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Ivabradine and Atrial Fibrillation: a Word of Caution?

Comprehensive Meta-analysis of RCTs

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Ivabradine

- Inhibits I_f ion current, which is highly expressed in the SA node
- Mixed Na^+– K^+ inward current activated by hyperpolarization and modulated by the autonomic nervous system
- Reducing the SA node activity, allowing for improved diastolic filling
- Increased binding with higher HR vs lower HR

DiFrancesco D, Camm JA. Heart rate lowering by specific and selective I(f) current inhibition with ivabradine: a new therapeutic perspective in cardiovascular disease. Drugs 2004;64:1757-65.

History

- 2005- Approved by European Medicines Agency
  - Stable angina with NSR who do not tolerate β -blocker therapy supported by Borer et al[1], INITIATIVE[2]
- 2010
  - Uncontrolled angina and a HR $\geq$60 bpm despite β -blocker therapy, following the results of BEAUTIFUL[3]

1) Borer JS[1], Fox K, Jaillon P, Lerebours G. Antianginal and antiischemic effects of ivabradine, an I(f) inhibitor, in stable angina: a randomized, double-blind, multicentered, placebo-controlled trial. Circulation. 2003 Feb 18;107(6):817-23.
2) Tardif JC, Ford I, Tendera M, Bourassa MG, Fox K. Efficacy of ivabradine, a new selective I(f) inhibitor, compared with atenolol in patients with chronic stable angina. Eur Heart J 2005 Dec;26:2529-36
3) Fox K, Ford I, Steg PG, Tendera M, Robertson M, Ferrari R. Relationship between ivabradine treatment and cardiovascular outcomes in patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina: a subgroup analysis of the randomized, controlled BEAUTIFUL trial.. Eur Heart J 2009 Oct;30:2337-45

History

- 2012
  - Systolic CHF (NYHA II–IV) in patients in NSR and whose HR ≥75, in combination with standard therapy or when β -blockers are contraindicated or not tolerated, SHIFT[1]
- 2015- Approved by US FDA
  - Stable patients with CHF and a HR of ≥70 on maximally tolerated β -blockers, SHIFT[1]

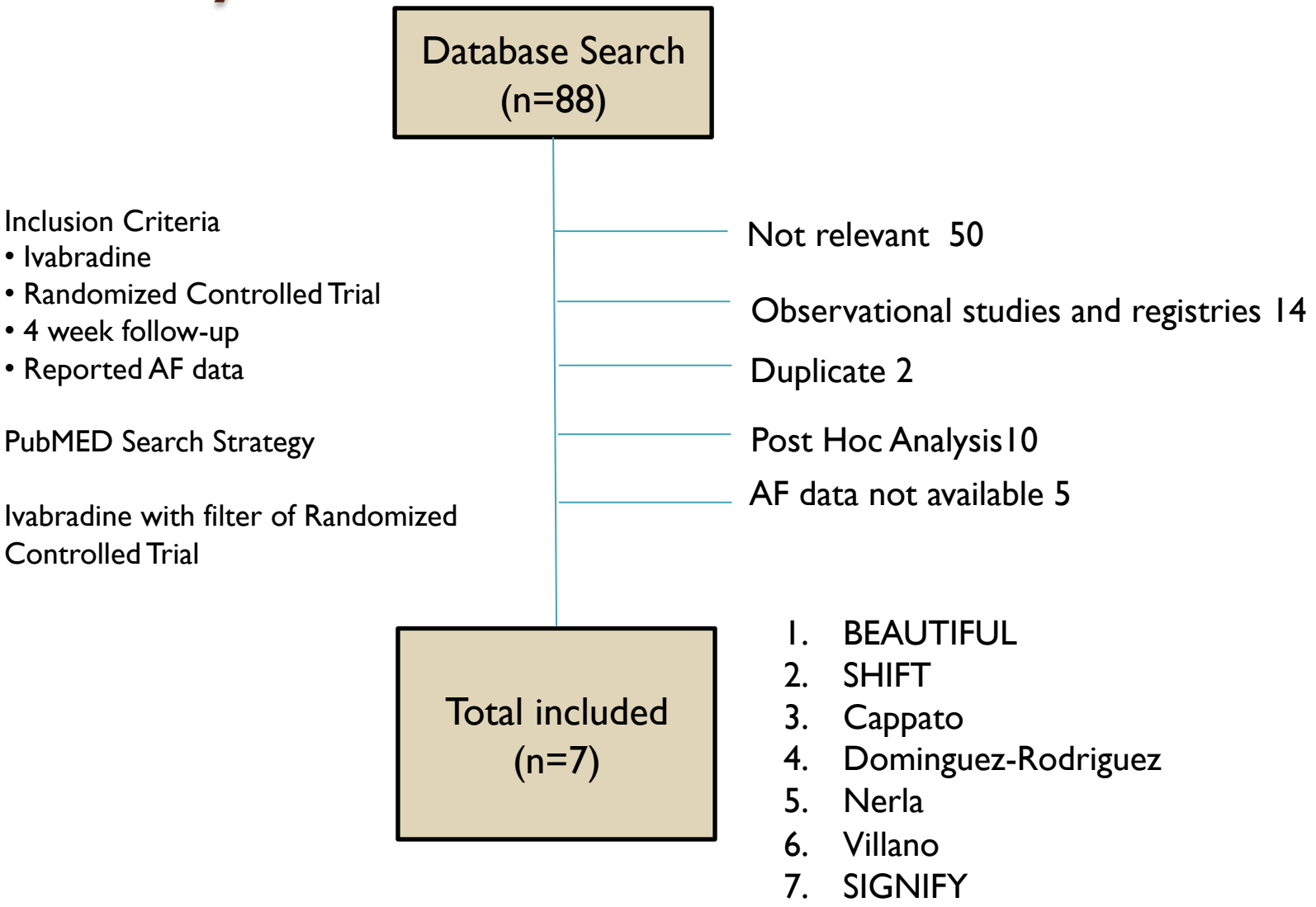
1) Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study.. Lancet 2010 Aug 27Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study.. Lancet 2010 Aug 27

