

# Clinical trials of ivabradine

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## 1 stable angina

Trial	Treatments	Patients	Trials design and methods
<b>ivabradine 10mg vs placebo</b>			
Borer (CL2-009) 10mg , 2003 n=91/91 follow-up: 2 weeks	Ivabradine 5 mg twice daily (10mg/d) versus placebo		double blind
<b>ivabradine 15mg vs placebo</b>			
BEAUTIFUL , 2008 [NCT00143507] n=5479/5438 follow-up: 19 months (range 16-24)	ivabradine target dose of 75 mg twice a day versus placebo	patients with coronary artery disease and left-ventricular systolic dysfunction (LVEF <=40% )	double blind 33 countries
<b>ivabradine 20mg vs placebo</b>			
SIGNIFY , 2014 [ISRCTN61576291] n=9550/9552 follow-up: 27.8 mo (median)	ivabradine, at a dose of up to 10 mg twice daily, with the dose adjusted to achieve a target heart rate of 55 to 60 beats per minute. versus placebo	patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more	Parallel groups double-blind
Borer (CL2-009) 20mg , 2003 n=88/91 follow-up: 2 weeks	ivabradine 10mg twice daily (20mg/d) versus placebo		double blind
<b>ivabradine 5mg vs placebo</b>			
Borer (CL2-009) 5mg , 2003  n=90/91 follow-up: 2 weeks	-	-	Parallel groups double blind
<b>ivabradine 15mg vs placebo (on top standard treatment)</b>			

continued...

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>BEAUTIFUL (angina subgroup)</b> n=734/773 follow-up: 19 months (range 16-24)	ivabradine target dose of 75 mg twice a day versus placebo	patients with stable coronary artery disease and left ventricular systolic dysfunction with limiting angina	double blind 33 countries
<b>ivabradine 10mg vs placebo on top of amlodipine</b>			
<b>CL3-018 10mg , 3000 unpublished</b> n=232/252 follow-up: 12 weeks	ivabradine 5mg twice daily (10mg/d) versus placebo	-	Parallel groups
<b>ivabradine 15mg vs placebo on top of amlodipine</b>			
<b>CL3-018 15mg , 3000 unpublished</b> n=244/252	ivabradine 7.5mg twice daily (15mg/d) versus placebo	-	
<b>ivabradine 15mg vs placebo on top of atenolol</b>			
<b>ASSOCIATE (Tardif) , 2009</b> [NCT00202566] n=449/440 follow-up: 4 months	ivabradine 5 mg b.i.d. for 2 months, increased to 7.5 mg b.i.d. for a further 2 months (on top atenolol 50 mg/day ) versus placebo on top atenolol 50 mg/day	patients with stable angina receiving atenolol 50 mg/day or another beta-blocker at equivalent doses for at least 3 months	Parallel groups double blind 20 countries
<b>ivabradine vs amlodipine</b>			
<b>CL3-023 (15mg) unpublished</b> n=381/398 follow-up: 3 months	ivabradine 7.5mg twice daily versus amlodipine		Parallel groups double-blind
<b>CL3-023 (20mg) unpublished</b> n=376/398 follow-up: 3 months	ivabradine 10mg twice daily versus amlodipine		double-blind
<b>ivabradine 15mg vs amlodipine</b>			
<b>Ruzylo (CL3-023) 15mg , 2007</b> n=400/404 follow-up: 3 months	ivabradine 7.5mg twice daily versus amlodipine 10mg once daily	Patients with a >/=3-month history of chronic, stable effort-induced angina	Parallel groups double-blind
<b>ivabradine 20mg vs amlodipine</b>			

