

Meta-Analysis of Digoxin Use and Risk of Mortality in Patients With Atrial Fibrillation



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There is an ongoing debate on the safety of digoxin use in patients with atrial fibrillation (AF). To address this issue, the investigators assembled a synthesis of the available evidence on the relation between digoxin and all-cause mortality in patients with AF. PubMed and the Embase database were systematically searched to identify all eligible studies examining the association between digoxin use and the mortality risk in AF. Overall hazard ratios and 95% confidence intervals were calculated using the random-effects model. Eleven observational studies were identified that met the inclusion criteria, 5 of which additionally used propensity score matching for statistical adjustment. In total, 318,191 patients were followed up for a mean of 2.8 years. Overall, digoxin use was associated with a 21% increased risk for mortality (hazard ratio 1.21, 95% confidence interval 1.12 to 1.30). Sensitivity analyses found the results to be robust. In the propensity score-matched AF patients, digoxin use was associated with a 17% greater risk for mortality (hazard ratio 1.17, 95% confidence interval 1.13 to 1.22). When the AF cohort was grouped into patients with and without heart failure, the use of digoxin was associated with an increase in mortality in patients with and those without heart failure, and no significant heterogeneity was seen between the groups ($p > 0.10$). In conclusion, the results suggest that digoxin use was associated with a greater risk for mortality in patients with AF, regardless of concomitant heart failure. A well-powered randomized trial is necessary to reveal the true effect of digoxin. © 2015 Elsevier Inc. All rights reserved. (Am J Cardiol 2015;115:901–906)

Digoxin has been used worldwide for decades to achieve rate control in patients with atrial fibrillation (AF), particularly in those with heart failure (HF). Clinical guidelines currently endorse the use of digoxin in AF,^{1,2} despite the lack of randomized trials of digoxin in AF patients. In the largest study, the Digitalis Investigation Group (DIG) study, digoxin was reported to have a neutral effect on mortality in patients with HF,³ but elevated serum levels of digoxin were found to be correlated with increased mortality in multiple patient population.^{4,5} Therefore, the safety of digoxin in patients with AF should be adequately addressed. Recently, a number of observational studies have focused on the safety of digoxin in patients with AF and generated mixed results.^{6–16} Therefore, we aimed to quantify the association between the use of digoxin and risk for mortality in AF and to discern whether the mortality risk differs between patients with and without HF.

Methods

Our systematic review was conducted according to the Meta-Analysis of Observational Studies in Epidemiology guidelines.¹⁷ Each investigator independently conducted

a systematic search of PubMed and Embase from their inception to December 29, 2014, using the following key words: “digitalis” OR “digoxin” AND “atrial fibrillation” AND “mortality” OR “death.” The search was limited to human research, with no restrictions on language. In addition, a manual search of the reference lists of all identified studies and review articles was performed to identify relevant studies.

Abstracts of identified reports were screened to exclude studies that clearly did not meet the eligibility criteria. The full text of those selected for further review was obtained and evaluated. Studies were considered for inclusion if they fulfilled the following criteria: (1) prospective or retrospective studies assessing the association between digoxin use and risk for all-cause mortality in patients with AF, (2) follow-up ≥ 1 year, (3) described adjustment for potential confounding, and (4) reported effect estimates with confidence intervals (CIs), standard errors, or sufficient information to calculate these.

Two investigators independently extracted data from each study. Discrepancies were discussed and resolved by agreement. The following data were extracted from each study: study name, year of publication, setting, study design, number of participants, mean age, study duration, methods for confounding adjustment and variables adjusted for, effect estimates, and CIs or standard errors (or information required to compute these). When multiple effect estimates were reported, maximally adjusted estimates were extracted.

The quality of each study was assessed independently by 2 investigators (A.-J.O., Y.-N.L.) using the Newcastle-Ottawa Scale (NOS).¹⁸ The NOS consists of 3 parameters of quality: selection, comparability, and outcome. The NOS assigns

Department of Pharmacy, The First Affiliated Hospital of Nanchang University, Nanchang, China. Manuscript received November 28, 2014; revised manuscript received and accepted January 3, 2015.

