

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Should we SHIFT our thinking about digoxin? Observations on ivabradine and heart rate reduction in heart failure.

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/134414> since

Published version:

DOI:10.1093/eurheartj/ehs004

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

**[Should we SHIFT our thinking about digoxin? Observations on
ivabradine and heart rate reduction in heart failure. Eur Heart J 2012;
33 (9): 1137-41. doi: 10.1093/eurheartj/ehs004.]**

The definitive version is available at:

La versione definitiva è disponibile alla URL:

<http://eurheartj.oxfordjournals.org/content/33/9/1137.long>

Title: Should we SHIFT our thinking about digoxin?
Observations on ivabradine and heart rate reduction in heart failure

Authors: Davide Castagno MD^{1,2}
Mark C Petrie MB ChB³
Brian Claggett AM⁴
John McMurray MD⁵

Affiliations: ¹ Cardiovascular Division, Brigham and Women's Hospital, Boston, Massachusetts, U.S.A. ² Division of Cardiology, Department of Internal Medicine – University of Turin, Turin, Italy. ³ Advanced Heart Failure Service, Golden Jubilee National Hospital, Clydebank, Glasgow, Scotland, UK. ⁴ Department of Biostatistics, Harvard School of Public Health, Boston, Massachusetts, U.S.A. ⁵ BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland, UK.

Corresponding author: BHF Cardiovascular Research Centre,
University of Glasgow,
Glasgow, Scotland,
United Kingdom, G12 8QQ.
Tel: +44 141 330 3479. Fax: +44 141 330 6955

email: john.mcmurray@glasgow.ac.uk

Word count :

Abstract = 171

Text (including references and figure legends) = 2638

Disclosure:

All authors have no conflicts of interest to disclose in connection with this article

Abstract

The importance of heart rate in the pathophysiology of heart failure with reduced LVEF has recently attracted attention. In particular, the findings of the Systolic Heart failure treatment with the *I_f* inhibitor ivabradine Trial (SHIFT), have put special emphasis on heart rate reduction with ivabradine for improvement in clinical outcomes. Of course there is a much older drug that reduces heart rate i.e. digoxin. In this short commentary we retrospectively analyse the Digitalis Investigation Group (DIG) Trial looking at the primary composite endpoint used in SHIFT (i.e. cardiovascular death or hospital admission for worsening heart failure) and compare the effect of digoxin on this endpoint with that of ivabradine. A remarkably similar risk reduction in the composite outcome and in its components appears evident amongst patients receiving the active treatment in both studies (although ivabradine was added to a beta-blocker whereas digoxin was not). This raises the question of whether the Cardiological community dismissed digoxin too readily and if we should reappraise its potential role in the treatment of heart failure.

Key Words

Heart failure

Heart rate

Digoxin

Ivabradine

Left ventricular ejection fraction

The key characteristics of the patients enrolled in the Systolic Heart failure treatment with the I_f-inhibitor Ivabradine Trial (SHIFT) and the Digitalis Investigation Group trial (DIG) trials are shown in Table 1. The remarkable similarity between the results of these 2 trials (Table 2) is a reminder that, in addition to beta-blockers and ivabradine, there is another treatment for heart failure which reduces heart rate i.e. digoxin.^{1,2}

Because it did not reduce mortality and perhaps because it was not promoted, digoxin has not been seen as a useful treatment for patients with systolic heart failure in sinus rhythm over recent years.³ Contemporaneous trials showing large benefits of spironolactone in patients with severe heart failure and similarly impressive benefits of beta-blockers across the whole spectrum of symptom severity eclipsed the findings of DIG.^{4,5-7}

Endpoints in DIG and SHIFT

DIG was also performed at a time when all-cause mortality was perceived to be the most appropriate end-point for trials in systolic heart failure. More recently the importance of morbidity, principally heart failure hospitalization, has been recognized and it is also now accepted that heart failure interventions are unlikely to reduce non-cardiovascular death.⁸ Consequently, the composite morbidity-mortality outcome of cardiovascular death or hospitalization for heart failure has become the most commonly used endpoint in recent heart failure trials, including SHIFT.^{2,9,10} Re-analysis of DIG shows that digoxin led to a highly significant 15 (9-21)% relative risk reduction in this composite outcome as compared with an 18 (10-25)% relative risk reduction in SHIFT, both p<0.001 (Figure 1 and Table 2). In both trials the primary effect was on heart failure hospitalization without any significant effect on

cardiovascular death. Heart failure hospitalization was reduced by 26 (17-34) % with ivabradine and by 28 (21-34) % with digoxin (both $p < 0.001$). Further inspection of the two trials shows very similar effects of digoxin on the other outcomes reported by the SHIFT investigators. Notably, both drugs reduced the proportion of patients admitted to hospital for any reason (Table 2).

