SERVIZIO SANITARIO REGIONALE
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Azienda Ospedaliero - Universitaria di Parma

DALL'ICTUS CRIPTOGENETICO ALLA CHIUSURA PERCUTANEA DEL FORAME OVALE PERVIO

Analisi dei Trials e Linee Guida

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Parma 21 ottobre 2014

TOAST

Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment

HP Adams, Jr, BH Bendixen, LJ Kappelle, J Biller, BB Love, DL Gordon and EE Marsh, 3d

Large-artery atherosclerosis (embolus/thrombosis)*

Cardioembolism (high-risk/medium-risk)*

Small-vessel occlusion (lacune)*

Stroke of other determined etiology*

Stroke of undetermined etiology

a. Two or more causes identified

b. Negative evaluation

c. Incomplete evaluation

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

Stroke. 1993;24:35-41

TABLE 3. TOAST Classification of High- and Medium-Risk Sources of Cardioembolism

High-risk sources	Medium-risk sources
Mechanical prosthetic valve	Mitral valve prolapse
Mitral stenosis with atrial fibrillation	Mitral annulus calcification
Atrial fibrillation (other than lone atrial fibrillation)	Mitral stenosis without atrial fibrillation
Left atrial/atrial appendage thrombus	Left atrial turbulence (smoke)
Sick sinus syndrome	Atrial septal aneurysm
Recent myocardial infarction (<4 weeks)	Patent foramen ovale
Left ventricular thrombus	Atrial flutter
Dilated cardiomyopathy	Lone atrial fibrillation
Akinetic left ventricular segment	Bioprosthetic cardiac valve
Atrial myxoma	Nonbacterial thrombotic endocarditis
Infective endocarditis	Congestive heart failure
	Hypokinetic left ventricular segment
	Myocardial infarction (>4 weeks, <6 months)

Stroke. 1993;24:35-41

An Evidence-Based Causative Classification System for Acute Ischemic Stroke

Hakan Ay, MD,[1,2] Karen L. Furie, MD,[2] Aneesh Singhal, MD,[2] Wade S. Smith, MD, PhD,[3] A. Gregory Sorensen, MD,[1] and Walter J. Koroshetz, MD[2]

Regular, evidence-based assignment of patients to etiologic stroke categories is essential to enable valid comparison among studies. We designed an algorithm (SSS-TOAST) that incorporated recent advances in stroke imaging and epidemiology to identify the most probable TOAST category in the presence of evidence for multiple mechanisms. Based on the weight of evidence, each TOAST subtype was subdivided into 3 subcategories as "evident", "probable", or "possible". Classification into the subcategories was determined via predefined specific clinical and imaging criteria. These criteria included published risks of ischemic stroke from various mechanisms and published reports of the strength of associations between clinical and imaging features and particular stroke mechanisms. Two neurologists independently assessed 50 consecutively admitted patients with acute ischemic stroke through reviews of abstracted data from medical records. The number of patients classified as "undetermined-unclassified" per the original TOAST system decreased from 38–40% to 4% using the SSS-TOAST system. The kappa value for interexaminer reliability was 0.78 and 0.90 for the original TOAST and SSS-TOAST respectively. The SSS-TOAST system successfully classifies patients with acute ischemic stroke into determined etiologic categories without sacrificing reliabilty. The SSS-TOAST is a dynamic algorithm that can accommodate modifications as new epidemiological data accumulate and diagnostic techniques advance.

Ann Neurol 2005;58:688–697

Table 2. Cardioaortic Sources of Cerebral Embolism

Sources with high primary risk for ischemic stroke
- *Sources of embolism of thrombotic origin*
  - [a]Left atrial thrombus[78,79]
  - [a]Left ventricular thrombus[80]
  - [a]Atrial fibrillation[81,82]
  - [a]Paroxysmal atrial fibrillation[82,83]
  - [a]Sick sinus syndrome[84,85]
  - [a]Sustained atrial flutter[44]
  - [a]Recent myocardial infarction[51,52] (within 1 month)
  - [a]Rheumatoid mitral or aortic valve disease[86]
  - [a]Bioprosthetic and mechanical heart valves[45–48]
  - [a]Chronic myocardial infarction together with low ejection fraction less than 28%[38]
  - [a]Symptomatic congestive heart failure with ejection fraction less than 30%[39]
  - [b]Dilated cardiomyopathy[87,88]
  - [b]Nonbacterial thrombotic endocarditis[49,50]
- *Sources with embolism not predominantly of thrombotic origin*
  - [a]Infective endocarditis[89,90]
  - [a]Papillary fibroelastoma[40]
  - [b]Left atrial myxoma[91]

Sources with low or uncertain primary risk for ischemic stroke
- *Cardiac sources of embolism*
  - [a]Mitral annular calcification[92]
  - [b]Patent foramen ovale[93]
  - Atrial septal aneurysm
  - Atrial septal aneurysm and patent foramen ovale
  - Left ventricular aneurysm without thrombus
  - Isolated left atrial smoke (no mitral stenosis or atrial fibrillation)
- *Aortic sources of embolism*
  - [a]Complex atheroma in the ascending aorta or proximal arch[41]

Cerebrovascular Diseases

Cerebrovasc Dis 2009;27:493–501
DOI: 10.1159/000210432

Received: October 2, 2008
Accepted: February 2, 2009
Published online: April 3, 2009

Classification of Stroke Subtypes

P. Amarenco[a] J. Bogousslavsky[b] L.R. Caplan[c] G.A. Donnan[d] M.G. Hennerici[e]

Cerebrovascular Diseases

Cerebrovasc Dis 2009;27:502–508
DOI: 10.1159/000210433

Received: February 2, 2009
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Published online: April 3, 2009

New Approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke

P. Amarenco[a] J. Bogousslavsky[b] L.R. Caplan[c] G.A. Donnan[d] M.G. Hennerici[e]

Principi

- Identificare la causa(e) più probabile senza ignorare le altre cause o malattie concomitanti (fenotipi misti)
- La classificazione deve essere basata sulla storia del paziente, esame fisico e tests diagnostici completi
- Livello di evidenza diagnostica

Stroke subtype classification: A-S-C-O

- A-S-C-O: acronym for
  - A = Atherosclerosis
  - S = Small vessel disease
  - C = Cardiac source
  - O = Other cause
- additional grading
  - 1 definitely a potential cause of the index stroke
  - 2 causality uncertain
  - 3 unlikely a direct cause of the index stroke (but disease is present)
  - 0 disease is completely absent
  - 9 grading not possible because of insufficient work-up
- Every patient gets a phenotypic (descriptive) score: e.g. A0 S3 C1 O0

- Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. Classification of Stroke Subtypes. Cerebrovasc Dis 2009. 27(5):493-501

  Amarenco P, Bogousslavsky J, Caplan LR, Donnan GA, Hennerici MG. New approach to Stroke Subtyping: The A-S-C-O (Phenotypic) Classification of Stroke. Cerebrovasc Dis 2009. 27(5):502-508

Grades of pathology		Levels of diagnostic evidence	
1	Definitely a potential cause of the index stroke	A	Direct demonstration by gold standard diagnostic tests or criteria
2	Causality uncertain	B	By indirect evidence or less sensitive or specific tests or criteria
3	Unlikely a direct cause of the index stroke (but disease is present)	C	By weak evidence

In the absence of disease the grade is 0. In case of insufficient work-up and that the patient cannot be graded, the grade is 9.

Further information can be found in table 2.

Grades for cardioembolism (C)	
1. Definitely a potential cause of the index stroke	Cardioembolic stroke – demonstration of: (a) Mitral stenosis; (b) Prosthetic heart valve; (c) Myocardial infarction within the past 4 weeks; (d) Mural thrombus in left cavities; (e) Left ventricular aneurysm; (f) Any documented history or permanent or transient atrial fibrillation or flutter with or without spontaneous echo contrast or left atrial thrombus; (g) Sick sinus syndrome;
	(h) Dilated cardiomyopathy; (i) Ejection fraction <35%; (j) Endocarditis; (k) Intracardiac mass; (l) PFO plus in situ thrombosis; (m) PFO plus concomitant PE or DVT preceding the brain infarction.
2. Causality uncertain	(a) PFO and ASA; (b) PFO and concomitant DVT or PE (but not preceding the index stroke); (c) Spontaneous echo contrast; (d) Apical akinesia of the left ventricle and impaired ejection fraction (but >35%); (e) Only suggested by history of myocardial infarction or palpitation and multiple repeated brain infarcts on both sides or in both the anterior and posterior circulation; (f) Only suggested by abdominal CT/MRI or autopsy demonstration of the presence of systemic infarction (e.g. kidney, splenic, mesenteric) or lower limb embolism (in addition to the index stroke).
3. Unlikely a direct cause of index stroke	One of the following abnormalities: PFO, ASA, valvular strands, mitral annulus calcification, calcified aortic valve, nonapical akinesia of the left ventricle.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

Guidelines for the Prevention of Stroke in Patients With Stroke or Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

AHA/ASA[23]	USA	2011	Prevenzione secondaria ictus cerebrale	Nei pazienti con ictus/TIA ischemico e POF, la terapia antiaggregante è ragionevole.	Classe IIa, Livello B
				Non ci sono dati sufficienti a definire il trattamento anticoagulante è equivalente o superiore all'aspirina nella prevenzione secondaria dello stroke in pazienti con PFO	Classe IIb, Livello B
				Non ci sono dati sufficienti per raccomandare la chiusura del PFO in pazienti con stroke e PFO	Classe IIb, Livello C

Prevenzione e trattamento ictus cerebrale 2012	Nei pazienti con ictus ischemico o TIA criptogenetico associato a FOP ed esenti da TVP e diatesi trombofilica, è indicato il trattamento con ASA 325 mg/die.	Raccomandazione 12.13 a **Grado A**
	Nei pazienti con ictus o TIA criptogenetico associato a FOP, che hanno altre indicazioni alla TAO, quali una diatesi trombofilica o evidenza di TVP, è indicato il trattamento con warfarin.	Raccomandazione 12.13 b **Grado A**
	Nei pazienti con ictus o TIA criptogenetico associato a FOP, con TVP o diatesi trombofilica e controindicazioni alla TAO è indicata la chiusura del FOP.	Raccomandazione 12.13 c **Grado D**
	Nei pazienti con recidiva di ictus o TIA associato a FOP, in presenza di trattamento con ASA o con TAO, dopo una rivalutazione multidisciplinare del caso e in accordo con il paziente è indicata la chiusura del FOP.	Raccomandazione 12.13 d **Grado D**