See page 905 for disclosure information.

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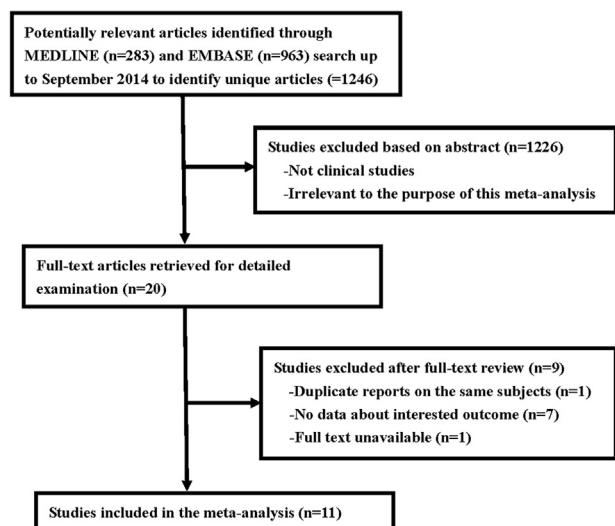


Figure 1. Search strategy and flowchart for studies included in the meta-analysis.

a maximum of 4 points for selection, 2 points for comparability, and 3 points for exposure or outcome. Therefore, a score of 9 points indicates the highest quality, 6 to 8 points indicates medium quality, and <6 points indicates low quality. Any discrepancies were resolved by consensus.

Our meta-analysis and statistical analyses were performed by using Stata 12.0 (StataCorp LP, College Station, Texas). A p value <0.05 was considered to indicate statistical significance, unless otherwise specified. Publication bias was assessed with funnel plots and Egger's regression asymmetry test. Heterogeneity was measured using Cochran's Q and the I^2 statistic; for the Q statistic, a p value <0.10 was considered to indicate statistical significance for heterogeneity, while for I^2 , a value >50% was considered to indicate significant heterogeneity.¹⁹ The primary measurement was the pooled hazard ratios (HR) of mortality from individual studies calculated using the random-effects model (DerSimonian and Laird method), which accounts for heterogeneity among studies.

We obtained the pooled risk estimate from studies using a Cox regression survival model to evaluate the association between digoxin use and mortality risk. Furthermore, because observational study designs are limited by an inherent imbalance of both known and unknown confounders, an additional pooled survival analysis was performed on the basis of the propensity score–matching method, which can balance all measured baseline characteristics across treatment groups. We also explored whether the association between digoxin and mortality risk was related to HF status (HF vs no HF).

To test the robustness of the results, we performed a 1-way sensitivity analysis. The scope of this analysis was to evaluate the influence of individual studies by estimating the average HR in the absence of each study.

Results

We retrieved 1,203 citations from database searches. After title and abstract screening, 1,184 were found not to be relevant to this meta-analysis and were excluded. After

detailed evaluation of the remaining 20 full-text reports, 9 were excluded for reasons described in Figure 1. Thus, 11 studies^{6–16} were included in the primary analyses.

Study and patient characteristics are summarized in Table 1. A total of 318,191 patients were involved. The participants were monitored for 1 to 4.6 years, and the studies were published from 2007 to 2014. Ten studies reported the association between digoxin use and mortality risk on the basis of Cox regression modeling and 5 studies^{6,7,11,12,16} additionally on the basis of propensity score matching. On the basis of the NOS, 6 studies^{6,7,10–12,15} were of high quality and 5 of medium quality.^{8,9,13,14,16}

The pooled analysis on the basis of Cox survival regression modeling showed that digoxin use was associated with a 21% increased risk for mortality (95% CI 1.12 to 1.30; Figure 2), and significant heterogeneity was detected for this outcome ($I^2 = 83.6\%$, $p < 0.001$). Sensitivity analysis showed that the HRs for mortality were similar, without great fluctuation (data not shown). Subgroup analysis showed that both prospective and retrospective studies exhibited significant findings. On the basis of propensity score matching, digoxin use was associated with a 17% increased risk for mortality (95% CI 1.13 to 1.22), but no significant heterogeneity was detected ($I^2 = 40.0\%$, $p = 0.154$).

