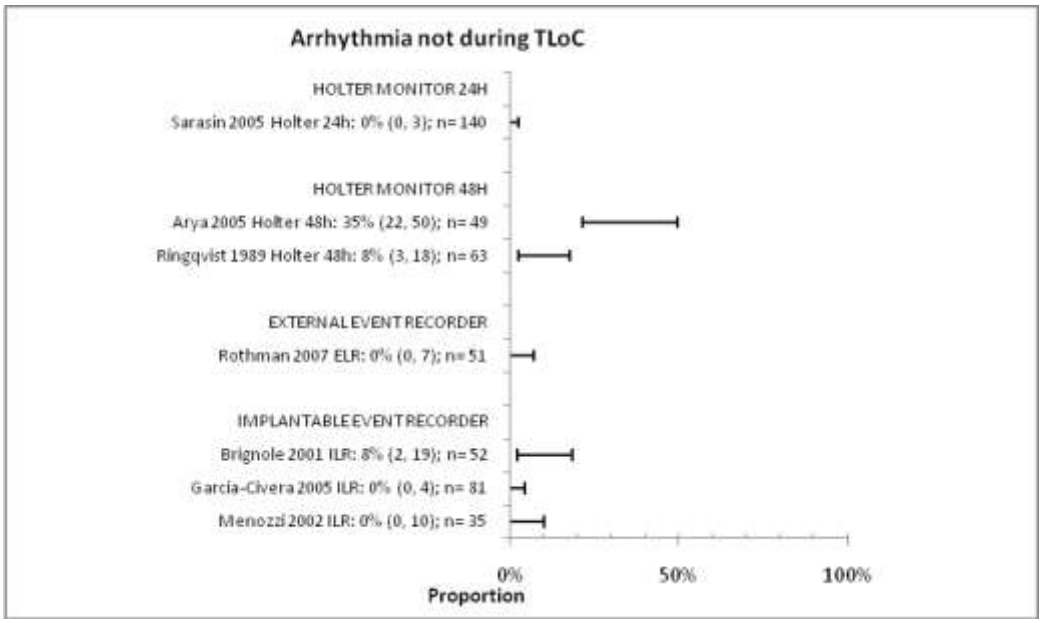
Figure 1: Normal rhythm during TLoC; subgroup by type of device



Arrhythmia recorded not during TLoC

One study (Ringqvist 1989) reported arrhythmia not during TLoC for Holter 48-hour monitoring; it had patients who had recurrent TLoC. One study (Rothman 2007) reported arrhythmia not during TLoC for EER, but none were significant arrhythmias, so these were not counted. One study (Brignole 2001) reported arrhythmia not during TLoC for implantable event recorders; patients had recurrent TLoC. One study (Menozzi 2002) examined this outcome for patients with recurrent TLoC on IER but there were no events.

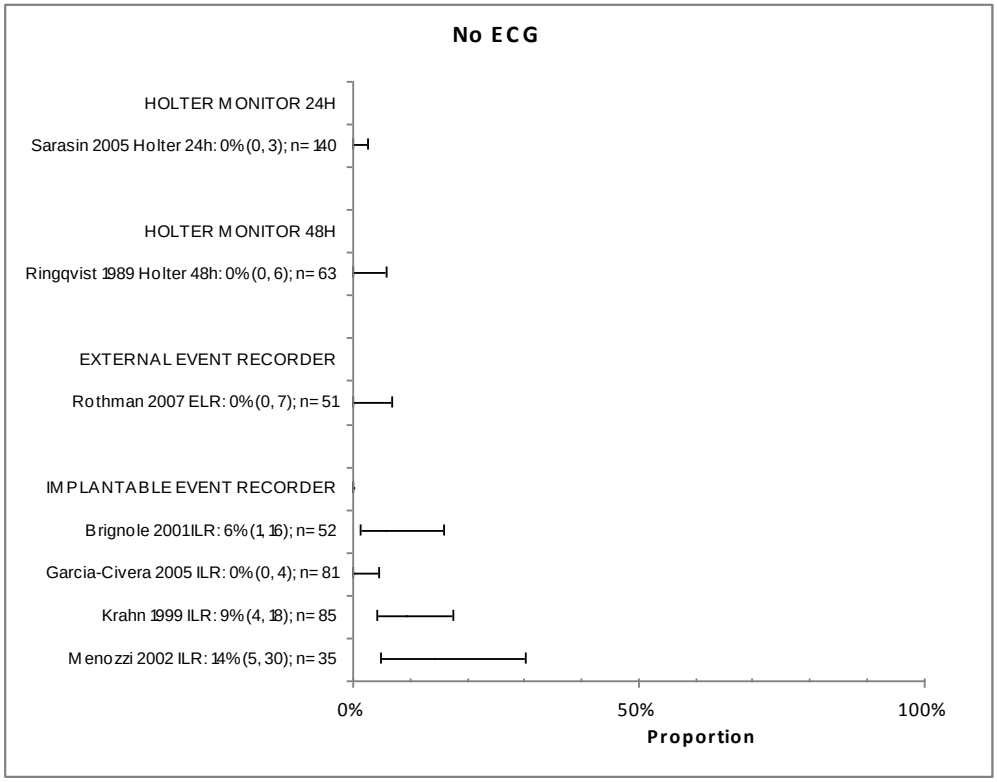
Figure 2: Arrhythmia recorded, but not during TLoC; subgroup by type of device



No ECG recorded

Two studies (Brignole 2001; Krahn 1999) reported the outcome, no ECG recorded during TLoC, for implantable event recorders; all patients had recurrent TLoC. Two other studies had no patients with no ECG recorded (Menozzi 2002; Rothman 2007).

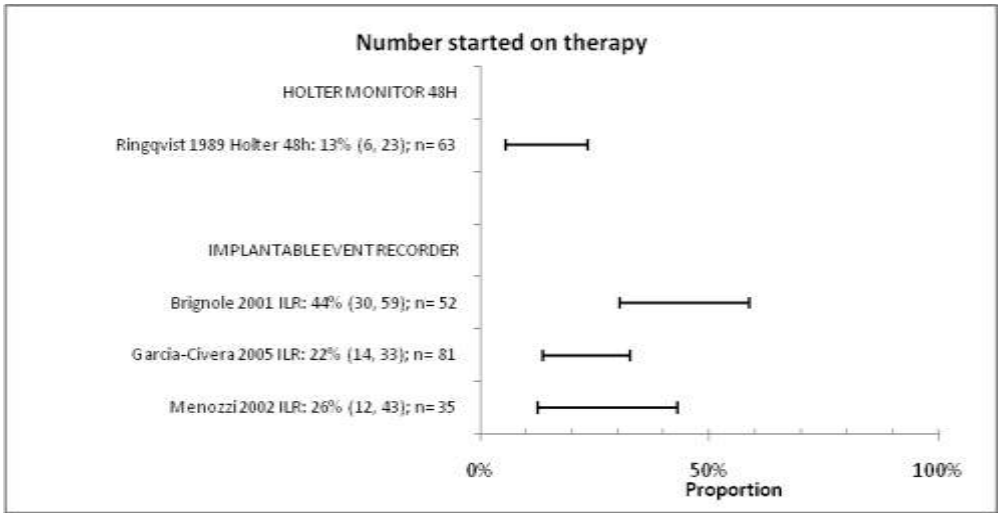
Figure 3: No ECG recorded



Number of patients started on therapy

One study assessing Holter 48-hours (Ringqvist 1989; recurrent TLoC) and 3 assessing implantable event recorders (Brignole 2001; Garcia-Civera 2005; Menozzi 2002; all patients had recurrent TLoC) reported the number of patients started on therapy. The therapy included pacemakers, implantable defibrillators and antiarrhythmic drugs.

Figure 4: number of patients started on therapy by type of device



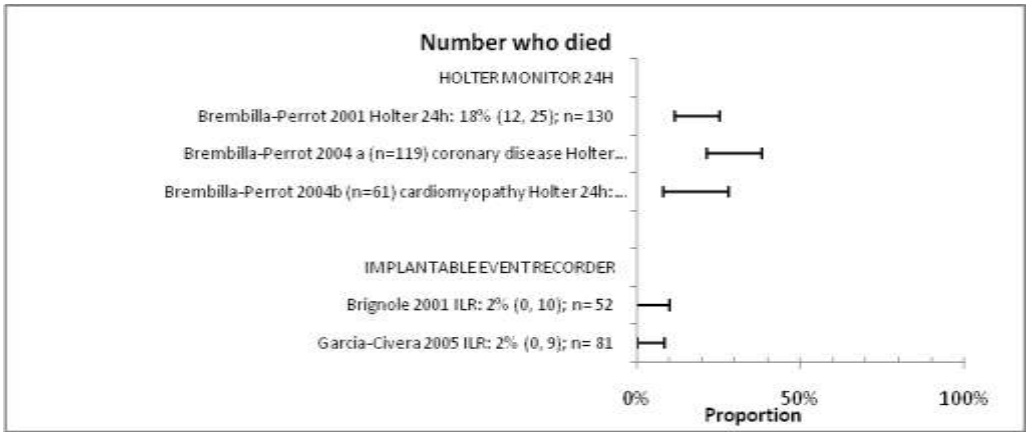
Adverse events

One study (Krahn 1999) reported 4 adverse events in 85 people with implantable event recorders; 3 patients had infections and one had pain.

Death

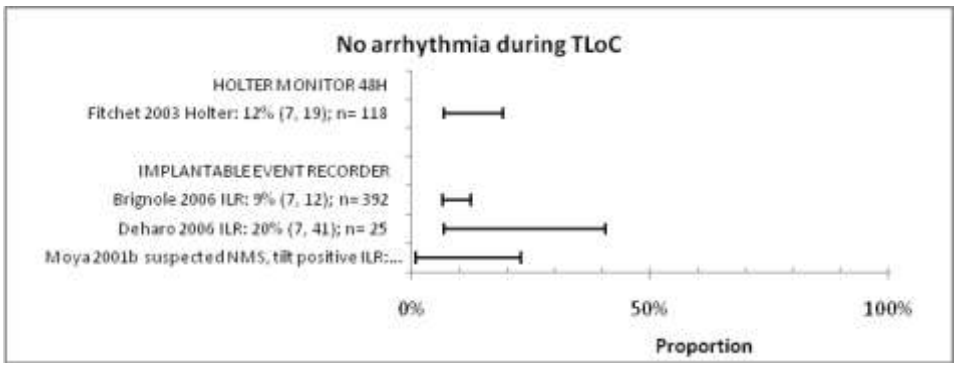
Three Holter studies (Brembilla-Perrot 2001; Brembilla-Perrot 2004a; Brembilla-Perrot 2004b) and three IER studies (Brignole 2001; Garcia-Civera 2005; Menozzi 2002) reported this outcome. The results are more likely to be due to the patient characteristics than the type of device.

Figure 5. Number of patients who died



1.2 Suspected neurally mediated syncope

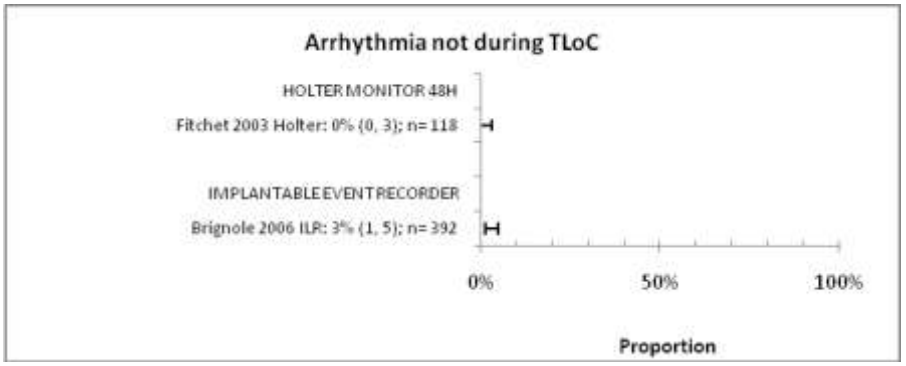
Figure 6. Normal rhythm during TLoC (suspected NM syncope)



B4. Arrhythmia not during TLoC

Two studies (Brignole 2006, Fitchet 2003) assessed this outcome. Results are reported only for 'good' arrhythmias. A single study reported no asymptomatic arrhythmias for the Holter monitor and a large single study reported 3%.

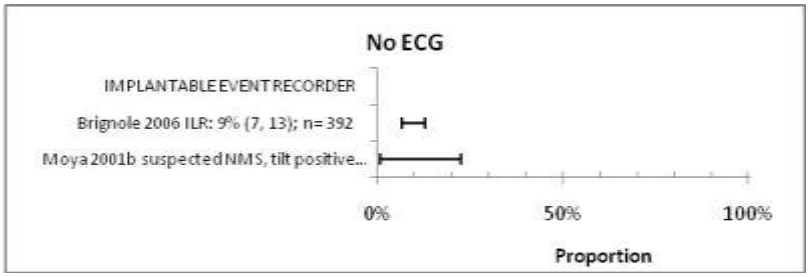
Figure 7. Arrhythmia not during TLoC (suspected NM syncope)



No ECG during TLoC

Two studies (Brignole 2006, Moya 2001) reported this outcome for an IER and had a yield of 9%.

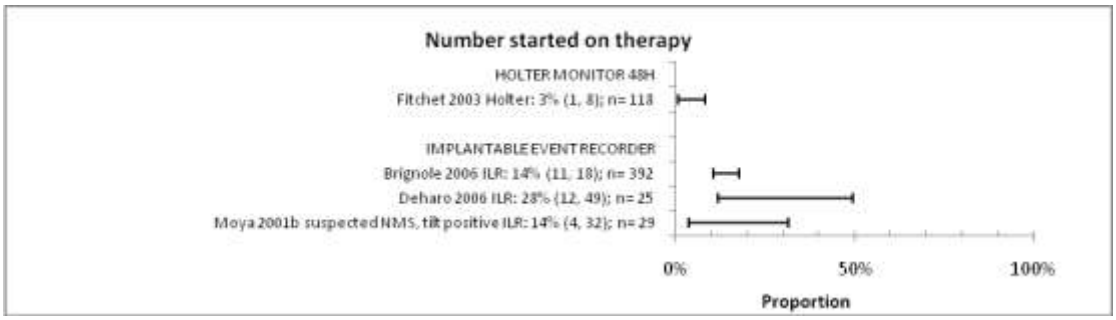
Figure 9. No ECG during TLoC (suspected NM syncope)



Number of patients started on therapy

Four studies reported this outcome (Brignole 2006, Deharo 2006, Fitchet 2003, Moya 2001).

Figure 10. Patients started on therapy (suspected NM syncope)



Adverse events

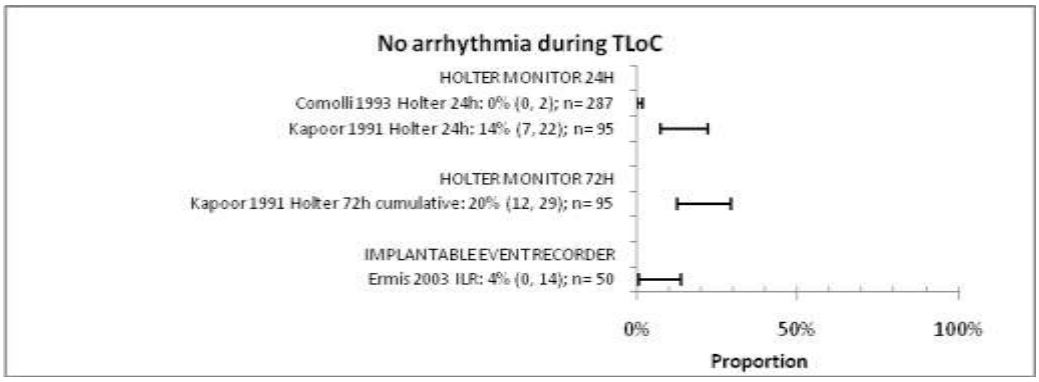
Two studies (Brignole 2006, Deharo 2006) reported adverse events: Brignole (2006) reported 4 pocket infections of 392 implantable event recorders, and Deharo (2006) reported one patient had an infection (out of 25 patients) and the implantable event recorder was explanted after 6 months.

Number of patients who died

One study (Moya 2001) reported that no patients died during the study period.

1.3 Unexplained after initial tests

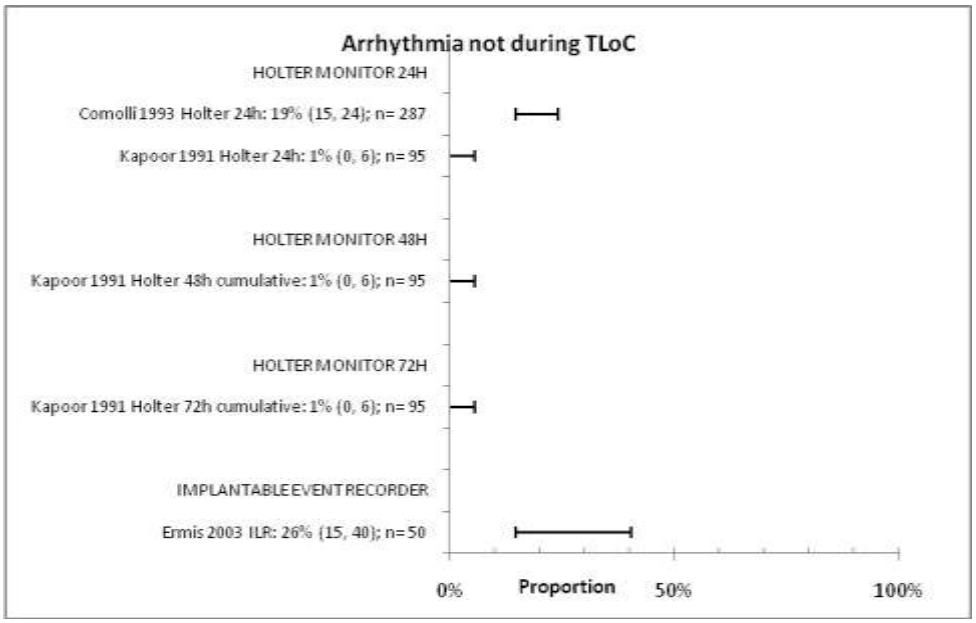
Figure 11. Normal rhythm during TLoC in patients with syncope unexplained after initial tests; subgroup by type of test



Arrhythmia not during TLoC

Three studes reported this outcome (Comolli 1993, Ermis 2003; Kapoor 1991). For the Comolli (1993) and Kapoor (1991) studies we only considered the ‘good’ arrhythmias, and the Ermis (2003) study was assessed to be ‘good’ arrhythmias if grades 0 and I were considered only.

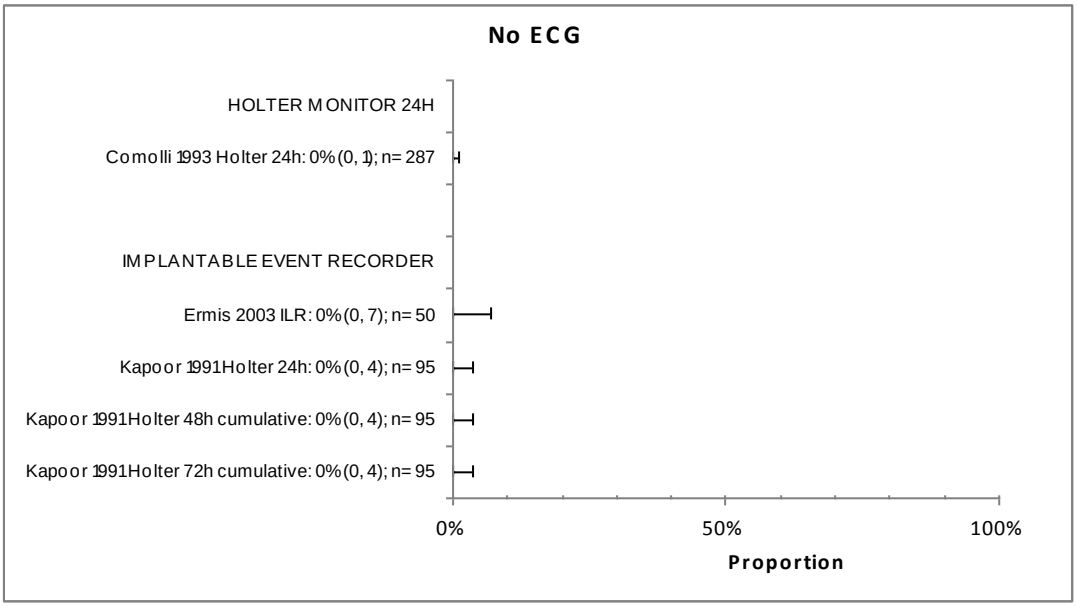
Figure 12. Arrhythmia not during TLoC in patients with syncope unexplained after initial tests; subgroup by type of device



No ECG during TLoC

One study reported this outcome for Holter monitoring and two for ILR (Comolli 1993, Ermis 2003, Kapoor 1991).

Figure 13. No ECG during TLoC in patients with syncope unexplained after initial tests; subgroup by type of test



C6 Number of patients started on therapy

One study (Ermis 2003) reported that 16 out of 50 patients were started on therapy.