Study	Closure device	Inclusion criteria	Primary end point	Follow-up (months)
Furlan *et al*	STARFlex	TIA, CS	Composite (stroke or TIA, early death from any cause*, late death from neurologic causes†)	24
Meier *et al*	Amplatzer PFO Occluder	TIA, CS, peripheral embolism	Composite (death, non-fatal stroke, TIA, peripheral embolism)	49.2/48.0 (PC/MTx)
Carroll *et al*	Amplatzer PFO Occluder	TIA, CS	Composite (stroke, early death)‡	31.2
Paciaroni *et al*	Amplatzer PFO Occluder PFO STAR Cardioseal/STARflex	TIA, CS	Composite (stroke, TIA)	24.0
Faggiano *et al*	na	TIA, CS, migraine	Composite (stroke, TIA, death from neurologic cause)	54.0
Mazucco *et al*	Amplatzer PFO Occluder Amplatzer Cribriform Occluder BioSTAR	CS	Composite (stroke, TIA)	27.5
Wahl *et al*	Amplatzer PFO Occluder PFO STAR Sideris Buttoned Angel Wing Amplatzer ASD CardioSEAL	TIA, CS	Composite (stroke, TIA, peripheral embolism)	108.0
Schuchlenz *et al*	Rashkind occluder, CardioSEAL, StarFlex, Amplatzer	CS, TIA	Composite (stroke or TIA)	33.6
Harrer *et al*	Rashkind, ASDOS, Sideris, Amplatzer, CardioSeal, PFO Star	CS, TIA	Composite (TIA or stroke)	25
Thanopoulos *et al*	Amplatzer	CS, TIA	composite (TIA or stroke)	24
Cerrato *et al*	NA	CS, TIA	Composite (stroke or TIA)	64
Horner *et al*	Amplatzer, CardioSeal, CardioStar	CS, TIA	Recurrent stroke	24
Lee *et al*	Amplatzer, CardioSeal	CS	Recurrent stroke	42
Casaubon *et al*	Amplatzer, CardioSeal	CS, TIA	Recurrent stroke	32

Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials

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Table I Trials baseline characteristics

Author	Study acronym	Enrolment	Country	Number of patients	Mean follow-up (months)	Lost to F/U	Intervention group	Medical therapy group	Study conclusions
Carroll *et al.*	RESPECT	2003–11 multicentre, randomized	USA and Canada	980	31	Medical group 17.2% 83/481 Device group 9.2% 46/499	Amplatzer PFO occluder + aspirin and clopidogrel for 1 month followed by aspirin for at least 5 months	Aspirin 46.5% Coumadin 25.2% Clopidogrel 14% Aspirin + dipyridamole 8.1% Aspirin + clopidogrel 6.2%	No significant benefit of PFO closure for recurrent stroke prevention
Meier *et al.*	PC	2000–09 multicentre randomization by web-based system	29 Centres in Europe, Canada, Brazil, and Australia	414	49	Medical group 15% 31/210 Device group 12% 24/204	Amplatzer PFO occluder + aspirin (5–6 months) and ticlopidine OR clopidogrel	Antiplatelet OR, AND coumadin (left at the discretion of treating physician)	No significant reduction in the risk of recurrent embolic events or death in the closure group, as compared with the medical therapy group
Furlan *et al.*	CLOSURE I	2003–08 multicentre, randomized	USA and Canada	909	44	Medical group 17% 77/462 Device group 5%, 24/447	STARFlex + aspirin (2 years) and clopidogrel (6 months)	Aspirin, coumadin OR aspirin and coumadin (left at the discretion of treating physician)	No significant difference between closure with a percutaneous device plus antiplatelet therapy and medical therapy alone with respect to the prevention of recurrent stroke or TIA

European Heart Journal (2013) 34, 3342–335

Percutaneous Closure versus Medical Therapy Alone for Cryptogenic Stroke Patients with a Patent Foramen Ovale: Meta-Analysis of Randomized Controlled Trials

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TABLE III. Definition of Primary Endpoint by Study

Variable	CLOSURE I[8]	PC Trial[10]	RESPECT[9]
Device	STARFlex Septal Closure System	AMPLATZER PFO Occluder	AMPLATZER PFO Occluder
Definition of primary endpoint	Sum of stroke + TIA + any death <30 d + death from neurologic cause >30 d	Sum of stroke + TIA + any death + peripheral embolism*	Sum of stroke + any death <30 d + stroke death

PFO = patent foramen ovale; TIA = transient ischemic attack

*No peripheral embolization occurred

(Tex Heart Inst J 2014;41(4):357-67)

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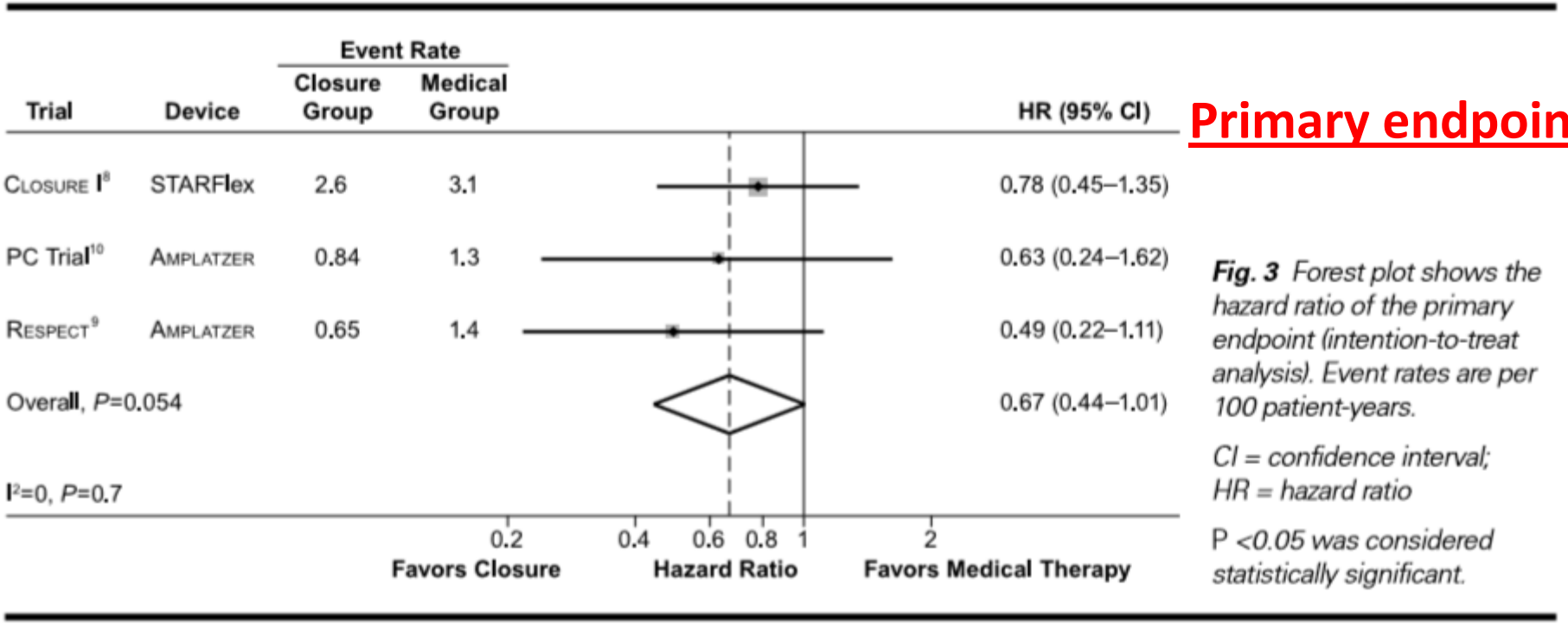

Primary endpoint

Fig. 3 *Forest plot shows the hazard ratio of the primary endpoint (intention-to-treat analysis). Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P <0.05 was considered statistically significant.

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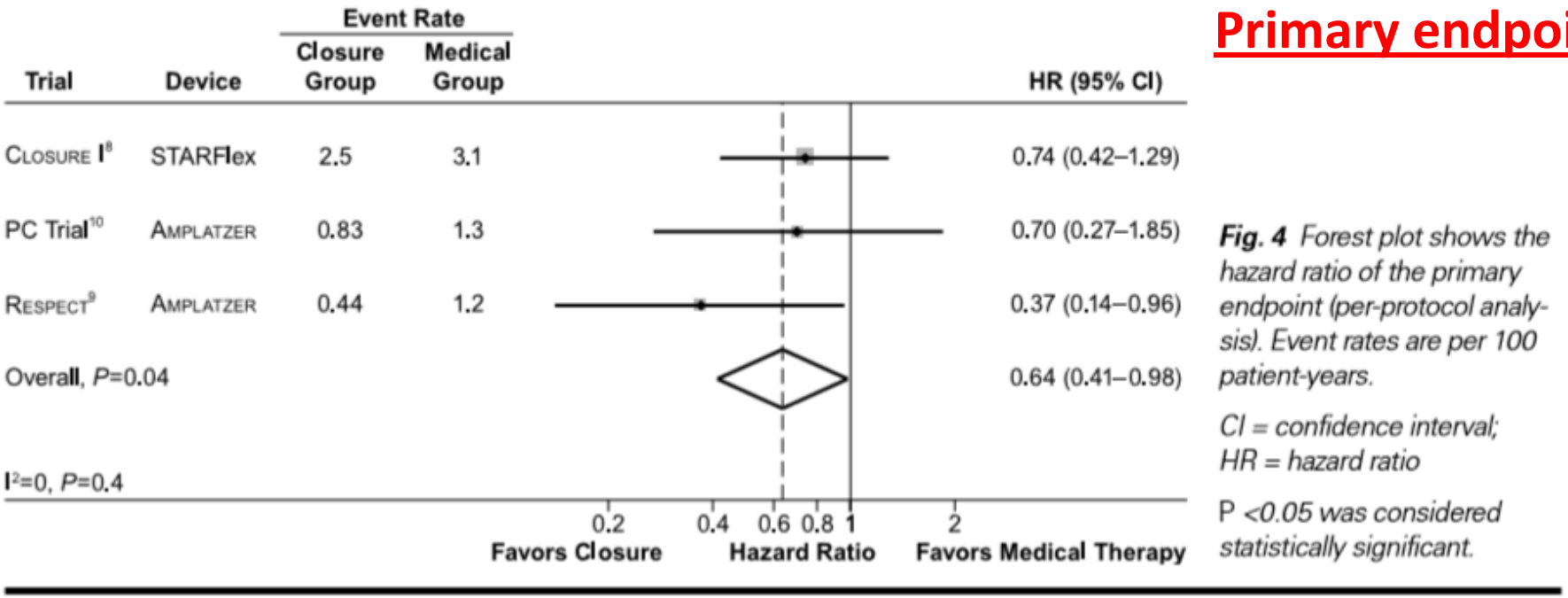

Primary endpoint

Fig. 4 *Forest plot shows the hazard ratio of the primary endpoint (per-protocol analysis). Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P <0.05 was considered statistically significant.

