The role of adenosine challenge in catheter ablation for atrial fibrillation: a systematic review and meta-analysis

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ABSTRACT

Aims

Adenosine may unmask dormant PV conduction and facilitate consolidation of PV isolation. We performed a meta-analysis to determine the impact of adenosine administration on clinical outcomes in patients undergoing PVI.

Methods

References and electronic databases reporting AF ablation and adenosine following PVI were searched through to 22nd November 2015. The impact of adenosine on freedom from AF was assessed in twenty publications after radiofrequency ablation (RFA), and in four publications after cryoablation to achieve PVI. Relative risks were calculated and combined in a meta-analysis using random effects modeling.

Results

In patients undergoing RFA with adenosine challenge, there was a significant reduction in freedom from AF in patients with versus without adenosine induced reconnection (RR 0.86; 95%CI 0.77-0.98; p=0.02) particularly if no further ablation was performed (RR 0.66; 95%CI 0.50-0.87; p<0.01). There was no difference when comparing outcomes in studies of routine adenosine challenge vs no adenosine (RR 1.07; 95%CI 0.93-1.22; p=0.36). There was a non-significant trend to an increase in freedom from AF in patients receiving routine adenosine challenge (RR 1.18 95%CI 0.99-1.42; p=0.07) in non-randomized studies using cryoablation.

Conclusion

Adenosine induced PV reconnection following PVI is associated with a significant increase in AF recurrence, particularly if the reconnection sites are not targeted for ablation. The routine use of adenosine may be beneficial in AF ablation if given early post PVI, at sufficient dose and reconnection is ablated.

KEYWORDS

Adenosine

ATP

Atrial fibrillation

Pulmonary vein isolation

Pulmonary vein reconnection

Dormant pulmonary vein conduction

ABBREVIATIONS

AF Atrial Fibrillation

PV Pulmonary Vein

PVI Pulmonary Vein Isolation

LA Left atrium

LVEF Left Ventricular Ejection Fraction

HT Hypertension

AAD Anti-arrhythmic drug

RFA Radiofrequency Ablation

INTRODUCTION

Pulmonary vein isolation is the cornerstone of AF ablation[1]. Despite operator experience, advances in catheter sensing and mapping technologies and alternative energy delivery sources the single procedure success remains limited to 70%[2]. At repeat procedures pulmonary vein reconnection is frequently present. Adenosine/ ATP may be administered following initial pulmonary vein isolation to unmask dormant pulmonary vein conduction with the premise that additional ablation at sites of acute reconnection may improve long term freedom from AF [3, 4]. Previous non-randomized studies[5-7] reported an improvement in outcome following catheter ablation for AF if adenosine was administered and sites of dormant reconnection ablated however recent large randomized controlled trials assessing the utility of adenosine in AF ablation have reported seemingly conflicting results[8, 9]. The aim of the present review and meta analysis was to examine the available literature to determine the role of adenosine challenge on freedom from AF following PVI.

METHODS

We searched The Cochrane Database of Systematic Reviews, Pubmed, Medline and Embase using the search term: '(adenosine or ATP) AND (pulmonary vein isolation OR ablation OR atrial fibrillation OR AF)'. The search strategy was limited to English language in human subjects where abstracts were available for review. Bibliographies of relevant articles were reviewed to assess for any further citations.

Articles were included if the study included an assessment of adenosine induced pulmonary vein reconnection after initial isolation , and reported freedom from AF beyond a minimum follow up

of 6 months in patients undergoing catheter ablation for AF. The studies made one of three comparisons to determine impact of adenosine/ATP on freedom from AF:

In patients undergoing radiofrequency ablation:

1) Adenosine/ATP given to *all* patients in a study cohort comparing outcomes between those without PV reconnection and those with reconnection
    a. where the reconnection was targeted for further ablation
    b. where the reconnection was not targeted for further ablation
2) Adenosine/ATP administration and ablation of PV reconnection compared to no adenosine administration.

In patients undergoing cryoablation:

3) Adenosine/ATP administration and ablation of PV reconnection compared to no adenosine administration.

Articles were excluded if only reported in abstract form or if the ablation procedure was not for atrial fibrillation. Data extracted from the articles included information relevant to the search criteria such as patient characteristics, details of adenosine/ATP dose and time, procedural characteristics, and outcomes.

The search was conducted by two reviewers (AM and SK) identifying 1359 citations. Abstracts and full text articles (where relevant) of these citations were independently assessed by the two reviewers, with discrepancies resolved through discussion between the study investigators.

Statistical Analysis

Statistical analyses assessed the dichotomous outcome of freedom from atrial fibrillation at follow up. Relative risks with 95% confidence intervals were calculated. Pooled effects of relative risk were calculated using the random effects model based on the Der-Simonian and Laird method. The random effects model assumes that each study is estimating a different effect, but that the effects come from the same underlying distribution of effects. This model fundamentally incorporates differences between studies. Heterogeneity was assessed using the I^2 statistic[10]. The I^2 measures the percentage of variation across the studies due to heterogeneity. The statistical analysis was performed using Stata Version 11 (StataCorp, Texas, USA).

RESULTS

The search strategy generated 1359 citations (see figure 1), and twenty-four publications including 3970 patients who fulfilled the inclusion/exclusion criteria. The energy source to achieve pulmonary vein isolation was radiofrequency ablation in 20 [3-9, 11-23] and cryoablation in four[24-27].

Radiofrequency Ablation

Twenty publications examined the role of adenosine in patients with AF undergoing pulmonary vein isolation by radiofrequency ablation. The study design was a randomized controlled trial in four and cohort study in 16. The studies were published between 2004 and 2015.

In 16 studies the format was adenosine/ATP given to *all* patients in the cohort and outcomes compared between those with PV reconnection and those without reconnection. Pulmonary vein reconnection was targeted for further ablation and adenosine repeated to confirm the absence of

dormant conduction following consolidation ablation in 14 studies. Sites of PV reconnection following adenosine were not targeted for further ablation in four and all combinations (of adenosine reconnection ablated or not ablated) examined in two studies.