Aim

- Martin RI, et al suggested a 15% increased RR of atrial fibrillation associated with ivabradine[1]
- Recently, SIGNIFY[2] published its study results with almost double the study population from the previous meta-analysis
- To update previous data and further investigate the increased risk of AF and use of ivabradine

1) Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. Heart 2014; 100:1506-10
2) Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014;371:1091-1099

Study Selection



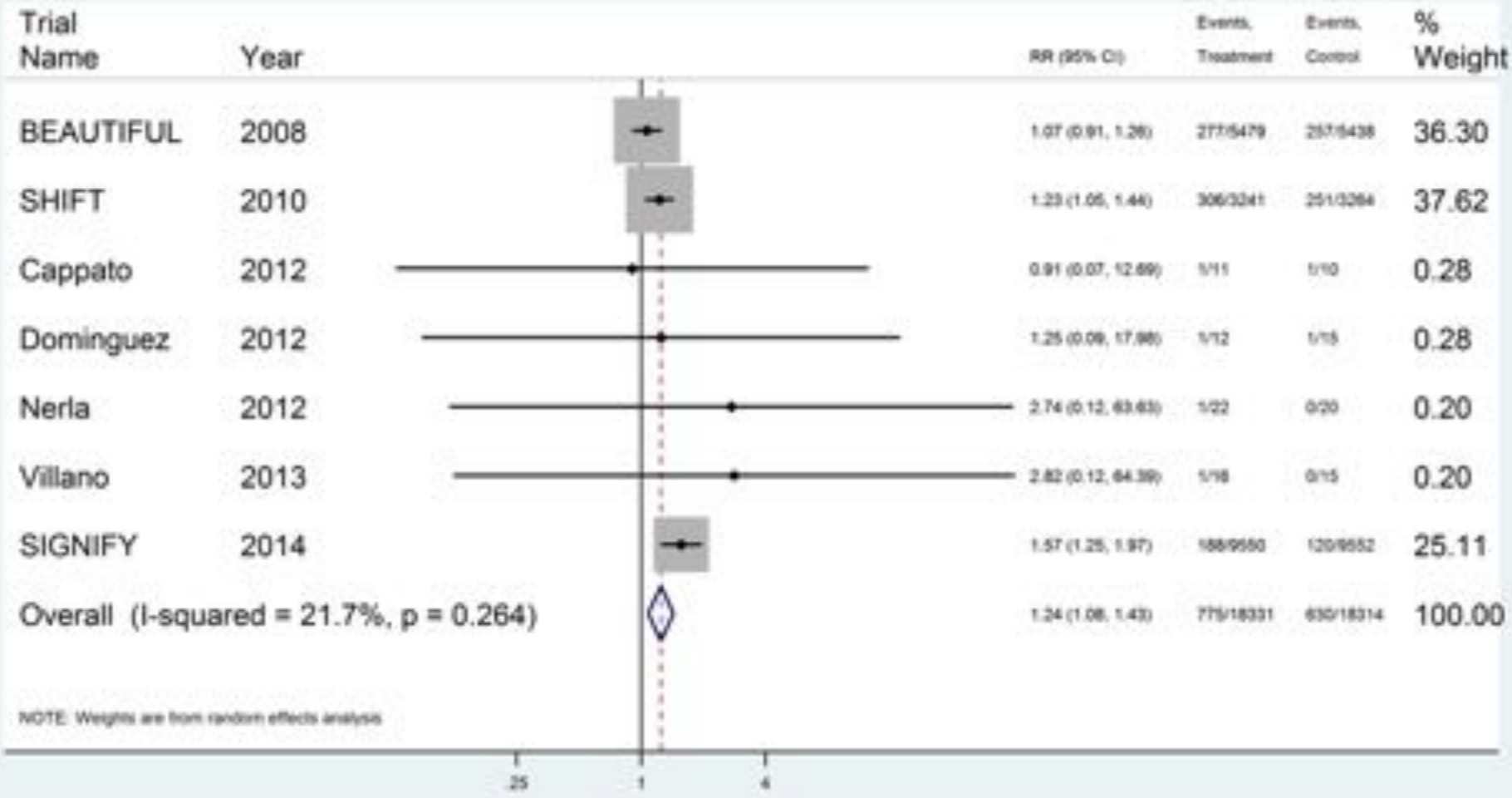
Meta-analysis Outcomes

- Primary outcome
  - Incidence of AF
- Secondary outcome
  - All cause mortality
  - Incidence of hospitalizations for HF

Statistical Review

- PRISMA-P-2015 (Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015)
- Intention-to-treat analysis for primary and secondary outcomes
- Relative risks and their corresponding 95% confidence intervals were computed for each dichotomous outcomes using random effect
- Used I^2 statistic and p-value for heterogeneity (p for heterogeneity <0.1 was considered significant)
- To evaluate publication bias for primary outcome we utilized comparison adjusted funnel plot
- All p-values were 2-tailed, with statistical significance set at 0.05