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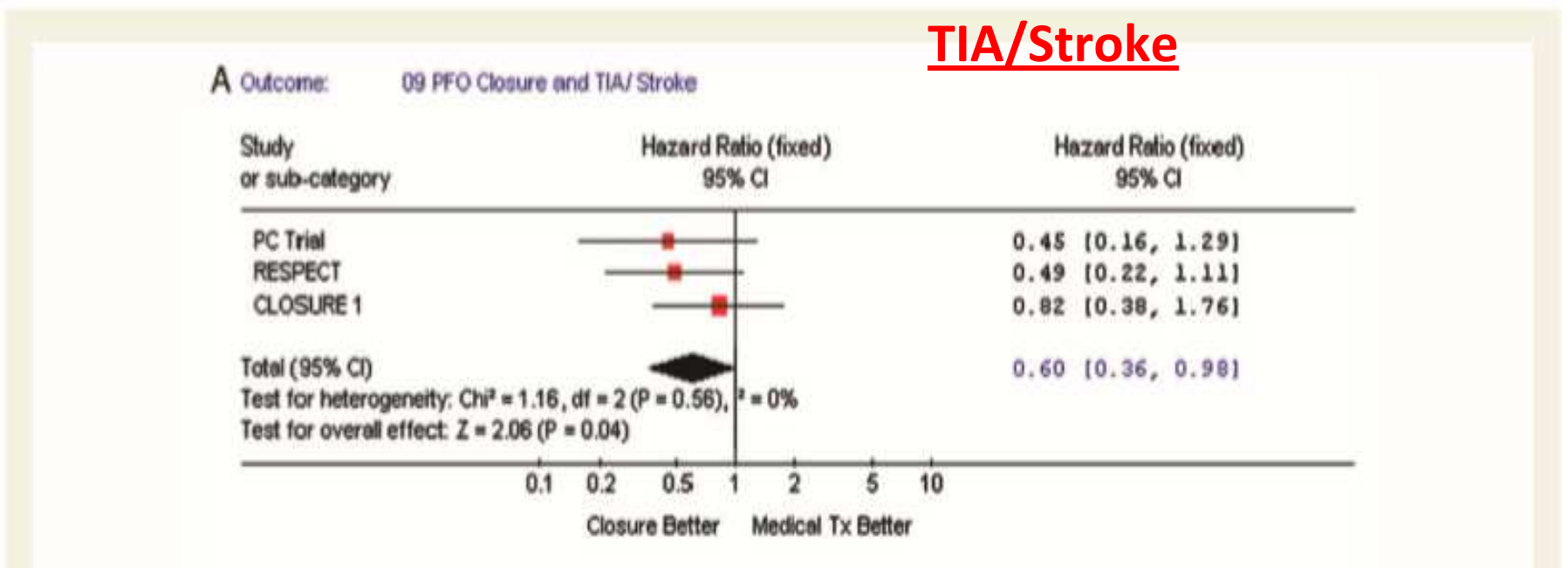
TIA/Stroke



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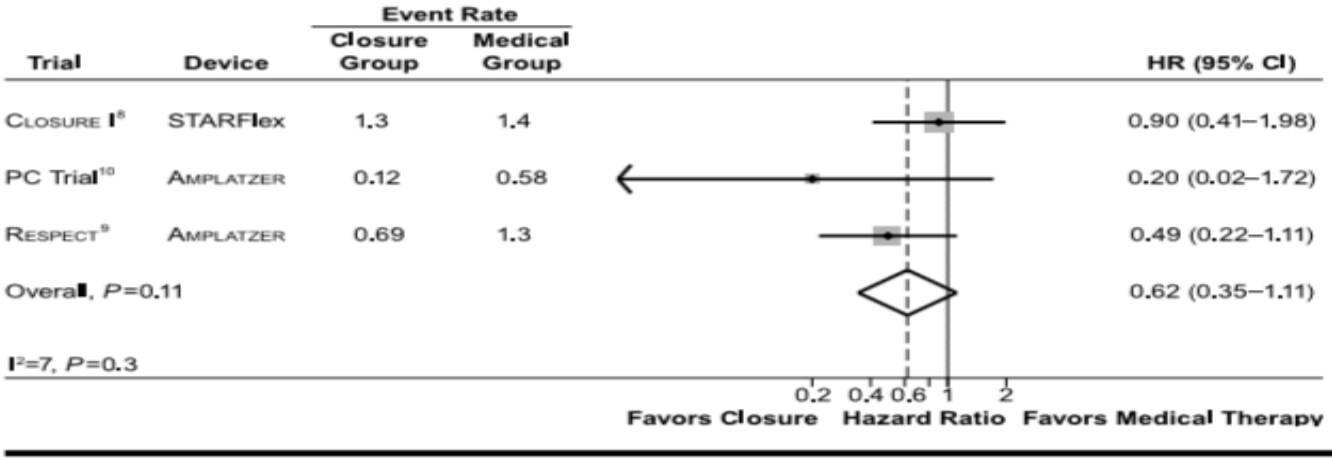
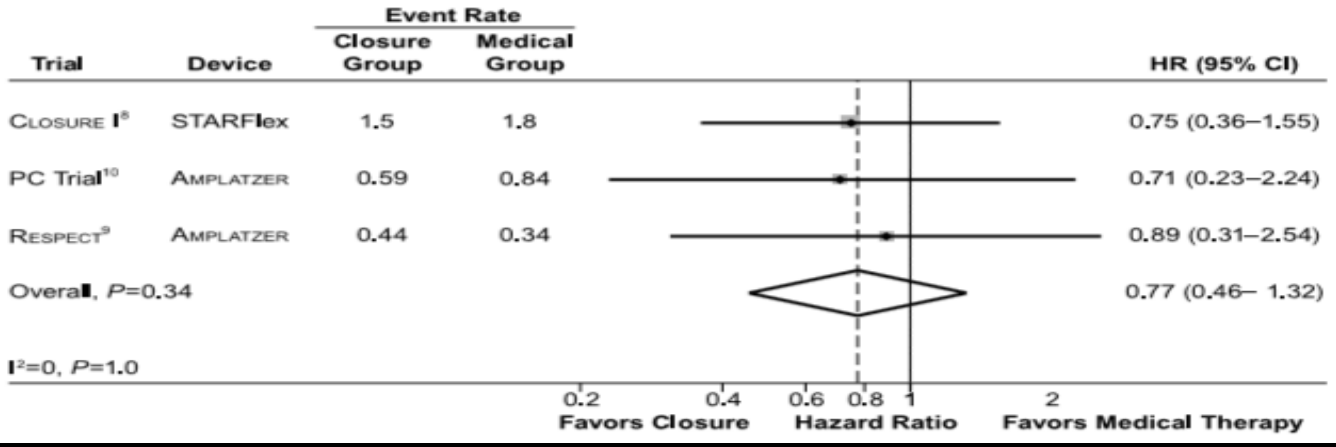


Stroke

Fig. 5 *Forest plot shows the hazard ratio of stroke. Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P <0.05 was considered statistically significant.



TIA

Fig. 6 *Forest plot shows the hazard ratio of transient ischemic attack. Event rates are per 100 patient-years.*

CI = confidence interval; HR = hazard ratio

P <0.05 was considered statistically significant.

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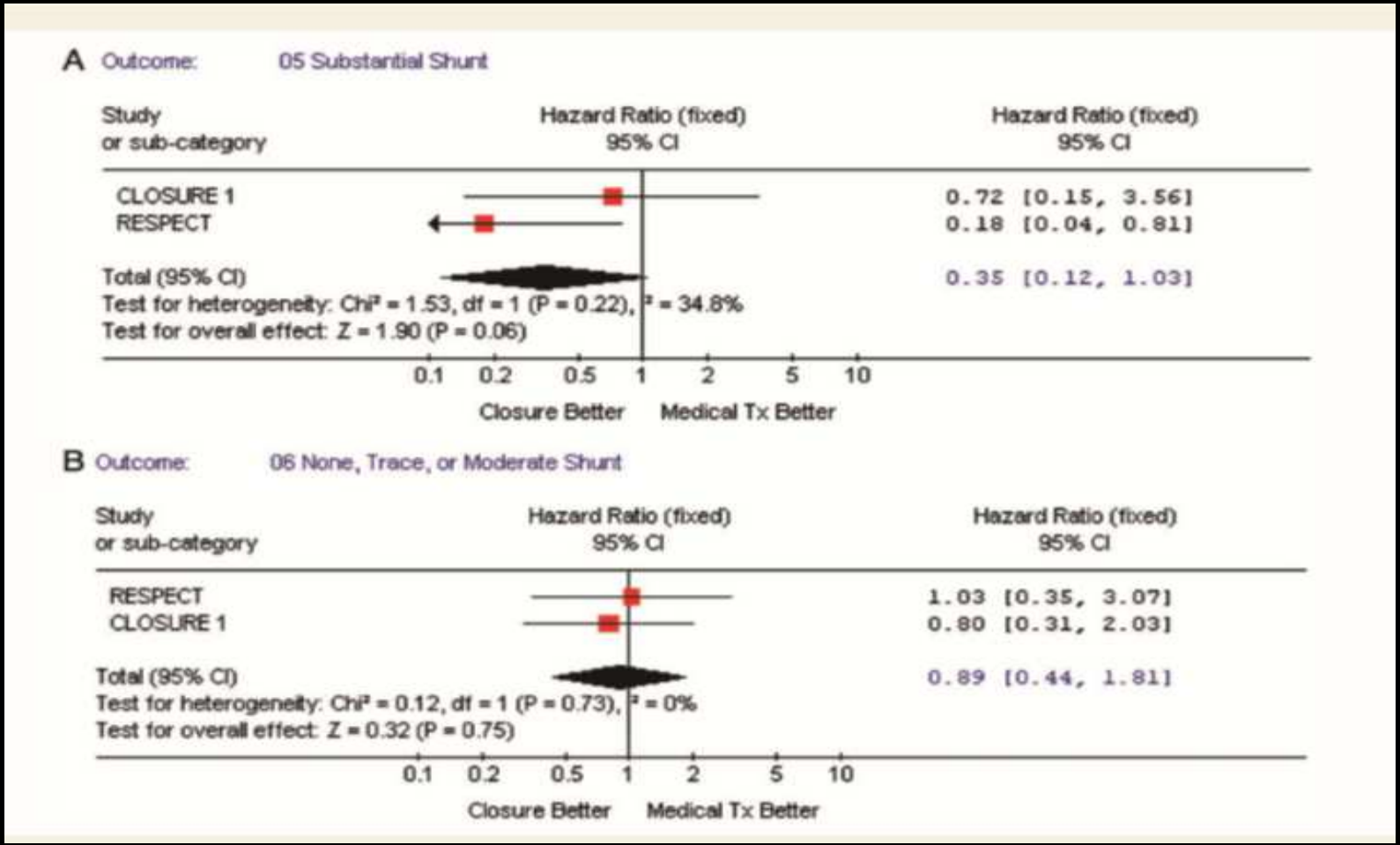