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Trial	Treatments	Patients	Trials design and methods
Ruzylo (CL3-023) 20mg , 2007 n=391/404 follow-up: 3 months	ivabradine 10mg twice daily versus amlodipine 10mg once daily	Patients with a $\geq$ 3-month history of chronic, stable effort-induced angina	Parallel groups double-blind
<b>ivabradine 15mg vs atenolol</b>			
INITIATIVE (CL3-017, Tardif) 15mg , 2005 n=315/307 follow-up: 16 weeks	ivabradine 5 mg bid for 4 weeks and then either 7.5 or 10 mg bid for 12 weeks versus atenolol 50 mg od for 4 weeks and then 100 mg od for 12 weeks	patients with stable angina	double-blind
<b>ivabradine 20mg vs atenolol</b>			
INITIATIVE (CL3-017, Tardif) 20mg , 2005 n=317/307 follow-up: 16 weeks	ivabradine 5 mg bid for 4 weeks and then 10 mg bid for 12 weeks versus atenolol 50 mg od for 4 weeks and then 100 mg od for 12 weeks	patients with stable angina	Parallel groups double-blind

∞ More details and results :

- HR-slowing agents for stable angina in patients with left ventricular dysfunction at <http://www.trialresultscenter.org/go-Q118>
- HR-slowing agents for stable angina in all type of patients at <http://www.trialresultscenter.org/go-Q262>

## References

### Borer (CL2-009) 10mg, 2003:

Borer JS, 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;107:817-23 [12591750]

### BEAUTIFUL, 2008:

Fox K, Ford I, Steg PG, Tendera M, Ferrari R Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008 Sep 6;372:807-16 [18757088]

### SIGNIFY, 2014:

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 Aug 31; [25176136] 10.1056/NEJMoa1406430

### Borer (CL2-009) 20mg, 2003:

### Borer (CL2-009) 5mg, 2003:

Borer JS, Fox K, Jaillon P, Lerebours G Circulation 2003 Feb 18;107:817-23 [12591750]

### **BEAUTIFUL (angina subgroup), :**

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 [[19720635](#)]

### **CL3-018 10mg, 3000:**

unpublished

### **CL3-018 15mg, 3000:**

unpublished

### **ASSOCIATE (Tardif), 2009:**

Tardif JC, Ponikowski P, Kahan T Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. Eur Heart J 2009 Mar;30:540-8 [[19136486](#)]

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unpublished

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unpublished

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Ruzylo W, Tendera M, Ford I, Fox KM Antianginal efficacy and safety of ivabradine compared with amlodipine in patients with stable effort angina pectoris: a 3-month randomised, double-blind, multicentre, noninferiority trial. Drugs 2007;67:393-405 [[17335297](#)]

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### **INITIATIVE (CL3-017, Tardif) 15mg, 2005:**

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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 [[16214830](#)]

## **2 heart failure**

<b>Trial</b>	<b>Treatments</b>	<b>Patients</b>	<b>Trials design and methods</b>
<b>ivabradine vs placebo</b>			

continued...

Trial	Treatments	Patients	Trials design and methods
<b>SHIFT , 2010</b> [ISRCTN70429960] n=3241/3264 follow-up: 23 months	ivabradine versus placebo	patients with NYHA class 2-4 heart failure, an LVEF <35% , a resting heart rate >70 bpm, and a heart-failure hospitalization within the previous year	Parallel groups double-blind 37 countries
<b>ivabradine 15mg vs placebo</b>			
<b>BEAUTIFUL , 2008</b> [NCT00143507] n=5479/5438 follow-up: 19 months (range 16-24)	ivabradine target dose of 75 mg twice a day versus placebo	patients with coronary artery disease and left-ventricular systolic dysfunction (LVEF <=40% )	double blind 33 countries

More details and results :

- HR-slowing agents for heart failure in all type of patients at <http://www.trialresultscenter.org/go-Q456>

## References

### SHIFT, 2010:

Swedberg K, Komajda M, Bhm M, Borer JS, Ford I, Tavazzi L Rationale and design of a randomized, double-blind, placebo-controlled outcome trial of ivabradine in chronic heart failure: the Systolic Heart Failure Treatment with the I(f) Inhibitor Ivabradine Trial (SHIFT). Eur J Heart Fail 2010;12:75-81 [19892778] [10.1093/eur-jhf/hfp154](https://doi.org/10.1093/eur-jhf/hfp154)

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Fox K, Ford I, Steg PG, Tendera M, Ferrari R Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. Lancet 2008 Sep 6;372:807-16 [18757088]

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