APPENDIX D3 – Additional forest plots and analyses

1 Forest plots showing predictors for diagnosis of TLoC or adverse events

1.1 Epileptic seizures versus syncope: signs and symptoms for differential diagnosis - univariate predictors (likelihood ratios or mean differences)

1.1.1 Patient characteristics

1.1.2 Medical history

1.1.3 Signs and symptoms at any time

1.1.4 Predisposing/Precipitating factors

1.1.5 TLoC history

The Sheldon (2002) authors also reported that there were significant differences in TLoC history:

- seizure patients had more episodes of TLoC than those with syncope: median 168 spells (IQR 20 to 450) versus 3 spells (IQR 2 to 8); $p < 0.001$
- seizure patients had a longer history of TLoC: median 186 months (IQR 67 to 352) versus 24 months (IQR 0.33 to 169); $p < 0.001$.

1.1.6 Prodromal symptoms pre-TLoC

1.1.7 Signs and symptoms during TLoC

1.1.8 Prodromal symptoms after TLoC

1.2 Epileptic seizures versus syncope: signs and symptoms for prediction of a diagnosis of seizures - multivariable predictors (odds ratios)

Thirty-eight variables were included in the multivariable analysis for epileptic seizures versus syncope; they were those with a p value below 0.05: age, cut tongue, head turning, bedwetting, blue colour observed by bystanders, prodromal trembling, prodromal preoccupation, prodromal hallucinations, prodromal déjà vu, prodromal mood changes, prodromal vertigo, LoC associated with stress, muscle pain, postictal confusion, postictal headaches, abnormal behaviours noted by bystanders (any one of witnessed: amnesia for abnormal behaviour; unresponsiveness, unusual posturing or limb jerking); presyncopal spells before LoC, self-reported high blood pressure, hypertension (physician reported), any chest pain coronary heart disease, any presyncope, presyncope with hot/warm environments, presyncope after exercise, warmth pre-TLoC, nausea pre-TLoC, diaphoresis pre-TLoC, chest pain pre-TLoC, presyncope with prolonged sitting/standing, remembered loss of consciousness, palpitations before LoC, dypsnoea before LoC, LoC with prolonged sitting/standing.

1.2.1 Symptom burden not known

The following factors were not significant factors in the multivariable analysis: age, bedwetting, blue colour observed by bystanders, prodromal trembling, prodromal preoccupation, prodromal hallucinations, prodromal mood changes, prodromal vertigo, behaviours not recalled, muscle pain, postictal headaches, self-reported high blood pressure, hypertension (physician reported), any chest pain, coronary heart disease, remembered loss of consciousness, palpitations before LoC, dypsnoea before LoC.

1.2.2 Symptom burden known

In addition to the variables listed above, two further variables were added: number of spells more than 30 and duration of history of TLoC and light-headed spells.

The following factors were not significant in multivariable analysis: age, cut tongue, unusual posturing, bedwetting, blue colour observed by bystanders, limb jerking noted by others, prodromal trembling, prodromal preoccupation, prodromal hallucinations, prodromal déjà vu, prodromal mood changes, prodromal vertigo, behaviours not recalled, muscle pain, postictal confusion, postictal headaches, abnormal behaviours noted by bystanders, self-reported high blood pressure, hypertension (physician reported), any chest pain coronary heart disease, remembered loss of consciousness, palpitations before LoC, dypsnoea before LoC.

1.3 Vasovagal syncope versus other syncope: signs and symptoms for differential diagnosis - univariate predictors (likelihood ratios or mean differences)

1.3.1 Patient characteristics

1.3.2 Medical history

1.3.3 TLoC history

The Sheldon (2006) study also reported that there were significant differences in TLoC history:

- Patients with tilt positive vasovagal syncope had more episodes of TLoC than those with other known forms of syncope (about 84% cardiac syncope): median 6 spells (IQR 3 to 20) versus 2 spells (IQR 1 to 5); $p < 0.001$
- Tilt positive patients had a longer history of TLoC: median 100 months (IQR 13 to 268) versus 1month (IQR 0 to 16); $p < 0.001$.

1.3.4 Predisposing/precipitating factors

We note that Sheldon (2006) reported pre-syncope after exercise.