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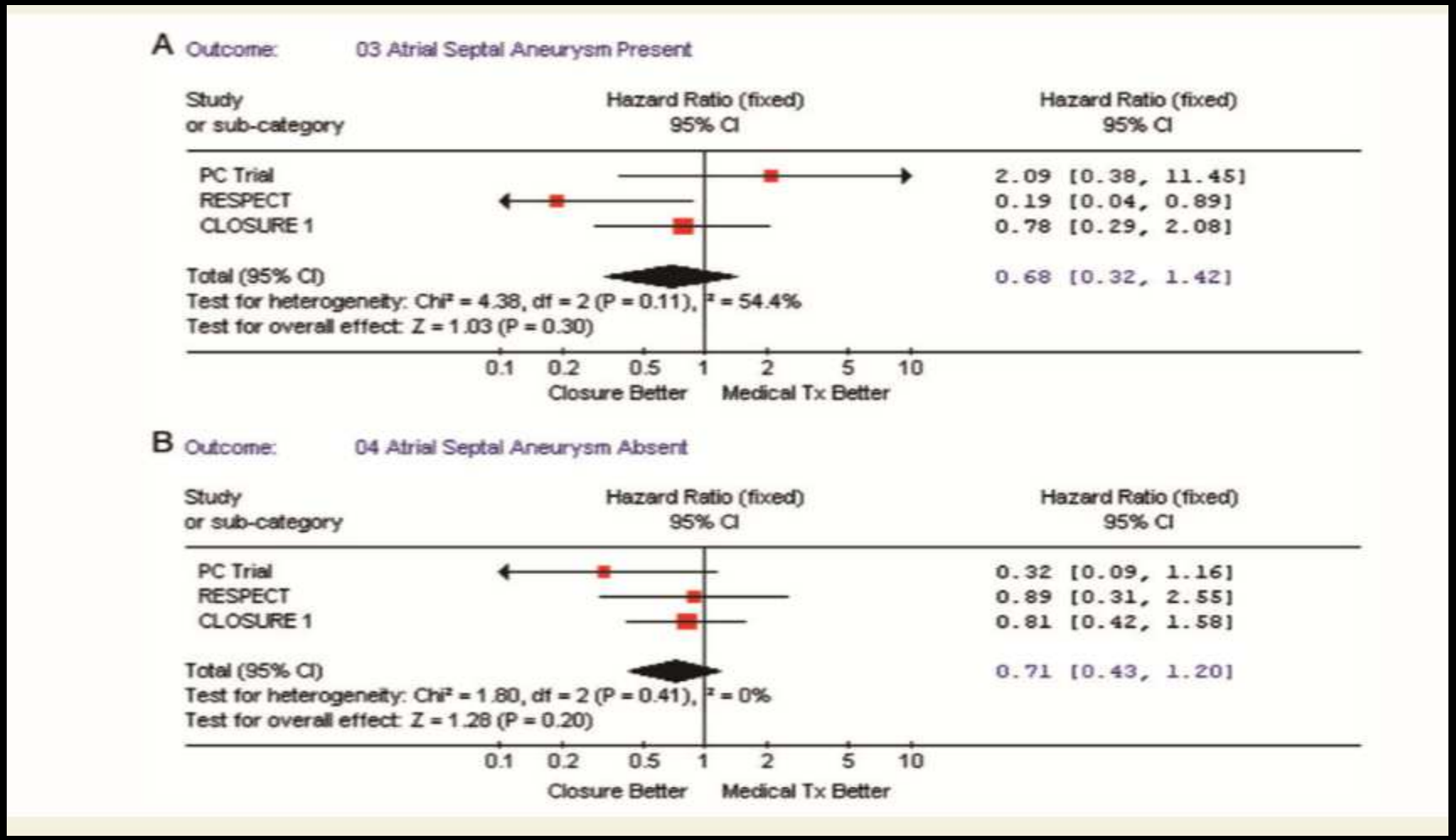

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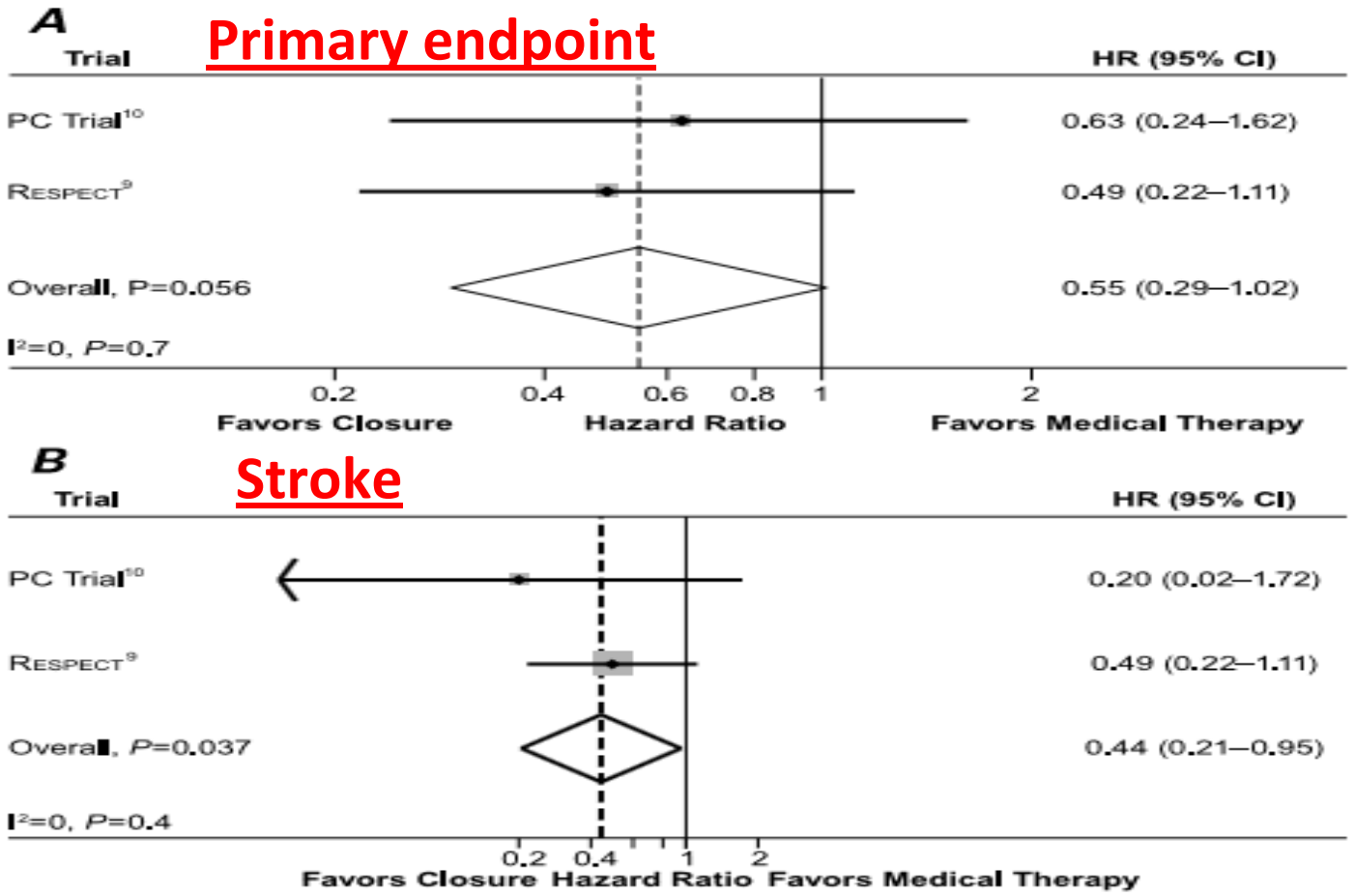
Amplatzer vs Medical Therapy



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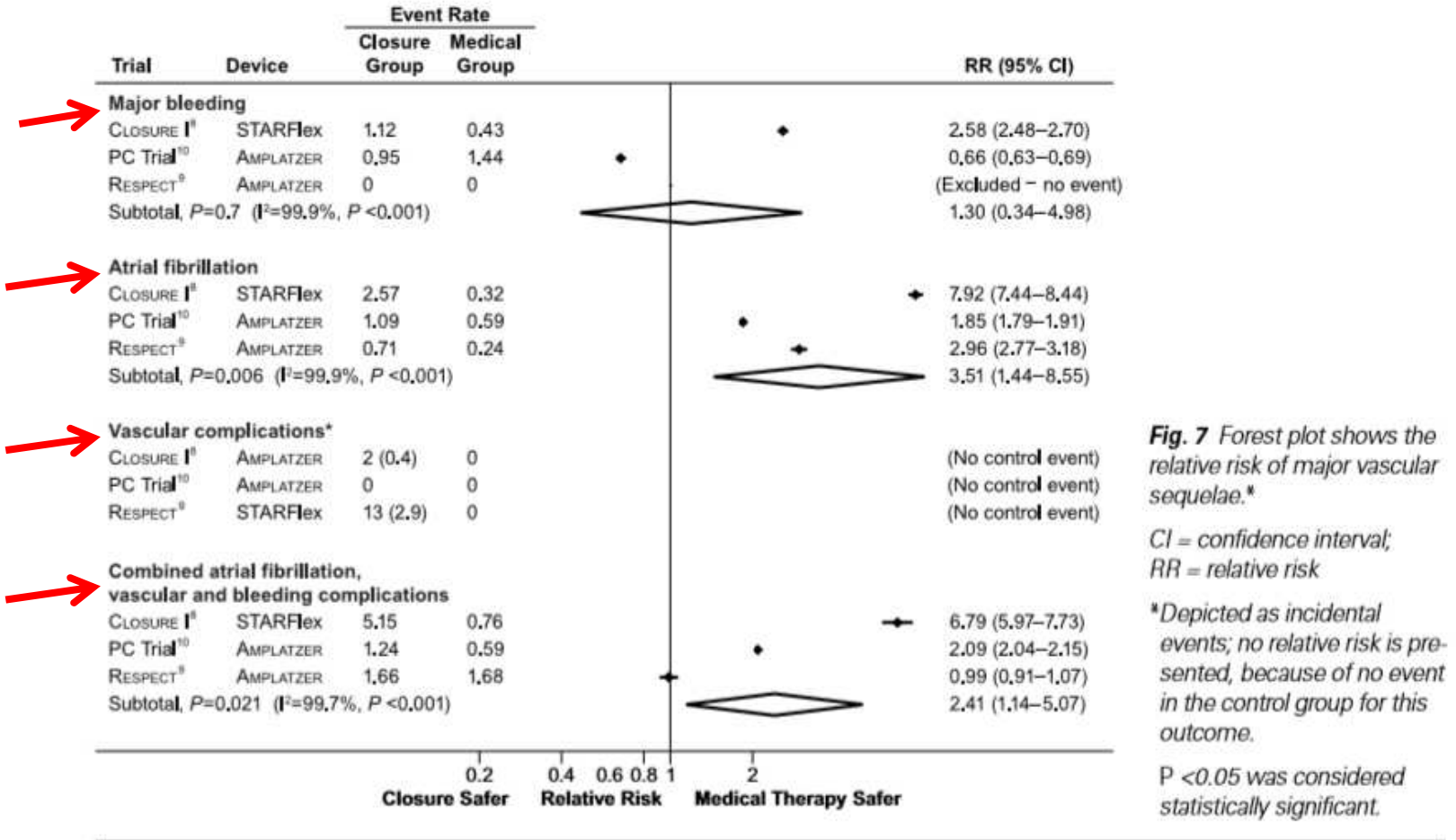

Fig. 7 *Forest plot shows the relative risk of major vascular sequelae.**

CI = confidence interval; RR = relative risk

**Depicted as incidental events; no relative risk is presented, because of no event in the control group for this outcome.*

P <0.05 was considered statistically significant.