An additional analysis was performed to determine whether the risk for mortality differed between patients with and without HF. As shown in Figure 3, we found that digoxin use was associated with a 15% increased mortality risk among AF patients with HF (95% CI 1.12 to 1.17) and an 18% increased risk among patients without HF (95% CI 1.15 to 1.21). There was no significant heterogeneity between groups ($p = 0.125$).

Funnel plots and Egger's tests indicated no significant publication bias in the meta-analyses (Egger's test = 0.921). A fail-safe N test indicated that it would take 421 unpublished null-result studies to bring the combined p to a nonsignificant level.

Discussion

This meta-analysis suggests that in patients with AF, digoxin is associated with increased risk for mortality after controlling for confounders and propensity scores. In addition, digoxin use in patients with AF was associated with 15% and 18% greater risk for mortality in the group of patients with HF compared with those without HF, respectively.

The DIG trial, which randomized patients with HF to digoxin, demonstrated a neutral effect on mortality compared with placebo.³ However, a post hoc analysis of the DIG trial showed that patients with serum digoxin concentrations ≥ 1.2 ng/ml had an 11.8% higher absolute mortality rate than patients receiving placebo.⁴ Because digoxin is widely prescribed to control heart rate in the AF population, the safety of digoxin in patients with AF should be adequately addressed. In the present analysis, increased mortality risk after digoxin use was observed in patients with AF. We hypothesize that arrhythmias, including ventricular arrhythmias and worsened sinus node dysfunction, are a potential source of mortality. The incidence of digoxin-induced arrhythmia was reported to be dose related: 10% at a level of 1.7 ng/ml and 50% at 2.5 ng/ml.²⁰

Table 1
 Characteristics of studies evaluating the association between digoxin use and risk of mortality in patients with atrial fibrillation

First Author	Study design	Country	Subjects				Follow-up (yrs)	Primary endpoints	Analysis method	Study quality
			N (digoxin/no digoxin)	Age (yrs)	Male	HF				
Turakhia (2014) ⁶	Prospective	USA	28,679/93,786	72.1±10.7	98.4%	15.8%	2.9	All-cause mortality	Cox regression model, Propensity score matching	High
Shah (2014) ⁷	Retrospective	Canada	38,381/101,730	79.6±7.3	47.6%	25.6%	3.5	All-cause mortality	Cox regression model, Propensity score matching	High
Mulder (2014) ⁸	Retrospective	The Netherlands	284/327	68±8	65.5%	14.9%	2.9	Composite of CV morbidity and mortality	Cox regression model	Medium
Rodríguez-Mañero (2014) ⁹	Retrospective	Spain	270/507	74.8±9.3	53.1%	12.3%	2.9	All-cause mortality, CV morbidities	Cox regression model	Medium
Whitbeck (2013) ¹⁰	Retrospective	USA	2,193/1,905	69.7±9	60.7%	23.1%	3.5	All-cause mortality	Cox regression model, Propensity score matching	High
Gheorghiadu (2013) ¹¹	Prospective	Sweden	802/2022	75.5±8	54.7%	44.6%	4.6	All-cause mortality	Cox regression model, Propensity score matching	High
Friberg (2010) ¹²	Prospective	Sweden	802/2022	75.5±8	54.7%	44.6%	4.6	All-cause mortality	Cox regression model, Propensity score matching	High
Georgiopoulou (2009) ¹³	Retrospective	USA	93/69	52.3±12.1	68.7%	100%	2.3	All-cause mortality	Cox regression model	Medium
Fauchier (2009) ¹⁴	Prospective	France	591/418	75.5±10.3	61%	100%	2.4	All-cause mortality	Cox regression model	Medium
Gjesdal (2008) ¹⁵	Retrospective	USA	3911/3418	70.9±8.3	69.2%	NA	1.5	All-cause mortality, strokes and systemic embolic events	Cox regression model	High
Hallberg (2007) ¹⁶	Prospective	Sweden	12,630/25,789	67±5.8	56.8%	44.1%	1	All-cause mortality	Cox regression model, Propensity score matching	Medium