In 6 studies the format was adenosine/ATP compared with no adenosine/ATP following pulmonary vein isolation with the primary endpoint of freedom from AF. Two of six studies also reported outcomes according to adenosine induced PV reconnection with consolidation ablation vs no PV reconnection (see Figure 1)

Adenosine induced transient reconnection post PVI

Study characteristics (table 1)

Sixteen studies (2970 patients) were identified with the design of randomized controlled trial in two, prospective studies in twelve and retrospective cohort in two. Adenosine reconnection was identified in 41% of patients across 16 studies.

Baseline patient characteristics, procedural details, adenosine/ATP protocol and follow-up are provided separately for each study in Table 1.

*Meta-analysis (figure 2)*There was significant heterogeneity based on the I-squared test (I^2 = 69%; p = 0.04) of 16 studies assessing adenosine induced PV reconnection versus no reconnection. Using random effects modeling there was a significant reduction in freedom from AF in patients with adenosine induced reconnection (RR 0.86; 95%CI 0.77-0.98; p=0.02).

We performed further analysis of these 16 studies based on whether the adenosine induced reconnection was targeted for further ablation (14 studies) or not (4 studies), with 2 studies including patient groups where adenosine reconnection was ablated or not ablated. Using

random effects modeling, there was a non-significant trend to reduction in freedom from AF (RR 0.91 with 95%CI 0.83-1.01; p=0.08) in the adenosine induced PV reconnection group who underwent further ablation at sites of PV reconnection compared with no adenosine induced PV reconnection. Adenosine induced reconnection without further ablation was associated with a significant reduction in freedom from AF (RR 0.66; 95%CI 0.50-0.87; p<0.01) compared with no adenosine induced PV reconnection.

Impact of Adenosine/ATP administration post PVI

Study characteristics (table 2).

Six articles including 3006 patients were identified that assessed freedom from AF between patients given or not given adenosine/ ATP[5-7, 9, 22, 23]. Three studies were randomized controlled trials comparing adenosine/ ATP versus no adenosine/ ATP[9, 22, 23]. An important difference in the randomized controlled trial by Theis et al was AF induction followed by ablation to terminate AF in the group randomized to no adenosine[23]. In the other three studies the design was a retrospective cohort where patients receiving adenosine were compared to historical controls in the era immediately preceding ATP challenge[5-7]. Baseline patient characteristics, procedural details, and follow-up are given separately for each study in Table 2.

Adenosine/ATP protocol

A range of doses of ATP (10-30mg) or adenosine (6-24mg) were administered generally with concurrent isoprenaline challenge except for the study by Theis et al[23]. Sites of PV reconnection were targeted for ablation and ATP/adenosine repeated following additional ablation in all studies. The time at which ATP/ adenosine was given post procedure ranged from immediately following PVI to 73 minutes after. Four of six studies reported procedure and

ablation duration. There was no significant difference in procedure duration between groups in any study except the study of Theis et al. In this study procedure duration was longer in patients not given ATP/adenosine due to additional ablation performed in the group with AF induction post PVI. Similarly there was no difference in ablation time between groups in any study except for the study by Theis et al where ablation time was longer in patients not given ATP/adenosine and the study by Matsuo et al where ablation time was longer in patients given ATP/ adenosine[6].

Meta-analysis (figure 3)

There was significant heterogeneity between studies prior to the meta-analysis based on the I-squared without exclusion of any studies ($I^2 = 0.78$; $p = 0.02$). Random effects modeling demonstrated that the routine administration of adenosine/ ATP post PVI to reveal PV reconnection with additional ablation to target sites of PV reconnection was not associated with an improvement in freedom from AF with a pooled relative risk of 1.07 (95% confidence interval: 0.93 to 1.22; p=0.36). There remained no significant benefit of adenosine when the meta analysis was confined to the 3 randomized controlled trials of adenosine given versus not given (relative risk 0.92; 95% CI 0.76-1.10; p=0.35). The overall freedom from AF at follow up in patients given adenosine with additional ablation at sites of reconnection was 70% versus 66% in patients not tested with adenosine.

Cryoablation

Study characteristics

Four cohort studies including 479 patients undergoing cryoablation comparing PVI with or without adenosine/ ATP challenge were included. Baseline characteristics, procedural details,

and follow-up are given separately for each study in supplementary table 1. Patients with adenosine reconnection received further ablation in all studies, however in one study patients without adenosine induced reconnection received a bonus freeze irrespectively[27]. The control group were retrospectively taken from the era prior to adenosine challenge in two studies[25, 27].

Meta-analysis

There was significant heterogeneity between studies based on the I-squared without exclusion of any studies ($I^2 = 0.62$; $p = 0.02$). Random effects modeling demonstrated that there was a non-significant trend to an improvement in freedom from AF in patients with versus without adenosine challenge (RR 1.18, 95% CI 0.99-1.42, p=0.07).

After excluding the study of Tebbenjohanns et al in which patients not given adenosine also received a bonus freeze, there was a borderline significant trend for improvement in freedom from AF in patients with versus without adenosine challenge (RR 1.27; 95% CI 1.00-1.62, p=0.05).

DISCUSSION

The major findings of this systematic review of the available literature examining the role of adenosine/ATP testing following pulmonary vein isolation for AF are:

1) adenosine/ATP induced PV reconnection is associated with a reduction in freedom from AF compared with no adenosine/ATP induced PV reconnection;
    a. in particular adenosine/ATP induced PV reconnection not targeted for ablation is associated with a significant reduction in freedom from AF,

   b. there was no significant difference in freedom from AF in patients with adenosine/ATP induced PV reconnection targeted for ablation compared with no adenosine induced PV reconnection;
2) routine adenosine/ATP challenge compared with no adenosine/ATP challenge is not associated with an improvement in freedom from AF in randomized control trials using RFA;
3) routine adenosine/ATP challenge is associated with a non-significant trend to improved freedom from AF (p=0.07) in non-randomized control trials using cryoablation.

Randomized controlled trial studies and the role of adenosine post PVI

The introduction of routine adenosine testing suggested an improvement in outcomes to AF ablation however earlier studies were limited by a cohort design. More recently four randomized controlled trials(RCT) have been completed to further determine the role of adenosine testing. Unfortunately there has been conflicting results between the two largest randomized controlled trials which has left the electrophysiology community with a quandary. Our review suggests adenosine induced PV reconnection and consolidation ablation improves outcomes compared with no further ablation at dormant sites and is not significantly different to no adenosine induced PV reconnection. Therefore additional or consolidation ablation leads to an outcome equivalent to no acute reconnection.