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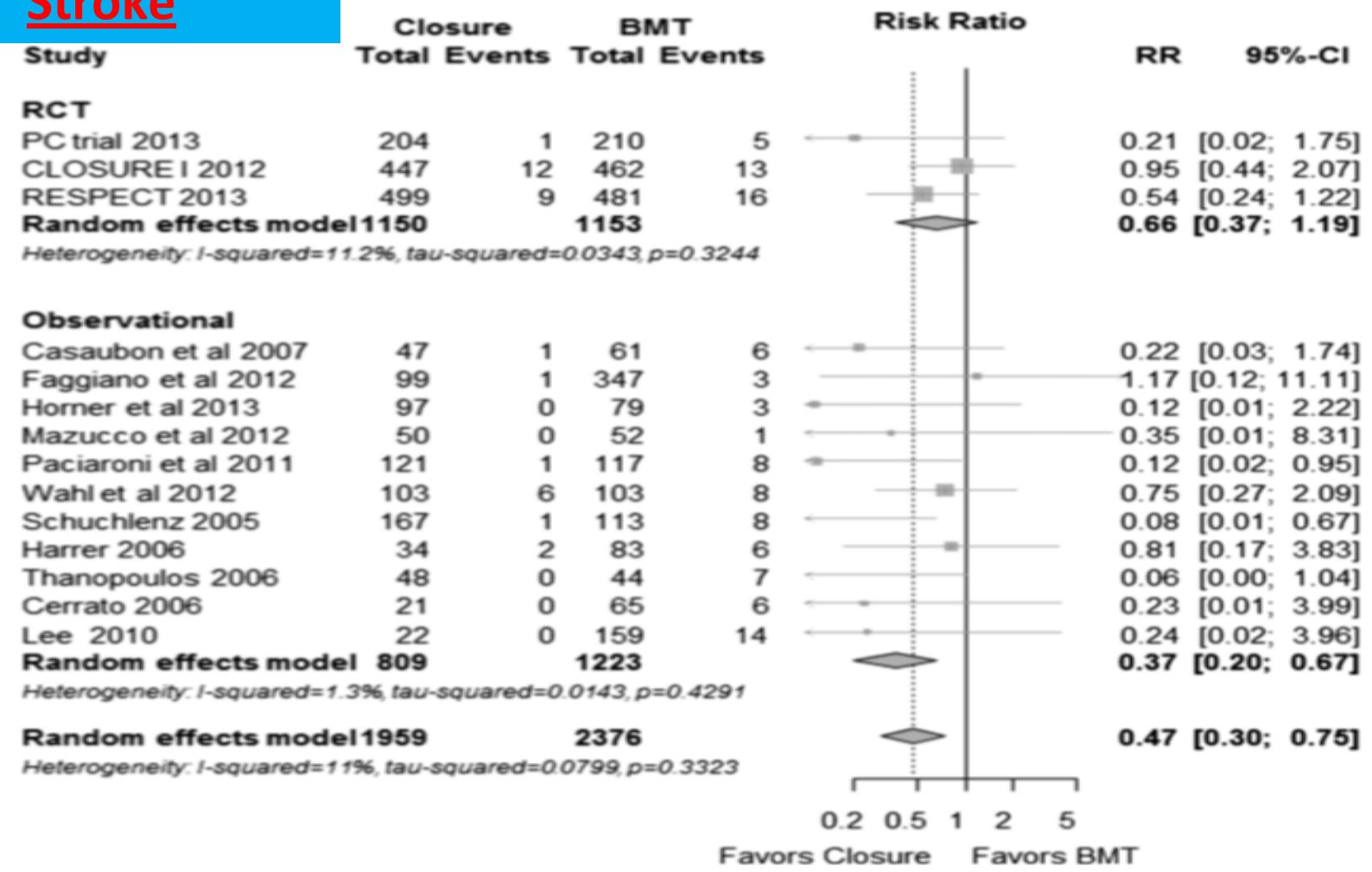
Stroke



Heart 2014;100:389–395

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Figure 3 Forest plot of time-to-event analyses. Hazard ratio (HR) for end point stroke. For observational studies, adjusted HR were used. RCT, randomised controlled trials.

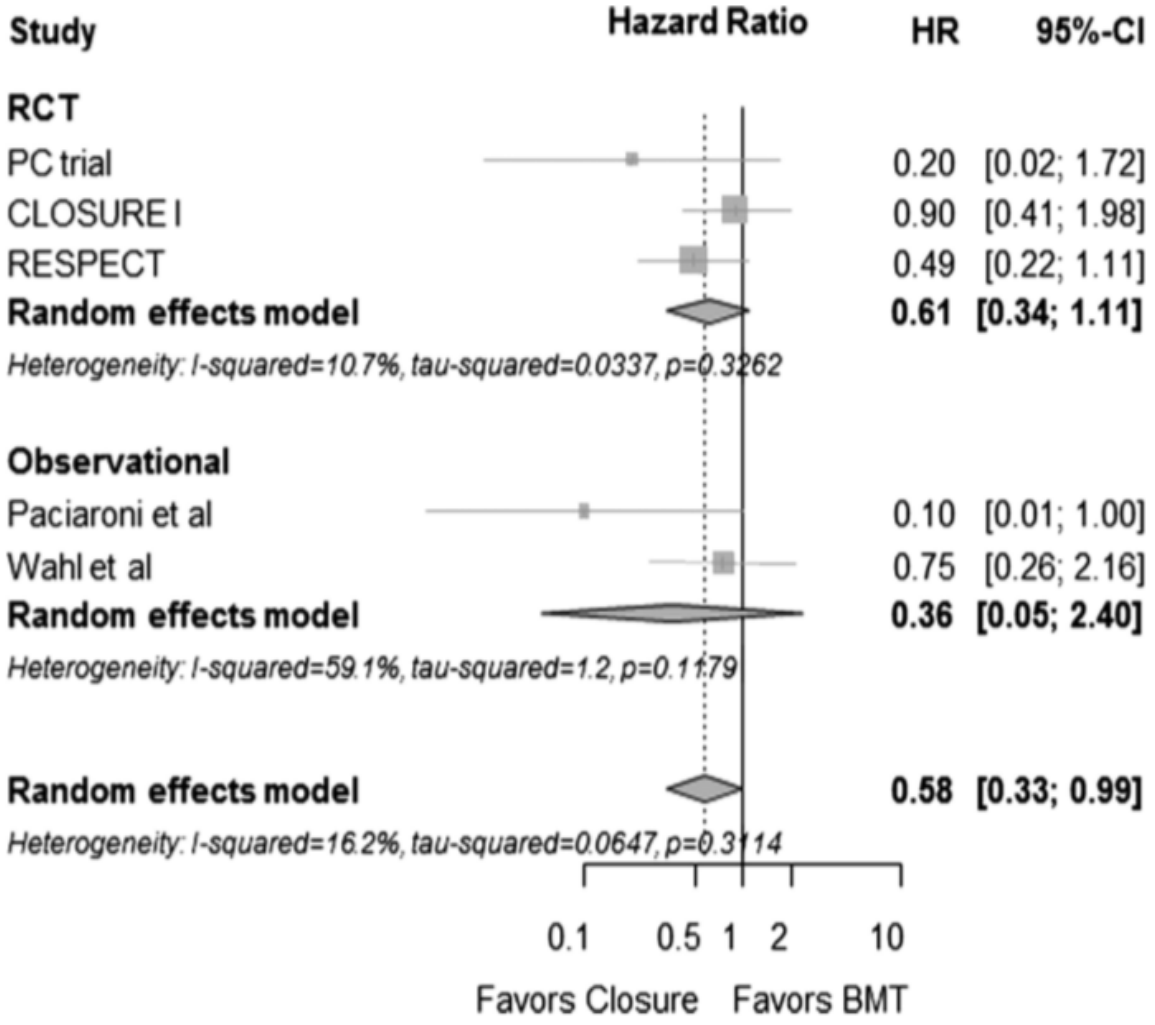

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Figure 5 Forest plot of risk ratios (RR) for bleeding. BMT, best medical therapy; RCT, randomised controlled trials.