1.3.5 Prodromal signs and symptoms pre-TLoC

1.3.6 Duration of TLoC

1.3.7 Signs and symptoms during TLoC

1.3.8 Recovery after TLoC

1.3.9 Prodromal symptoms after TLoC

1.4 Vasovagal syncope versus non-VV syncope: signs and symptoms for prediction of a diagnosis of vasovagal syncope - multivariable predictors (odds ratios)

For the Alboni (2001) study, six variables were included in the multivariable analysis for people with suspected heart disease: time between first and last episode > 4y; history of presyncope; abdominal discomfort; pallor pre-TLoC; nausea post-TLoC; diaphoresis post TLoC. Two variables were included for people without suspected heart disease (≥ 3 syncopal episodes; duration of prodromes > 10s).

For the Sheldon (2006) study, 34 variables were included in the multivariable analysis; these were: age at first syncopal spell ≤ 35 years; less than 5s warning; tired after a syncopal spell; syncope/presyncope with pain or medical procedure; syncope/presyncope with hot or warm environments; syncope/presyncope with stress; syncope/presyncope with headaches; syncope/presyncope with prolonged standing/sitting; syncope/presyncope on way to the toilet; syncope/presyncope after using the toilet; presyncope after exercise; cannot remember behaviour during syncope; unresponsive during syncope; no memory about syncope; confusion after a spell; cyanotic during syncope; white or pale colour noted by bystander; valvular heart disease; atrial fibrillation or flutter; any one of bifascicular block, asystole, SVT, diabetes; hypertension; nausea or vomiting pre-TLoC; sweating or warm feeling pre-TLoC; headache pre-TLoC; visual distortion pre-TLoC; auditory distortion pre-TLoC; heart racing pre-TLoC; abdominal rising sensation pre-TLoC; numbness or tingling pre-TLoC; mood changes or preoccupation pre-TLoC; sweating or warm feeling post-TLoC; mood changes post-TLoC; numbness or tingling post-TLoC; nausea or vomiting post-TLoC.

For the Graf (2008) study, 15 variables were included for vasovagal/psychogenic pseudosyncope; these were: age (3 categories: ≤ 45; 46-64; ≥65 years); P-wave duration <120ms; number of prodromes ≤1; nausea or vomiting; diaphoresis; sudation; blurred vision; paresthesia;

palpitations; vertigo/dizziness; dypsnoea; anxiety; asthenia/weakness; headache.

1.4.1 Patient characteristics

1.4.2 History of TLoC

1.4.3 Heart disease or abnormal ECG or both

The following factors were not significant in the multivariable analysis in the Sheldon (2006) study: valvular heart disease; atrial fibrillation or flutter.

1.4.4 Predisposing/precipitating factors

The following precipitating factors were not significant in the Sheldon (2006) study: syncope/presyncope with hot or warm environments;

syncope/presyncope with stress; syncope/presyncope on way to the toilet; syncope/presyncope after using the toilet; presyncope after exercise..

1.4.5 Prodromal signs and symptom pre-TLoC

The following prodromal factors were not significant for vasovagal syncope/psychogenic pseudosyncope in the Graf (2008) study: nausea / vomiting; diaphoresis; sudation; blurred vision; paresthesia; palpitations; vertigo/dizziness; dypsnoea; anxiety; weakness/asthenia and headache.

The following prodromal factors were not significant in the Sheldon (2006) study: less than 5 s warning; white or pale colour noted by bystander; nausea or vomiting pre-TLoC; headache pre-TLoC; visual distortion pre-TLoC; auditory distortion pre-TLoC; heart racing pre-TLoC; abdominal rising sensation pre-TLoC; numbness or tingling pre-TLoC; mood changes or preoccupation pre-TLoC.

1.4.6 Signs and symptoms during TLoC

The factor, white or pale colour noted by bystander, was not a significant predictor in the Sheldon (2006) study.

1.4.7 Signs and symptoms post TLoC

The following prodromal symptoms post-TLoC were not significant in the Sheldon (2006) study: cannot remember behaviour during syncope; confusion after a spell; sweating or warm feeling post-TLoC; mood changes post-TLoC; numbness or tingling post-TLoC; nausea or vomiting post-TLoC.

1.5 Cardiac syncope versus other syncope: signs and symptoms for differential diagnosis - univariate predictors (likelihood ratios or mean differences)

1.5.1 Patient characteristics

1.5.2 Predisposing/precipitating factors

1.5.3 Prodromal symptoms pre-TLoC

1.5.4 Signs and symptoms during TLoC

1.5.5 Duration of TLoC

1.5.6 Recovery after TLoC

1.5.7 Prodromal symptoms after TLoC

1.6 Cardiac syncope versus non-cardiac syncope: signs and symptoms for prediction of a diagnosis of cardiac syncope - multivariable predictors (odds ratios)

The Alboni (2001) study first investigated non-syncope variables in a multivariable analysis for cardiac syncope, of all patients and included age, gender and suspected or certain heart disease. The patients were then divided into two subgroups: six variables were included in the multivariable analysis for people with suspected heart disease: time between first and last episode ≤ 4y; convulsions; TLoC during supine position; TLoC during effort; blurred vision (prodrome). Only one variable was significant in the univariate analysis for people without suspected heart disease (palpitations before TLoC).