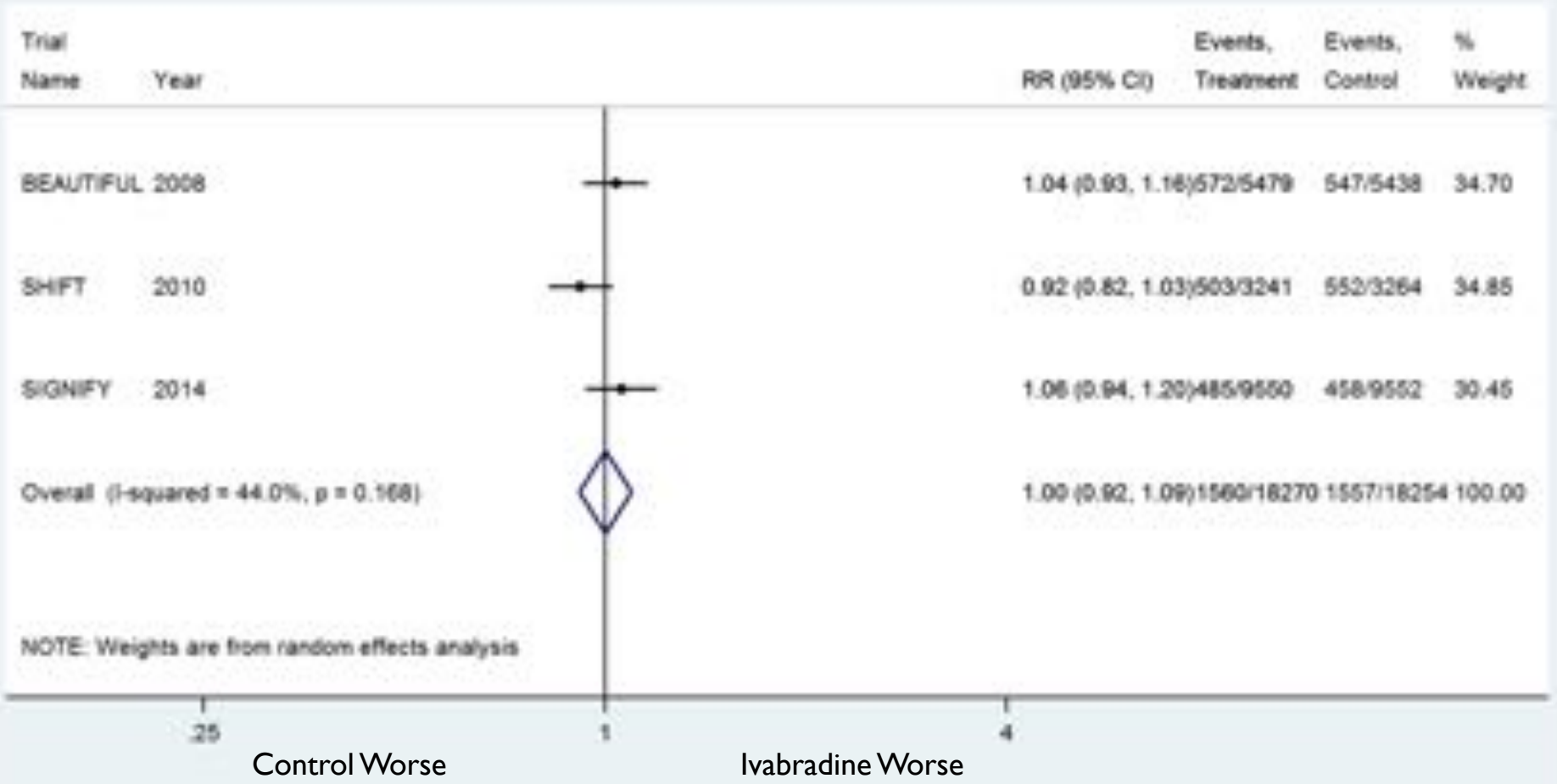
Atrial Fibrillation



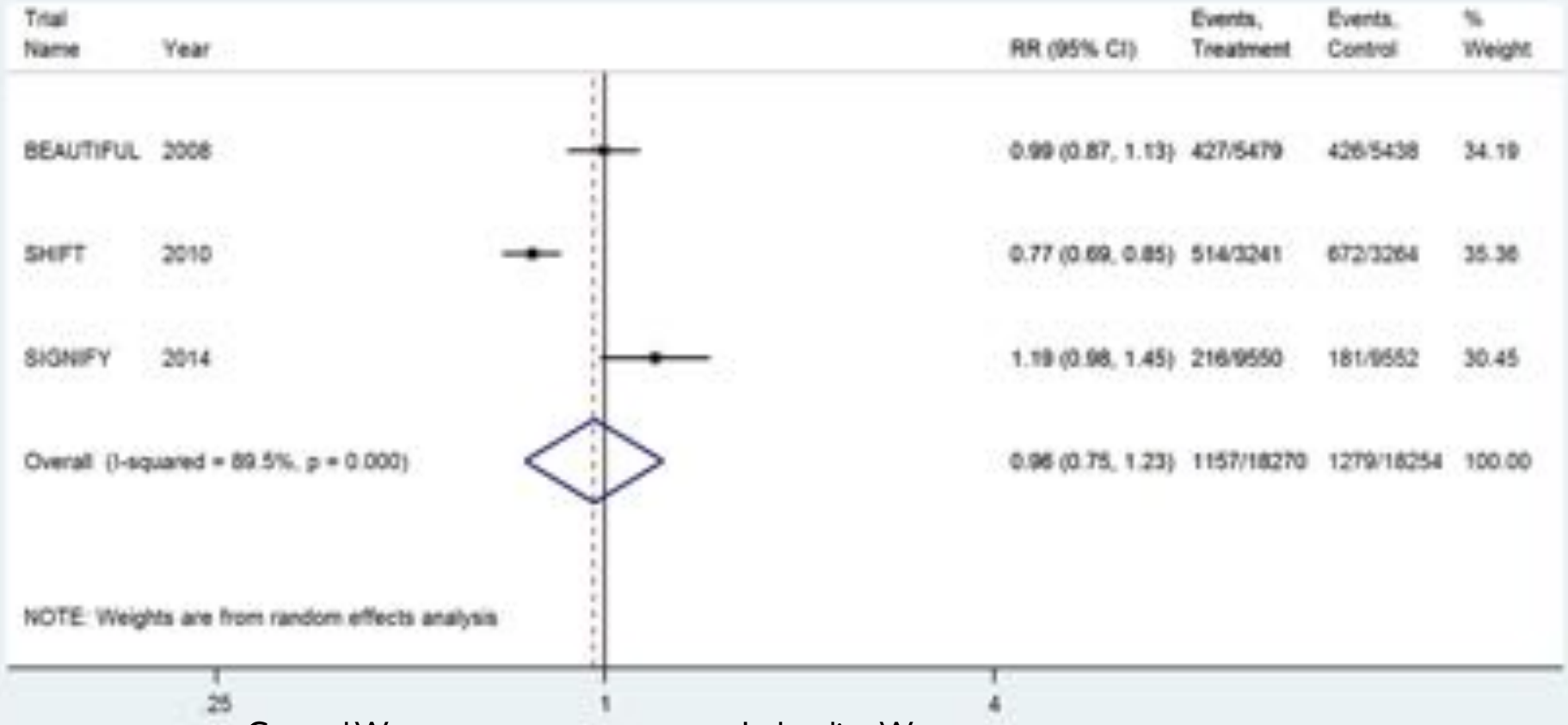
Results

- Seven trials published from 2008 to 2015 involving 36,622 patients
- Significantly higher incidence of atrial fibrillation in ivabradine group (4.2% vs. 3.4%, RR 1.24 (95% CI 1.08-1.43), $p<0.002$
- No evidence of significant heterogeneity ($I2=21.7\%$, $p=0.26$) or publication bias ($p=0.89$) noted
- Number needed to harm was 127

Mortality


Trial Name
Year
RR (95% CI)
Events, Treatment
Events, Control
% Weight
BEAUTIFUL 2008 1.04 (0.93, 1.16) 572/5479 547/5438 34.70
SHIFT 2010 0.92 (0.82, 1.03) 503/3241 552/3264 34.85
SIGNIFY 2014 1.06 (0.94, 1.20) 485/9550 458/9552 30.45
Overall (I-squared = 44.0%, p = 0.168) 1.00 (0.92, 1.09) 1560/18270 1557/18254 100.00
NOTE: Weights are from random effects analysis
.25
1
4
Control Worse
Ivabradine Worse

Heart Failure



Discussion