Ivabradine and heart rate reduction

An entry criterion for SHIFT was a heart rate ≥ 70 beats per minute.² As a consequence, the mean baseline heart rate was 80 beats per minute. Compared with placebo, ivabradine reduced heart rate by 11 beats per minute at 28 days and 9 beats per minute at 1 year, a greater reduction in heart rate than achieved with digoxin (see below). An earlier trial, morbidity-mortality Evaluation of the I_f inhibitor ivabradine in patients with coronary disease and left-ventricular dysfunction (BEAUTIFUL), required patients to have a heart rate entry of at least 60 beats per minute.¹¹ The mean baseline heart rate in BEAUTIFUL was 72 beats per minute and the placebo-corrected reduction in heart rate was 7 beats per minute at 6 months and 6 beats per minute at 12 months. This latter finding is consistent with the observation that the heart rate reduction with ivabradine is greater in patients with a higher starting heart rate.^{2,12} In both trials, the reduction in heart rate was achieved despite the use of background beta-blocker therapy (although not always in a recommended dose¹³).

Digoxin and heart rate reduction in sinus rhythm

The baseline heart rate in DIG was 78 beats per minute. The use of beta-blockers was not recorded but was likely to have been very infrequent. Although change in heart rate was not reported in DIG, prior studies reported the effect of digoxin in patients

with heart failure in sinus rhythm. The largest study to do so was the Randomized Assessment of Digoxin on Inhibitors of the Angiotensin Converting Enzyme trial (RADIANCE), although this was a trial of digoxin withdrawal.¹⁴ Compared with continuation of digoxin, withdrawal of digoxin in RADIANCE led to a significant increase in heart rate of 7 beats per minute over 3 months from a baseline of 77 per minute. Two smaller placebo-controlled cross-over studies showed significant reductions in heart rate of 5 to 6 beats per minute.^{15,16}

The Dutch Ibopamine Multicenter Trial (DIMIT) investigators carried out ambulatory ECG monitoring in a subset of 50 patients receiving no background heart failure therapy.¹⁷ These patients were randomized to placebo, ibopamine or digoxin. Mean heart rate over 24 hours did not change from baseline in the placebo or ibopamine group but was reduced from 78 ± 7 to 74 ± 8 beats per minute in the digoxin group ($p=0.005$).

Digoxin is thought to reduce heart rate mainly by enhancing activity of the parasympathetic nervous system although it probably also inhibits the sympathetic nervous system as it lowers plasma norepinephrine levels.¹⁸⁻²¹ The vagal actions of digoxin also enhance heart-rate variability, an effect that is obtained even with low doses.²²⁻²⁴ In contrast to ivabradine, the addition of digoxin to a beta-blocker has not been studied in patients with systolic heart failure in sinus rhythm. As some of the heart rate reducing action of digoxin is due to an anti-sympathetic effect, concomitant beta-blockade may attenuate the bradycardic response to digoxin. However it is unlikely that beta-blocker treatment will eliminate the heart rate lowering action of digoxin which is probably mainly vagally driven.¹⁹ Certainly, the combination of digoxin and a beta-blocker gives greater heart rate reduction than either drug alone in

patients with atrial fibrillation, which is a frequent co-morbidity in patients with heart failure (and in which ivabradine is ineffective).^{25,26}

Left ventricular ejection fraction (LVEF)

As ivabradine's only known effect is to reduce heart rate, it was surprising that its use in SHIFT led to a placebo-corrected increase in LVEF of 2.7% ($p < 0.001$).²⁷ The placebo-corrected change in BEAUTIFUL (in which the reduction in heart rate was less) was smaller 1.6% ($p = 0.009$).²⁸ Two of the larger controlled trials with digoxin showed a placebo-corrected change in LVEF of 3.5% over 6 months ($p < 0.001$) and 3.7% over 3 months ($p < 0.01$), respectively.^{29,30} Although it has long been assumed that the increase in LVEF with digoxin is due an inotropic action of the drug, the findings of SHIFT raise the possibility that some of this effect of digoxin may be related to heart rate reduction (although the increase in LVEF with digoxin was somewhat greater than in SHIFT despite smaller reductions in heart rate).