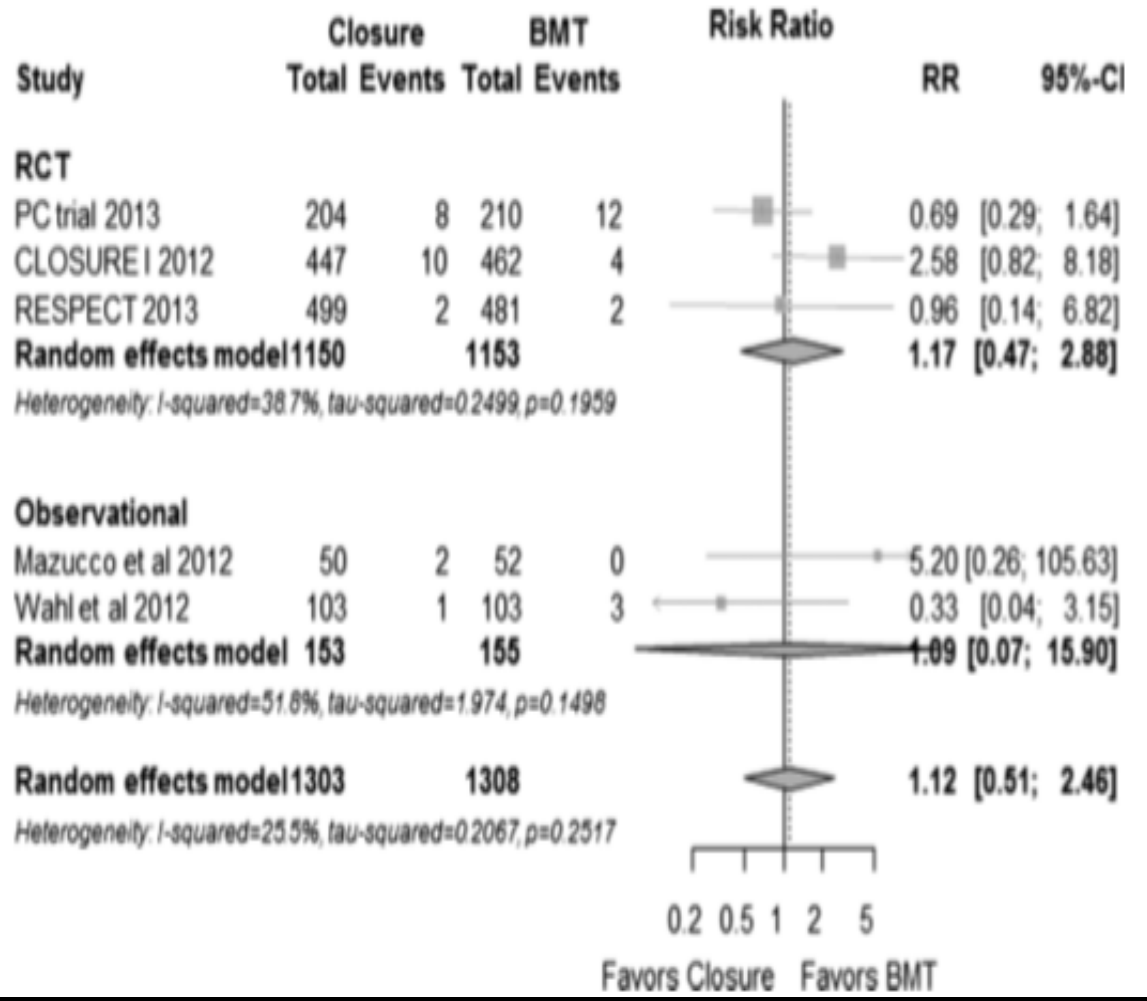

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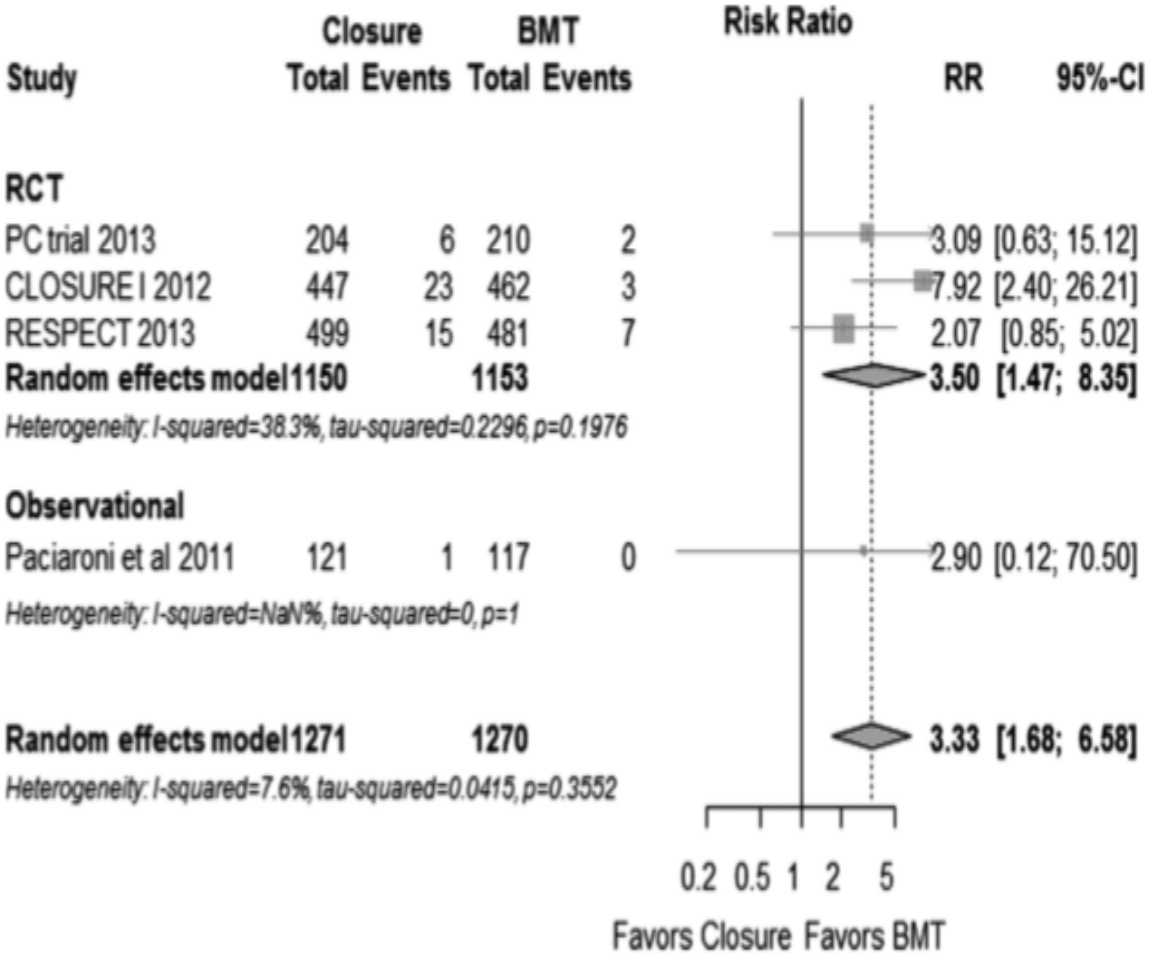
Figure 6 Forest plot of risk ratios (RR) for atrial fibrillation. BMT, best medical therapy; RCT, randomised controlled trials.



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BENEFICIO ASSOLUTO

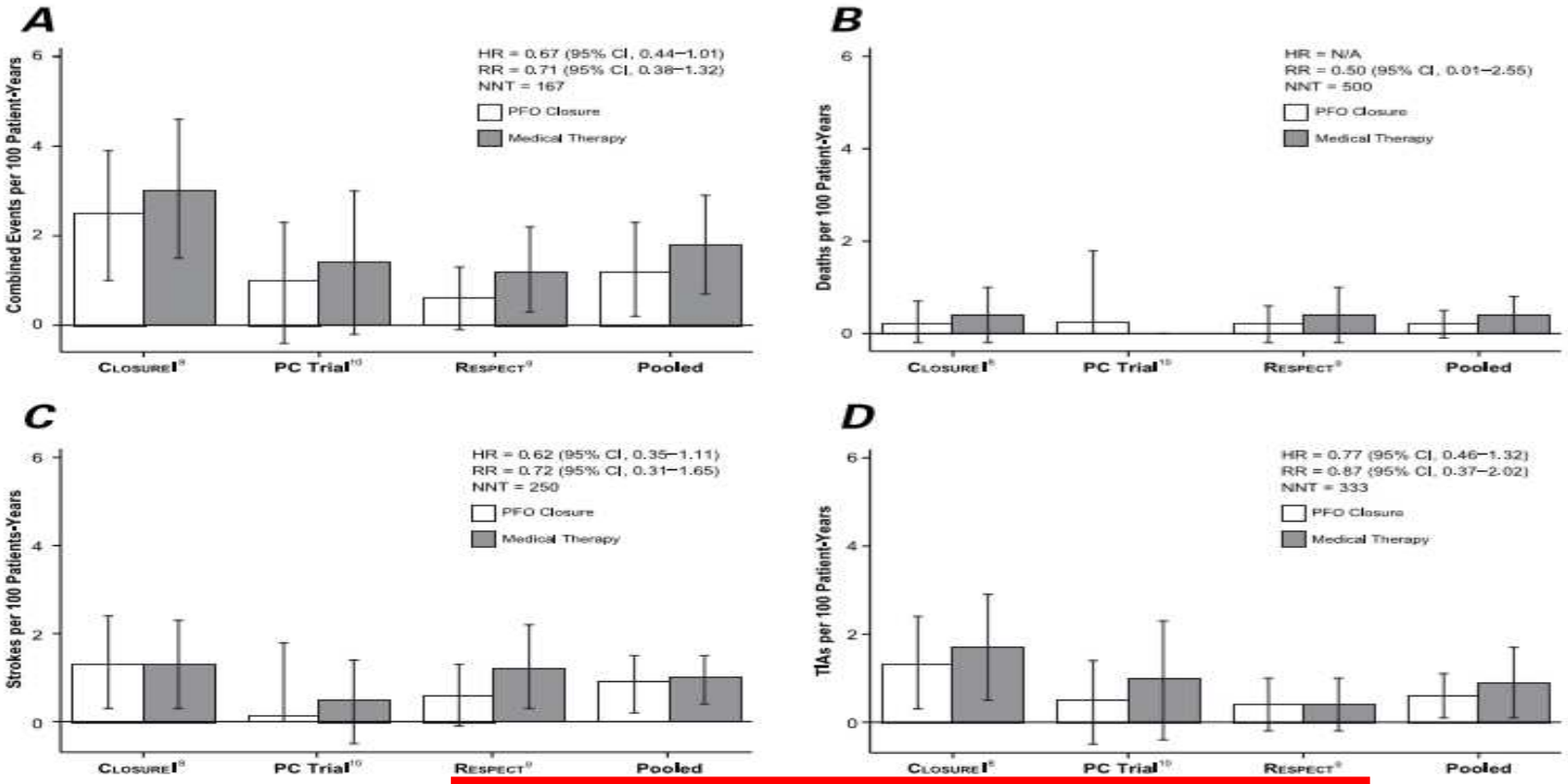

Fig. 2 *Graphs show the pooled rates of **A)** the primary endpoint, **B)** death, **C)** stroke, and **D)** transient ischemic attack, per 100 patient-years. The upper limit of NNT could not be estimated, because the 95% CI for the pooled absolute risk difference crosses zero.*

CI = confidence interval; HR = hazard ratio; NNT = number needed to treat; PFO = patent foramen ovale; RR = relative risk; TIA = transient ischemic attack

Tex Heart Inst J 2014;41(4):357-67

LIMITI

- numero di pazienti relativamente basso
- esiguo numero di eventi nel follow-up
- durata del follow-up relativamente breve
- eccessiva durata dell'arruolamento
- disomogeneità terapeutica (ASA, tienopiridine, TAO)
- discreta percentuale di drop out

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA

RegioneEmilia-Romagna

Agenzia sanitaria e sociale regionale

Il percorso diagnostico-terapeutico del Forame Ovale Pervio

Documento di indirizzo

a cura della Commissione Cardiologica e Cardiochirurgica Regionale

Aprile 2014

FLOW CHART DIAGNOSTICO-TERAPEUTICA

- Età < 55 anni
- TIA/ICTUS criptogenetico, infarto emicranico, embolia sistemica criptogenetica