For the del Rosso (2008) study, 13 variables were included in the multivariable analysis; these were: age 65 years and over; heart disease or abnormal ECG or both; precipitating or predisposing factors or both (warm-crowded place / prolonged orthostasis / fear-pain-emotion; palpitations pre-TLoC; syncope during effort; syncope while supine; autonomic prodromes (nausea/vomiting); absence of prodromes; dypsnoea pre-TLoC; sweating pre-TLoC; fractures; incontinence; blurred vision.

For the Sarasin (2003) study, 5 variables were included for arrhythmic syncope; these were: abnormal ECG; age ≥ 65y; history of congestive heart failure; history of MI; history of cardiac disease (any type).

1.6.1 Patient characteristics

Age and gender were not significant factors in either the Alboni (2001) analysis of all patients for cardiac syncope (low quality) or the del Rosso

(2008) analysis for cardiac syncope (moderate quality). A fracture (unspecified) was not a significant factor in the del Rosso (2008) analysis.

1.6.2 Heart disease or abnormal ECG or both

History of myocardial infarction and history of cardiac disease (any type) were not significant multivariable factors in the Sarasin (2003) analysis for arrhythmic syncope (moderate quality).

1.6.3 TLoC history

'Two or fewer syncopal episodes' was not a significant factor for cardiac syncope in the multivariable analysis in the Alboni (2001) subgroup of people with suspected or certain heart disease.

1.6.4 Predisposing / precipitating factors

Syncope during effort was not a significant factor for cardiac syncope in the multivariable analysis in the Alboni (2001) subgroup of people with suspected or certain heart disease.

1.6.5 Prodromal symptoms and signs pre-TLoC

Convulsions during TLoC was not a significant predictor in the multivariable analysis for cardiac syncope in the subgroup, people with suspected/certain heart disease in the Alboni (2001) study (low quality).

1.7 Signs and symptoms that indicate an increased risk of death at 12 months (relative to the risk for not having this symptom) - univariate predictors (relative risks) and age as a risk factor for death at 30 days and 3 and 6 months

We report relative risks for death and also give the likelihood ratios for these signs and symptoms.

1.7.1 Patient characteristics

Likelihood ratios

1.7.2 Medical history

Likelihood ratios

1.7.3 TLoC history

Likelihood ratios

1.7.4 Prodromal symptoms and signs

Likelihood ratios

1.7.5 ECG findings

Likelihood ratios

1.7.6 Signs and symptoms post-TLoC

Likelihood ratios

1.8 Signs and symptoms, and laboratory and ECG results that indicate an increased risk of death at 12 months (relative to the risk for those without the symptom) - multivariable predictors (relative risks)

1.8.1 Patient characteristics

1.8.2 ECG findings

1.9 Signs and symptoms, and laboratory and ECG results that indicate an increased risk of adverse events (relative to the risk for those without the symptom) - univariate predictors (relative risks)

1.9.1 Patient Characteristics

1.9.2 Family history

1.9.3 Medications

1.9.4 Medical history

1.9.5 History of TLoC

1.9.6 Predisposing / precipitating factors

1.9.7 Prodromal symptoms

1.9.8 Physical examination

1.9.9 Laboratory and other initial tests

One study (Quinn 2004) also reported that there was a significant difference in glucose level, with higher levels predicting the adverse outcome (153 mg/dl versus 122 mg/dl).

1.9.10 ECG findings

1.10 Signs and symptoms, and laboratory and ECG results that indicate an increased risk of adverse events - Multivariable predictors (odds ratios)

For the Reed (2010) study, eight covariables were included in the multivariable analysis for serious adverse events at 1 month; these were: B-type natriurectic peptide (BNP – marker for prognosis in heart failure and cardiac disease) concentration ≥ 300pg/ml; rectal examination showing faecal occult blood; haemoglobin ≤ 90g/l; Q-waves (25% R wave) / left bundle branch block; gender; oxygen saturation ≤ 94% on room air; albumin <37g/l; white cell count > 14 x 10^9 cells/litre.

The Costantino (2008) study carried out two multivariable analyses for different time points, up to 10 days and 11 days to 1 year. We note that the population excluded people who had serious conditions that would have been diagnosed in the ED regardless of whether the person had TLoC.