CV=cardiovascular; HF=heart failure; NA = not available.

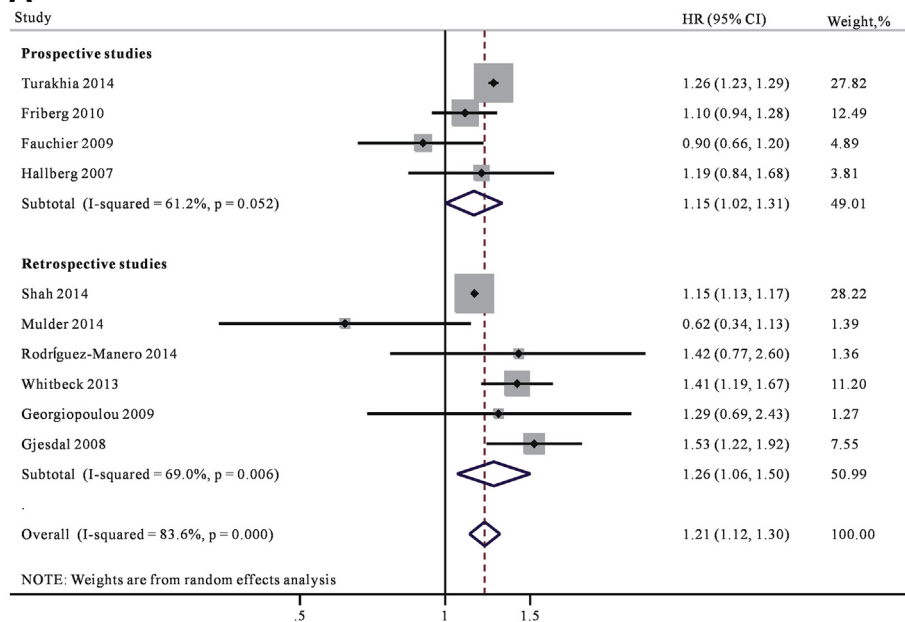
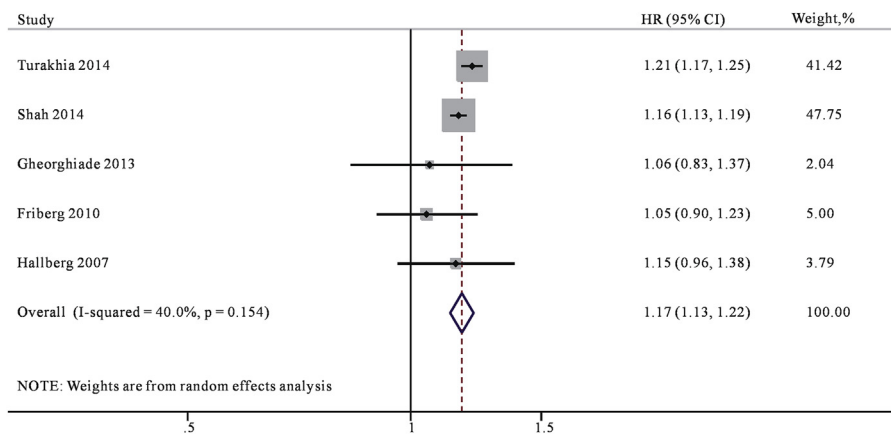
A Cox regression model**B Propensity score matching**

Figure 2. Combined estimate of HRs and 95% CIs of digoxin associated with risk for all-cause mortality in patients with AF on the basis of Cox regression survival model (A) and propensity score matching (B).