Perspective

The recent finding that lowering heart rate with ivabradine reduces the risk of hospitalization for worsening heart failure should make us revisit the role of digoxin in the management of heart failure. Although probably not as potently bradycardic as ivabradine, digoxin also improves heart rate variability and seems to increase LVEF to a greater degree. The benefit of digoxin was demonstrated across the full range of heart rates in DIG, although patients in DIG were not treated with a beta-blocker. Conversely, in SHIFT, the benefit of ivabradine was shown only in patients with a persistently high heart rate, although most patients in that trial were on a beta-blocker. Indeed there was a significant interaction between baseline heart rate and the effect of

ivabradine in SHIFT, whereby there was a greater benefit of treatment in patients with a heart rate of ≥ 77 beats per minute.² Interestingly, a recent study has shown patients with a persistently high heart rate constitute a small minority of adequately beta-blocked patients.³¹ Digoxin is, of course, of value in patients with atrial fibrillation whereas ivabradine does not work in these patients. On the other hand, the toxicity of digoxin is well recognized and it also has interactions with many other drugs. Combination with a beta-blocker has the potential to cause atrioventricular block in particular, although more than half of patients in the pivotal beta-blocker trials were receiving background digoxin therapy and this problem was reported infrequently.⁵⁻⁷ Perhaps the findings of SHIFT, together with our retrospective hypothesis-generating analysis of DIG, should make us concerned that we dismissed digoxin too readily and that we should reconsider whether this inexpensive and generally well tolerated and safe agent still has a role to play as a treatment for heart failure? It is worth reflecting that in DIG there were 8 fewer patients admitted and 18 fewer admissions per 100 patients treated with digoxin compared with placebo. In other words, treatment of 13 patients for 3 years prevented 1 patient being admitted at least once with worsening heart failure i.e. the number needed to treat (NNT) for 3 years was only 13. For patients in sinus rhythm, the treatment algorithms in current guidelines recommend digoxin almost as a “last resort” in patients who remain significantly symptomatic despite everything else – maybe we should reconsider this?³

REFERENCES

1. [No authors listed]. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med* 1997; 336: 525-33.
2. Swedberg K, Komajda M, Böhm M, Borer JS, Ford I, Dubost-Brama A, Lerebours G, Tavazzi L; SHIFT Investigators. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet* 2010; 376: 875-85.
3. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail* 2008; 10: 933-89.
4. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med* 1999; 341: 709-17.

5. [No authors listed]. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet* 1999; 353: 9-13.
6. [No authors listed]. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet* 1999; 353: 2001-7.
7. Packer M, Coats AJ, Fowler MB, Katus HA, Krum H, Mohacsi P, Rouleau JL, Tendera M, Castaigne A, Roecker EB, Schultz MK, DeMets DL; Carvedilol Prospective Randomized Cumulative Survival Study Group. Effect of carvedilol on survival in severe chronic heart failure. *N Engl J Med* 2001; 344: 1651-8.
8. Yusuf S, Negassa A. Choice of clinical outcomes in randomized trials of heart failure therapies: disease-specific or overall outcomes? *Am Heart J* 2002; 143: 22-8.
9. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA; CHARM Investigators and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet* 2003; 362: 767-71.
10. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B; EMPHASIS-HF Study Group. Eplerenone in

- patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011; 364: 11-21.
11. Fox K, Ford I, Steg PG, Tendera M, Ferrari R; BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL): a randomised, double-blind, placebo-controlled trial. *Lancet* 2008; 372: 807-16.
 12. Borer JS, Le Heuzey JY. Characterization of the heart rate-lowering action of ivabradine, a selective I(f) current inhibitor. *Am J Ther* 2008; 15: 461-73.
 13. Teerlink JR. Ivabradine in heart failure--no paradigm SHIFT...yet. *Lancet* 2010; 376: 847-9.
 14. Packer M, Gheorghiu M, Young JB, Costantini PJ, Adams KF, Cody RJ, Smith LK, Van Voorhees L, Gourley LA, Jolly MK. Withdrawal of digoxin from patients with chronic heart failure treated with angiotensin-converting-enzyme inhibitors. RADIANCE Study. *N Engl J Med* 1993; 329: 1-7.
 15. Lee DC, Johnson RA, Bingham JB, Leahy M, Dinsmore RE, Goroll AH, Newell JB, Strauss HW, Haber E. Heart failure in outpatients: a randomized trial of digoxin versus placebo. *N Engl J Med* 1982; 306: 699-705.