For the short term analysis there were eight covariables: age over 65 years; male gender; heart failure; structural heart disease; COPD, trauma; abnormal ECG; absence of preceding symptoms.

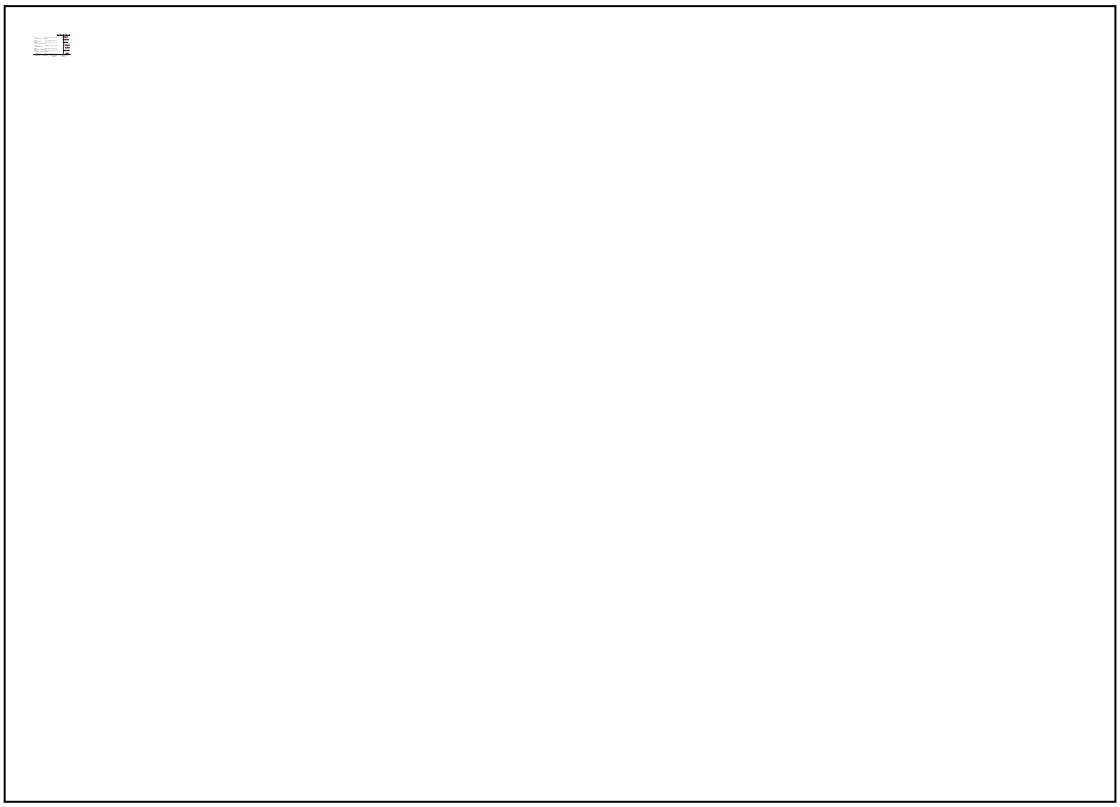
For the longer term analysis there were nine covariables: age over 65 years; history of hypertension; structural heart disease; heart failure; ventricular arrhythmias; cerebrovascular diseases; COPD; neoplasms; abnormal ECG.

Short term analysis

1.10.1 Patient characteristics

1.10.2 Prodromal symptoms pre-TLoC

1.10.3 Physical examination and tests



Longer term outcomes

1.10.4 Patient characteristics

1.10.5 Comorbidities

2 DTA statistics for decision rules for diagnosis

2.1 Target condition: epilepsy / seizures

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Sheldon 2002 Initial symptoms decision rule Rule 1 symptoms only	94 (89-97)	94 (89-97)	94	94	15.8 (8.0-30.9)	0.06 (0.03 - 0.12)	50	94	6.0	248.1	50
Sheldon 2002 Initial symptoms decision rule Rule 2 symptoms + TLoC history	92 (86-96)	83 (75-89)	86	90	5.3 (3.6-7.7)	0.09 (0.05 - 0.17)	53	86	9.6	55.9	57
van Dijk 2008 ESC guidelines certain only	100 (16-100)	100 (99-100)	67	100	NA	0.17 (0.01 - 2.10)	0.4	67	0.0	NA	1
van Dijk 2008 ESC guidelines Highly likely	67 (30-93)	100 (99-100)	86	99	NA	0.33 (0.13 - 0.84)	1.8	86	0.6	NA	1
van Dijk 2008 ESC guidelines certain and highly likely	73 (39-94)	100 (99-100)	80	99	NA	0.27 (0.10 - 0.72)	2.2	80	0.6	NA	2