However routine adenosine testing does not improve outcome compared to not testing at all. To understand these apparent inconsistencies a critical review of the two large randomized studies which vary in a number of important ways is crucial. Macle et al administered IV adenosine to

534 patients following PVI for paroxysmal AF[8]. Patients with adenosine induced PV reconnection (284 patients or 53%) were randomised to additional ablation or not. Ablation of adenosine induced PV reconnection was associated with higher freedom from AF(69%) compared with adenosine induced PV reconnection without additional ablation(42%) and the registry group without adenosine induced PV reconnection(56%). In contrast Kobori et al randomized 2113 patients undergoing PVI for paroxysmal, persistent and long standing persistent AF to ATP at a weight determined dose after a longer waiting period. ATP induced PV reconnection was present in 307 patients (28%) with no difference in freedom from AF between patients with or without ATP challenge or between patients with or without ATP induced PV reconnection[9].

Important differences between the studies of Macle et al and Kobori et al include:

1) *Study design*: although both are RCT in design randomization was different. In the study by Macle et al all patients received adenosine and randomization was between additional ablation vs no further ablation in the adenosine induced PV reconnection group. In contrast the study by Kobori et al randomized patients to ATP guided PVI vs no ATP administration;
2) *Patient and Procedural characteristics*: the study by Macle et al included only paroxysmal AF patients with ablation largely confined to PVI with additional LA ablation in 3% and cavotricuspid isthmus ablation in 17%. In contrast Kobori et al included patients with paroxysmal and persistent AF (33%) who underwent more extensive ablation beyond PVI in more than 30%. Linear LA roof ablation was significantly more common in the conventional PVI group and cavotricuspid isthmus ablation was performed in more than 70%;

3) *Dose of adenosine or ATP*: Macle et al administered Adenosine doses according to the physiologic endpoint of atrioventricular block in contrast to a standardized weight adjusted dose of ATP which may be insufficient to demonstrate reconnection in the study by Kobori et al;
4) *Timing of adenosine or ATP*: in the study by Macle et al adenosine was given following a standardized 20 minute waiting period during which spontaneous reconnection occurred in 27% and adenosine induced PV reconnection in 53%. The median waiting time was substantially longer in the study by Kobori et al at 57minutes from PVI to ATP challenge during which spontaneous reconnection occurred in 42% and adenosine induced PV reconnection in 28%. The importance of waiting time post PVI to the outcome of adenosine challenge was demonstrated in a smaller RCT by Ghanbari et al of 129 patients randomized to adenosine or no adenosine post PVI. Dormant PV conduction was present in 37% of patients randomized to adenosine given 39-73 minutes post PVI. Adenosine induced PV reconnection was significantly higher when performed less than 60minutes post PVI (75% vs 9% more than 60 minutes) [22]. In this study there was no difference in procedure time, ablation time or freedom from AF between groups. These fundamental differences between studies in part explain the apparent contrast in conclusions that:

(1) additional ablation at sites of PV reconnection "rescues" an outcome to that of no acute reconnection however (2) routine adenosine testing does not improve outcome compared to not testing at all. A randomized study of adenosine guided PVI at doses sufficient to cause AV block confined to paroxysmal AF ablation is required to provide clarity to the role of adenosine in PVI.

Mechanisms of Pulmonary vein reconnection

Although pulmonary vein isolation is the well established cornerstone for AF ablation, achieving enduring pulmonary vein disconnection is challenging. Spontaneous acute pulmonary vein reconnection with further ablation to achieve PVI has been associated with reduced freedom from AF at follow-up[15, 28]. The present review confirms that patients with adenosine induced PV reconnection have an increase in recurrent AF following catheter ablation particularly if no further ablation is performed. Following consolidation ablation there is no longer a difference in outcome between adenosine induced reconnection and no adenosine induced reconnection. To explain these observations it is important to appreciate potential differences in the mechanism of PV reconnection. Adenosine induced reconnection involves selective activation of the I_{KAdo} inward rectifier current that hyperpolarizes the resting membrane potential in dormant PVs to establish transient PV reconnection[29] whereas pulmonary vein reconnection may also occur after resolution of acute tissue injury, oedema and inflammation[8]. Contact force sensing catheters may provide insights into anatomic regions vulnerable to dormant conduction or PV reconnection[30]. In a routine assessment of PV reconnection irrespective of AF recurrence, 26 of 40 (65%) patients had at least one 'gap' causing PV reconnection associated with reduced CF and force-time integral[30]. Dormant conduction was associated with lower contact force (5g vs 11g) and force time integral (225 vs 415gram.seconds) and indeed 86% of dormant reconduction was associated with CF < 10g[18]. In the present review, Andrade et al randomized patients to hydrocortisone or no hydrocortisone and all patients were challenged with adenosine post PVI[20]. Patients in the hydrocortisone group had higher rates of adenosine induced PV reconnection with consequently longer ablation times, however freedom from AF was not different between groups. One may speculate that hydrocortisone reduces tissue oedema

resulting in acute PV reconnection followed by further ablation without impact on longer term outcome.

Clinical implications

Although there are significant differences in study design, patient and procedural characteristics and the timing and dose of adenosine/ATP post PVI some conclusions may be drawn from the present report. Firstly patients with adenosine induced PV reconnection not targeted for ablation have significantly worse outcome than patients with no adenosine induced PV reconnection. Secondly, adenosine administration becomes less useful the longer the observation period post PVI for spontaneous PV reconnection. While it is enticing to consider the role of adenosine testing in lieu of an adequate observation period following PVI there is insufficient data to support this strategy; indeed in the non randomised studies by Yamaguchi et al and Miyazaki et al where adenosine/ ATP was given post PVI without a waiting period and adenosine induced PV reconnections were re-ablated, there was a significant reduction in freedom from AF in patients with versus without adenosine induced PV reconnection[4, 17]. Unfortunately due to the differences between studies the present review is not conclusive in determining whether adenosine/ATP should be administered or not but rather if administered the major benefits are if administered earlier in the waiting period post PVI given to a dose associated with AV block and that additional ablation is completed to obliterate sites of dormant conduction. Noting less than ¼ of the taskforce for the 2012 AF ablation guidelines utilized adenosine/ATP to assess for PV reconnection[1], our practice is to assess for adenosine induced PV reconnection shortly after achieving PVI, with ablation at sites of reconnection until repeat adenosine challenge is negative, and to subsequently incorporate a standard waiting period for assessment of PV reconnection.