In addition, increased intracellular calcium plays a key role in platelet activation,²¹ and this might be associated with the greater incidence of thromboembolic events in AF patients. Digoxin could inhibit the membrane-bound Na^+/K^+ adenosine triphosphatases, thereby ultimately increasing intracellular calcium.²² In patients with AF, digoxin use was found to be associated with increased platelet activation, which may contribute to a predisposition to thrombosis and vascular events.²³ This is supported by the results of a large cohort study in which digoxin use was linked to an increased risk for stroke in patients with AF.²⁴ Therefore, it is reasonable to speculate that the increased platelet activity induced by digoxin might be a contributor to vascular events and mortality in AF.

The use of digoxin to control heart rate during rest in patients with HF and AF is recommended, according to the current guidelines for management of chronic HF.^{25,26} Although digoxin treatment can improve the left ventricular

ejection fraction and symptoms in HF patients^{27,28} and reduce the rest heart rate in AF, in our analysis, digoxin was associated with a 15% increase in mortality in patients with AF and HF. It may be hypothesized that potential benefits are offset by deleterious effects. HF patients with AF may result in more frequent hemodynamic disorder, frequent electrolyte disturbances, and varying degrees of kidney impairment that render them more susceptible to digoxin toxicity.²⁹ Furthermore, these patients are frequently prescribed a number of medications (e.g., amiodarone, diuretics, and calcium channel blockers), which may interact with digoxin and reduce renal clearance, decrease the volume of distribution, and increase serum concentration.³⁰ These could be the reasons for the increased risk for mortality in AF patients with HF.

Two studies^{8,14} included in the meta-analysis showed a trend toward a decreased mortality rate in patients using digoxin, although it did not reach statistical significance. The study by Mulder et al⁸ reported an unadjusted HR, and

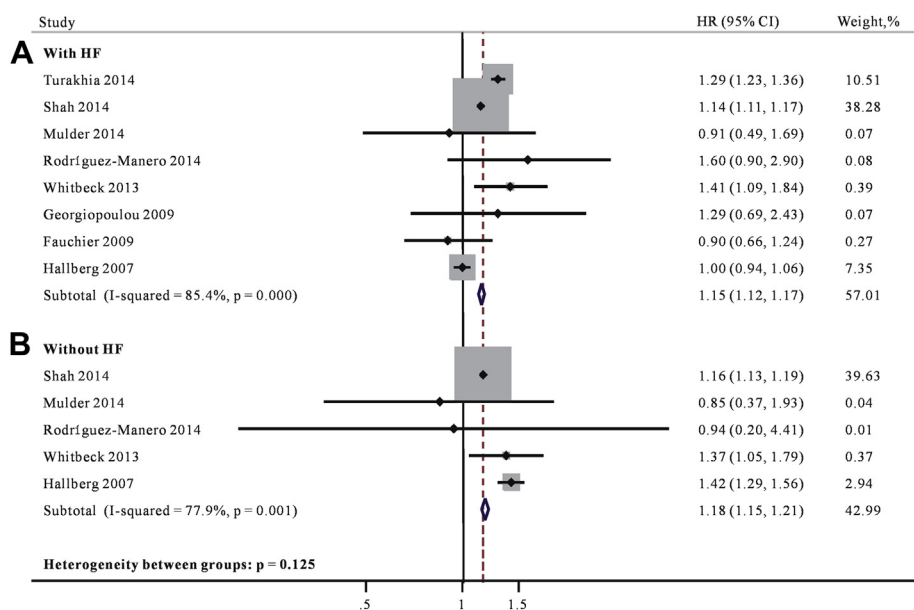


Figure 3. Combined estimate of HRs and 95% CIs of digoxin associated with risk for all-cause mortality in AF patients with (A) and without (B) HF.

thus the potential confounders may have biased the results. Furthermore, the heart rate target was not achieved at all costs in these AF cohorts, and this may have prevented high serum concentrations and possible toxicity of digoxin. In the work of Fauchier et al,¹⁴ almost half of patients not using digoxin were taking antiarrhythmic agents, which could worsen outcomes. And the proportion of anticoagulants was higher in the digoxin group, which creates the possibility that digoxin users were managed better. Thus, these factors may create bias and influence the results.