2.2 Target condition: psychiatric cause of TLoC

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
van Dijk 2008 ESC guidelines certain and highly likely	86 (57-98)	100 (99-100)	100	100	NA	0.17 (0.05-0.52)	2.8	100	0.4	NA	2

2.3 Target condition: vasovagal syncope

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Graf 2008 Initial symptoms decision rule VV/Psychogenic model; validation cohort	84 (64-95)	50 (34-66)	51	83	1.7 (1.2-2.4)	0.32 (0.12-0.83)	39	51	16.7	5.3	63
Sheldon 2006 Initial symptoms decision rule for vasovagal syncope; cut off above -2;	89 (85-93)	91 (83-96)	96	76	9.8 (5.1-19.1)	0.12 (0.08-0.17)	73	96	23.8	84.0	67
Romme 2009 validation of Sheldon 2006	87 (82-91)	31 (24-40)	68	59	1.3 (1.1-1.4)	0.42 (0.28-0.62)	62	68	40.8	3.1	80
van Dijk 2008 ESC guidelines certain only	97 (91-100)	100 (98-100)	97	100	208.3 (52.2-830.6)	0.03 (0.01-0.11)	15	97	0.47	7774	15
van Dijk 2008 ESC guidelines Highly likely only	98 (93-100)	97 (94-98)	91	99	30.4 (17.4-53.2)	0.02 (0.01-0.07)	26	91	0.82	1267	27
van Dijk 2008 ESC guidelines certain and highly likely	98 (94-99)	95 (92-97)	93	98	20.8 (12.5-34.8)	0.03 (0.01-0.06)	41	93	1.7	810	42

2.4 Target condition: cardiac syncope

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
van Dijk 2008 ESC guidelines certain only	71 (29-96)	100 (99-100)	100	100	NA	0.31 (0.11-0.87)	1.4	100	0.4	NA	1
van Dijk 2008 ESC guidelines Highly likely only	74 (52-90)	99 (97-99)	71	99	50.7 (23.4-110.0)	0.26 (0.13-0.53)	4.6	71	1.3	191.5	5
van Dijk 2008 ESC guidelines certain and highly likely	73 (54-88)	99 (97-99)	76	98	49.6 (23.0-106.6)	0.27 (0.15-0.49)	6.0	76	1.7	183.1	6
Elseber 2005 ACEP guidelines ACEP level B	100 (86-100)	81 (75-87)	42	100	5.2 (3.8-7.1)	0.02 (0.00-0.38)	12	42	0.0	100000	29
Elseber 2005 ACEP guidelines ACEP level B + C	100 (86-100)	33 (26-40)	17	100	1.5 (1.3-1.7)	0.06 (0.00-0.95)	12	17	0.0	100000	71
del Rosso 2008 EGSYS score >2	91 (77-98)	69 (63-75)	32	98	3.0 (2.4-3.7)	0.12 (0.04-0.37)	14	32	1.9	24.0	39
del Rosso 2008 EGSYS score >4	29 (15-46)	99 (96-100)	77	90	21.0 (6.1-72.7)	0.72 (0.61-0.94)	14	77	10.3	29.1	5
Sarasin 2003 decision rule >0 Arrhythmic	96 (85-99)	42 (35-49)	26	98	1.7 (1.5-1.9)	0.10 (0.03-0.40)	18	26	2.1	16.1	65
Sarasin 2003 decision rule >1 Arrhythmic	66 (51-79)	72 (66-78)	34	91	2.4 (1.8-3.2)	0.47 (0.31-0.71)	18	34	9.1	5.1	34

2.5 Target condition: orthostatic hypotension

Study and analysis details Sens Spec PPV NPV LR+ LR- pre test prob post test prob (rule in) post test prob (rule out) Diag OR Diag yield

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
van Dijk 2008 ESC guidelines certain only	100 (63-100)	99 (98-100)	62	100	85.2 (36.6-198.5)	0.06 (0.00-0.83)	1.6	62	0.0	100000	3
van Dijk 2008 ESC guidelines Highly likely only	80 (44-97)	99 (97-100)	57	100	65.7 (28.0-154.3)	0.20 (0.06-0.70)	2.0	57	0.4	324.7	3
van Dijk 2008 ESC guidelines certain and highly likely	89 (65-99)	98 (96-99)	59	100	39.2 (21.4-71.9)	0.11 (0.03-0.42)	3.6	59	0.4	344.7	5