Study Limitations

The findings of the meta-analysis are based on the synthesis of randomized and non-randomized studies which includes considerable variation in the doses of adenosine/ATP and administration times post isolation. We performed sensitivity analyses to exclude studies with significant confounders for the comparison of adenosine or not following PVI. Of the non-randomized studies, several are retrospective and involve the comparison of non-contemporaneous cohorts and may include bias such as procedural learning curve and difference in procedural technology. The present review primarily assessed adenosine induced reconnection at index PVI, and does not make any conclusions regarding the utility of adenosine induced PV reconnection during redo procedures; limited studies have suggested the utility of adenosine PV reconnection following PVI at redo procedure[31]. We acknowledge there are some limitations of assessing PV signals during cryoablation procedures that may potentially affect the accuracy of adenosine induced PV reconnection, and potentially contribute to the reduced rates of adenosine PV reconnection during cryoablation compared to radiofrequency ablation procedures.

CONCLUSIONS

In this meta-analysis of heterogeneous studies, adenosine induced PV reconnection following PVI is associated with a significant increase in AF recurrence, particularly if the reconnection sites are not targeted for ablation. The routine use of adenosine may be beneficial in AF ablation if given early post PVI, at sufficient dose and reconnection is ablated however does not replace a routine observation period for surveillance of spontaneous PV recovery.

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Table 1: Adenosine/ ATP given with or without pulmonary vein reconnection

Article	Study type	N	Comparator groups	n	Age	Male n (%)	AF type – paroxysmal n (%)	LA diameter mm	Adenosine protocol	Follow up (months)	Follow up	Freedom from AF# n (%)	P	Repeat Procedure n (%)
Tritto (2004)[11]	Prospective cohort	29	Adenosine induced reconnection	16	55±8*	21 (72)*	21 (72)*	43.3±4.2*	Adenosine 12mg after 10 min waiting period	6.3±2.4*	Clinical review + Holter 1,2 months and then every 3 months	11 (69)	1.0	6 (21)*
			No induced adenosine reconnection	13	-	-	-	-	as above	-	as above	9 (69)		
Arentz (2004)[3]	Prospective cohort	29	Adenosine induced reconnection	13	54±10*	21 (72)*	20 (69)*	-	Adenosine 12-18 mg rapid bolus IV post isolation	12	Clinical review + ECG + 24hr Holter 3 and 12 month. Event monitor if symptoms	5 (38)	1.0	14 (48)*
			No Adenosine reconnection	16	-		-	-	as above	12	as above	7 (44)		
Hachiya (2007)[5]	Retrospective Cohort	252	ATP given Subgroup with reconnection without reconnection	82 34 48	56±9	67 (82)	62 (76)	41.7±6	30mg ATP post isolation, during isoproterenol continuous infusion (1-3µg/min)	6.1±3.3	Clinical review + Holter at 2 weeks, then monthly	60 (73) 23 (68) 37 (77)	0.04 (ATP given vs. not given)	-
			ATP not given	170	54±9	143 (84)	135 (79)	41.3±6	N/A	6.1±3.3	as above	102 (60)		-
Matsuo (2010)[12]	Retrospective Cohort	233	ATP dormant PV conduction	139	54.3±9.6	122 (88)	89 (64)	38.5±5.5	20mg ATP during isoproterenol continuous infusion (5-20 µg/min), > 20minutes post isolation	29.7±13.0*	Clinical review + ECG + 24hr Holter at 1,3,6,9,12,18, 24 months ± 5 day event recorder if symptoms	87 (63)	0.69	43 (31)
			No ATP dormant PV conduction	94	54.2±10.9	84 (89)	55 (58)	39.7±5.7	as above		as above	62 (66)		28 (30)
Gula (2011)[13]	Prospective cohort	72	Adenosine transient reconnection	25	56.7±9.2*	61 (85)*	25 (100)	39.7±5.6*	12mg adenosine 30 min post isolation	12	Clinical review + ECG at 3 months, with 48hr Holter at 12 months	19 (76)	1.0	6 (24)
			No adenosine transient reconnection	47	-	-	47 (100)	-	as above	12	as above	35 (74)		12 (26)
Miyazaki (2012)[4]	Prospective cohort	109	ATP reconnection	39	59.4±10.3	33 (85)	39 (100)	39.4±5.5	40 mg ATP no waiting period	12	Holter at 2, 6, 10, 14, 24, 36, and 48 weeks after discharge, then every 3 months. Event monitor if symptoms	20(51)	0.03	10 (26)
			No ATP reconnection	70	61.4 ±11.2	58 (83)	70 (100)	38.1±5.4	as above	12	as above	51(73)		22 (31)
Cheung (2013)[14]	Prospective cohort	152	Adenosine reconnection	44	62±9	34 (77)	29 (66)	40±6	Adenosine 12mg post isolation	12	7-14 day ambulatory ECG at 3,6 and 12 months.	28 (64)	0.06	5 (11)
			No adenosine reconnection	108	60±11	86 (80)	67 (62)	43±7	as above	12	as above	82 (76)		13 (12)
Anter (2014)[15]	Prospective	44	Adenosine	16	60±6.9	22 (50)*	24 (55)*	-	Isoprenaline then	12	≥two 14day	8 (50)	<0.01	3 (19)