C7 Number with Adverse events

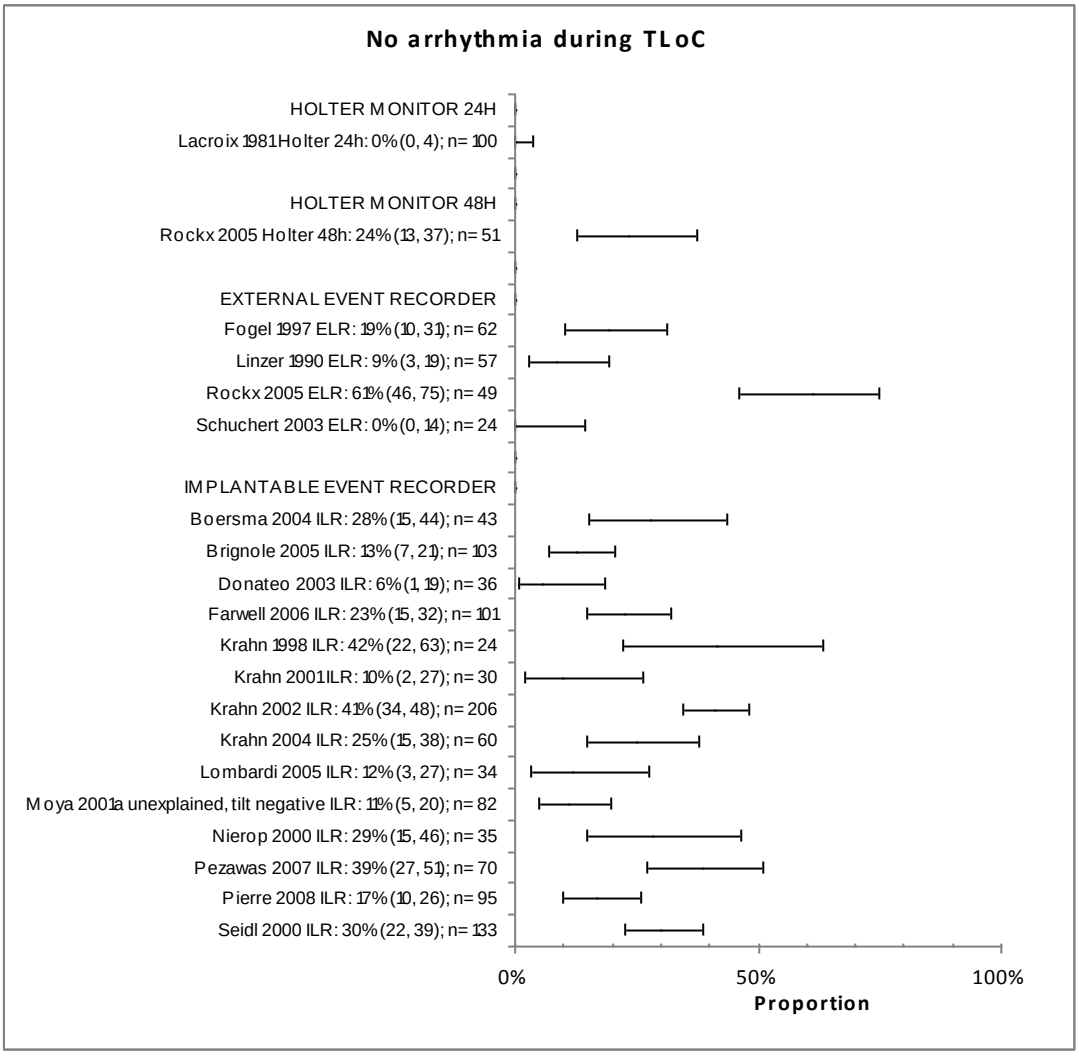
No study reported this outcome.

C8 Number of patients who died

One study (Ermis 2003) reported that 3 out of 50 patients died

1.4 Unexplained after secondary tests

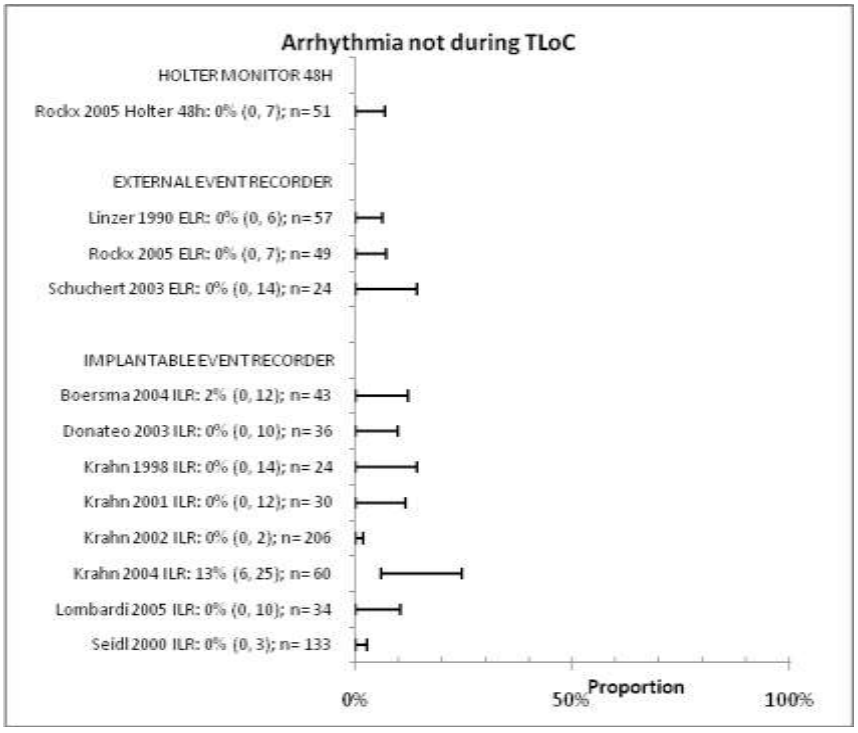
Figure 14. Normal rhythm during TLoC (unexplained after secondary tests); subgroup by type of device



D4 Arrhythmia not during TLoC

Few studies identified arrhythmias not during TLoC for this population.

Figure 15: arrhythmia not during TLoC unexplained after secondary tests



Adverse events

Seidl (2000) reported that 12 patients out of 130 had an adverse event.

No ECG during TLoC

The studies included for this outcome all had self consistent results. There was no heterogeneity for the IER group and the proportion for this outcome ranged from 4 to 11%.

Figure 17. No ECG during TLoC (unexplained after secondary tests); subgroup by type of device

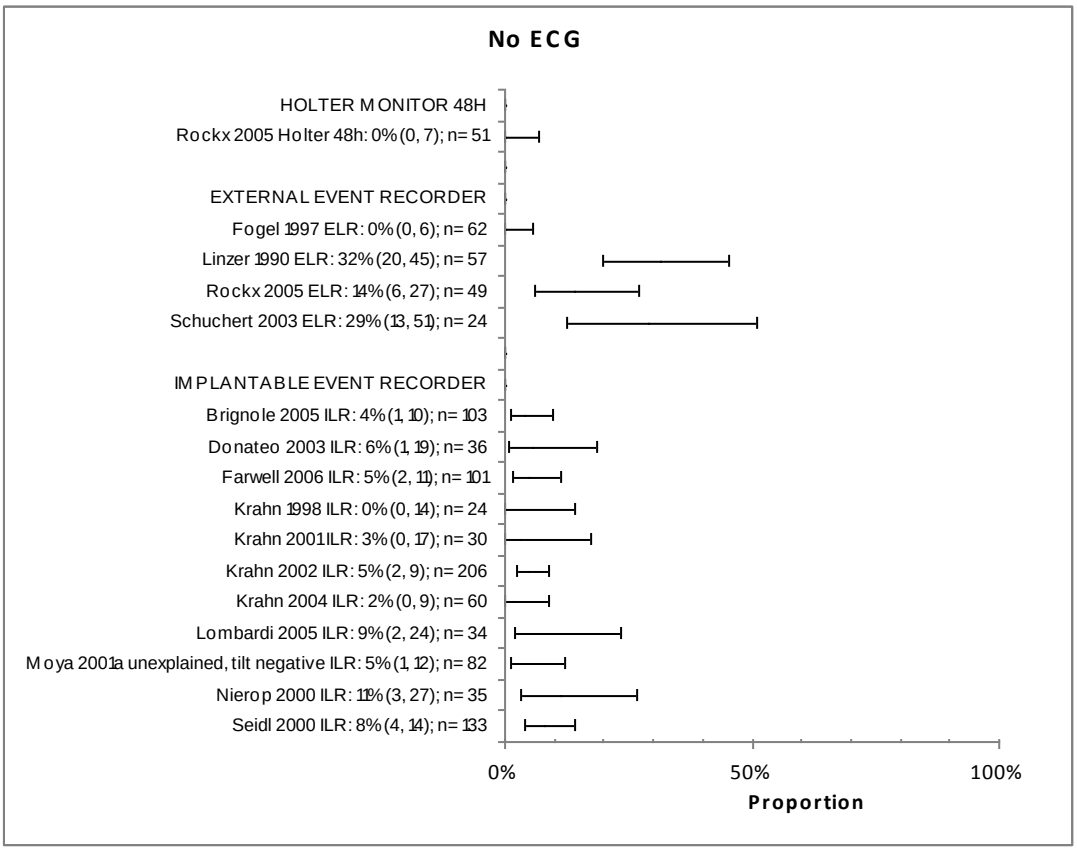


Figure 18. Number of patients started on therapy (unexplained after secondary testing); subgroup by type of device

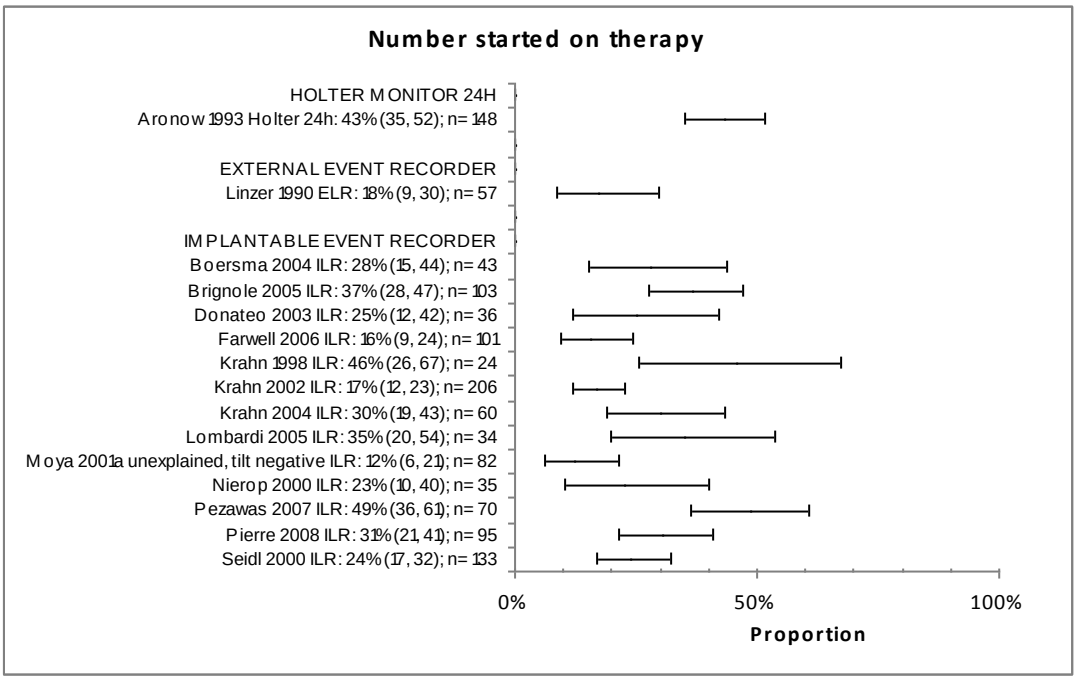
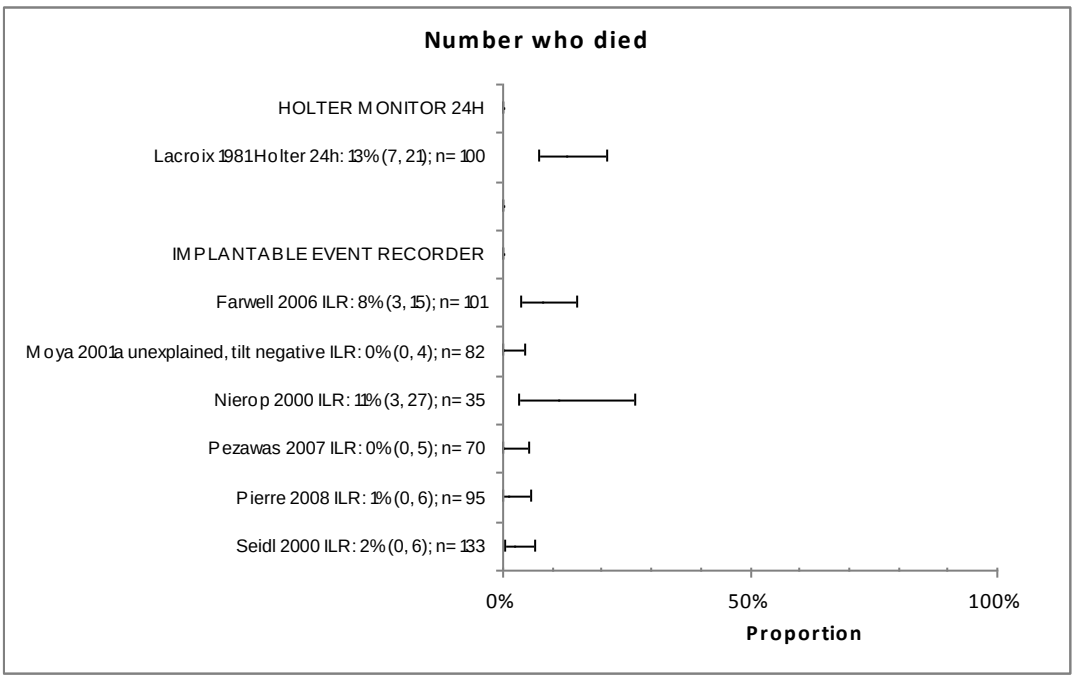


Figure 19. Number of patients who died (unexplained after secondary tests).

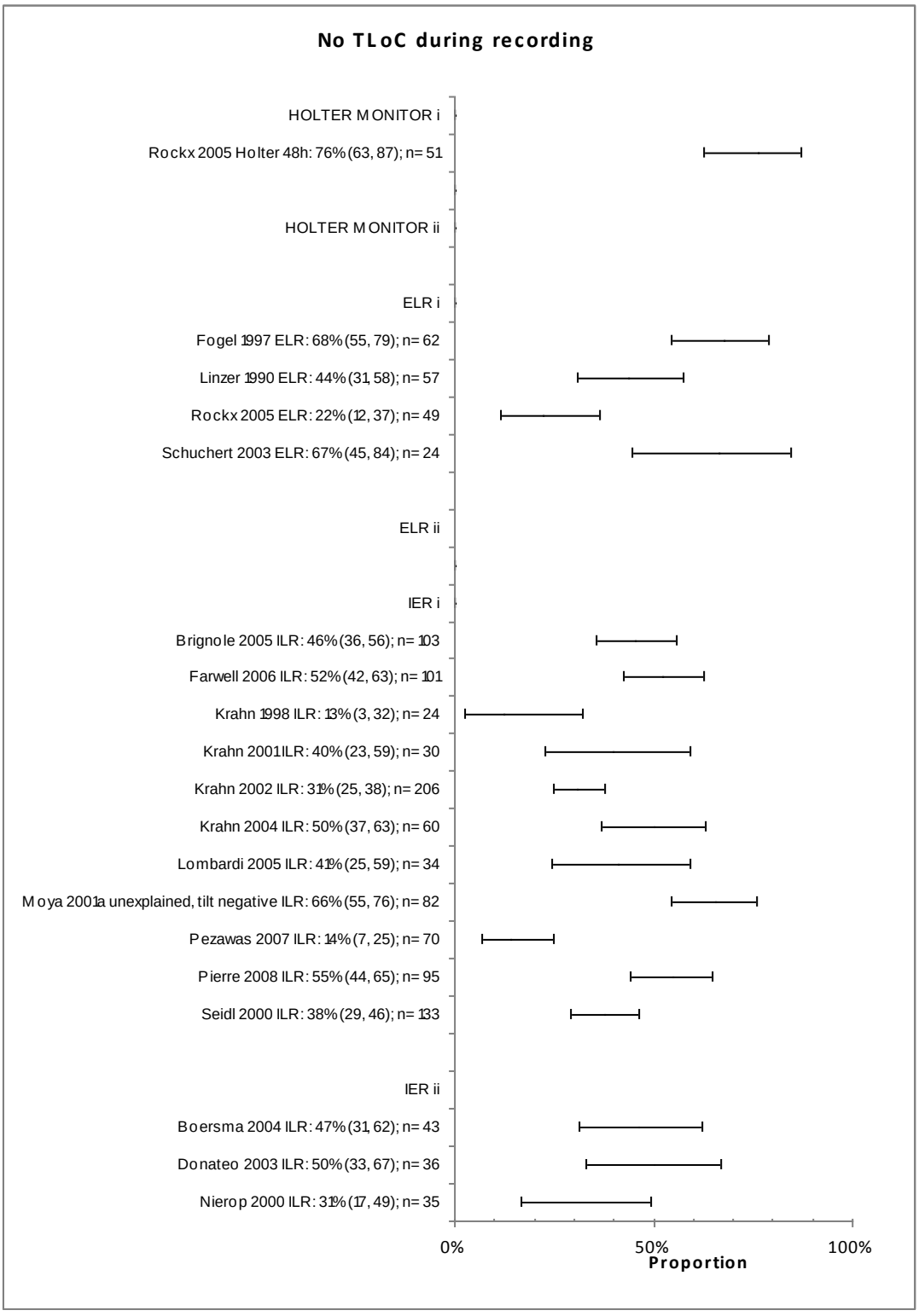


2 Ambulatory ECG review – further analyses

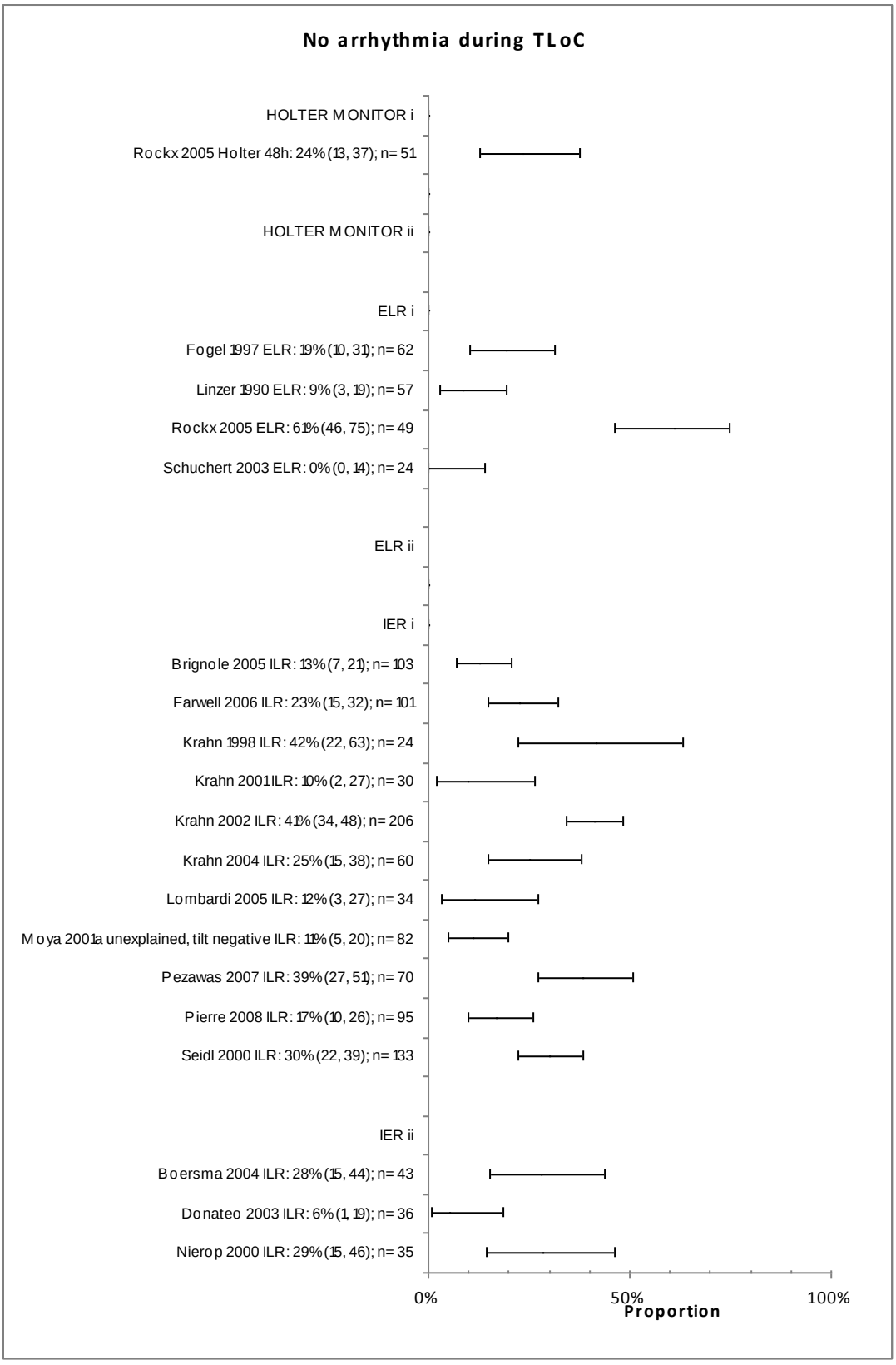
2.1 Subgroup analysis: studies for which patients were included or excluded following secondary tests