3 Diagnostic test accuracy statistics - risk stratification tools

3.1 Decision rules for risk stratification (death)

3.1.1 Target condition: death as the only outcome

3.1.1.1 Index test: San Francisco Syncope Rule

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Quinn 2008 San Francisco Syncope Rule deaths related to syncope at 6 months	100 (89-100)	52 (49-55)	5	100	2.1 (1.9-2.2)	0.03 (0.00-0.44)	2.3	5	0.0	100000	49
Quinn 2008 San Francisco Syncope Rule all cause deaths at 6 months	89 (78-95)	52 (49-55)	8	99	1.9 (1.7-2.1)	0.22 (0.11-0.44)	4.3	8	0.9	9.2	49
Quinn 2008 San Francisco Syncope Rule deaths related to syncope at 12 months	93 (82-98)	53 (50-56)	7	100	2.0 (1.8-2.2)	0.14 (0.05-0.36)	3.8	7	0.5	14.7	49
Quinn 2008 San Francisco Syncope Rule all cause deaths at 12 months	83 (75-90)	54 (51-57)	13	98	1.8 (1.6-2.0)	0.31 (0.20-0.47)	7.6	13	2.5	5.8	49

3.1.1.2 Index test: OESIL score

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Colivicchi 2003 OESIL score 12 months OESIL > 1	97 (83-100)	73 (67-78)	32	99	3.6 (2.9-4.$)	0.04 (0.01-0.31)	11	31	0.5	80.3	35

3.1.1.3 Index test: ACP guidelines

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Crane 2002 ACP guidelines ACP guidelines, high risk group; death 12 months	67 (45-84)	83 (76-88)	36	95	3.9 (2.5-6.1)	0.40 (0.23 - 0.71)	13	36	5.5	9.8	23
Crane 2002 ACP guidelines ACP guidelines, moderate risk; death 12 months	33 (16-55)	70 (63-77)	14	88	1.1 (0.6-2.1)	0.95 (0.70 - 1.28)	13	14	12.1	1.2	30
Crane 2002 ACP guidelines ACP guidelines, high + moderate risk; 12 months	100 (86-100)	53 (45-61)	24	100	2.1 (1.8-2.5)	0.04 (0.00 - 0.59)	13	24	0.0	100 000	53
Crane 2002 ACP guidelines ACP guidelines; low risk group; death 12 months	0 (0-14)	47 (39-55)	0	76	0.04 (0.0-0.6)	2.14 (1.77 - 2.49)	13	0	23.8	0.0	47

3.1.1.4 Index test: EGSYS score

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
del Rosso 2008 EGSYS score EGSYS score ≥ 3; 21-24 months	82 (57-96)	82 (76-87)	30	98	4.6 (3.1-6.7)	0.22 (0.08 - 0.60)	8.7	30	2.0	21.3	24

3.1.2 Target condition: all adverse outcomes

3.1.2.1 Index test: San Francisco Syncope Rule for outcomes in and out of ED

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Birnbaum 2008 San Francisco Syncope Rule; 7 day outcomes, in and out of ED.	74 (61-84]	57 (53-61]	14	96	1.7 (1.5-2.1)	0.46 (0.30-0.70)	9.0	15	4.3	3.8	45
Cosgriff 2007 San Francisco Syncope Rule; 7 day follow up	90 (55-100)	57 (45-68)	21	98	2.1 (1.5-2.9)	0.18 (0.03-1.14)	11	21	2.1	11.9	48
Quinn 2005 San Francisco Syncope Rule; ED and post-ED outcomes at 7 days, in and out of ED	96 (89-99)	62 (58-66)	25	99	2.5 (2.3-2.8)	0.06 (0.02-0.19)	12	26	0.8	41.3	45
Quinn 2006 San Francisco Syncope Rule; serious outcomes after ED visit; 30 days follow up	98 (90,-100])	56 (52-60)	15	100	2.2 (2.0-2.5)	0.03 (0.00-0.23)	7.0	14	0.3	66.3	48
Reed 2007 (ROSE pilot) San Francisco Syncope Rule; 3 months follow up	100 (72-100)	45 (35-56)	19	100	1.8 (1.4-2.2)	0.09 (0.01-1.39)	11	18	0.0	100000	60

Schladenhaufen 2008 San Francisco Syncope Rule Older people; 7 days follow up	77 (67-85)	37 (32-42)	22	87	1.2 (1.0-1.4)	0.64 (0.44-0.93)	19	22	13.0	1.9	66
Sun 2007 San Francisco Syncope Rule; 7 day outcomes in and out of ED	89 (78-96)	42 (36-48)	22	95	1.5 (1.4-1.8)	0.25 (0.12-0.55)	16	22	4.7	5.9	64