- Use of ivabradine was associated with an increased RR of 24% of AF, higher than noted as 15% by Martin RI[1] with addition of SIGNIFY[2]
- HCN*4* gene coding for I_f channel; mutation also associated with AF[3]

1) Martin RI, Pogoryelova O, Koref MS, Bourke JP, Teare MD, Keavney BD. Atrial fibrillation associated with ivabradine treatment: meta-analysis of randomised controlled trials. Heart 2014; 100:1506-10
2) Fox K, Ford I, Steg PG, Tardif JC, Tendera M, Ferrari R. Ivabradine in stable coronary artery disease without clinical heart failure. N Engl J Med 2014;371:1091-1099
3) den Hoed M, Eijgelsheim M, Esko T, et al. Identification of heart rate-associated loci and their effects on cardiac conduction and rhythm disorders. Nat Genet 2013;45:621–31.

Discussion

- Bradycardia increases risk of AF; APC's propagate AF[1]
  - Pauses, short coupling cycles, short-long-short cycle
- RR of AF
  - SIGNIFY > SHIFT

	Mean LVEF (%)	Mean Age (Yrs)	HTN	Mean Dosage (mg BID)	BB Use (%)	Mean Baseline HR (bpm)	Mean Endpoint HR (bpm)
BEAUTIFUL	32.3	65.2	71.0	6.2	87.0	71.6	64.0
SHIFT	29.0	60.4	67.0	6.5	89.0	79.9	67.0
SIGNIFY	56.4	65.0	86.2	8.2	83.0	77.1	60.7

1) Lau C-P. Pacing for atrial fibrillation. Heart 2003;89:106–12.

Discussion

- Benefit of ivabradine vs harm(AF):
  - SHIFT
    - HF Hospitalization NNT 20
    - AF NNH 59
  - SIGNIFY
    - CV death/MI No benefit
    - AF NNH 141
- Benefit of ivabradine vs harm(HF):
  - SIGNIFY, 4 more hospitalizations would make it significant
    - No benefit, NNH 224

Conclusion

- Doubling the number of patients studied in RCTs comparing ivabradine with placebo made the higher incidence of atrial fibrillation in the ivabradine group quite noticeable
- Further studies needed to identify patients more susceptible to atrial fibrillation who may benefit from ivabradine therapy

Aknowledgements

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