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

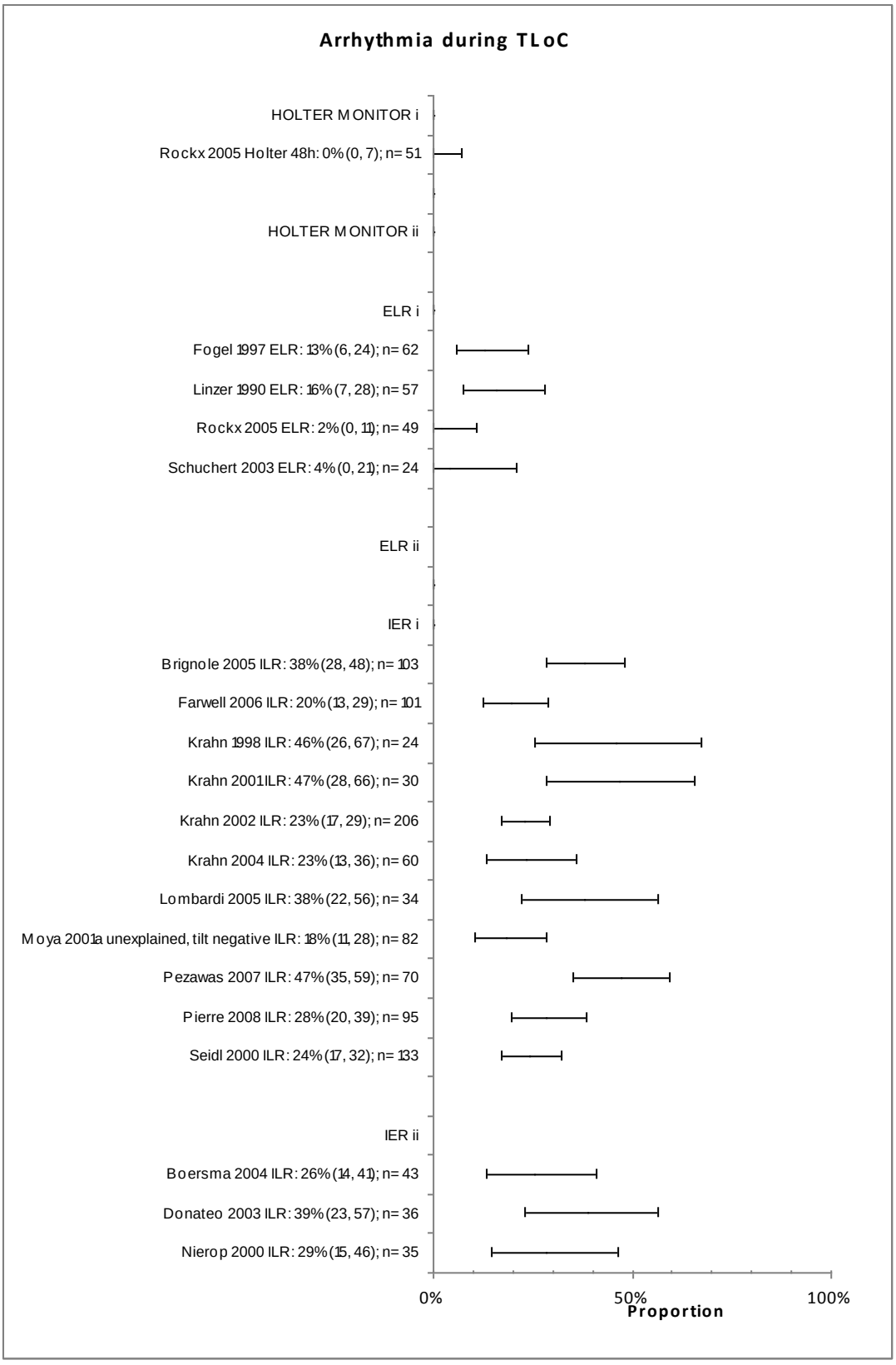
2.1.1 No TLoC during monitoring; unexplained TLoC following secondary tests



2.1.2 Normal Rhythm during TLoC; unexplained TLoC following secondary tests



2.1.3 Arrhythmia during TLoC; unexplained TLoC following secondary tests

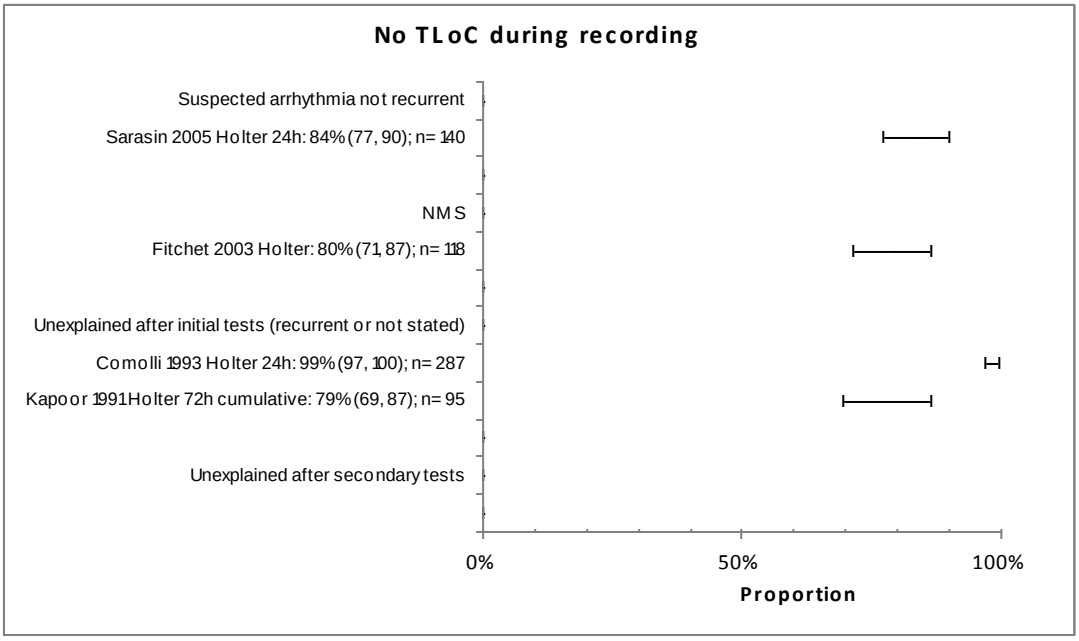


2.2 Ambulatory ECG – results for each type of test, by population

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

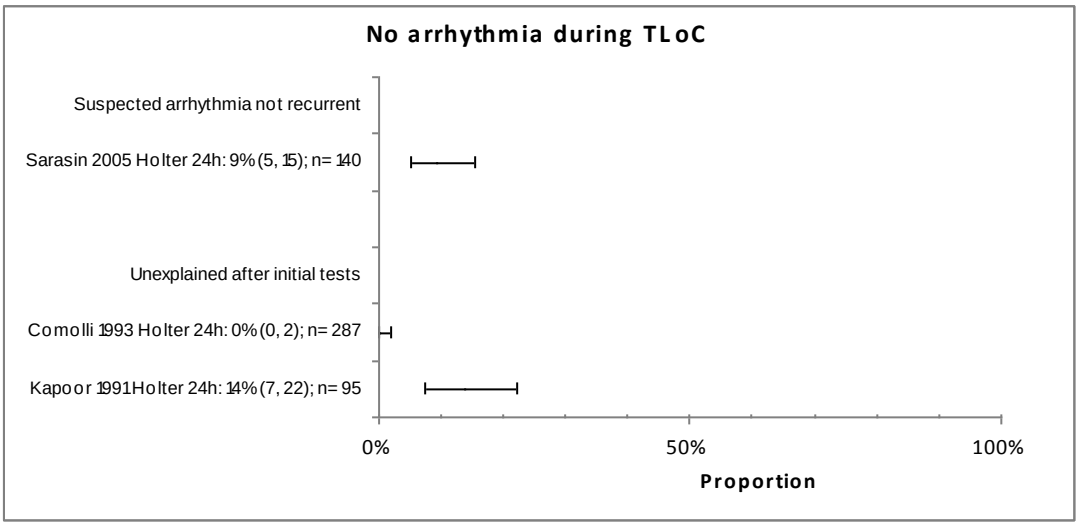
2.2.1 Holter 24-hour monitoring

2.2.1.1 No TLoC during monitoring

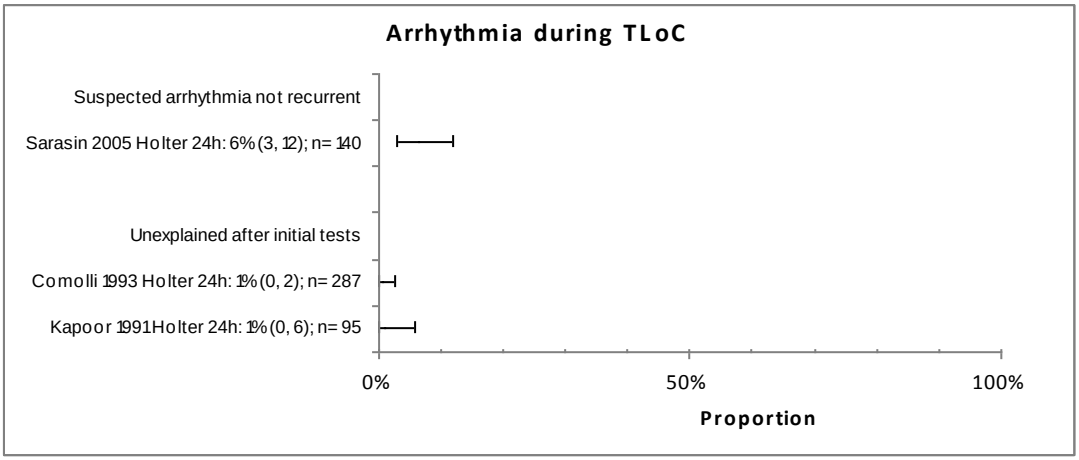


2.2.1.2 Normal rhythm during TLoC

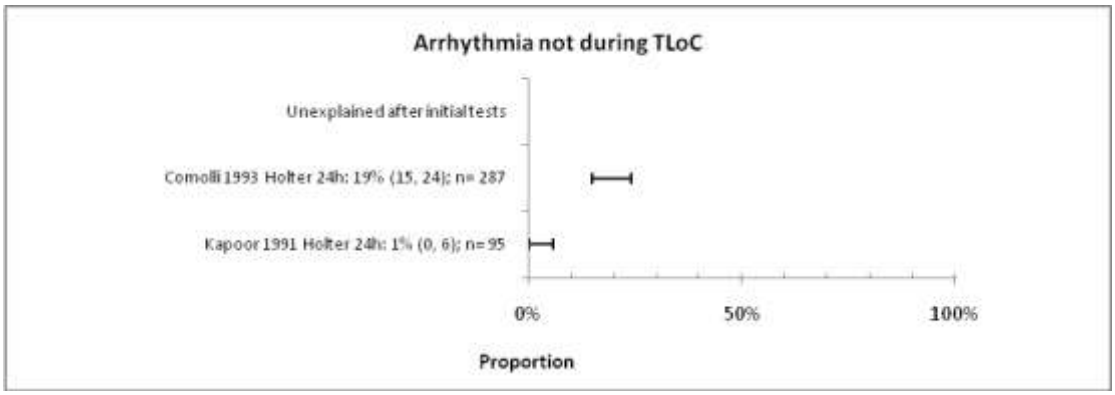
No NM syncope patients had Holter monitoring and reported this outcome