This study is the first meta-analysis to address the safety of digoxin on mortality risk in patients with HF. On the basis of the data from nearly 318,191 subjects, the results demonstrated an increased risk for mortality in digoxin users. Moreover, the results remained stable even after sensitivity analysis. Further observational studies will be useful for improving the precision of effect estimates. Importantly, our findings highlight the need for future randomized trials to confirm the safety of digoxin in AF.

Several limitations of this meta-analysis must be considered. First, our results suggest that serum digoxin concentration is the critical factor that predisposes AF patients to increased mortality risk, but the data on digoxin dosage or serum digoxin concentration was unavailable in most of the included studies. Second, there was limited information on renal function or the left ventricular ejection fraction, 2 important determinants of mortality. Third, although the random-effects pooling method adjusts for heterogeneity, another limitation of this meta-analysis was the substantial heterogeneity observed among studies. Overall, pooling can be fraught with significant heterogeneity and should thus be viewed with caution and as hypothesis generating.

Disclosures

The authors have no conflicts of interest to disclose.

1. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorennek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369–2429.
2. January CT, Wann LS, Alpert JS, Calkins H, Cleveland JC Jr, Cigarroa JE, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: Executive Summary: a report of the American college of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:2071–2104.
3. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity. *N Engl J Med* 1997;336:525–533.
4. Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. *JAMA* 2003;289:871–878.
5. Chan KE, Lazarus JM, Hakim RM. Digoxin associates with mortality in ESRD. *J Am Soc Nephrol* 2010;21:1550–1559.
6. Turakhia MP, Santangeli P, Winkelmayer WC, Xu X, Ullal AJ, Than CT, Schmitt S, Holmes TH, Frayne SM, Phibbs CS, Yang F, Hoang DD, Ho PM, Heidenreich PA. Increased mortality associated with digoxin in contemporary patients with atrial fibrillation: findings from the TREAT-AF study. *J Am Coll Cardiol* 2014;64:660–668.
7. Shah M, Avgil Tsadok M, Jacevicius CA, Essebag V, Behloul HL, Pilote L. Relation of digoxin use in atrial fibrillation and the risk of all-cause mortality in patients ≥ 65 years of age with versus without heart failure. *Am J Cardiol* 2014;114:401–406.
8. Mulder BA, Van Veldhuisen DJ, Crijns HJ, Tijssen JG, Hillege HL, Alings M, Rienstra M, Van den Berg MP, Van Gelder IC. Digoxin in patients with permanent atrial fibrillation: data from the RACE II study. *Heart Rhythm* 2014;11:1543–1550.
9. Rodríguez-Mañero M, Otero-Raviña F, García-Seara J, Zugaza-Guruchaga L, Rodríguez-García JM, Blanco-Rodríguez R, Turrado Turrado V, Fernández-Villaverde JM, Vidal-Pérez RC, González-Juanatey JR. Outcomes of a contemporary sample of patients with atrial fibrillation taking digoxin: results from the AFBAR study. *Rev Esp Cardiol* 2014;67:890–897.
10. Whitbeck MG, Charnigo RJ, Khairy P, Ziada K, Bailey AL, Zegarra MM, Shah J, Morales G, Macaulay T, Sorrell VL, Campbell CL, Gurley J, Anaya P, Nasr H, Bai R, Di Biase L, Booth DC, Jondeau G, Natale A, Roy D, Smyth S, Moliterno DJ, Elayi CS. Increased