16. Taggart AJ, Johnston GD, McDevitt DG. Digoxin withdrawal after cardiac failure in patients with sinus rhythm. *J Cardiovasc Pharmacol* 1983; 5: 229-34.
17. van Veldhuisen DJ, Brouwer J, Man in 't Veld AJ, Dunselman PH, Boomsma F, Lie KI. Progression of mild untreated heart failure during six months follow-up and clinical and neurohumoral effects of ibopamine and digoxin as monotherapy. DIMT Study Group. Dutch Ibopamine Multicenter Trial. *Am J Cardiol* 1995 Apr 15; 75: 796-800.
18. Kim YI, Noble RJ, Zipes DP. Dissociation of the inotropic effect of digitalis from its effect on atrioventricular conduction. *Am J Cardiol* 1975; 36: 459-67.
19. Watanabe AM. Digitalis and the autonomic nervous system. *J Am Coll Cardiol* 1985; 5(5 Suppl A): 35A-42A.
20. Ferguson DW, Berg WJ, Sanders JS, Roach PJ, Kempf JS, Kienzle MG. Sympathoinhibitory responses to digitalis glycosides in heart failure patients. Direct evidence from sympathetic neural recordings. *Circulation* 1989; 80: 65-77.
21. van Veldhuisen DJ, Man in 't Veld AJ, Dunselman PH, Lok DJ, Dohmen HJ, Poortermans JC, Withagen AJ, Pasterkamp WH, Brouwer J, Lie KI. Double-blind placebo-controlled study of ibopamine and digoxin in patients with mild

- to moderate heart failure: results of the Dutch Ibopamine Multicenter Trial (DIMIT). *J Am Coll Cardiol*. 1993; 22:1564-73.
22. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ, Dunselman PH, Boomsma F, Haaksma J, Lie KI. Heart rate variability in patients with mild to moderate heart failure: effects of neurohormonal modulation by digoxin and ibopamine. The Dutch Ibopamine Multicenter Trial (DIMIT) Study Group. *J Am Coll Cardiol* 1995; 26: 983-90.
23. Krum H, Bigger JT Jr, Goldsmith RL, Packer M. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *J Am Coll Cardiol* 1995; 25: 289-94.
24. Slatton ML, Irani WN, Hall SA, Marcoux LG, Page RL, Grayburn PA, Eichhorn EJ. Does digoxin provide additional hemodynamic and autonomic benefit at higher doses in patients with mild to moderate heart failure and normal sinus rhythm? *J Am Coll Cardiol* 1997; 29: 1206-13.
25. Farshi R, Kistner D, Sarma JS, Longmate JA, Singh BN. Ventricular rate control in chronic atrial fibrillation during daily activity and programmed exercise: a crossover open-label study of five drug regimens. *J Am Coll Cardiol* 1999; 33: 304-10.
26. Khand AU, Rankin AC, Martin W, Taylor J, Gemmell I, Cleland JG. Carvedilol alone or in combination with digoxin for the management of atrial

- fibrillation in patients with heart failure? *J Am Coll Cardiol* 2003; 42: 1944-51.
27. Tardif JC, O'Meara E, Komajda M, Böhm M, Borer JS, Ford I, Tavazzi L, Swedberg K; on behalf of the SHIFT Investigators. Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy. *Eur Heart J* 2011 Aug 29. [Epub ahead of print].
28. Ceconi C, Freedman SB, Tardif JC, Hildebrandt P, McDonagh T, Gueret P, Parrinello G, Robertson M, Steg PG, Tendera M, Ford I, Fox K, Ferrari R; BEAUTIFUL Echo-BNP Investigators. Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL. *Int J Cardiol* 2011; 146: 408-14.
29. [No authors listed]. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. *JAMA* 1988; 259: 539-44.
30. DiBianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R. A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. *N Engl J Med* 1989; 320: 677-83.

31. Cullington D, Goode KM, Cleland JG, Clark AL. Rate criteria provide limited application for ivabradine in chronic heart failure. *Heart* 2011 Sep 13. [Epub ahead of print]

FIGURE LEGEND.

Figure 1. Kaplan-Meier cumulative event curves for the composite outcome of cardiovascular death or heart failure hospitalization in the Digitalis Investigation Group trial (DIG) [A] and the Systolic Heart failure treatment with the I_finhibitor Ivabradine Trial (SHIFT) [B*].

* Adapted from Lancet 2010; 376: 875-85.

Table 1. Baseline characteristics of the patients enrolled in the Digitalis Investigation

Group trial (DIG) and in the Systolic Heart failure treatment with the I_f inhibitor Ivabradine Trial (SHIFT).