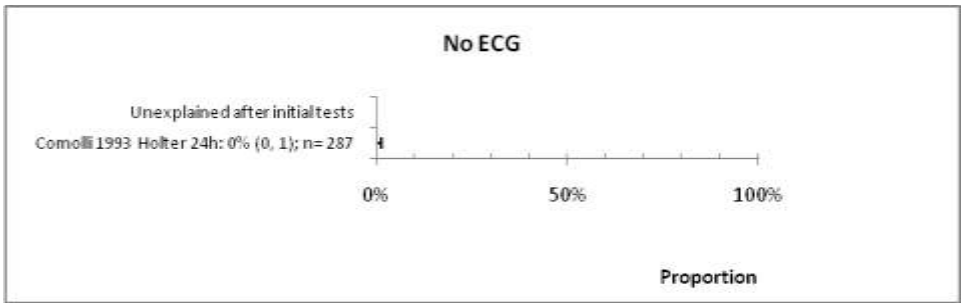
2.2.1.3 Arrhythmia during TLoC



2.2.1.4 Arrhythmia not during TLoC



2.2.1.5 No ECG during TLoC

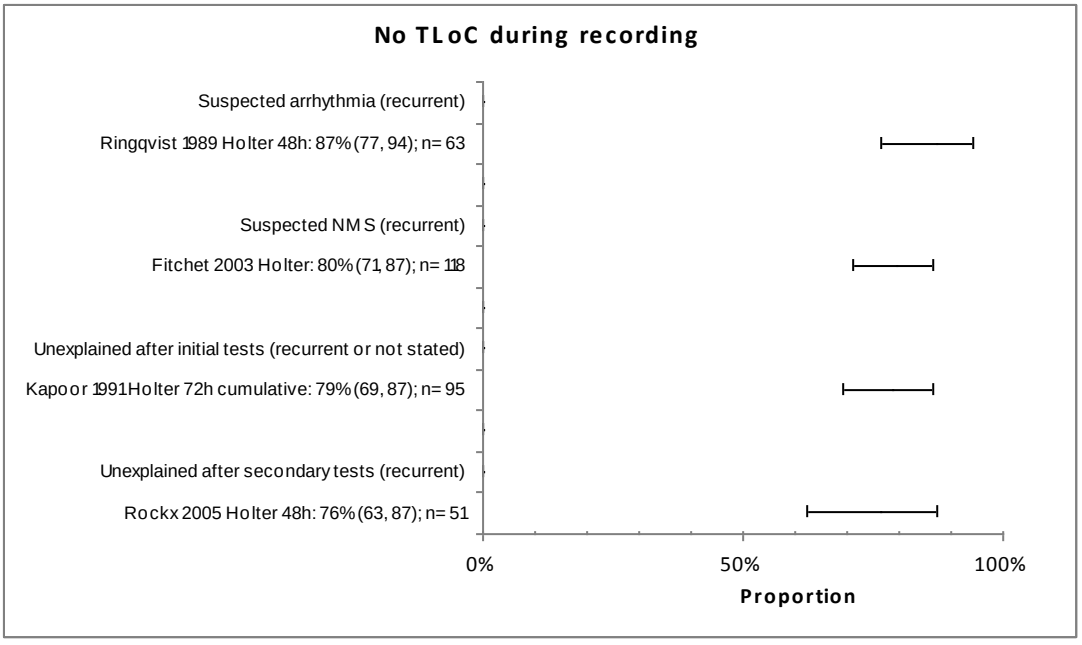


2.2.1.6 Adverse events

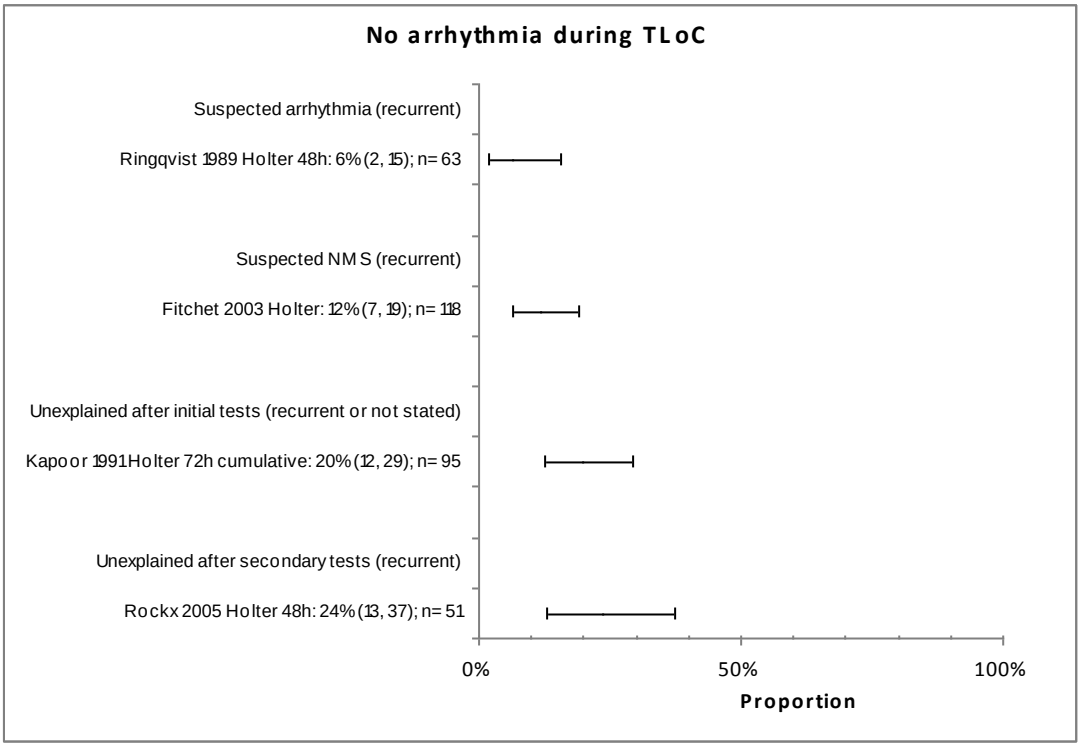
No studies reported this outcome

2.2.2 48-hour Holter monitoring or longer

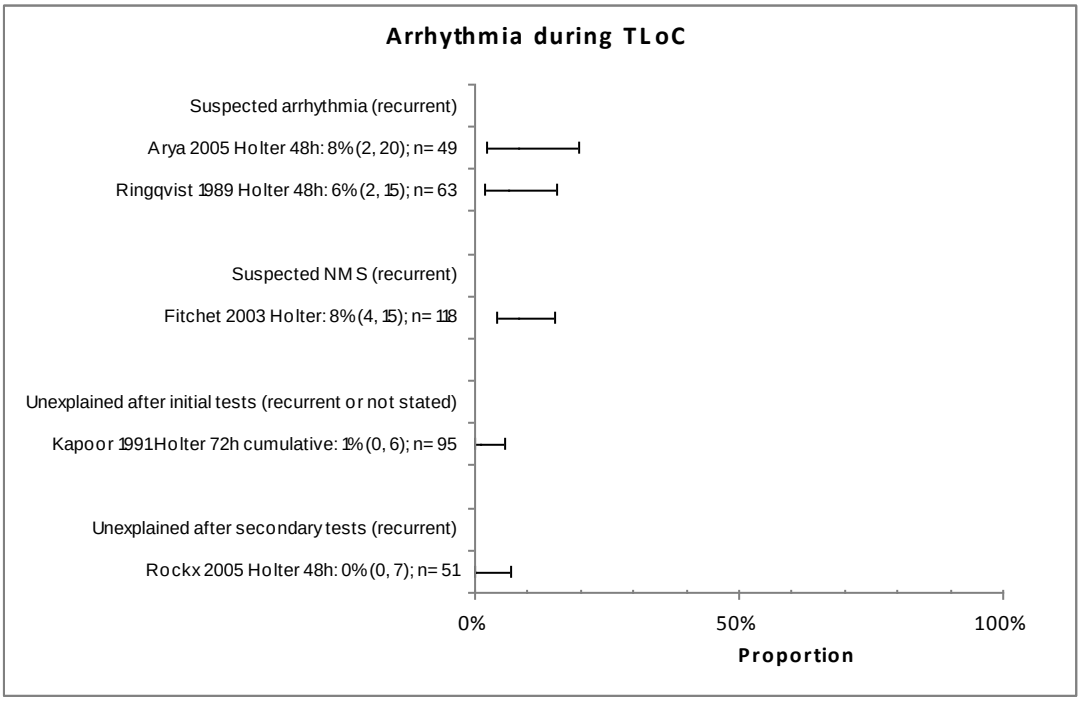
2.2.2.1 No TLoC during recording period



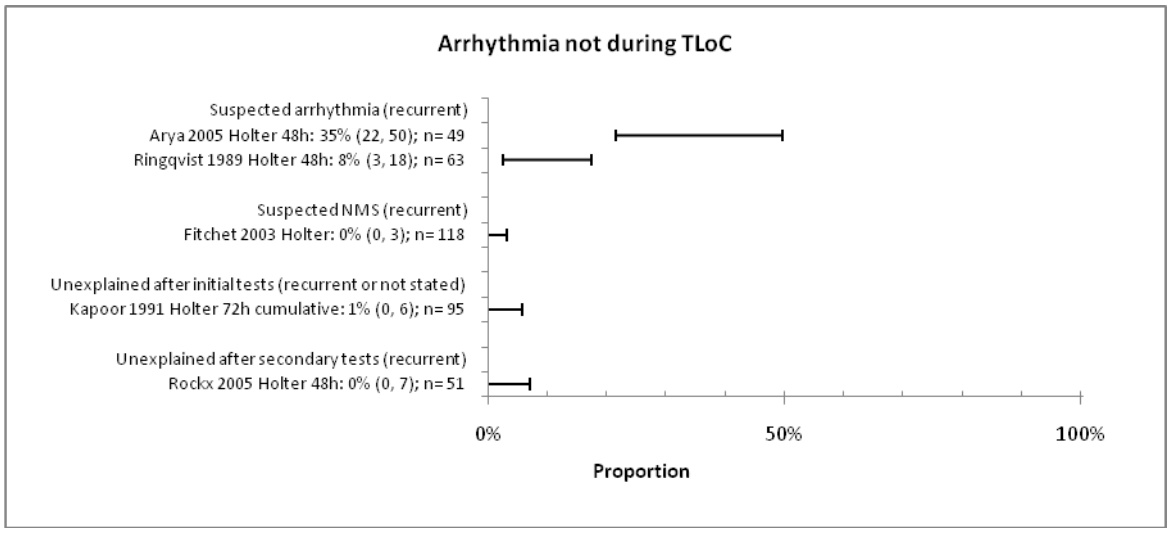
2.2.2.2 Normal rhythm during TLoC



2.2.2.3 Arrhythmia during TLoC



2.2.2.4 Arrhythmia not during TLoC



2.2.2.5 No ECG during TLoC

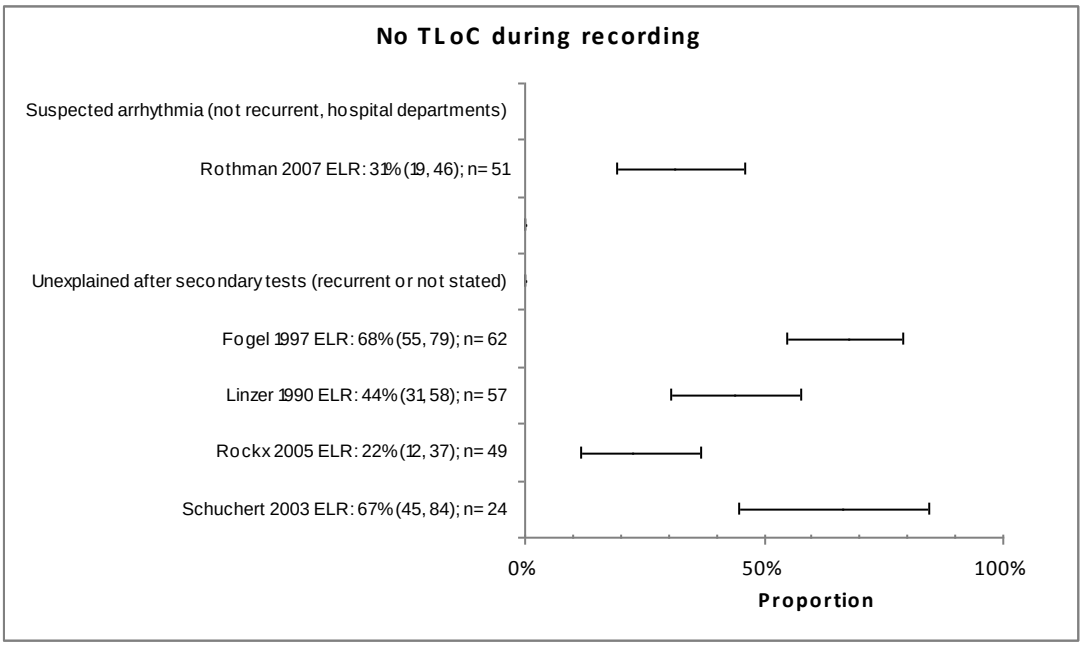
No studies reported this outcome.

2.2.2.6 Adverse events

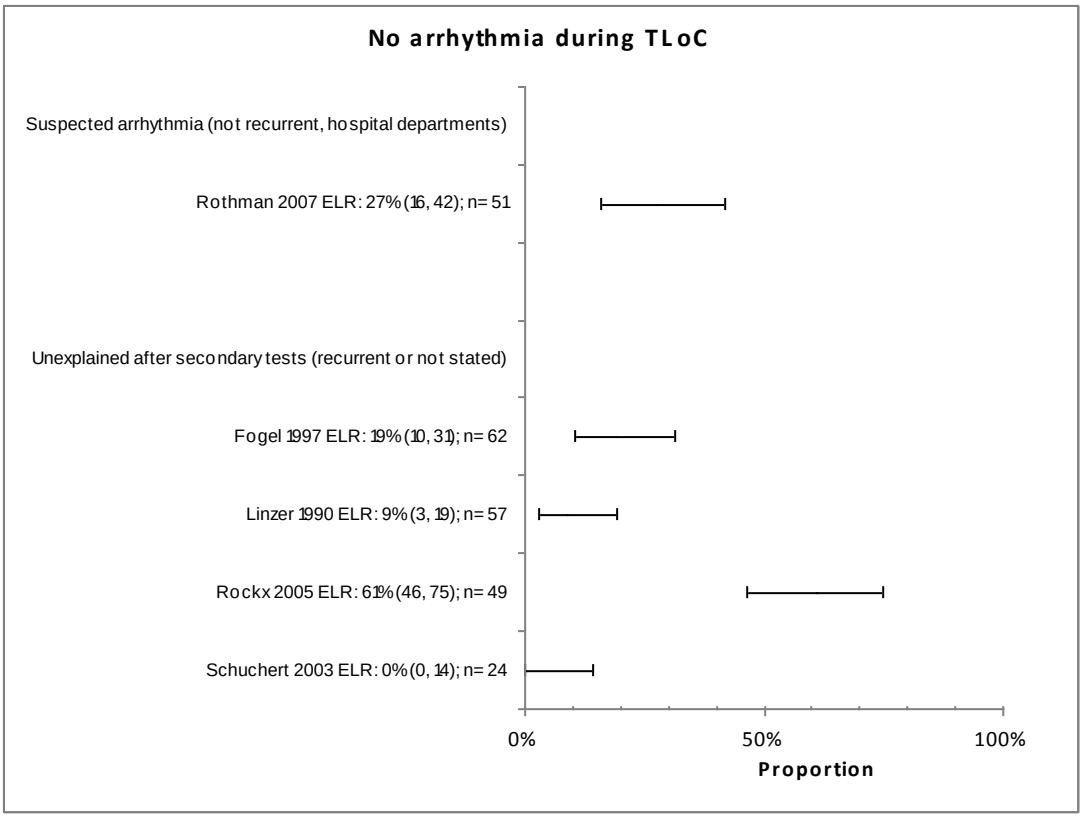
No studies reported this outcome.

2.2.3 External event recorder

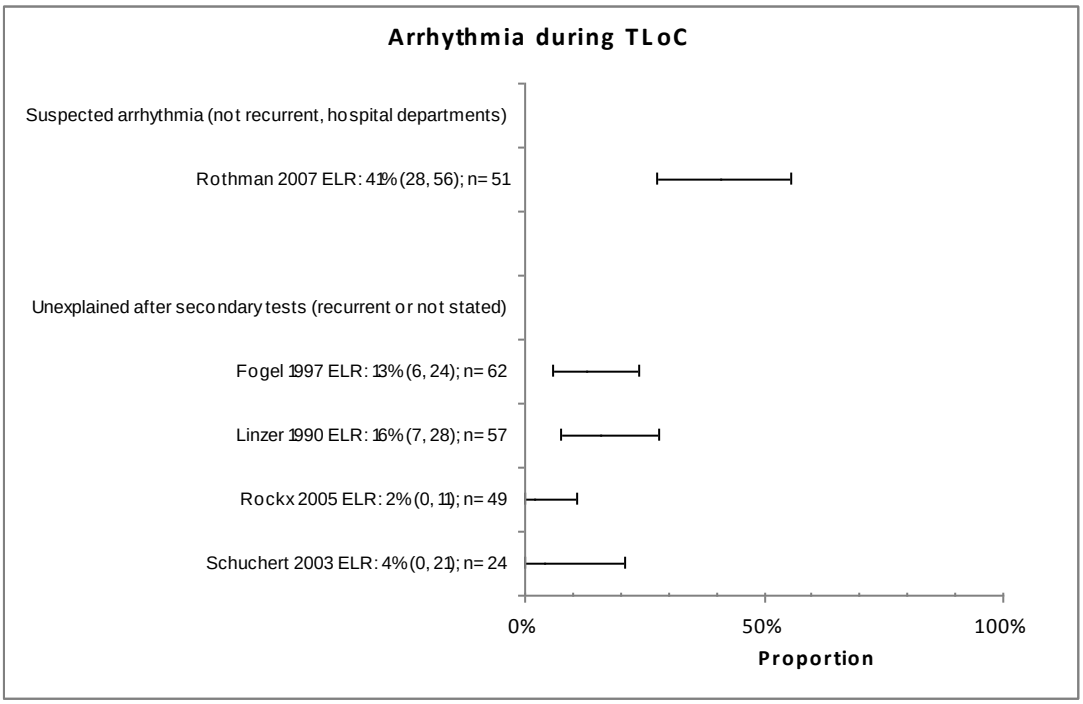
2.2.3.1 No TLoC during recording period



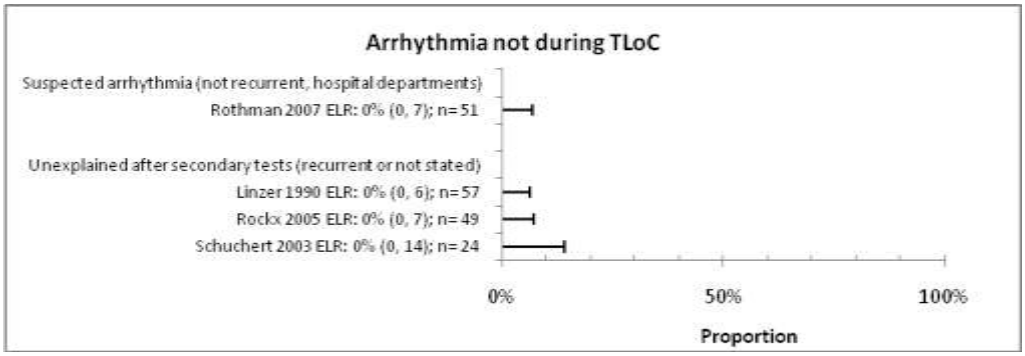
2.2.3.2 Normal rhythm during TLoC



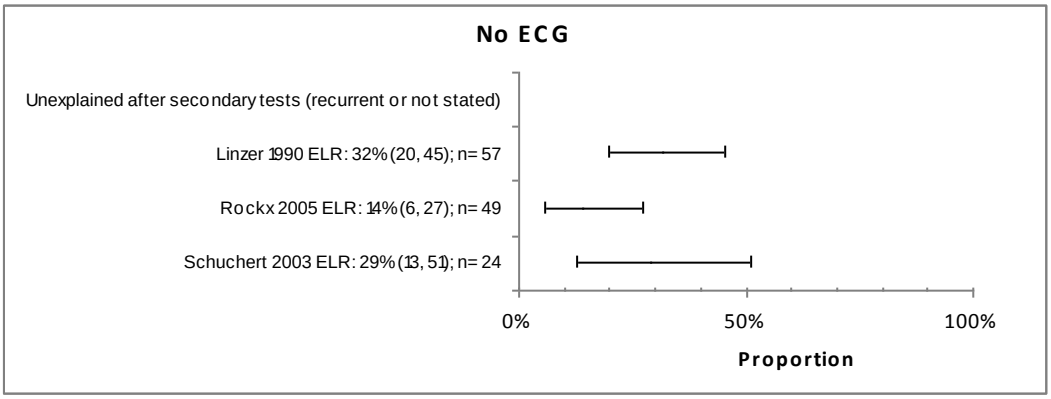
2.2.3.3 Arrhythmia during TLoC



2.2.3.4 Arrhythmia not during TLoC



2.2.3.5 No ECG during TLoC

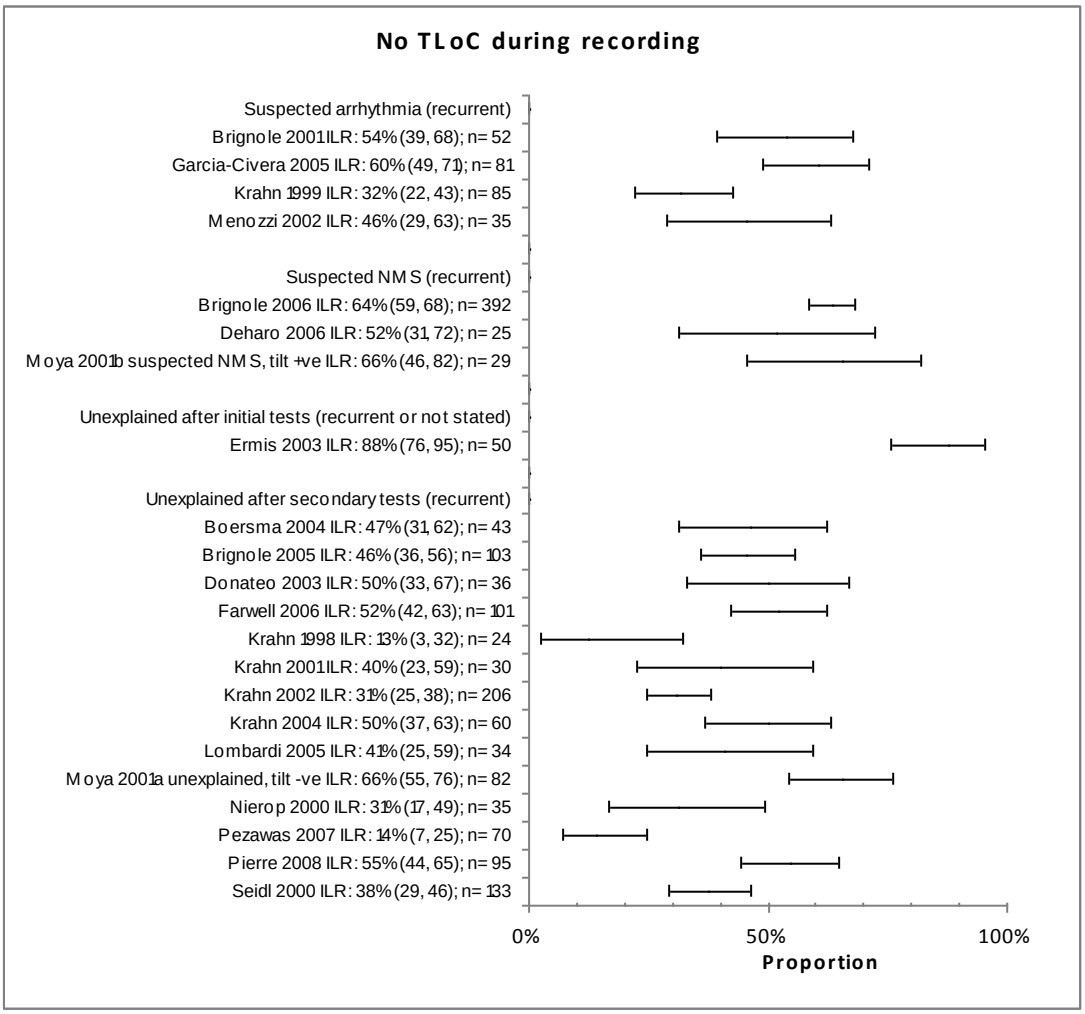


2.2.3.6 Adverse events

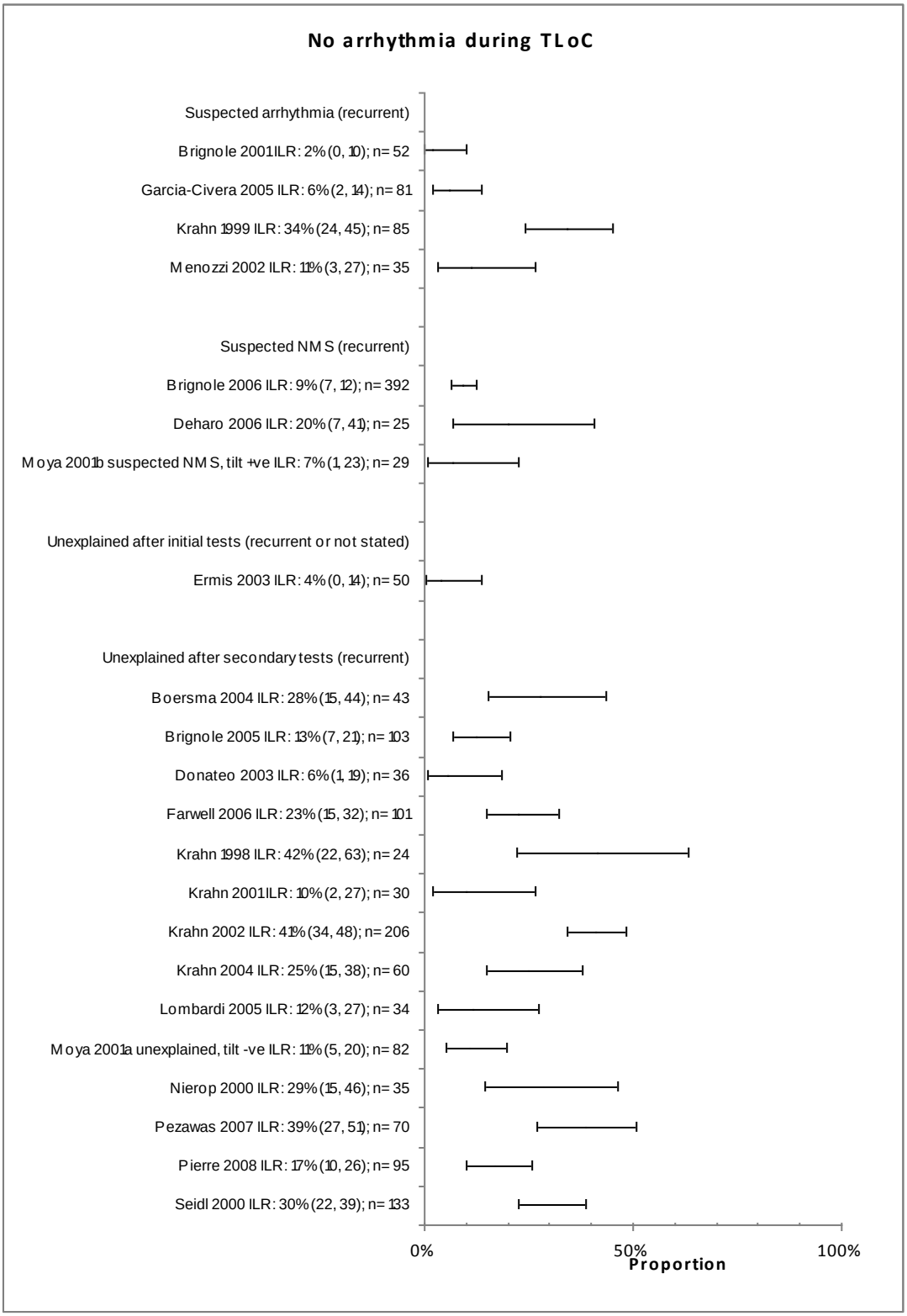
No studies reported this outcome.