- mortality among patients taking digoxin—analysis from the AFFIRM study. *Eur Heart J* 2013;34:1481–1488.
11. Gheorghide M, Fonarow GC, van Veldhuisen DJ, Cleland JG, Butler J, Epstein AE, Patel K, Aban IB, Aronow WS, Anker SD, Ahmed A. Lack of evidence of increased mortality among patients with atrial fibrillation taking digoxin: findings from post hoc propensity-matched analysis of the AFFIRM trial. *Eur Heart J* 2013;34:1489–1497.
 12. Friberg L, Hammar N, Rosenqvist M. Digoxin in atrial fibrillation: report from the Stockholm Cohort study of Atrial Fibrillation (SCAF). *Heart* 2010;96:275–280.
 13. Georgiopolou VV, Kalogeropoulos AP, Giamouzis G, Agha SA, Rashad MA, Waheed S, Laskar S, Smith AL, Butler J. Digoxin therapy does not improve outcomes in patients with advanced heart failure on contemporary medical therapy. *Circ Heart Fail* 2009;2:90–97.
 14. Fauchier L, Grimard C, Pierre B, Nonin E, Gorin L, Rauzy B, Cosnay P, Babuty D, Charbonnier B. Comparison of beta blocker and digoxin alone and in combination for management of patients with atrial fibrillation and heart failure. *Am J Cardiol* 2009;103:248–254.
 15. Gjesdal K, Feyzi J, Olsson SB. Digitalis: a dangerous drug in atrial fibrillation? an analysis of the SPORTIF III and V data. *Heart* 2008;94:191–196.
 16. Hallberg P, Lindbäck J, Lindahl B, Stenstrand U, Melhus H. Digoxin and mortality in atrial fibrillation: a prospective cohort study. *Eur J Clin Pharmacol* 2007;63:959–971.
 17. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-Analysis of Observational Studies in Epidemiology: a proposal for reporting. Meta-Analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–2012.
 18. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed on October 8, 2012.
 19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557–560.
 20. Thummel KE, Shen DD. Design and optimization of dosage regime. Pharmacologic data. In: Hardman JG, Kimbird LE, eds. Goodman and Gilman's the Pharmacological Basis of Therapeutics. New York: McGraw Hill, 2001.
 21. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med* 2007;357:2482–2494.
 22. Schwartz A, Whitmer K, Grupp G, Grupp I, Adams RJ, Lee SW. Mechanism of action of digitalis: is the Na,K-ATPase the pharmacological receptor? *Ann N Y Acad Sci* 1982;402:253–271.
 23. Chirinos JA, Castellon A, Zambrano JP, Jimenez JJ, Jy W, Horstman LL, Willens HJ, Castellanos A, Myerburg RJ, Ahn YS. Digoxin use is associated with increased platelet and endothelial cell activation in patients with nonvalvular atrial fibrillation. *Heart Rhythm* 2005;2:525–529.
 24. Chang SS, Chang KC, Wang YC, Muo CH, Pai PY, Chang CB, Li CY, Sung FC. Digoxin use is associated with increased risk of stroke in patients with non-valvular atrial fibrillation—a nationwide population-based cohort study. *Int J Cardiol* 2013;169:e26–e27.
 25. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787–1847.
 26. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Dickstein K, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:e147–e239.
 27. Packer M, Gheorghide 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.
 28. Guyatt GH, Sullivan MJ, Fallen EL, Tihal H, Rideout E, Halcrow S, Nogradi S, Townsend M, Taylor DW. A controlled trial of digoxin in congestive heart failure. *Am J Cardiol* 1988;61:371–375.
 29. Binder L, Fredrickson L. Poisonings in laboratory personnel and health care professionals. *Am J Emerg Med* 1991;9:11–15.
 30. Englund G, Hallberg P, Artursson P, Michaëlsson K, Melhus H. Association between the number of coadministered P-glycoprotein inhibitors and serum digoxin levels in patients on therapeutic drug monitoring. *BMC Med* 2004;2:8.