	cohort		reconnection					adenosine 12-48mg at least 30minutes post PVI		transtelephonic rhythm monitoring at 3, 6 or 12 months			
			No adenosine reconnection	28	60±6.9	22 (50)*	24 (55)*	-	as above	12	as above	25 (89)		0
Kaitani (2014)[16]	Prospective cohort	110	Adenosine reconnection	35	61.8±9.2	26 (74.3)	35 (100)	38.7±0.5	ISP+40mg bolus ATP >15minutes post PVI (range 43-64 minutes)	27.1±15*	Holter monitor or event recorder if symptoms.	28 (80)	0.12	4 (11)
			No adenosine reconnection	75	62.5±9.8	55 (73.3)	75 (100)	38.2±6	as above	27.1±15*	as above	50 (67)		24 (32)
Yamaguchi (2014)[17]	Prospective cohort	74	ATP reconnection	42	57±12*	63 (85)*	65 (88)*	38±5*	20mgATP +ISP post PVI (no waiting period)	24±7*	24Hr Holter 3months then 6 monthly	24 (57)	0.01	14 (33)
			No ATP reconnection	32	57±12*	63 (85)*	65 (88)*	38±5*	as above	24±7*	as above	27 (84)		3 (9)
Park (2014)[18]	Prospective cohort	40	Adenosine reconnection	24	60.1±10.4	18 (75)	16 (67)	42±4.9	Adenosine (dose not specified) 30 min post PVI	18±3*	24Hr Holter 3,6 and 12 months	16 (67)	1.0	-
			No adenosine reconnection	16	63.8±9.2	14 (88)	9 (56)	42±3.9	as above	18±3*	as above	11 (69)		-
Lin (2015)[19]	Prospective cohort	152	Adenosine reconnection	45	61 ±9	35 (78)	30 (67)	-	Adenosine 12-24mg post PVI (time not specified)	20±9*	7-14 Day ambulatory ECG monitoring 3, 6 and 12 months	21 (47)	0.12	10 (22)
			No adenosine reconnection	107	59±11	85 (79)	66 (62)	-	as above	20±9*		65 (61)		16 (15)
Kobori (2015)[9]	RCT	1112	ATP reconnection	307	58.6±8.6*	856 (77)*	737 (66.3)*	38.9±6.3*	ATP 0.4mg/kg bolus+/-ISP, post PVI (median 57 minutes)	15	24Hr Holter 6 and 12 months. 1 channel ambulatory ECG for 2 weeks, twice daily and when symptoms 6 and 12 months.	195 (62)	0.09	66 (26)
			No ATP reconnection	805	58.6±8.6*	856 (77)*	737 (66.3)*	38.9±6.3*	as above	15	as above	557 (67)		133 (19)
Andrade (2013)[20]	Prospective &	90	Adenosine reconnection ablated	35	58.4±9.5*	64 (71)*	35 (100)	38.0±5.7*	Adenosine 12mg 20minutes post PVI – ablation at discretion of operator	12	Transtelephonic, ECG and 24-hour Holter at 3, 6 and 12 months.	23 (66)	-	-
			Adenosine reconnection not ablated	25	58.4±9.5*	64 (71)*	25 (100)	38.0±5.7*	as above	12	as above	14 (56)	-	-
			No adenosine reconnection	30	58.4±9.5*	64 (71)*	30 (100)	38.0±5.7*	as above	12	as above	23 (77)		-
Okishige (2015)[21]	Prospective cohort	91	ATP reconnection not ablated	56	60±12*	62 (68)*	73 (80)*	41±6*	ATP 20mg bolus + ISP 20minutes post PVI	9*	ECG and 24Hr Holter 1 month then 2 monthly.	27 (48)	-	29 (52)
			No ATP reconnection	35	60±12*	62 (68)*	73 (80)*	41±6*	as above	9*	as above	35 (100)		0
Macle (2015)[8]	RCT^	534	Adenosine reconnection ablated	147	60·2±9·9	108 (74)	147 (100)	40·1±4·5	Adenosine 12mg 20 minute post PVI.	12	24Hr Holter 3, 6, 12 months + transtelephonic monitoring	102 (69)	<0.001[a], 0.02[c]	30 (20)

Adenosine reconnection not ablated	137	58·4±9·7	97 (71)	137 (100)	39·6±5·9	as above	12	as above	58 (42)	0.02[b]	48 (35)
No adenosine reconnection	250 (117)[$]	58·9±10·9	87 (74)	250 (100)	40·1±4·9	as above	12	as above	64 (56)		

AF atrial fibrillation; LA left atrium; ATP Adenosine Triphosphate; ISP isoprenaline; ECG electrocardiogram; RCT randomized controlled trial; PVI Pulmonary Vein Isolation; [#] freedom from AF after initial ablation; * characteristic reported for whole cohort, not for comparator groups; [&] randomized to hydrocortisone or no hydrocortisone. [^] patients with dormant conduction randomized to ablation or no ablation (of dormant conduction); [$] 117 of 250 patients assigned to registry; 115 in primary analysis; [a] dormant conduction ablated versus not ablated; [c] dormant conduction ablated versus no dormant conduction; [b] dormant conduction not ablated versus no dormant conduction. Values represent mean±SD or number (and average) unless otherwise stated.