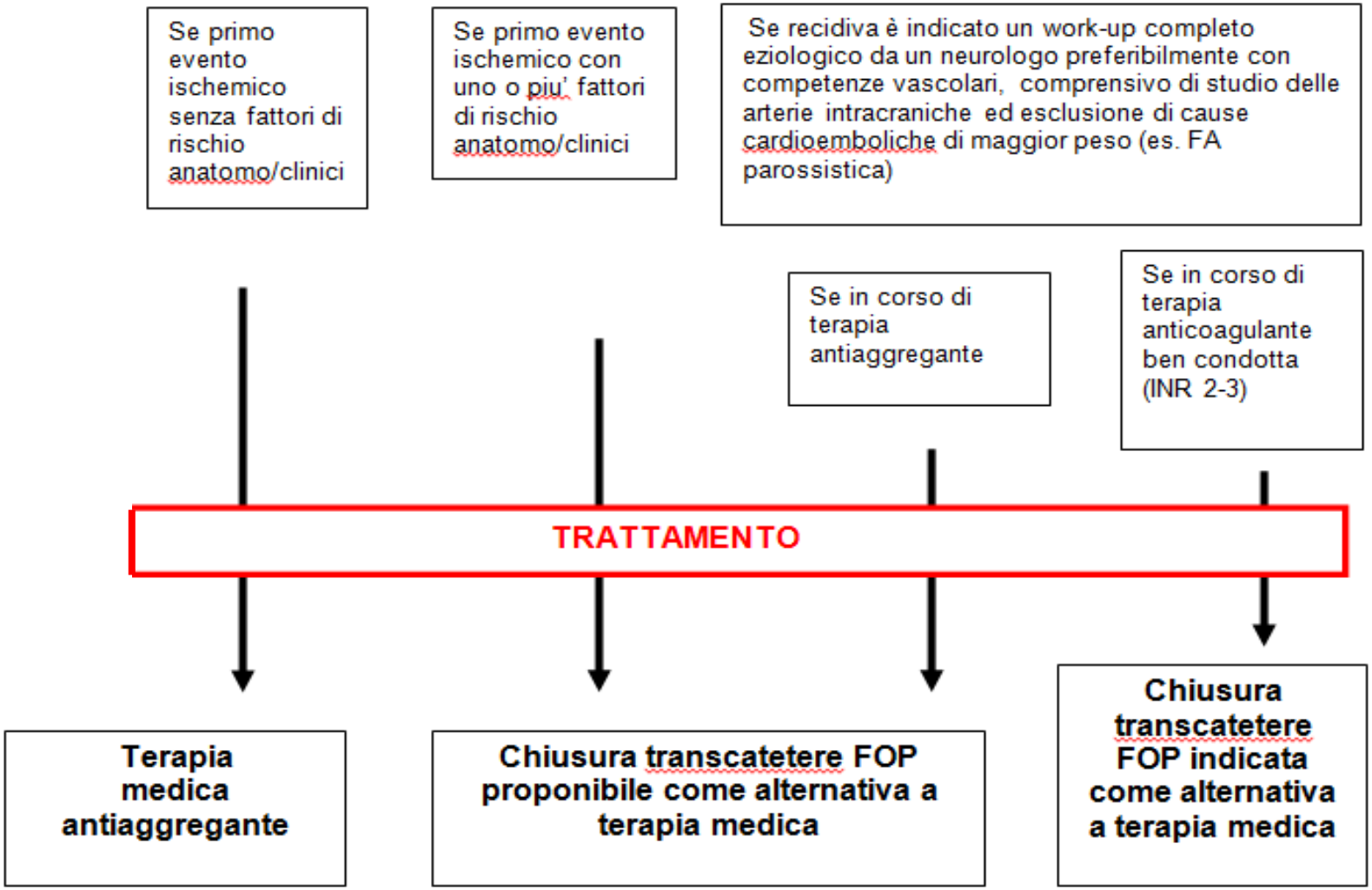

TABLE 1. RoPE SCORE CALCULATOR		
Characteristic	**Points**	**Score**
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age (y)		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥ 70	0	
Total score (sum of individual points)		
Maximum score (a patient < 30 y without vascular risk factors, no history of stroke or TIA, and cortical infarct)		10
Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct)		0

Kent DM, Thaler DE.
The Risk of Paradoxical Embolism (RoPE) study: developing risk models for application to ongoing randomized trials of percutaneous patent foramen ovale closure for cryptogenic stroke.
Trials. 2011;12:185-194.

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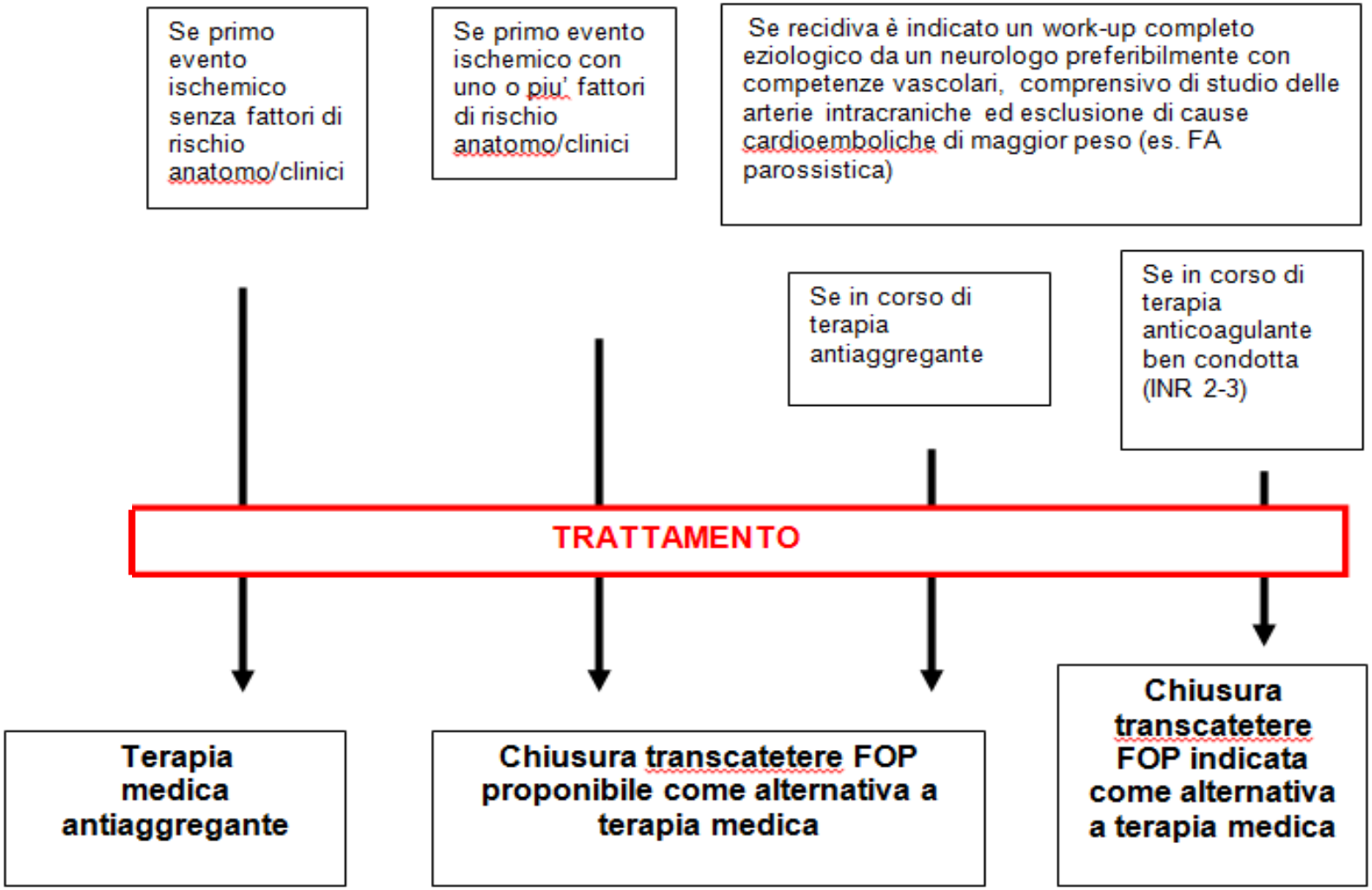

Terapia farmacologica post procedura

Nei pazienti sottoposti a chiusura trans catetere, il gruppo di studio ritiene di proporre il seguente schema di trattamento:

- **doppia terapia antiaggregante con Aspirina 100 mg/die e Clopidogrel 75 mg al giorno nei primi 3 mesi**
- **terapia antiaggregante singola preferibilmente con Aspirina 100-300 mg/die (in caso di intolleranza all'Aspirina: Clopidogrel 75 mg/die) dopo i primi 3 mesi e per almeno un anno dopo la procedura**

- **La prosecuzione della terapia antiaggregante oltre l'anno è consigliata in caso di shunt residuo significativo. In caso di occlusione completa ad un anno, l'eventuale prosecuzione della terapia antiaggregante andrà valutata collegialmente, caso per caso.**

CONCLUSIONI

- Debolezza delle evidenze
- Amplatzer meglio
- Ininfluenza delle caratteristiche anatomiche
- Rischio di complicanze
- Rigorosa selezione dei pazienti candidati alla chiusura
- Dopo chiusura ASA o clopidogrel in cronico !

Grazie per l'attenzione

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EMILIA-ROMAGNA

RegioneEmilia-Romagna

Indicazioni cliniche raccomandate

Agenzia sanitaria e sociale regionale

Pazienti con primo evento ischemico cerebrale/ sistemico criptogenetico

- Nei pazienti di qualsiasi età che vanno incontro ad un primo evento ischemico cerebrale/sistemico criptogenetico è indicata, come prima terapia, **quella antiaggregante**

- Nei pazienti di età inferiore o uguale a 55 anni che presentano uno o più fattori di rischio anatomo/clinici (ROPE SCORE > 7) e vanno incontro ad un primo evento ischemico cerebrale/sistemico criptogenetico è proponibile il trattamento di chiusura trans catetere del forame ovale pervio come alternativa alla terapia anticoagulante orale cronica.

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Pazienti con secondo evento ischemico cerebrale/ sistemico criptogenetico

- I pazienti che presentano recidiva di evento ischemico cerebrale e/o sistemico criptogenetico, in particolare se di età inferiore/uguale a 55 anni, sono candidati in prima istanza ad effettuare un nuovo work-up diagnostico da un neurologo preferibilmente con competenze vascolari, e solo al termine di tali indagini, (comprensive di studio delle arterie intracraniche, esclusione di cause cardioemboliche di maggior peso fra cui FA parossistica, studio dell'arco aortico studio neuroimaging con TC o preferibilmente RM cerebrale) l'eventuale proposta di chiusura trans catetere potrà essere valutata.

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Pazienti con secondo evento ischemico cerebrale/ sistemico criptogenetico

Nei pazienti di età inferiore/uguale a 55 anni (o > 55 anni a giudizio del clinico), recidiva di evento ischemico cerebrale e/o sistemico criptogenetico verificatosi in trattamento con terapia antiaggregante, nuovo work up diagnostico negativo e shunt dx/sn > 10 bolle al Doppler TC, è proponibile il trattamento di chiusura trans catetere del forame ovale pervio come alternativa alla terapia anticoagulante orale cronica che, generalmente, viene consigliata in questi casi pur in assenza di evidenze certe di superiorità della terapia anticoagulante su quella antiaggregante (23-26).