2.2.4 Implantable Event Recorder

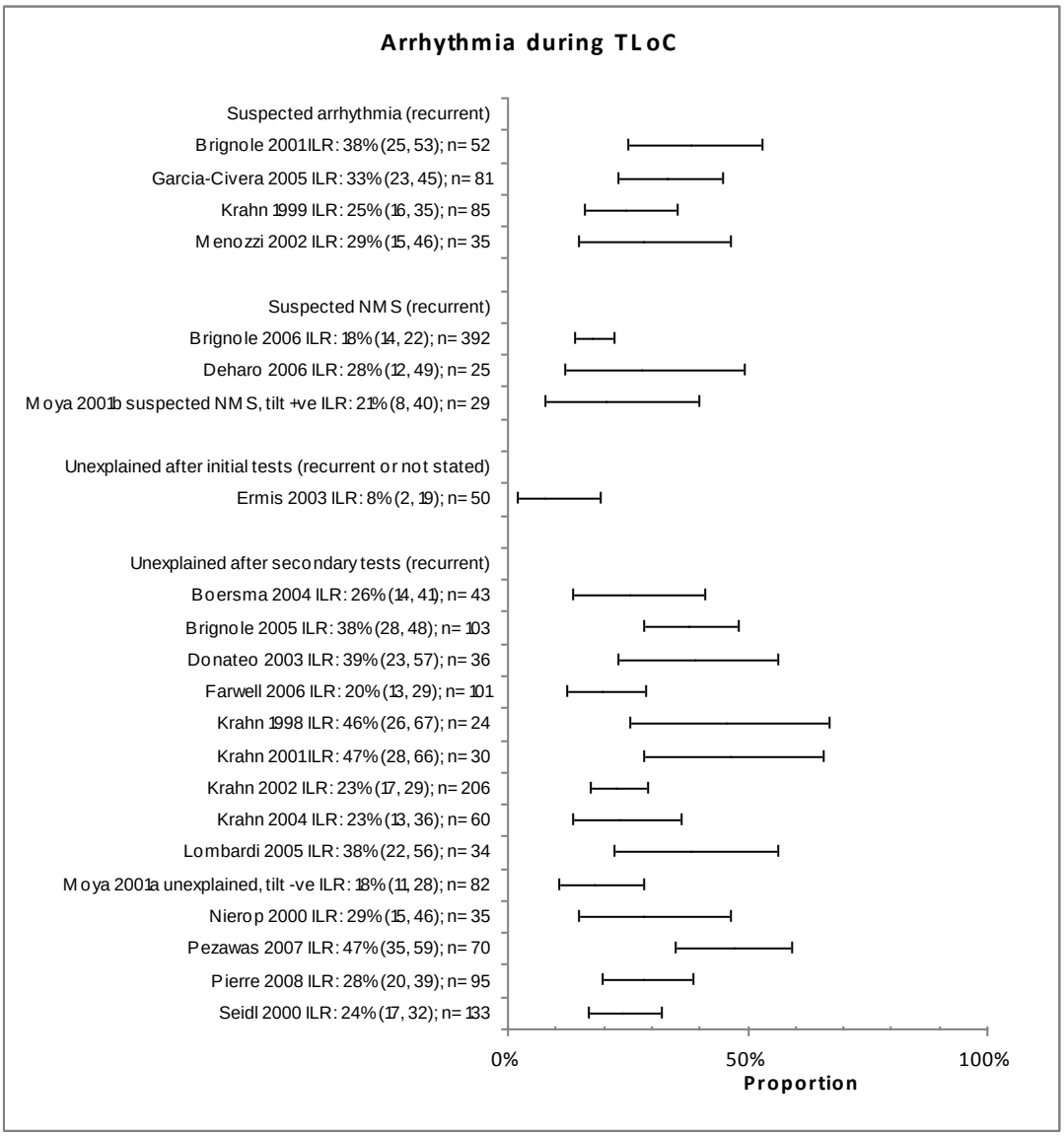
2.2.4.1 No TLoC during recording period



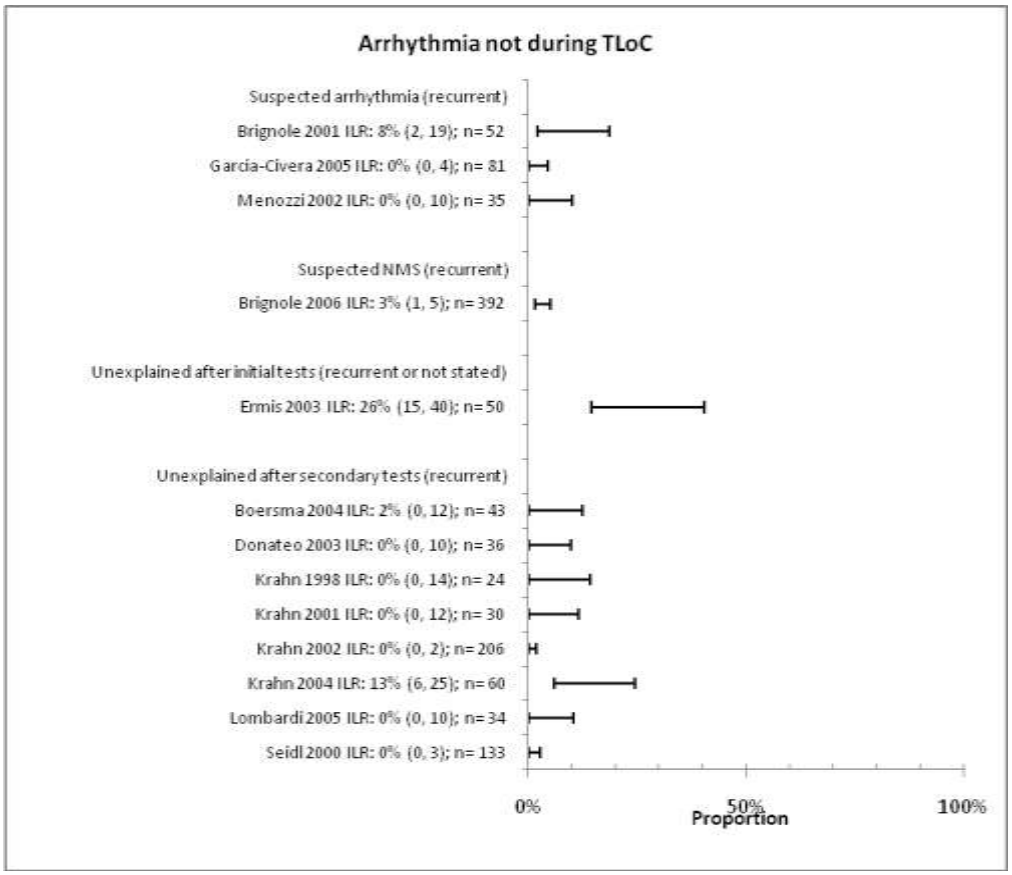
2.2.4.2 Normal rhythm during TLoC



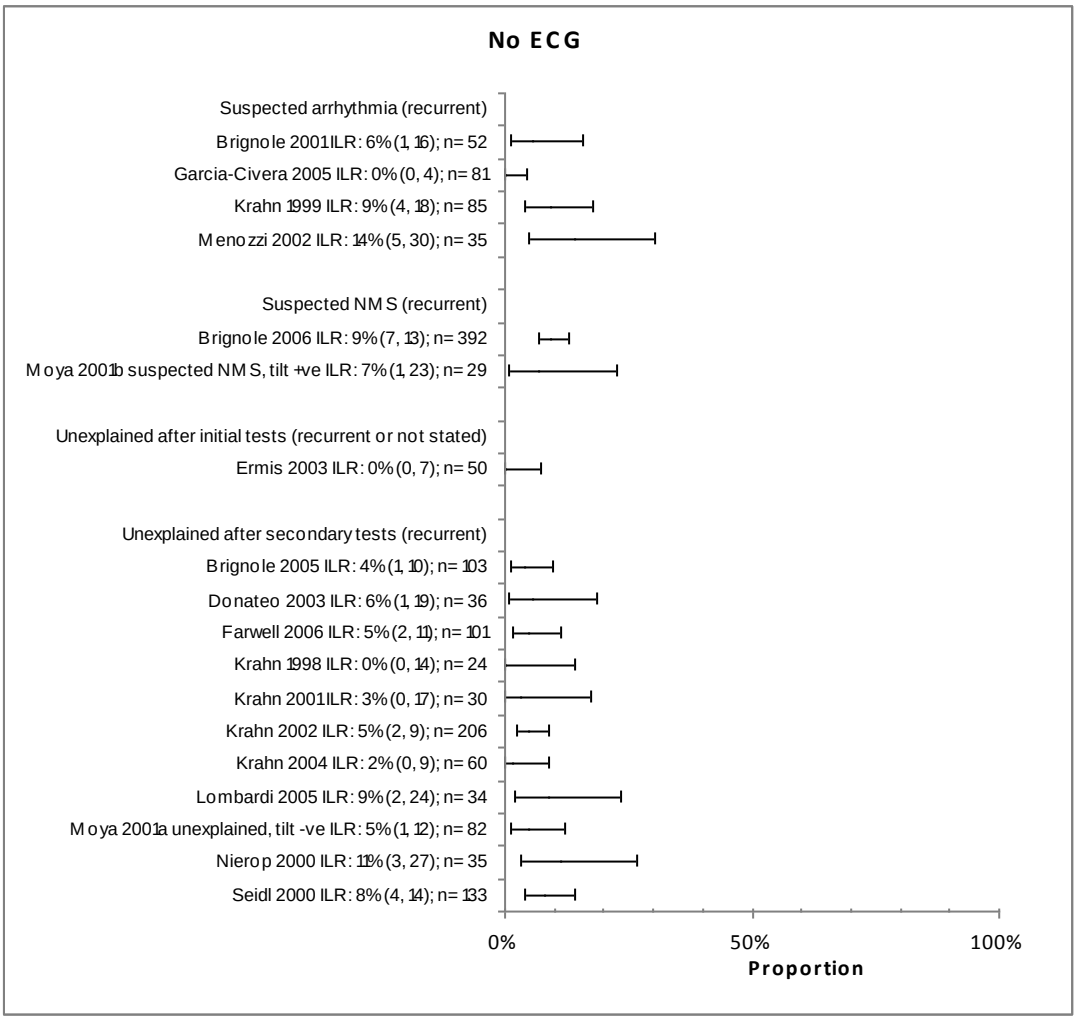
2.2.4.3 Arrhythmia during TLoC



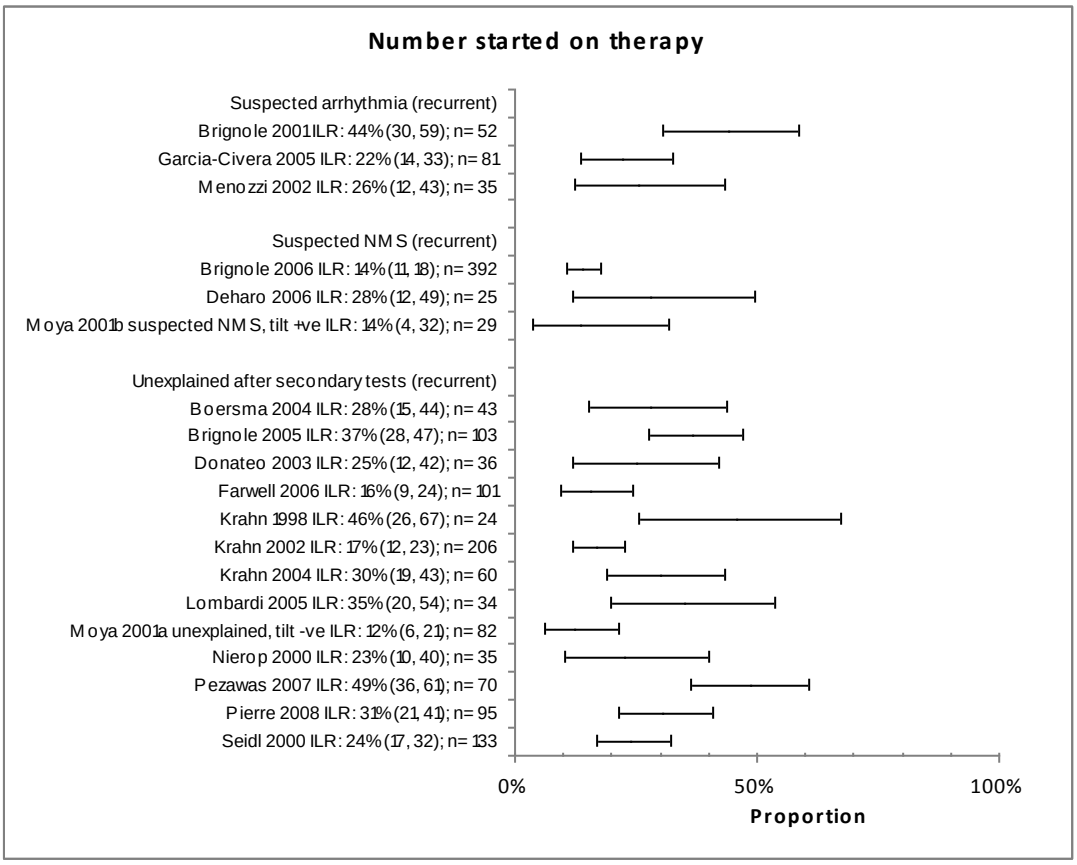
2.2.4.4 Arrhythmia not during TLoC



2.2.4.5 No ECG during TLoC



2.2.4.6 Number of patients started on therapy

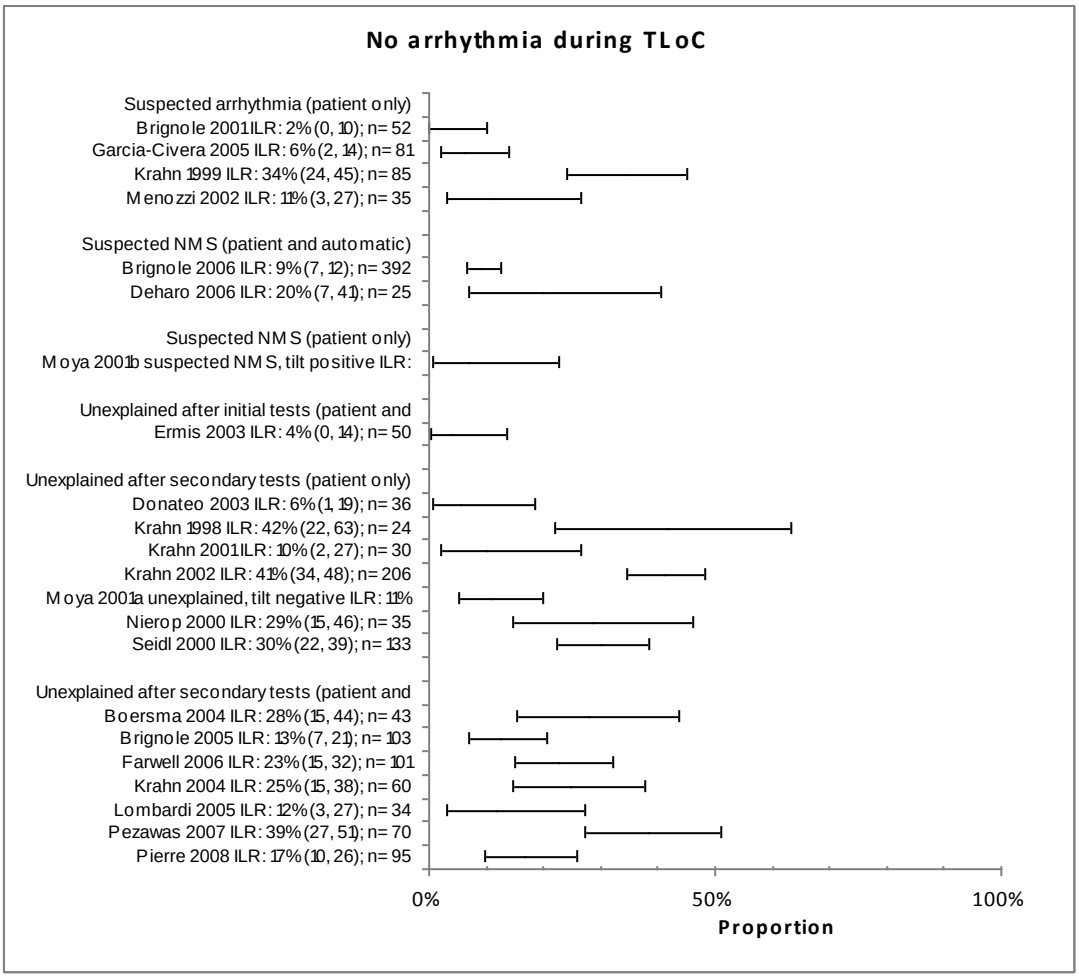


2.2.4.7 Adverse events

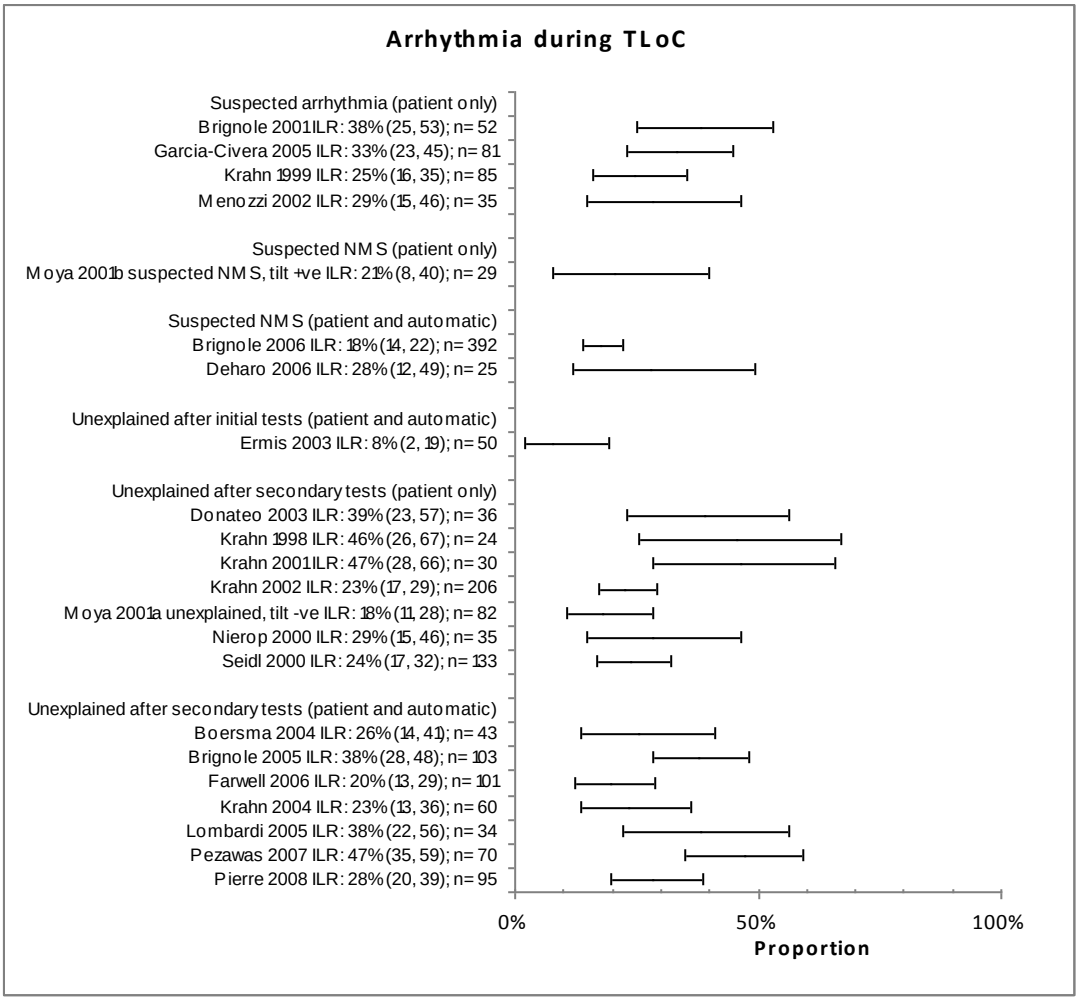
No studies reported this outcome.