Table 2: Adenosine/ATP given or not given

Article	Study type	n	Comparator groups	n	age	Male n (%)	AF type – paroxysmal n (%)	LA diameter mm	Adenosine protocol	Acute reconnection Pts.: n (%)	Follow up (months)	Follow up	Freedom from AF# n (%)	P	Repeat Procedure n (%)
Hachiya (2007)[5]	Retrospective	252	ATP given	82	56±9	67 (82)	62 (76)	41.7±6	30mg ATP plus ISP (1-3µg/min). Time post PVI not specified.	34 (41)	6.1±3.3	Clinical r/v + Holter at 2 weeks, then monthly	60 (73)	0.04	-
			ATP not given	170	54±9	143 (84)	135 (79)	41.3±6	N/A	-	6.1±3.3	as above	102 (60)	-	-
Matsuo (2007)[6]	Retrospective	148	ATP given	54	53.9±9.1	44 (81)	36 (67)	38.4±4.5	20mg ATP plus ISP (20 µg/min) at least 20 min post PVI	30 (56)	19.9±6	Clinical + ECG + 24Hr Holter at 1,3,6,9, 12 months + Event monitor 5/7 if symptoms	43 (80)	< 0.05	9 (17)
			ATP not given	94	52.7±10.1	80 (85)	60 (64)	37.4±5.1	N/A	-	19.9±6	as above	56 (60)	-	36 (38)
Kumagai (2010)[7]	Retrospective	212	ATP given	106	58±11	74 (70)	94 (89)	39.4±5.4	10 mg ATP Plus ISP (5 µg/min). Time post PVI not specified.	54 (51)	16±5.2	Hospitalized at 2 weeks, then 1-2monthly. ECG + Holter if symptoms	81 (76)	0.03	11 (10)
			ATP not given	106	59±10	83 (78)	86 (81)	39.7±5.7	N/A		16±6.9	as above	66 (62)	-	10 (9)
Kobori (2015)[9]	RCT, 2x2 factorial[#]	2113	ATP given	1112	59±9	856 (77)	737 (66)	38.9±6.3	ATP 0.4mg/kg bolus+/-ISP, post PVI (median 57 minutes)	307 (28)	12	24Hr Holter 6 and 12 months. 1 channel ambulatory ECG for 2 weeks, twice daily and when symptoms 6 + 12 months.	764 (69)	0.25	
			ATP not given	1001	69±9	723 (73)	683 (68)	39.2±6.2	N/A	-	12	as above	672 (67)		
Ghanbari (2015)[22]	RCT	129	Adenosine	61	59.7±8.7	37 (61)	61 (100)	41.0±5.3	6-24mg adenosine; post PVI (average 39-73minutes). ISP post.	23 (37)	9.9±7.3	4 week event monitor at 12months	37 (61)	0.83	12 (57)
			Adenosine not given	68	58.9±10.7	53 (78)	68 (100)	41.2±6.4	ISP.5-20 µg/min	-	8.7±6.9	as above	45 (66)		9 (43)
Theis (2015)[23]	RCT	152	Adenosine	76	63±10	45 (59)	76 (100)	22.2±5.2 cm^2	Adenosine >10mg, post PVI time not specified	31 (41)	12	Two 48hour Holter monitor	52 (68)	<0.01	24 (32)
			Adenosine not given: AF induction+ ablation to sinus	76	64±9	33 (43)	76 (100)	23.2±4.8 cm^2	N/A		12	as above	66 (87)		12 (16)

Abbreviations as per table 1. [#] Patients randomized to ATP or no ATP were also randomized to 90 days of anti-arrhythmic drug or not.

Figure Legend

Figure 1: Search Flow Diagram

Figure 2: Figure 2A: Relative risk of freedom from AF post ablation: Adenosine/ATP *acute reconnection vs. no acute reconnection*; Figure 2B (14 studies) where adenosine reconnection was ablated; Figure 2C (4 studies) where adenosine reconnection was not ablated.

Figure 3: Relative risk of freedom from AF post ablation: *Adenosine/ATP given vs. not given*