	SHIFT n=6505	DIG n=6800
Age (years)	60	64
Sex (male)	76%	78%
Ethnic origin		
White	89%	85%
Nonwhite	11%	15%
BMI	28	27
Heart rate	80	79
SBP	122	126
LVEF	29%	28%
eGFR	75	64
NYHA		
Class I	-	13%
Class II	49%	54%
Class III	49%	31%
Class IV	2%	2%
Primary cause of HF		
Ischaemic	68%	71%
Non-ischaemic	32%	29%
Prior myocardial infarction	56%	65%
Hypertension	66%	45%
Diabetes	30%	28%
Beta-blocker	89%	N/A
Ace-inhibitor	79%	94%
ARB	14%	0
Diuretic	83%	82%
Antialdosterone agents	60%	N/A*
Cardiac glycosides	22%	N/A

ICD	3%	0
CRT	1%	0

* Potassium sparing diuretic = 8%

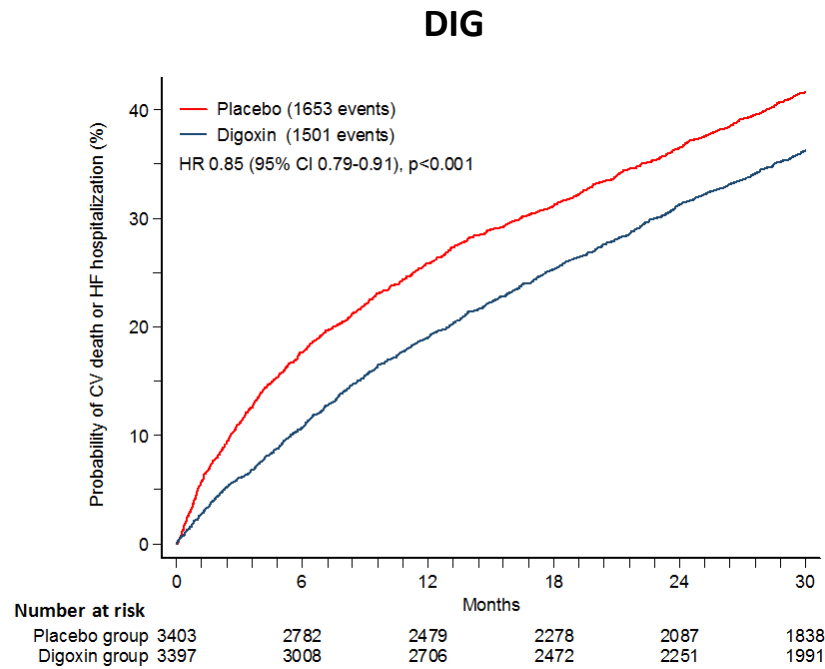
Table 2: Clinical outcomes in the Digitalis Investigation Group trial (DIG) and the Systolic Heart failure treatment with the I_finhibitor Ivabradine Trial (SHIFT).

Outcome	SHIFT				DIG			
	Ivabradine (n=3241)	Placebo (n=3264)	HR (95% CI)	P value	Digoxin (n=3397)	Placebo (n=3403)	HR (95% CI)	P value
	n (%)	n (%)			n (%)	n (%)		
Primary composite outcome in SHIFT								
Cardiovascular death or heart failure hospitalization	793 (24)	937 (29)	0.82 (0.75,0.90)	<0.001	1501 (44)	1653 (49)	0.85 (0.79,0.91)	<0.001
Hospitalization								
Heart failure hospitalization	514 (16)	672 (21)	0.74 (0.66,0.83)	<0.001	910 (27)	1180 (35)	0.72 (0.66,0.79)	<0.001
Cardiovascular hospitalization	977 (30)	1122 (34)	0.85 (0.78,0.92)	<0.001	1694 (50)	1850 (54)	0.87 (0.81,0.93)	<0.001
All-cause hospitalization	1231 (38)	1356 (42)	0.89 (0.82,0.96)	<0.01	2184 (64)	2282 (67)	0.92 (0.87,0.98)	<0.01
Deaths								
Heart failure death	113 (3)	151 (5)	0.74 (0.58,0.94)	0.01	394 (12)	449 (13)	0.88 (0.77,1.01)	0.06
Cardiovascular death	449 (14)	491 (15)	0.91 (0.80,1.03)	0.13	1016 (30)	1004 (30)	1.01 (0.93,1.10)	0.78
All-cause death	503 (16)	552 (17)	0.90 (0.80,1.02)	0.09	1181 (35)	1194 (35)	0.99 (0.91,1.07)	0.80

HR = hazard ratio CI = confidence interval

Figure 1: Kaplan-Meier cumulative event curves for the composite outcome of cardiovascular death or heart failure hospitalization in the Digitalis Investigation Group trial (DIG) [A] and the Systolic Heart failure treatment with the I_f-inhibitor Ivabradine Trial (SHIFT) [B*]. * Adapted from Lancet 2010; 376: 875-85.

A



B