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

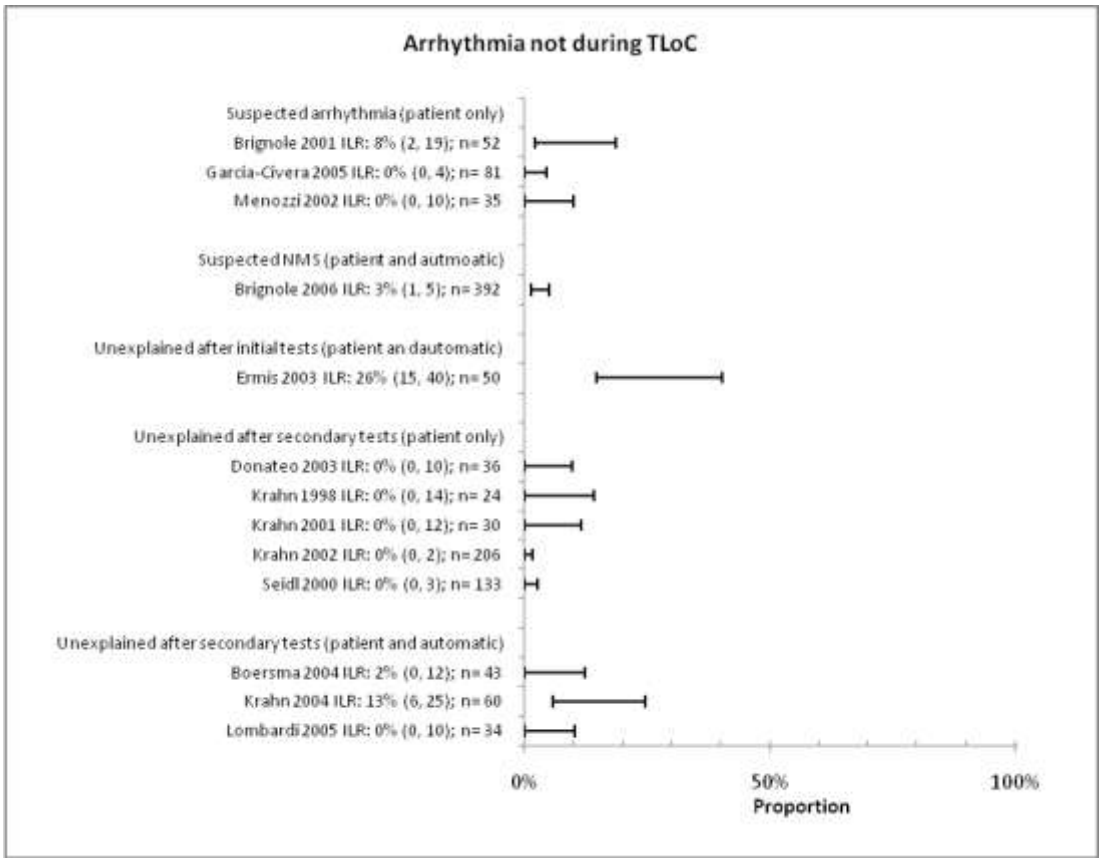
2.3.1 Normal rhythm during TLoC



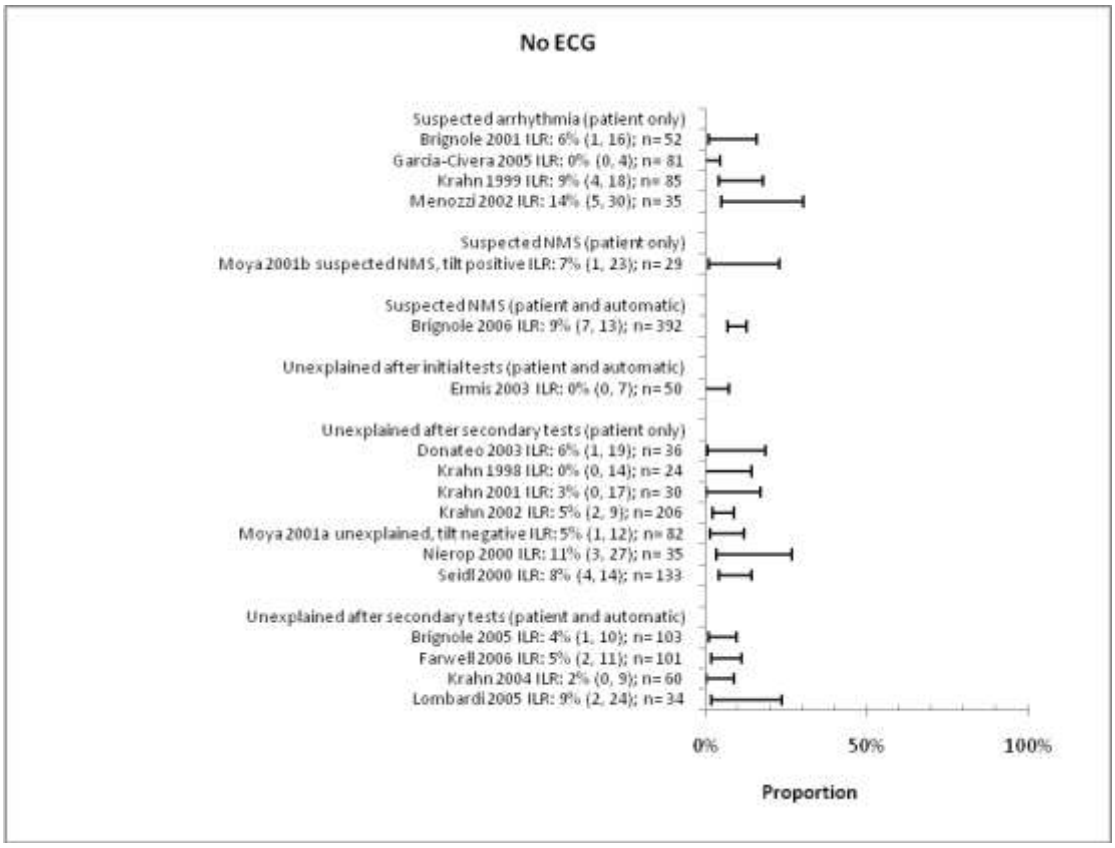
2.3.2 Arrhythmia during TLoC



2.3.3 Arrhythmia not during TLoC



2.3.4 No ECG during TLoC

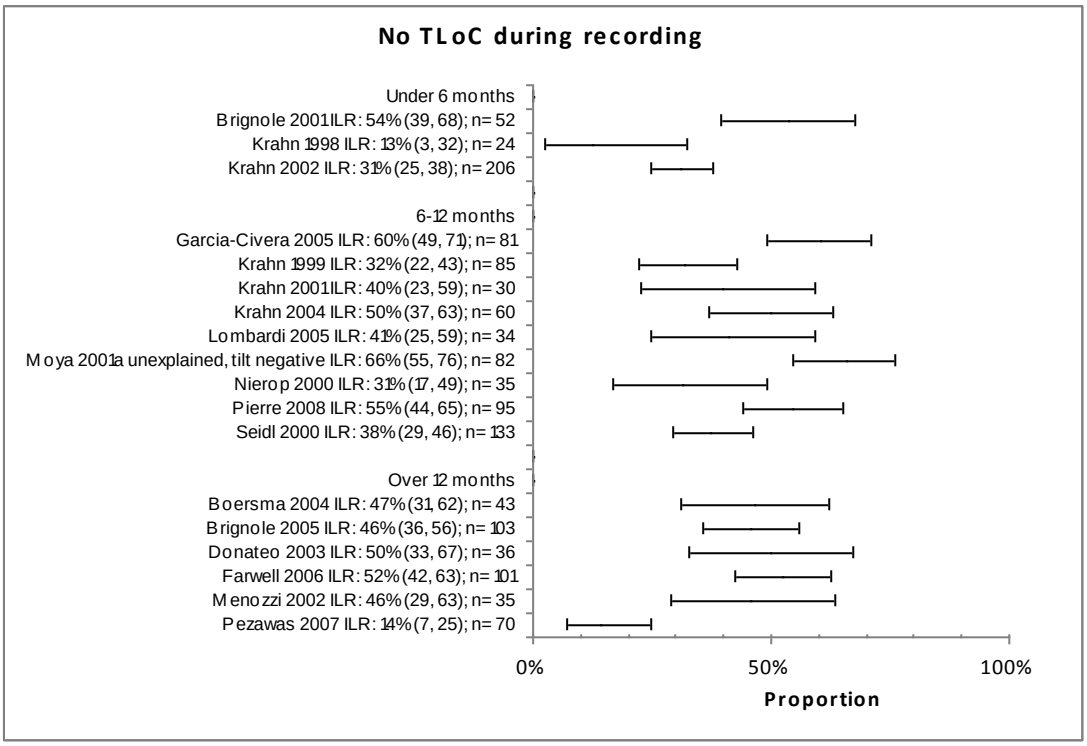


2.4 Implantable Event Recorder results only: subgroup analyses by duration, frequency and their product

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.

2.4.1 Subgroup analysis by duration for IER: populations combined

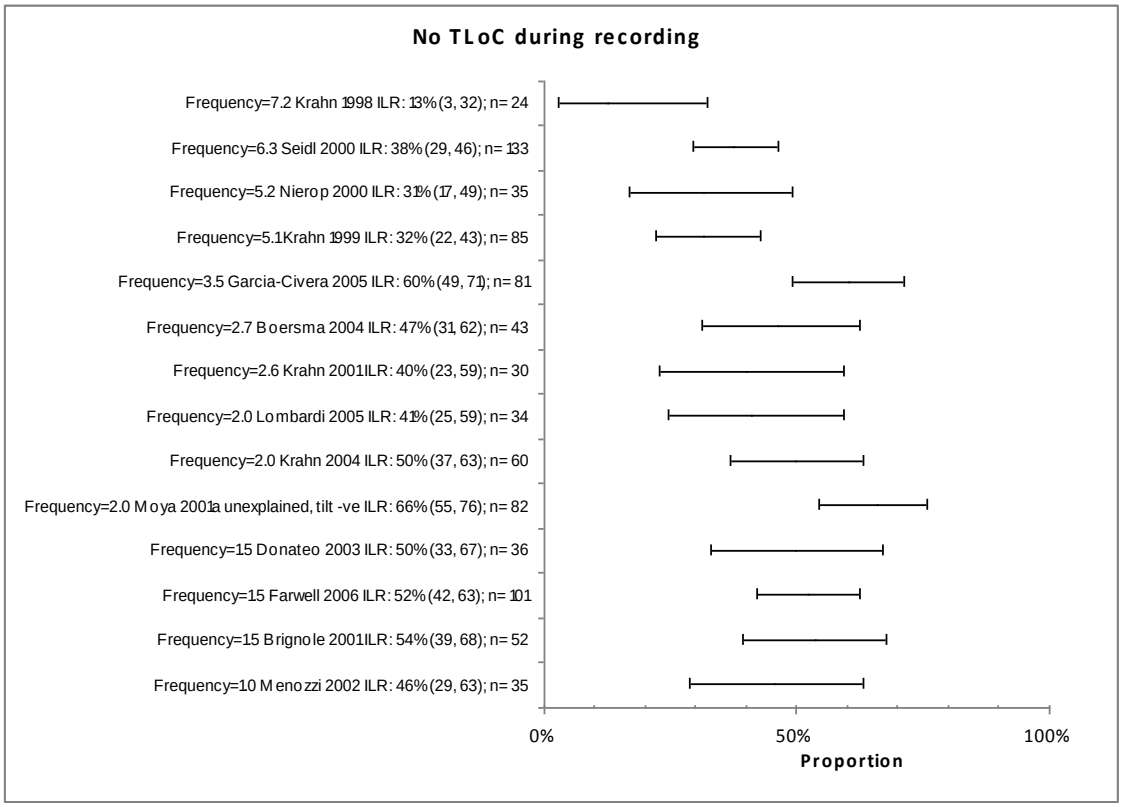
Subgroup analysis was carried out for the pre-specified durations, but this did not explain the heterogeneity.



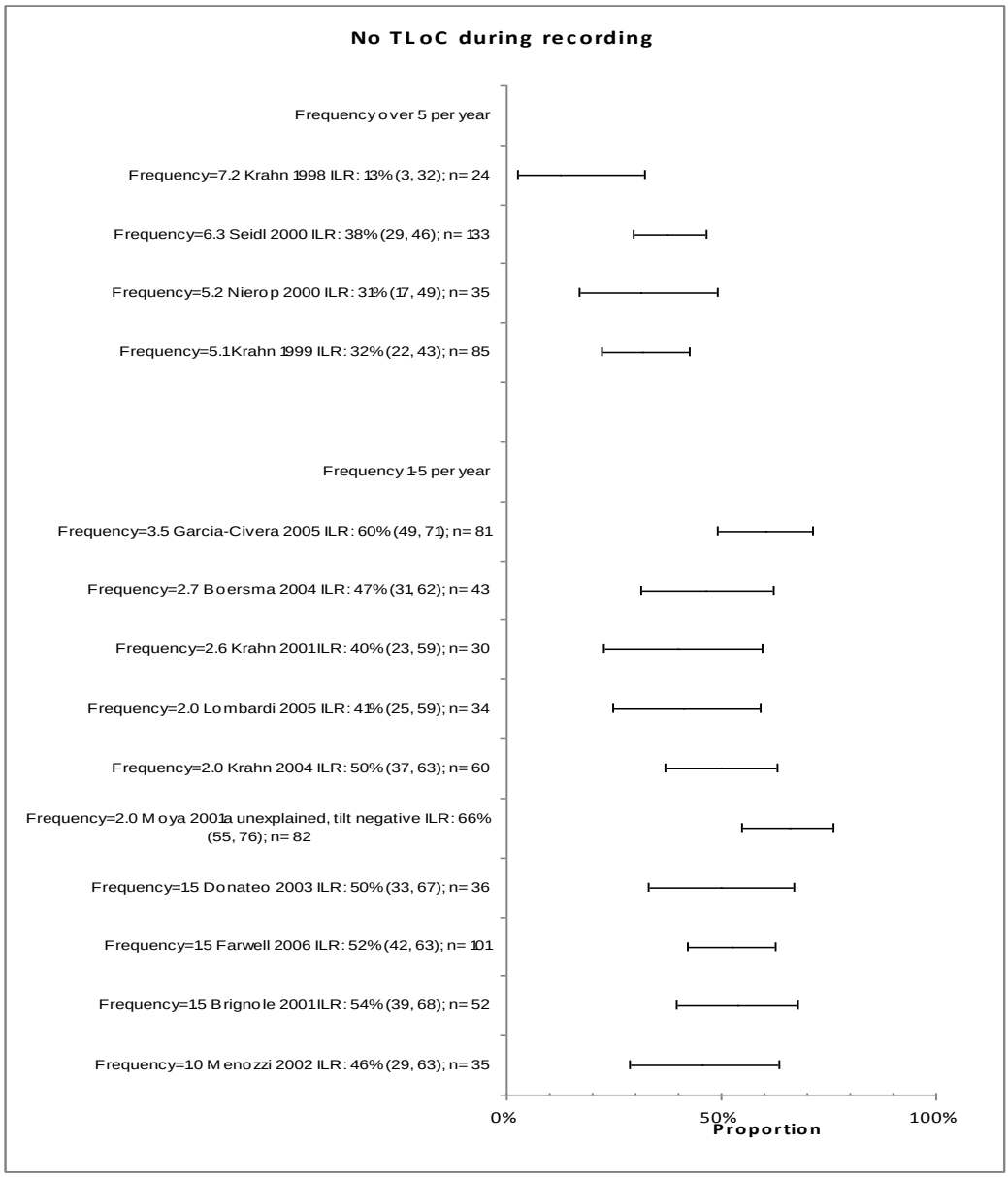
2.4.2 Subgroup analysis by frequency for IER: populations combined

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.

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



2.4.2.2 Post hoc subgroup analysis by frequency of TLoC

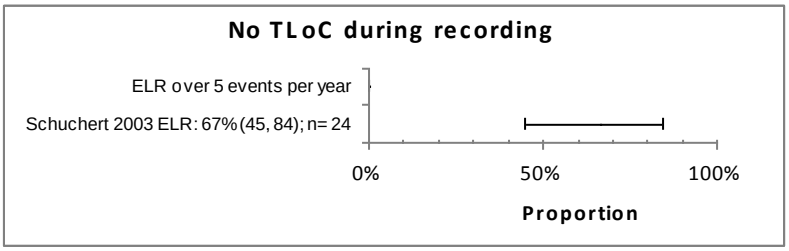


2.4.3 Sensitivity analysis taking into consideration frequency of previous TLoC – IER and EER

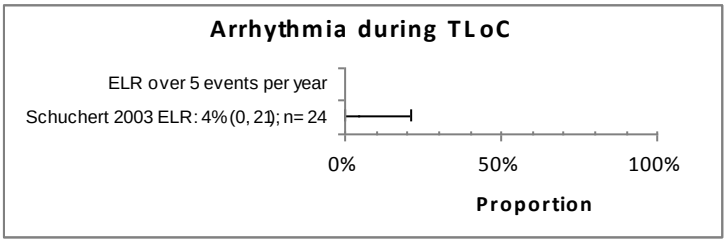
All the studies that reported the frequency of previous TLoC fall into the 'infrequent' category (i.e. less than 24 events per year). We carried out a sensitivity analysis, including only the studies that reported more than 5 events per year, this restricts the analyses to the following studies: Boersma

(2004), Deharo (2006), Krahn (1999), Nierop (2000), Schuchert (2003) and Seidl (2000).

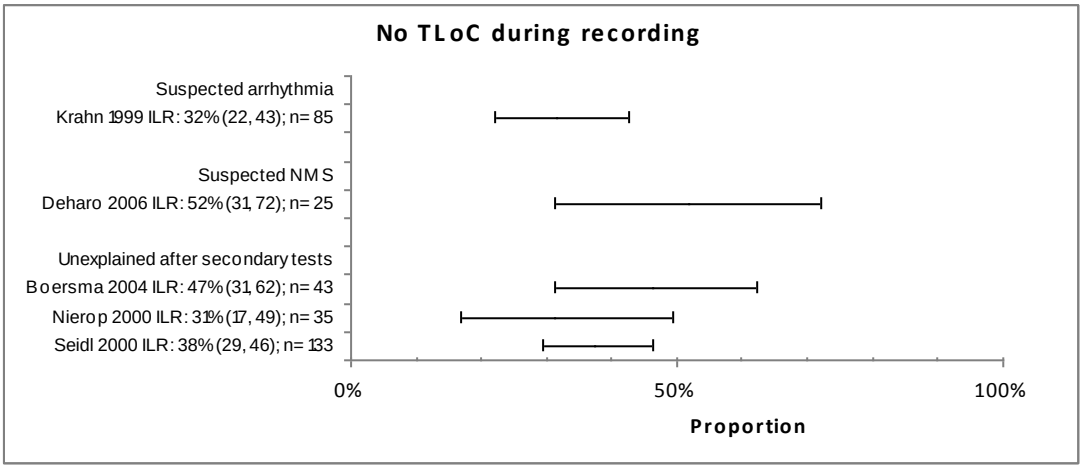
2.4.3.1 External event recorder: no TLoC during monitoring



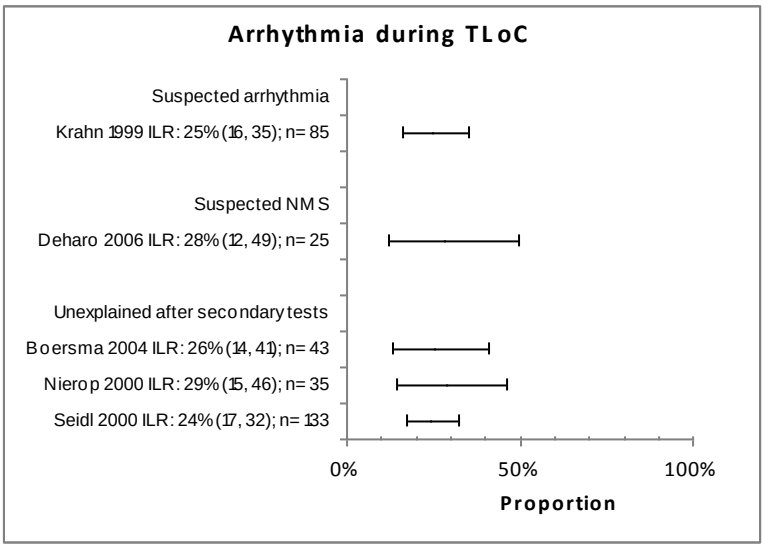
2.4.3.2 External event recorder: arrhythmia during TLoC



2.4.3.3 Implantable event recorder: no TLoC during monitoring



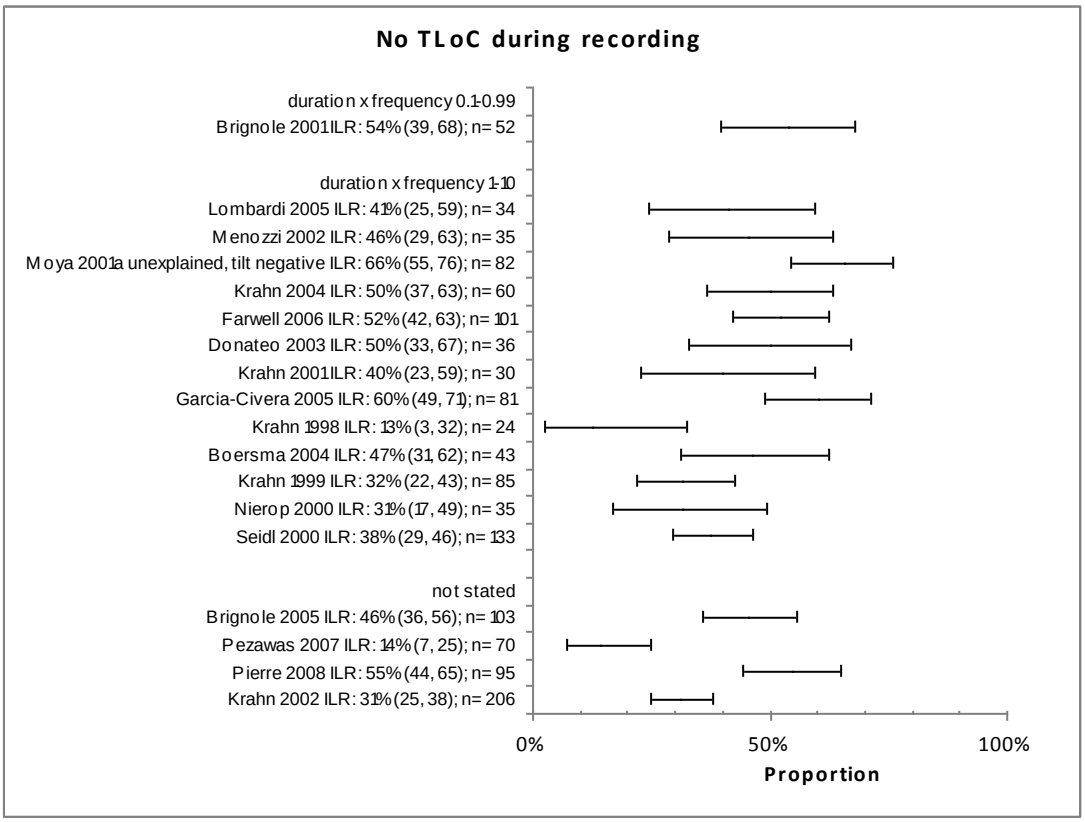
2.4.3.4 Implantable event recorder: Arrhythmia during TLoC



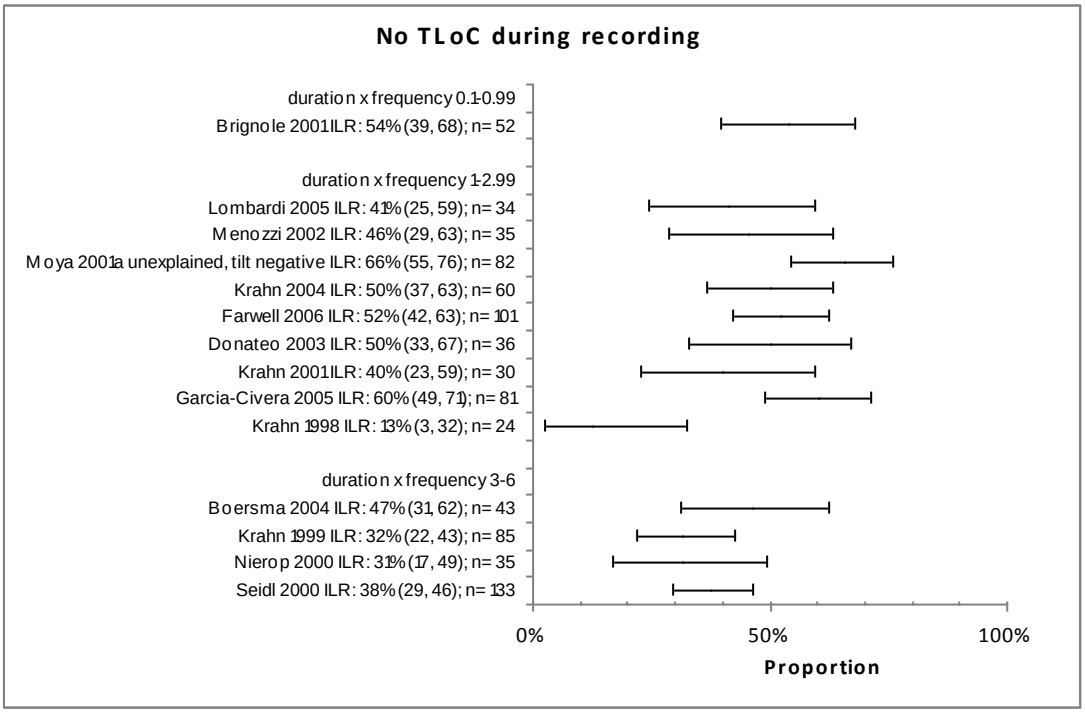
2.4.4 Subgroup analysis by the product of duration x frequency for the outcome, no TLoC during monitoring

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.