Supplementary Figure 1

Search Strategy

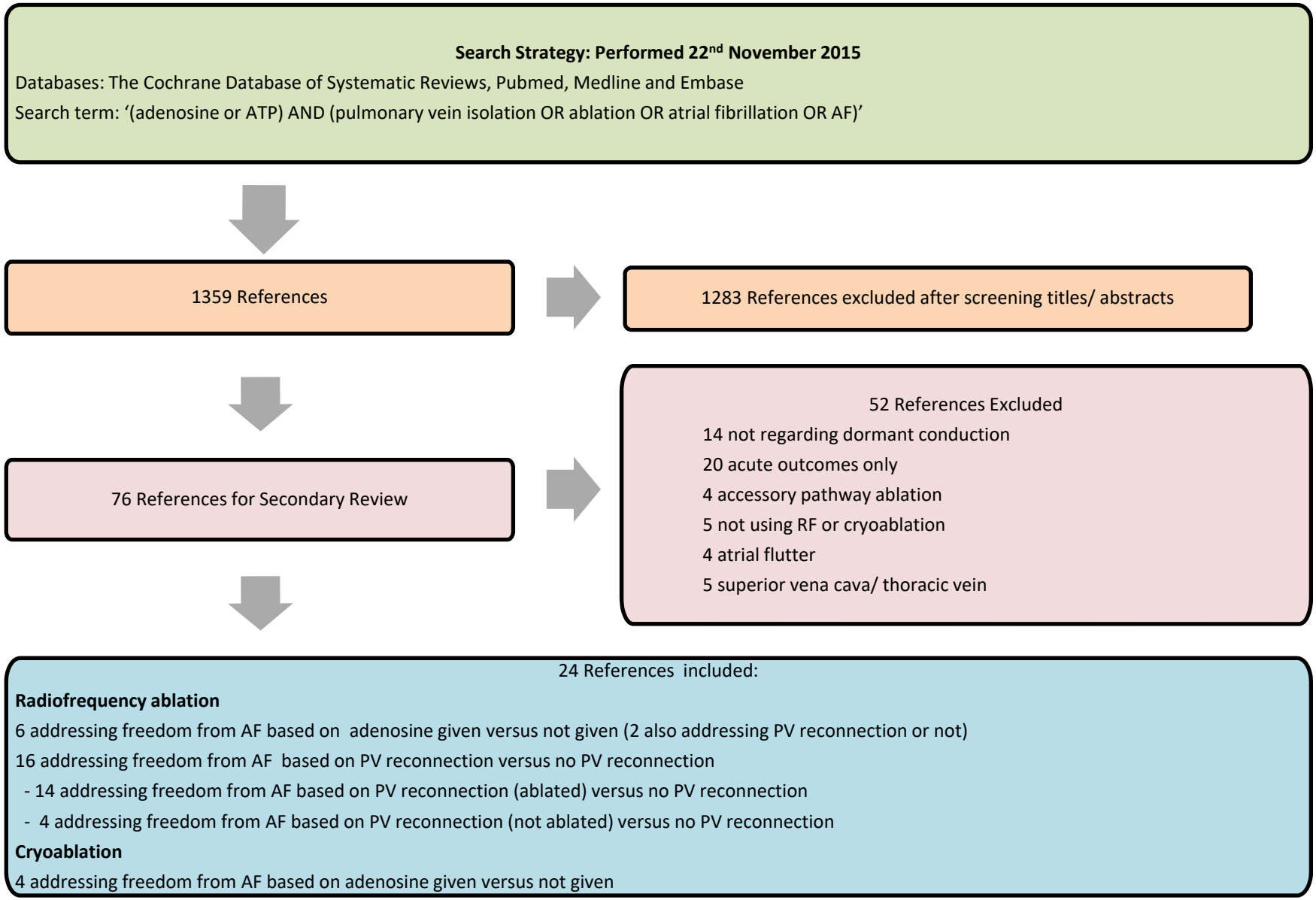
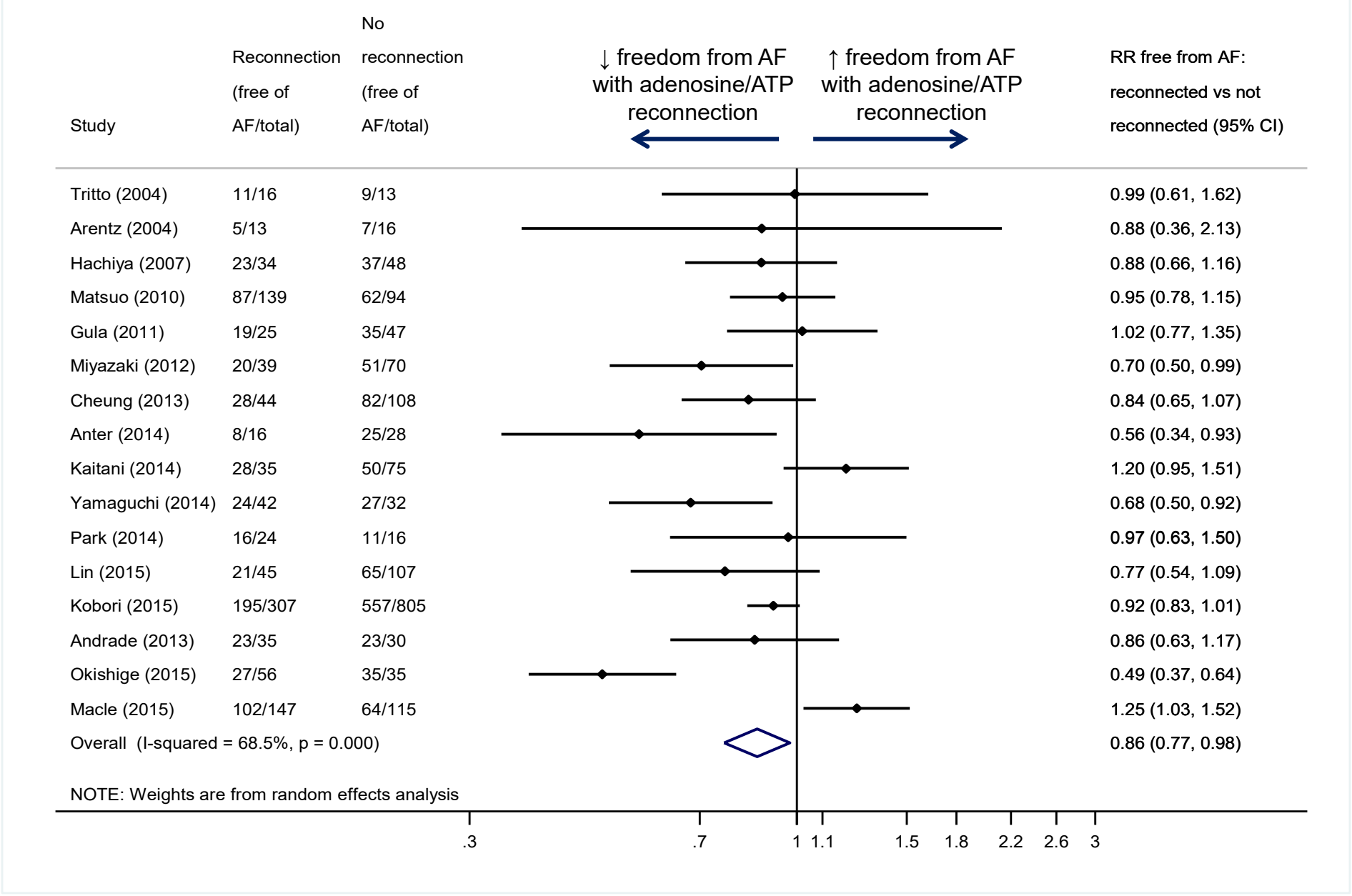