3.1.2.2 Index test: San Francisco Syncope Rule for outcomes out of ED (i.e. patients with outcomes in ED excluded)

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Birnbaum 2008 San Francisco Syncope Rule; 7 day outcomes, out of ED.	74 (61-84)	57 (53-61)	14	96	1.7 (1.5-2.1)	0.46 (0.30-0.70)	9.0	15	4.3	3.8	45
Quinn 2006 San Francisco Syncope Rule; serious outcomes after ED visit; 30 days follow up	98 (90-100)	56 (52-60)	15	100	2.2 (2.0-2.5)	0.03 (0.00-0.23)	7.0	14	0.3	66.3	48
Sun 2007 San Francisco Syncope Rule; 7 day outcomes in and out of ED	89 (78-96)	41 (36-47)	22	95	1.5 (1.4-1.8)	0.26 (0.12-0.55)	16	22	4.7	5.9	64

3.1.2.3 Index test: Boston Syncope Criteria

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Grossman 2007 Boston Syncope Criteria 30 days	97 (90-100)	62 (56-69)	44	99	2.6 (2.2-3.1)	0.05 (0.01 - 0.19)	23	43	1.4	54.4	52

3.1.2.4 Index test: OESIL score

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Reed 2007 (ROSE pilot) OESIL score OESIL score >1; 3 months follow up	91 (59-100)	49 (38-60)	18	98	1.8 (1.4-2.3)	0.19 (0.03 - 1.22)	11	18	2.2	9.6	56

3.1.2.5 Index test: Initial evaluation based on ESC, AAP & ACEP guidelines

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Reed 2010 (ROSE validation) ROSE rule from standardised patient assessment; adults presenting with acute syncope to ED 1 month serious outcomes	87 (73-96)	66 (61-70)	17	98	2.5 (2.1-3.0)	0.20 (0.09 - 0.44)	7.2	17	1.5	12.9	38

3.1.3 Target condition: death and cardiac outcomes

3.1.3.1 Index test: OESIL score

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Hing 2005 OESIL score OESIL score >1; cardiac outcomes	78 (56-93)	64 (52-74)	39.	91	2.2 (1.5-3.1)	0.34 (0.15 - 0.76)	23	39	9.3	6.3	46

4 Diagnostic test accuracy statistics: 12-lead ECG

4.1 Target condition: death as the only outcome

4.1.1 Index test: 12 lead ECG

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Colivicchi 2003 12 lead ECG death 12 months	61 (42-78)	74 (68-79)	23	94	2.3 (1.6-3.3)	0.53 (0.34 - 0.82)	12	23	6.4	4.4	30

4.2 Target condition: all adverse outcomes

4.2.1 Index test: 12 lead ECG

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Grossman 2007 12 lead ECG ischaemic ECG; all adverse events	1 (0-8)	98 (95-99)	17	77	0.7 (0.1-5.6)	1.01 (0.97 - 1.04)	23	17	23.3	0.7	2
Grossman 2007 12 lead ECG abnormal rhythm / new ECG changes; all adverse	15 (7-25)	85 (80-89)	23	77	1.0 (0.5-1.9)	1.00 (0.90 - 1.13)	23	23	23.3	1.0	15
Grossman 2007 12 lead ECG QT interval > 500ms; all adverse events	0 (0-5)	100 (98-100)	0	77	NA	1.00	23	100	23.2	NA	0
Grossman 2007 12 lead ECG heart block; all adverse events	1 (0-8)	98 (95-99)	17	77	0.7 (0.1-5.6)	1.01 (0.97 - 1.04)	23	17	23.4	0.7	2
Grossman 2007 12 lead ECG abnormal sinus rate	6 (2-14)	95 (91-98)	27	77	1.2 (0.4-3.7)	0.99 (0.93 - 1.06)	23	27	23.0	1.2	5
Quinn 2004 12 lead ECG Abnormal ECG	66 (54-76)	73 (69-76)	24	94	2.4 (2.0-2.9)	0.47 (0.35 - 0.64)	12	24	5.8	5.1	32
Quinn 2004 12 lead ECG Abnormal rhythm (non sinus); 7 days	43 (32-55)	81 (78-84)	23	92	2.3 (1.7-3.1)	0.70 (0.58 - 0.85)	12	23	8.4	3.3	21
Quinn 2004 12 lead ECG abnormal ECG, new changes	56 (44-67)	82 (79-85)	29	93	3.2 (2.5-4.1)	0.54 (0.42 - 0.69)	12	29	6.6	5.9	22
Reed 2007 (ROSE pilot)d 12 lead ECG 3 months follow up	82 (48-98)	45 (35-56)	16	95	1.5 (1.1-2.1)	0.40 (0.11 - 1.43)	11	16	4.7	3.8	58