2.4.4.1 Pre-specified subgroup analysis



2.4.4.2 Post-hoc subgroup analysis



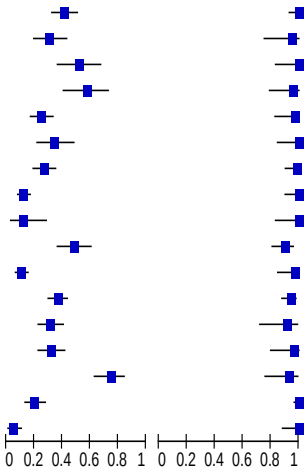
3 Tilt test additional analyses

3.1 HUT-passive

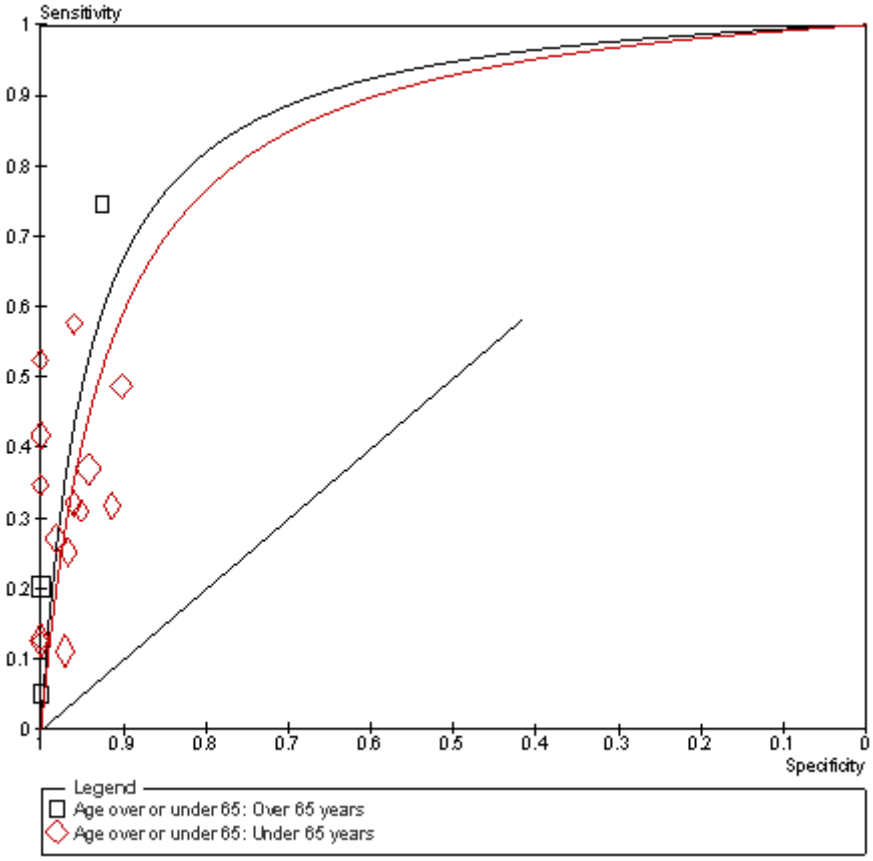
3.1.1 Age over or under 65 years (sorted by mean age in studies ('age continuous'); youngest to oldest)

3.1.1.1 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]



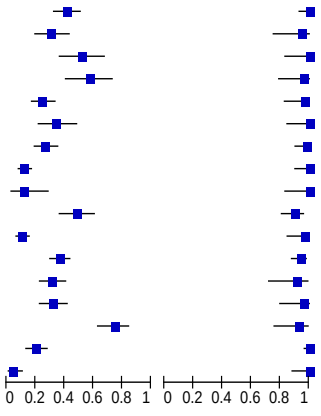
3.1.1.2 ROC curve (over versus under 65 years)



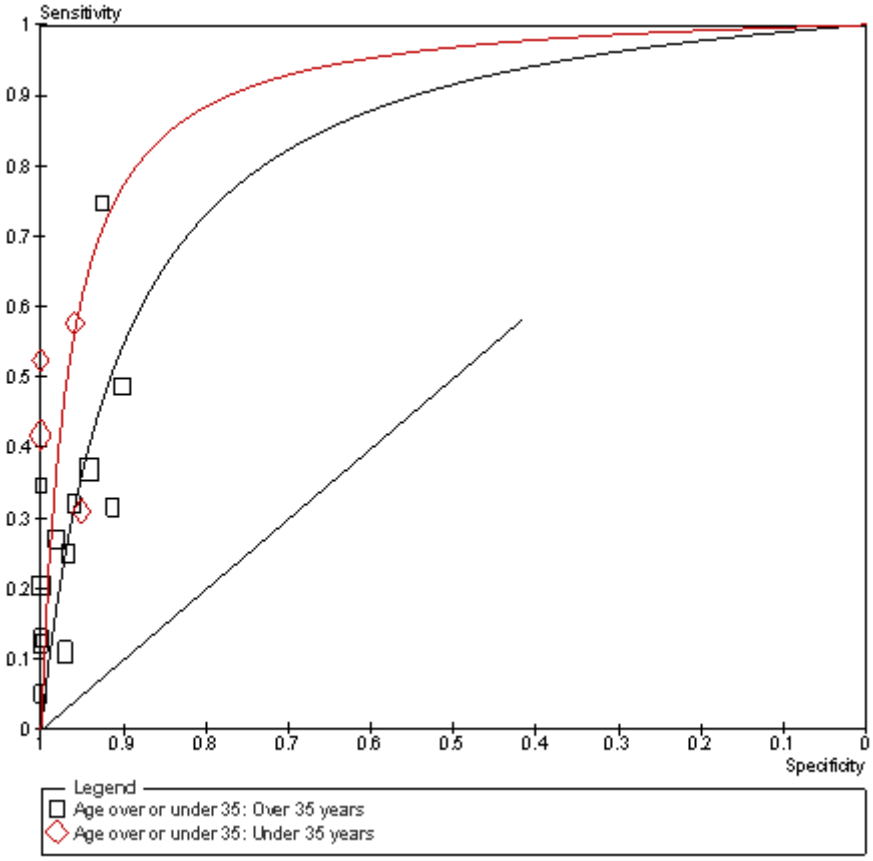
3.1.2 Age over or under 35 years

3.1.2.1 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]



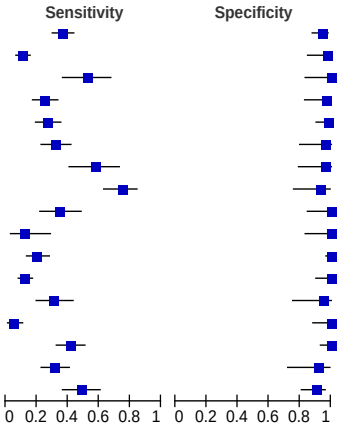
3.1.2.2 ROC curve (over versus under 35 years)



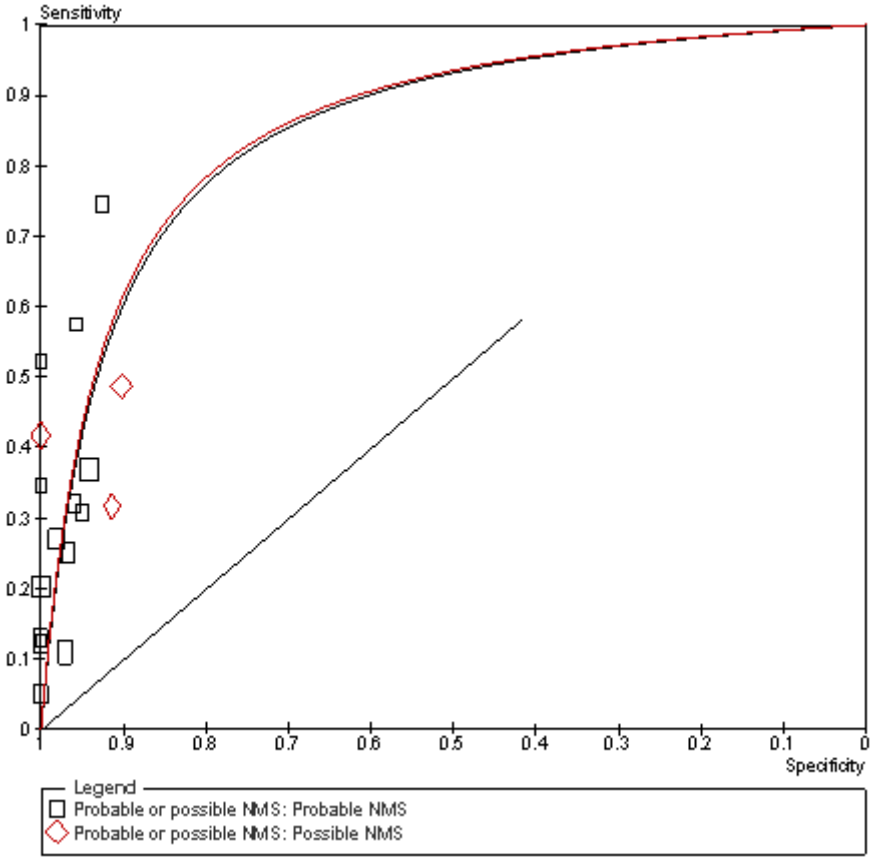
3.1.3 Subgroups for possible/probable NMS

3.1.3.1 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]



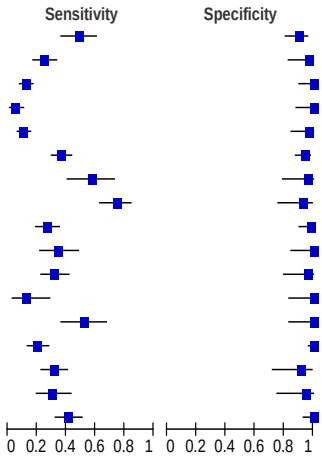
3.1.3.2 ROC curve (probable versus possible NMS)



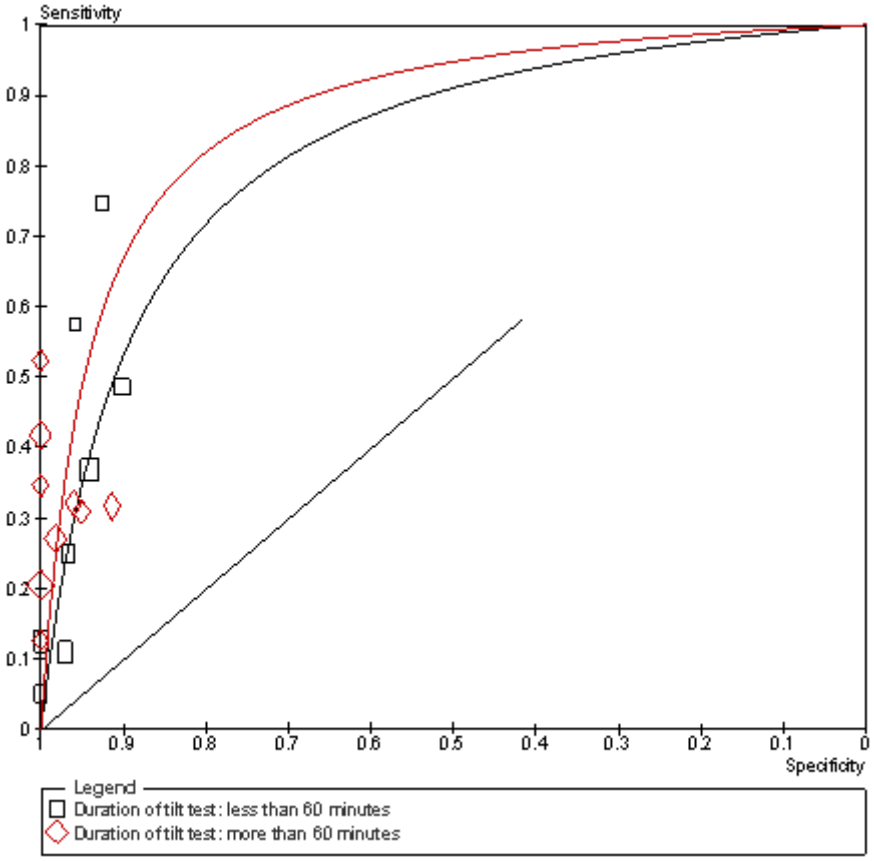
3.1.4 Subgroup analysis by duration of tilt test (more or less than 60 minutes – median value)

3.1.4.1 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]



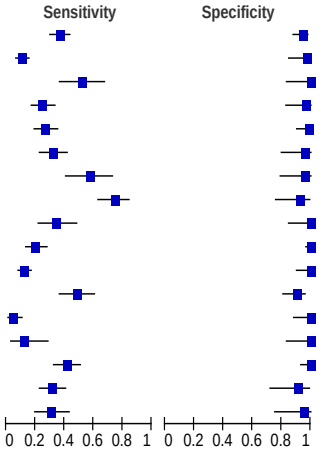
3.1.4.2 ROC curve (over versus under 60 minutes duration)



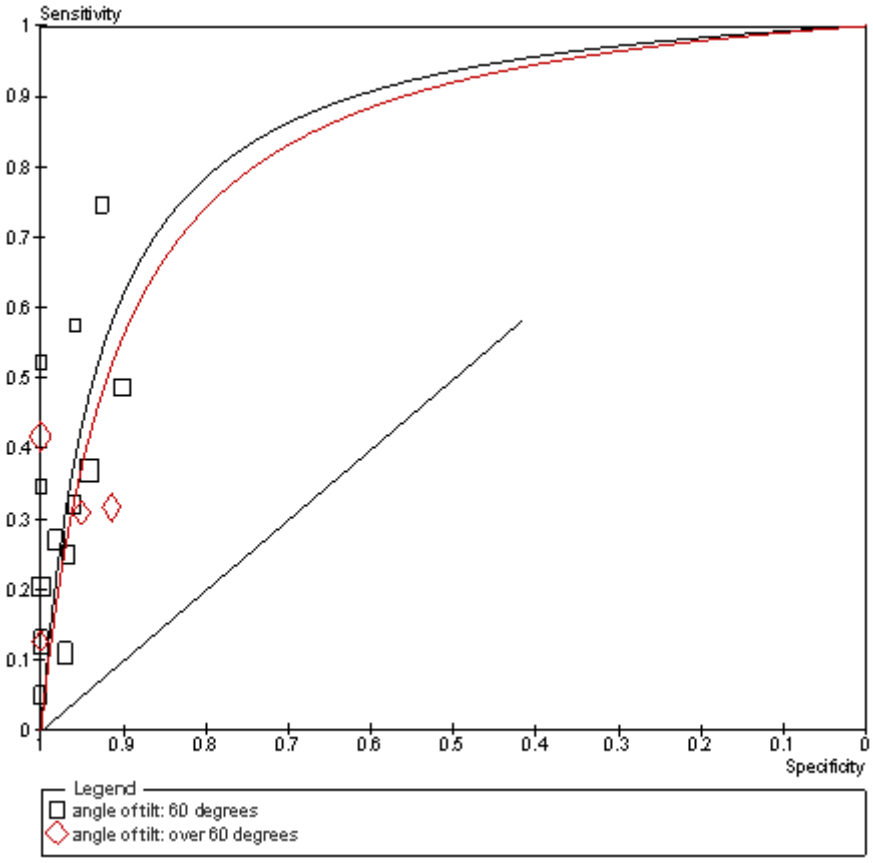
3.1.5 Subgroup analysis by angle of tilt (above and below 60 degrees – median value)

3.1.5.1 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]



3.1.5.2 ROC curve

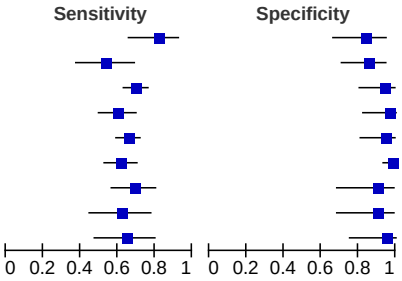


3.2 HUT-GTN

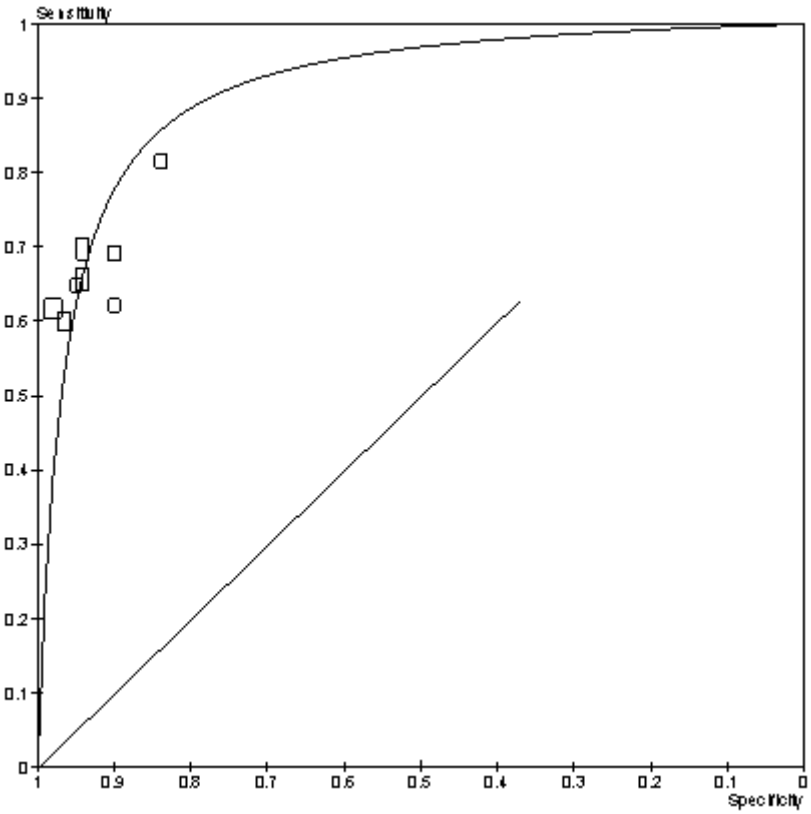
Nine studies used GTN stimulated HUT. There was high specificity for each study, and the studies were generally fairly homogeneous.

3.2.1.1 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]



3.2.1.2 ROC curve for all studies of HUT-GTN



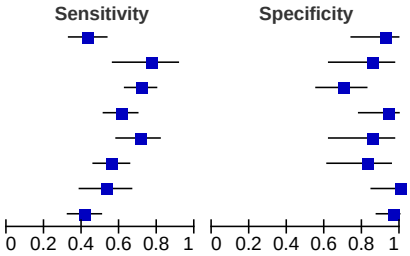
3.3 HUT-IPN

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.