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Nei pazienti di età inferiore/uguale a 55 anni (o > 55 anni a giudizio del clinico), recidiva di evento ischemico cerebrale e/o sistemico criptogenetico verificatosi in trattamento con terapia anticoagulante ben condotta (INR 2-3), nuovo work up diagnostico negativo, e shunt dx/sn > 10 bolle al Doppler TC, è indicato il trattamento

Pazienti con storia di trombosi venosa profonda e/o embolia polmonare

- Nei pazienti con storia di trombosi venosa profonda e/o embolia polmonare idiopatica, in presenza o meno di trombofilia, qualora il clinico ritenga indicata una terapia anticoagulante cronica, non vi è indicazione a chiusura transcatetere del forame ovale.

Pazienti con positività ai LAC o sindrome da anticorpi antifosfolipidi

- Nei pazienti con positività dei LAC o sindrome da anticorpi antifosfolipidi che abbiano presentato uno o più episodi di ischemia cerebrale/sistemica anche in assenza di storia di trombosi venosa profonda/embolia polmonare, qualora il clinico ritenga indicata una terapia anticoagulante cronica, non vi è indicazione a chiusura transcatetere del forame ovale.

Patent foramen ovale transcatheter closure vs. medical therapy on recurrent vascular events: a systematic review and meta-analysis of randomized controlled trials

Pablo Rengifo-Moreno1, Igor F. Palacios2, Parichart Junpaparp3, Christian F. Witzke1, D. Lynn Morris1,4, and Abel Romero-Corral1,5*

Table 3 Outcomes for included trials

	Events	Intervention group (%)	Medical therapy (%)	Hazard ratio	Confidence interval	*P*-value
RESPECT intention-to-treat	Non-fatal ischaemic stroke	9/499	16/481	0.49	0.22–1.11	0.08
RESPECT per protocol		6/471	14/473	0.37	0.14–0.96	0.03
RESPECT as-treated		5/474	16/484	0.27	0.1–0.75	0.007
PC	Composite: death, stroke, TIA or peripheral embolism	7 (3.4)	11 (5.2)	0.63	0.24–1.62	0.34
	Death	2 (1.0)	0	5.2	0.25–107.61	0.24
	Stroke	1 (0.5)	5 (2.4)	0.2	0.02–1.72	0.14
	TIA	5 (2.5)	7 (3.3)	0.71	0.23–2.24	0.56
	Composite stroke, TIA, peripheral embolism	5 (2.5)	11 (5.2)	0.45	0.16–1.29	0.14
CLOSURE I intention-to-treat	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	23 (5.5)	29 (6.8)	0.78	0.45–1.35	0.37
	Stroke	12 (2.9)	13 (3.1)	0.9	0.41–1.98	0.79
	TIA	13 (3.1)	17 (4.1)	0.75	0.36–1.55	0.44
CLOSURE I modified intention-to-treat	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	22/400 (5.6)	29/451 (6.9)	0.78	0.44–1.35	0.37
	Stroke	12/400 (3.1)	13/451 (3.1)	0.94	0.43–2.07	0.88
	TIA	12/400 (3.0)	17/451 (4.2)	0.72	0.34–1.51	0.38
CLOSURE I per protocol	Composite: death from any cause during first 30 days, death from neurological causes between 31 days and 2 years, stroke, and TIA	22/378	29/375	0.74	0.42–1.29	0.28
	Stroke	12/378	13/375	0.91	0.41–1.99	0.8
	TIA	12/378	17/375	0.68	0.33–1.43	0.31

European Heart Journal (2013) 34, 3342–335

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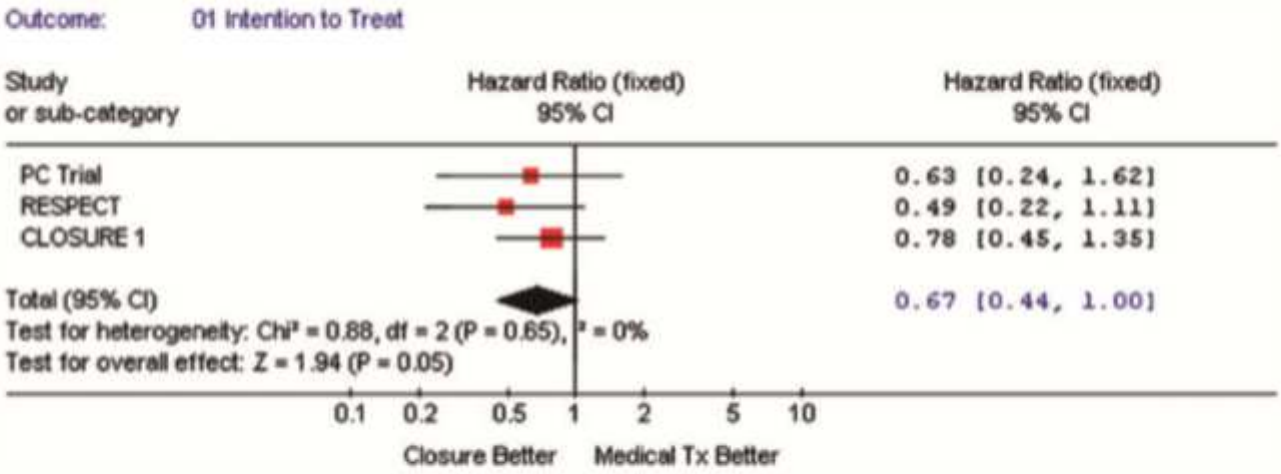


Figure 3 The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) between transcatheter patent foramen ovale closure vs. medical treatment (intention-to-treat).

European Heart Journal (2013) 34, 3342–335

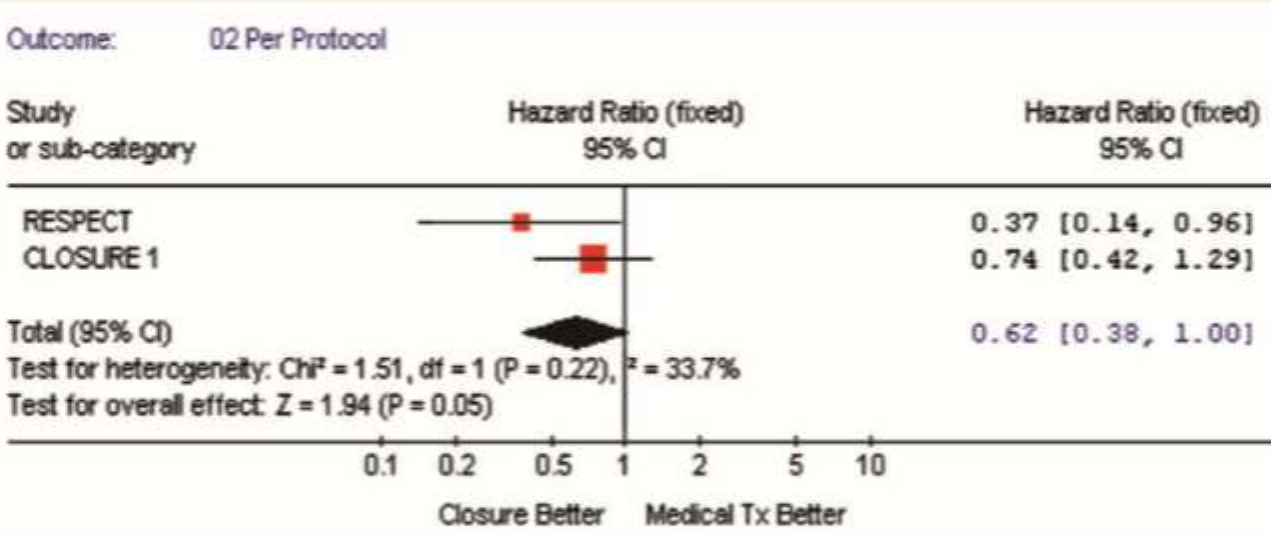
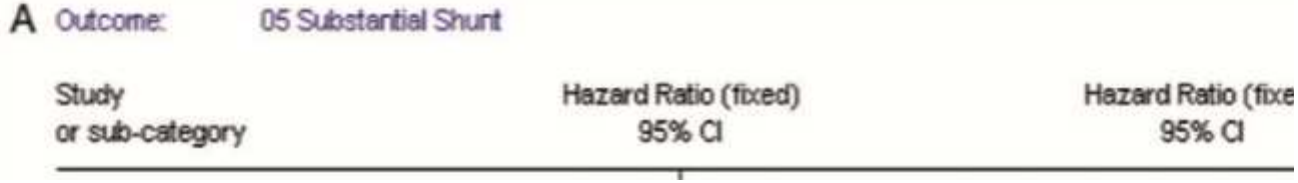


Figure 4 The forest plot of randomized controlled trial comparing composite outcome (death/vascular events) b
foramen ovale closure vs. medical treatment (per protocol).



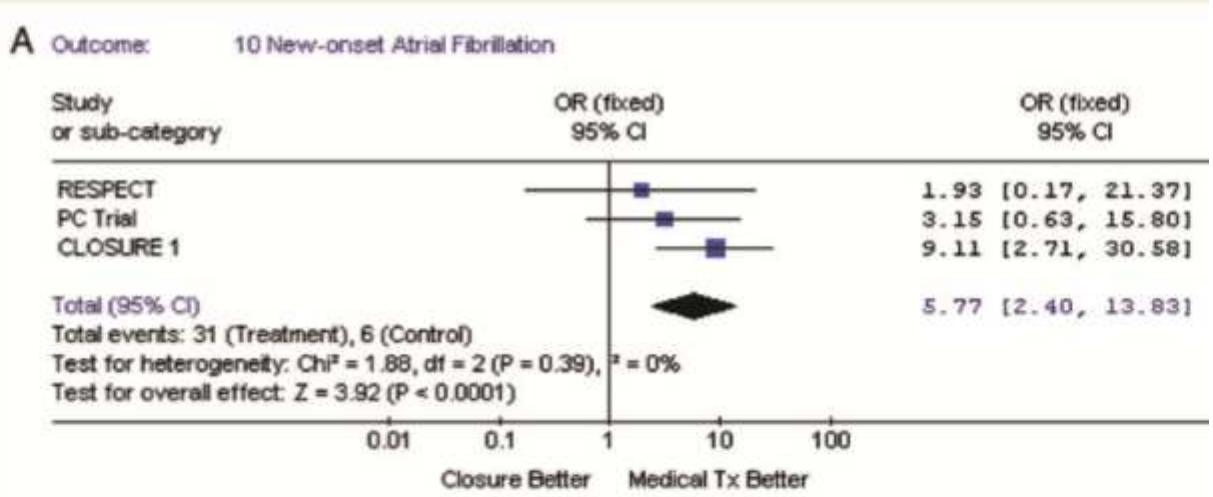


Figure 8 (*A*) The forest plot of randomized controlled trial comparing new-onset atrial fibrillation between transcath closure vs. medical treatment. (*B*) The forest plot of randomized controlled trial comparing new-onset atrial fibrillat patent foramen ovale closure vs. medical treatment excluding STARFLEX closure device.

are consistent with a recently reported meta-analysis of observational studies showing that STARFlex or CardioISEAL, but not the Amplatzer device were associated with an increased risk of develop-

data are needed, not only to support the clarify the role of 'high-risk PFO features cular events. Such data might also shed