4.3 Target condition: death and cardiac outcomes

4.3.1 Index test: 12 lead ECG

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Hing 2005 12 lead ECG 12-lead ECG cardiac outcomes	74 (52-90)	69 (57-79)	41	90	2.4 (1.6-3.6)	0.38 (0.19 - 0.77)	23	42	10.2	6.3	41
Sun 2008 12 lead ECG all ages; 14 days follow up	76 (60-87)	76 (71-80)	27	96	3.1 (2.5-4.0)	0.32 (0.19 - 0.54)	10	26	3.5	9.7	30

4.3.2 12-lead ECG – effect of patient age and operator expertise

Study and analysis details	Sens	Spec	PPV	NPV	LR+	LR-	pre test prob	post test prob (rule in)	post test prob (rule out)	Diag OR	Diag yield
Sun 2008 12 lead ECG age 18-39y; 14 days follow up Test operator: treating physician	50 (1-99)	88 (80-93)	7	99	4.1 (0.9-17.9)	0.57 (0.14 - 2.28)	2.0	8	1.1	7.2	13
Sun 2008 12 lead ECG age 40-59y; 14 days follow up Test operator: treating physician	90 (55-100)	88 (79-94)	45	99	7.3 (4.0-13.1)	0.11 (0.02 - 0.73)	10	45	1.3	63.8	20
Sun 2008 12 lead ECG age 60-79y; 14 days follow up Test operator: treating physician	71 (42-92)	67 (57-76)	23	94	2.2 (1.4-3.3)	0.43 (0.18 - 0.99)	12	23	5.5	5.1	38
Sun 2008 12 lead ECG age 80 and above; 14 days follow up Test operator: treating physician	72 (47-90)	60 (50-71)	27	92	1.8 (1.2-2.7)	0.46 (0.21 - 0.99)	17	27	8.6	4.0	45
Sun 2008 12 lead ECG age 18-39y; attending physician; 14 days follow up	0 (0-97)	88 (76-95)	0	98	1.9 (0.1-23.0)	0.86 (0.39 - 1.93)	2.0	0	2.3	0.0	12
Sun 2008 12 lead ECG age 18-39y; resident physician; 14 days follow up	0 (0-97)	82 (70-91)	0	98	1.4 (0.1-15.9)	0.92 (0.41 - 2.07)	2.0	0	2.4	0.0	18
Sun 2008 12 lead ECG age 40-59y; attending physician; 14 days follow up	50 (7-93)	80 (66-91)	18	95	2.6 (0.8-8.0)	0.62 (0.23 - 1.67)	8.0	18	5.1	4.1	22
Sun 2008 12 lead ECG age 40-59y; resident physician; 14 days follow up	100 (40-100)	85 (70-91)	36	100	5.6 (2.8-11.6)	0.12 (0.01 - 1.65)	8.0	36	0.0	100 000	22

Sun 2008 12 lead ECG age 60-79y; attending physician; 14 days follow up	67 (35-90)	55 (40-69)	27	87	1.5 (0.9-2.5)	0.60 (0.26 - 1.40)	20	27	13.1	2.5	49
Sun 2008 12 lead ECG age 60-79y; resident physician; 14 days follow up	67 (35-90)	67 (52-80)	33	89	2.0 (1.1-3.5)	0.48 (0.21 - 1.10)	20	34	11.0	4.1	39
Sun 2008 12 lead ECG age over 80y; attending physician; 14 days	58 (28-85)	65 (50-78)	28	87	1.7 (0.9-3.0)	0.64 (0.32 - 1.30)	19	28	13.1	2.6	40
Sun 2008 12 lead ECG age over 80y; resident physician; 14 days	75 (43-95)	61 (46-74)	3	91	1.9 (1.2-3.1)	0.41 (0.15 - 1.12)	19	31	8.8	4.7	46
Sun 2008 12 lead ECG all ages attending physician; 14 days follow up	59 (39-76)	72 (65-78)	23	92	2.1 (1.4-3.1)	0.57 (0.37 - 0.89)	13	24	7.9	3.7	32
Sun 2008 12 lead ECG all ages resident physician; 14 days follow up	72 (53-87)	74 (67-80)	28	95	2.8 (2.0-3.8)	0.37 (0.21 - 0.68)	13	29	5.3	7.3	32