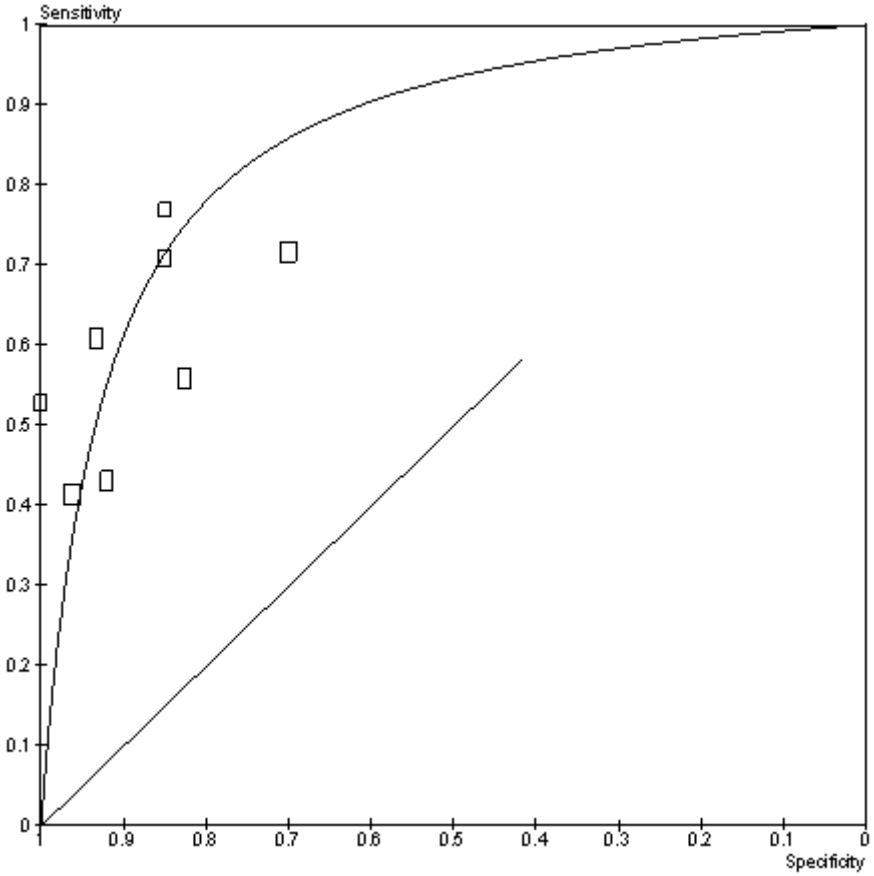
3.3.1 All IPN studies

3.3.1.1 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]



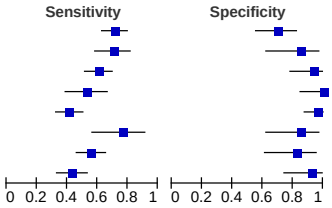
3.3.1.2 ROC curve for all HUT-IPN studies



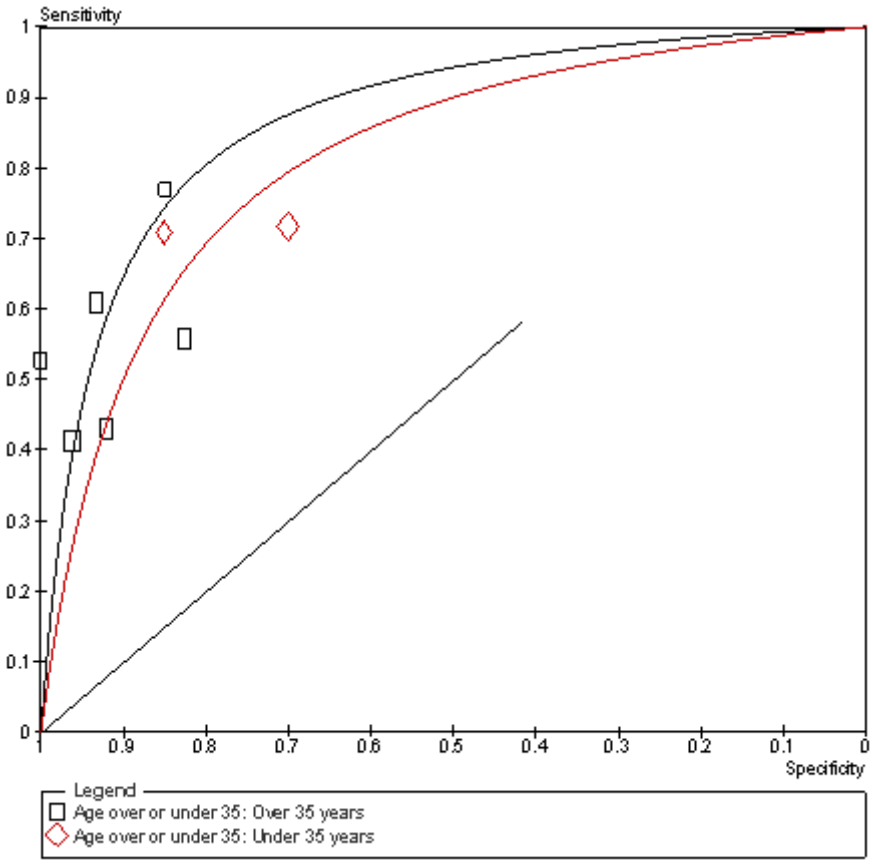
3.3.2 Subgroup analysis by age over or under 35 years

3.3.2.1 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]



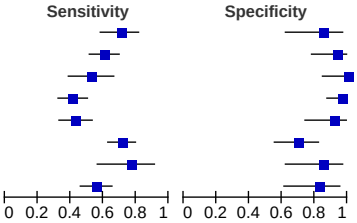
3.3.2.2 ROC curve (over versus under 35 years)



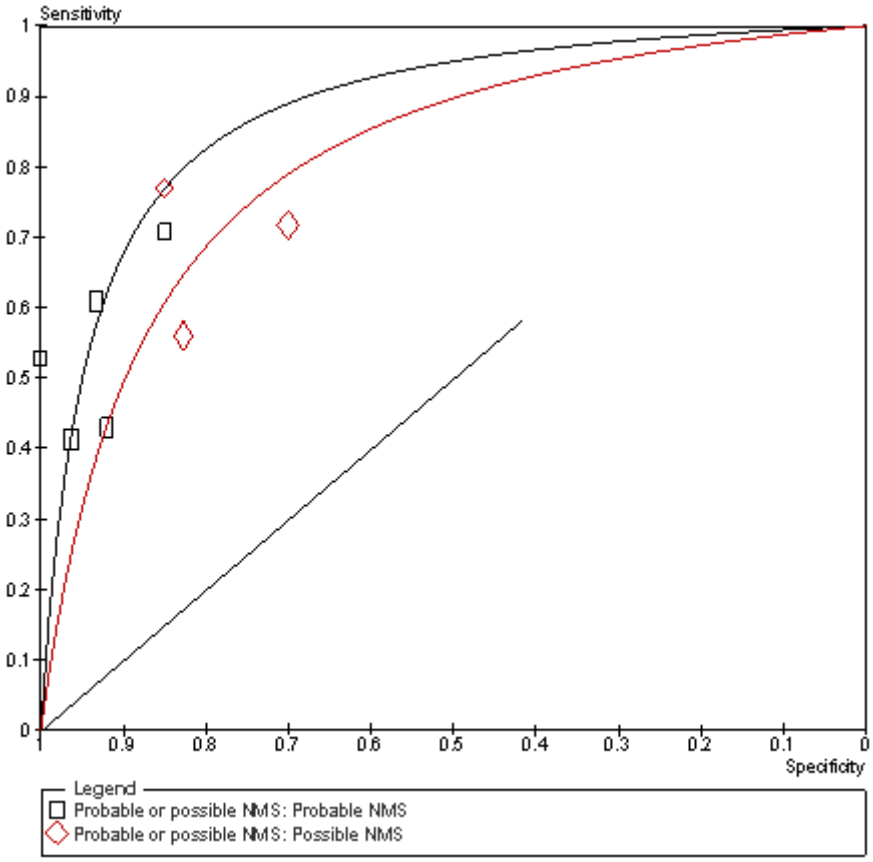
3.3.3 Subgroup analysis by probable or possible NM syncope

3.3.3.1 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]



3.3.3.2 ROC curve (probable versus possible NMS)

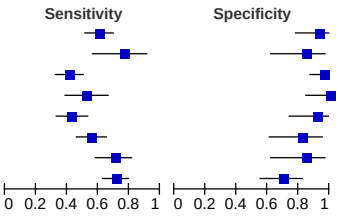


3.3.4 Subgroup analysis comparing duration of tilt over or under 60 minutes

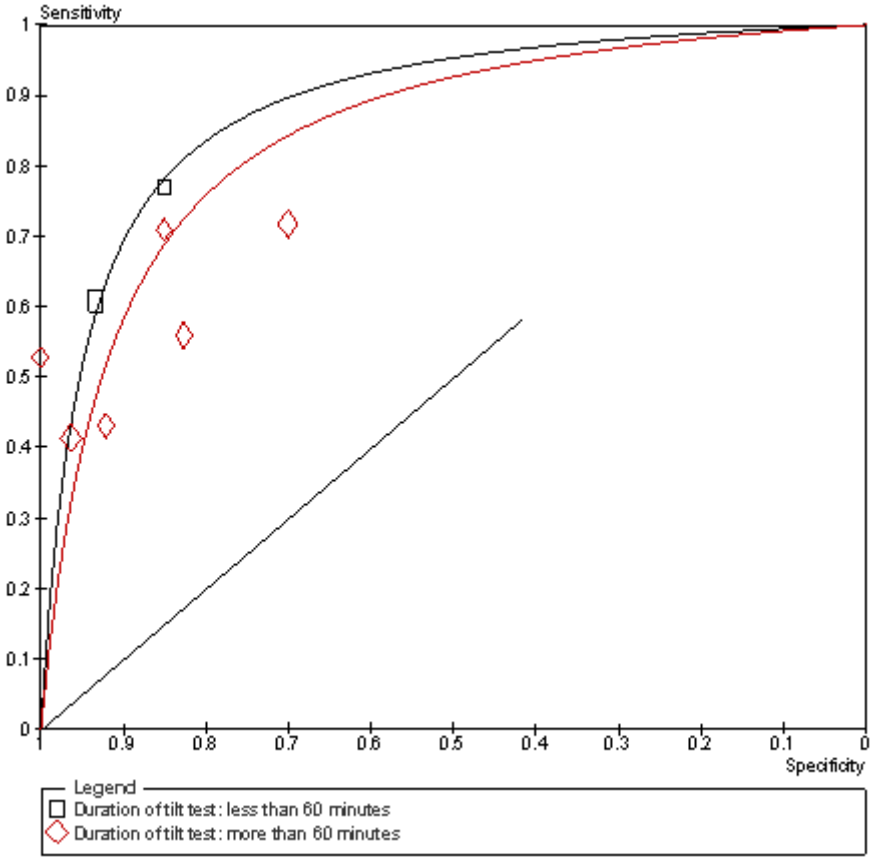
We note that there are only two studies with a duration of tilt below 60 minutes, so the subgroup analysis is not really meaningful.

3.3.4.1 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]



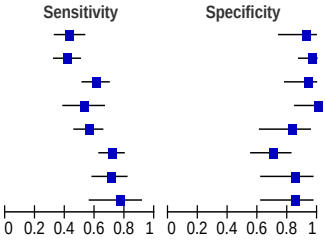
3.3.4.2 ROC curve (over versus under 60 min duration)



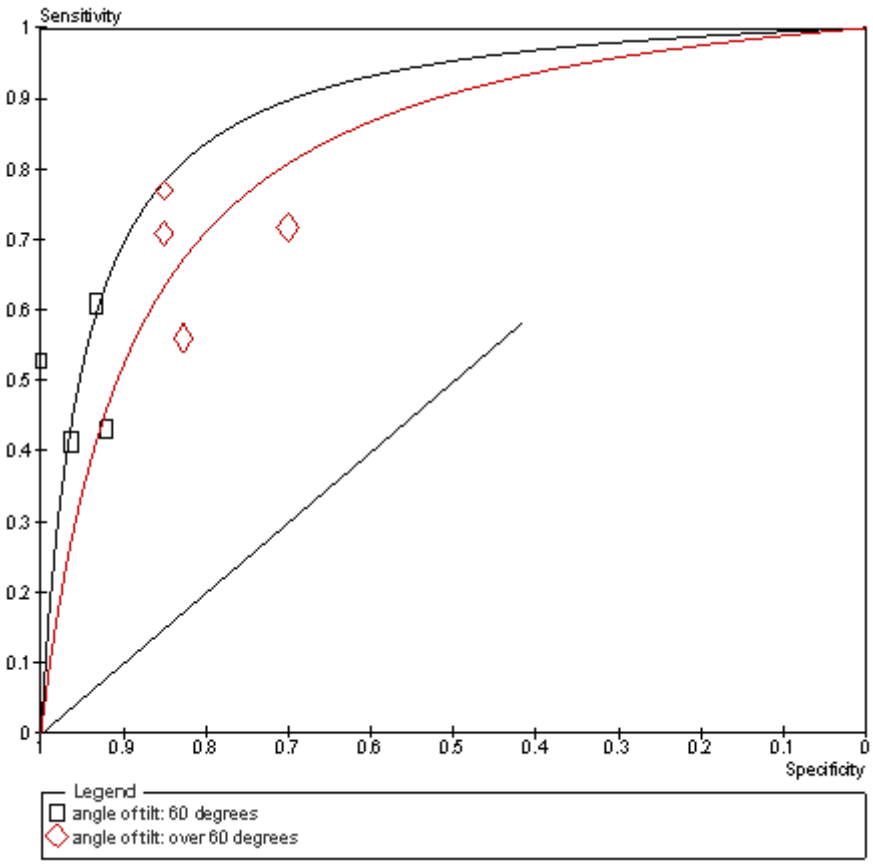
3.3.5 Subgroup analysis comparing angle of tilt over or under 60 degrees

3.3.5.1 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]



3.3.5.2 ROC curve (over versus under 60 degrees tilt)



Appendix D5: Interactive diagnostic simulation

In order to understand the context of initial stage assessment and to elicit GDG views in the early stages of guideline development, the GDG took part in an interactive diagnostic simulation exercise.

General practitioner (GP) training has focussed on the importance of what happens within a typical patient consultation. This is usually recorded and analysed to enable new GPs to reflect on the detail within the consultation, in particular, the quality of verbal and non-verbal behaviour, the sequencing of questions and information gathered to enable diagnosis. This is based around simulation and objective structured clinical examination methodology and has effectively enabled GP trainees to experience and develop understanding related to the importance of clinical history prior to physical examination.

In order to test the usefulness of different aspects of patient history including eye witness account, the technical team ran an interactive diagnostic simulation with members of the GDG. A patient profile, based on detailed notes kept by a real patient with recurrent TLoC, was shared by an actor. The patient profile used is given in the appendix to this section.

Four GDG members (a GP, an ED physician, and two cardiologists, one of whom worked in a specialist blackout clinic) then role-played a consultation, with an actor playing the part of the patient, timed at about 10 minutes consultation. All the clinicians observed each others' consultations, three of whom carried out full consultations and the consultant in the Blackout clinic asked additional questions to which he required answers, to avoid repetition. In the consultation in ED, another GDG member played the part of the patient's husband, and gave an eye witness account. During each of the role-plays, GDG members were asked to observe the consultation.

The technical team then discussed with the GDG what aspects of patient history had been considered and how these could be used to inform

management of the patient, moving towards a possible diagnosis/view of the cause of the TLoC.

The content was analysed and grouped in patient history themes, including eye witness accounts. The number of clinicians addressing each issue is also reported.

1. Pre-TLoC	**No. of clini-cians**	**comments**
How did the attack start?	1	
Any precipitating factors, e.g stress	3	
Pre-TLoC symptoms, e.g. light headed, feeling weak, cold and clammy, breathless and sick	4	
Of eye witness, did patient look pale?	2	
Did patient know it was about to happen? ("like a bird knows it's going to rain")	0	Additional suggestion by GDG
How did eye witness describe it? "I thought she was dying"	1	Indicates seriousness
How long was pre-TLoC warning?	2	Including how long was the chest pain before blackout. Relates to driving, & usefulness of external recorder
Were there auras preceding the event	1	
Were there palpitations preceding the event?	1	

2. The TLoC event itself	**No. of clini-cians**	**comments**
First determine if it was TLoC	1	
How long was attack?	2	30 minutes is unlikely to be syncope
How long unconscious? (of eye witness)	2	
Pain	1	
What is the tone of the body during blackout?	1	Stiffer tone with epilepsy; floppy and pale => syncope
Was there incontinence, tongue biting, abnormal movements, injuries on black out?	1	Syncope can be associated with abnormal movements and incontinence too
Was blackout related to posture or environment?	1	
Could patient abort an attack?	1	
Details about chest pain and pressure in chest	1	
Epilepsy can probably be diagnosed	0	GDG: Clear epileptic seizure can probably be diagnosed from initial information
3. Eye witness account	**No. of clini-cians**	**comments**
Did patient look pale?	2	
How did eye witness describe it? “I thought she was dying”	1	Indicates seriousness
How long was patient unconscious?	1	
Record with mobile phone	0	GDG: recommended that the eye witness should record event with mobile phone video if possible

4. Post-TLoC	**No. of clini-cians**	**comments**
How quickly came round/how long till felt normal	2	
Were there prolonged symptoms?	1	Epilepsy more likely to have post symptoms
How did patient feel?	1	
What did patient remember on coming round	1	Lack of memory of the event is more likely to be epilepsy
Any palpitations or fast heart beat	1	
Was oxygen given in the ambulance?	1	
Was ECG done in the ambulance?	1	
Ambulance investigation notes need to stay with the patient	1	Lot of the assessment is done by ambulance staff
Ambulance staff can give information on home environment e.g. presence of intoxicating substances	0	GDG suggestion
5. Patient history of TLoC	**No. of clini-cians**	**comments**
How many previous occasions?	3	
How frequent?	3	
How long had it been going on?	2	Long duration (11y) suggested less likely to be structural heart disease or ischaemia
Has it changed with time?	1	Same each time is more likely to be cardiac cause
What is difference between attacks (chest pain) with and without TLoC?	1	
How many times admitted because of blackout?	1	
How did it all start?	1	

6. Other aspects of patient history	**No. of clini-cians**	**comments**
How patient was when giving information, e.g. calm?	1	Was there a need for acute care/resuscitation?
Did the patient have any symptoms during consultation?	1	
Need to take into consideration the patient themself	0	GDG: could be psychogenic after 11 years
What happens when patient at rest? (re chest pain and any irregular heart flutters)	1	
What happens when walking up hill, any chest pain?	1	
Any other comorbidities?	2	Looking for serious medical conditions, e.g. diabetes, hypertension, rheumatic fever, smoking; also exploring other causes of loss of consciousness
Family history e.g. of early death	1	
Questions re previous investigations what were they and findings	3	Were the following done: treadmill, ECG, ambulatory ECG; external recorder
Any allergies?	1	Routine question
Any head injuries		GDG question
Previous history of myocardial infarction	1	
Age	1	Take into consideration
7. Drugs	**No. of clini-cians**	**comments**
Investigate different prescribed drugs – what are they for?	3	e.g. amitriptylene is antidepressant GDG: is the TLoC drug induced?
Prescribed drugs	0	Looking for history not reported by patient (e.g. psychiatric); confirmation of other indications
Alcohol intake?	1	

8. Clinical examination the clinicians would carry out	**No. of clini-cians**	**comments**
Blood pressure	1	
Bp sitting down and standing up	1	Cardiac, postural hypotension
Neurology questions (basic)	1	
Listen to heart	1	
Unspecified	1	
9. Routine tests the clinicians would order	**No. of clini-cians**	**comments**
12-lead ECG	2	GDG agreed that should be done for all patients
Finger prick test	1	diabetes

Both the GP and the ED consultant stated that their approach to the consultation was to determine if there were any areas requiring urgent action, so they focussed immediately on the chest pain symptoms.

The GP used the consultation to determine if the patient should be referred to secondary care for further investigation, and this was based on the perceived seriousness of symptoms, in this case, the chest pain. In some ways it was more difficult for the GP **not** to refer the patient.

The ED consultant, however, commented it was more difficult to admit the patient for further investigation; e.g. there was no direct route from ED into cardiology.

The GDG was concerned about referral patterns.

The clinicians concluded that the patient should not be considered to be in urgent need for referral because the events had been going on for 11 years, but she should be followed up fairly soon (a few weeks). The GDG noted that there was a need to ensure follow up if the patient was discharged, and there was a need to give lifestyle and safety advice.

The GDG concluded that there was a low chance of structural heart disease or ischaemia because the events had been going on for 11 years, the 12-lead ECG was normal, and problems did not occur on exertion. They suspected an infrequent arrhythmia (tachycardia) which they would investigate either with an external ECG recorder (used when the patient had another attack) or an implantable event recorder.

Appendix: 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.