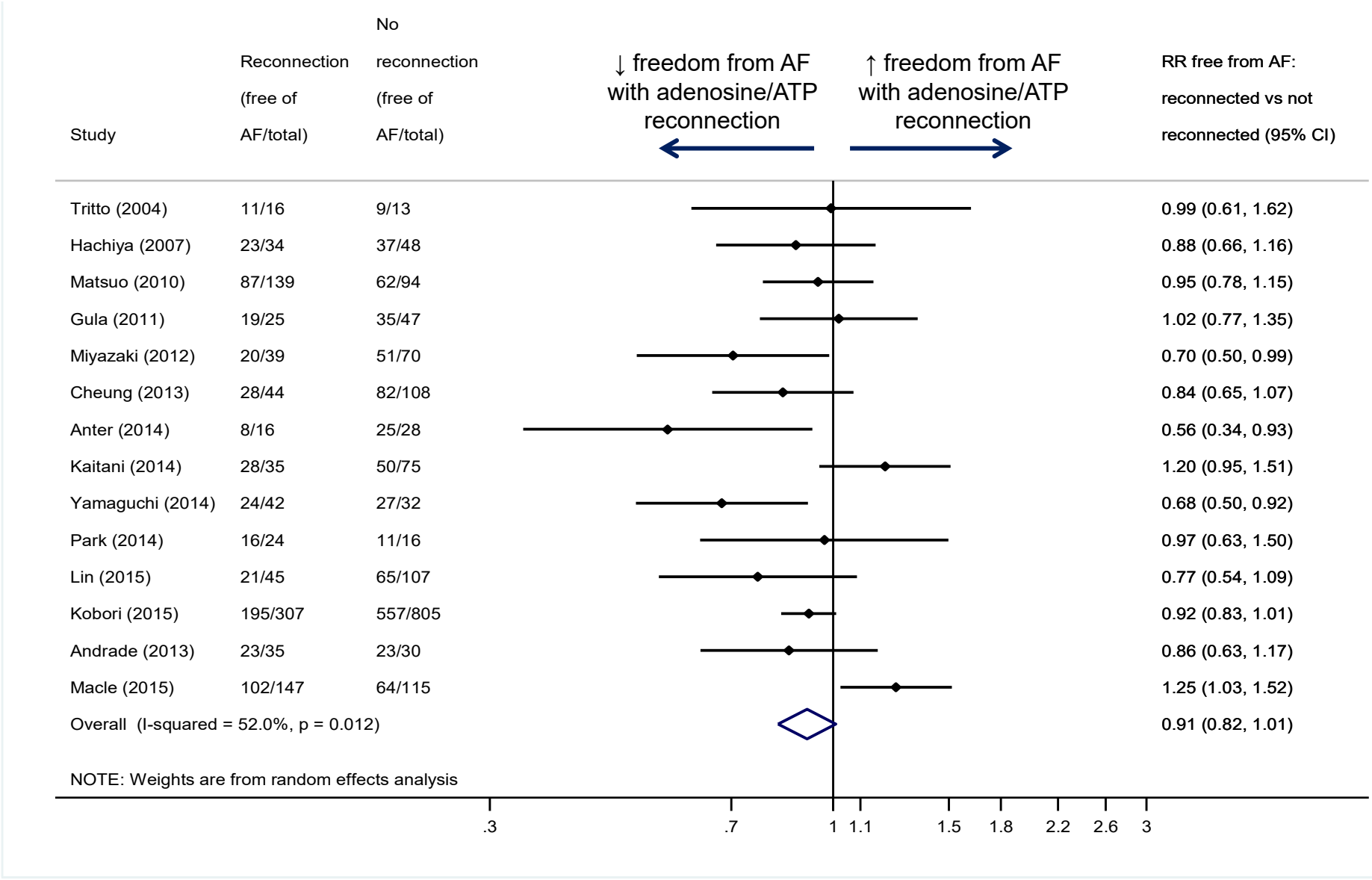
Figure 1

Relative risk of freedom from AF post ablation: Adenosine/ATP acute reconnection vs. no acute reconnection



Supplementary Figure 2A

Relative risk of freedom from AF post ablation: Adenosine/ATP acute reconnection vs. no acute reconnection: adenosine reconnection ablated



Supplementary Figure 2B

Relative risk of freedom from AF post ablation: Adenosine/ATP acute reconnection vs. no acute reconnection: adenosine reconnection not ablated

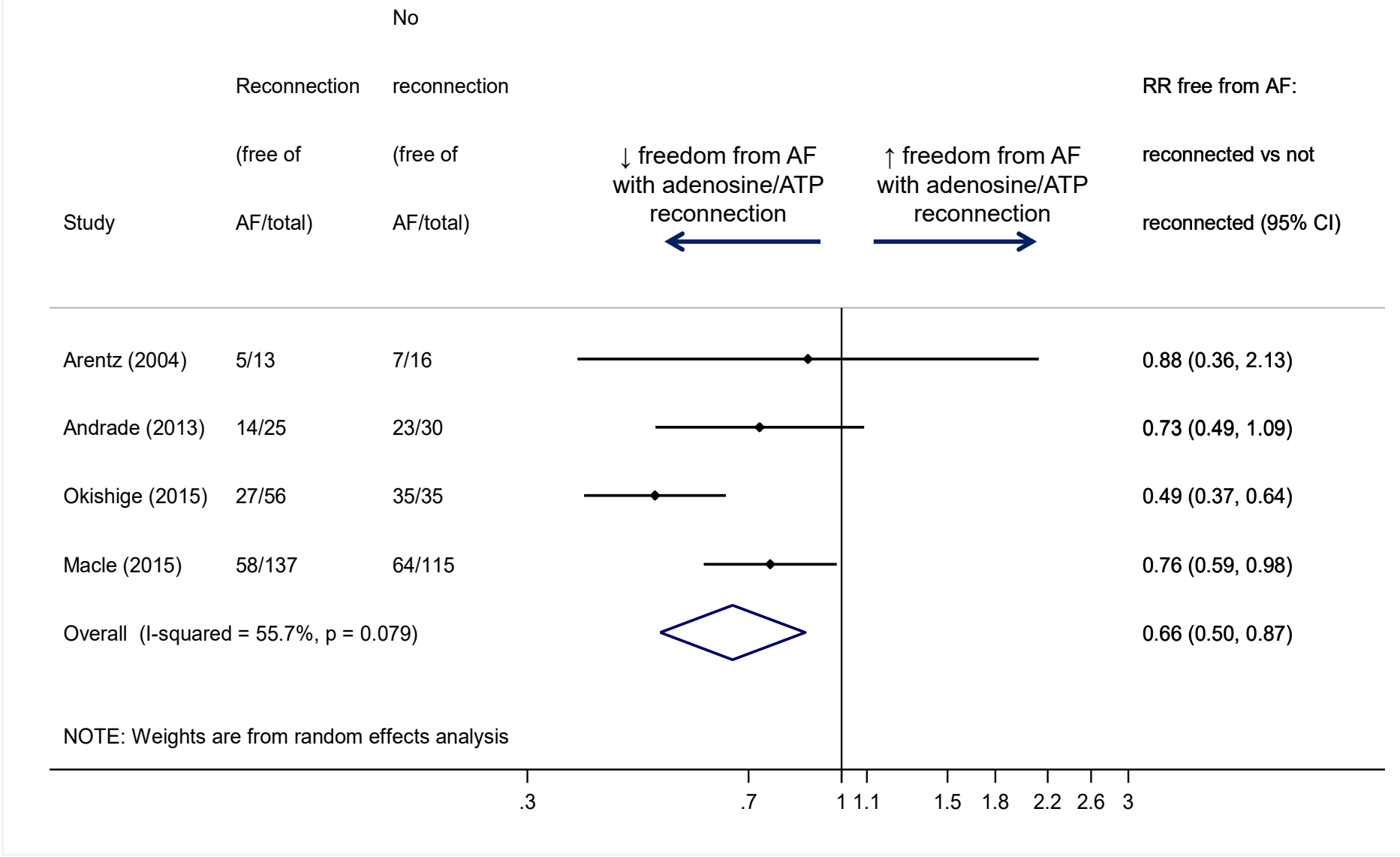


Figure 2

Relative risk of freedom from AF post ablation: Adenosine/ATP given vs. not given