AHC Media

Clinical Cardiology

Critical analysis of the latest clinical research in cardiovascular medicine [ALERT]

Vol. 34, Issue 11, November 2015
AHCMedia.com

ABSTRACT & COMMENTARY

Reduced Leaflet Motion in Bioprosthetic Valves: What Does It All Mean?

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

Dr. Zimmet reports no financial relationships relevant to this field of study.

SOURCES: Makkar RR, et al, Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. *N Engl J Med* 2015 Oct 5. [Epub ahead of print].

Holmes DR, Mack MJ. Uncertainty and possible subclinical valve leaflet thrombosis. *N Eng J Med* 2015 Oct 5. [Epub ahead of print].

Laschinger JD, et al. Reduced leaflet motion in bioprosthetic aortic valves — The FDA perspective. *N Eng J Med* 2015 Oct 5. [Epub ahead of print].

Is more information always better? That is one question for cardiologists and regulatory agencies alike since the recent publication of the above report. Transcatheter aortic valve replacement (TAVR) is currently available in the United States with two commercially available bioprostheses: the Edwards Sapien series of bovine balloon-expandable valves and the CoreValve line of self-expanding porcine valves. The PORTICO IDE trial is an ongoing prospective, clinical trial examining the safety and efficacy of another valve — the investigational Portico device — for TAVR. As part of this trial, a prespecified subgroup underwent post-implant CT scans to examine the valve frame. These scans demonstrated the unanticipated finding of reduced leaflet motion in several patients. A detailed analysis of all CT and imaging data ensued, leading also to the formation of two separate registries to evaluate bioprosthetic leaflet function after transcatheter or surgical aortic valve replacement: the Assessment of Transcatheter and Surgical Aortic Bioprosthetic Valve Thrombosis and Its Treatment with Anticoagulation (RESOLVE) registry and the Subclinical Aortic Valve Bioprosthesis Thrombosis Assessed with Four-Dimensional

Financial Disclosure: *Clinical Cardiology Alert*'s editor Michael H. Crawford, MD, peer reviewer Susan Zhao, MD, associate managing editor Jonathan Springston, and executive editor Leslie Coplin report no financial relationships relevant to this field of study.

Clinical Cardiology [ALERT]
Critical analysis of the latest clinical research in cardiovascular medicine

Clinical Cardiology Alert, ISSN 0741-4218, is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850 Atlanta, GA 30326.

GST Registration Number: R128870672. Periodicals Postage Paid at Atlanta, GA, and at additional mailing offices.

POSTMASTER: Send address changes to *Clinical Cardiology Alert*, P.O. Box 550669, Atlanta, GA 30355.

SUBSCRIBER INFORMATION
(800) 688-2421
customerservice@ahcmedia.com
AHCMedia.com

Questions & Comments:
Please contact Associate Managing Editor **Jonathan Springston** at jonathan.springston@ahcmedia.com

Subscription Prices
United States
Print: 1 year with ***free*** *AMA PRA Category 1 Credits™*: $349
Add $19.99 for shipping & handling.
Online only, single user: with ***free*** *AMA PRA Category 1 Credits™*: $299

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at (404) 262-5482.

Back issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of ***2.25*** *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the cardiologist. It is in effect for 36 months from the date of the publication.

AHC Media

Computed Tomography (SAVORY) registry.

The findings thus far are striking. Of the 55 patients in the PORTICO IDE trial with complete contrast CT data, 22 showed reduced aortic leaflet motion. The mix included 16 of 37 with Portico valves, 6 of 14 with Sapien XT valves, and none of the four Corevalve patients. All patients with reduced leaflet motion had hypodense opacities at the base of the corresponding leaflets. The 10 patients from this group of 22 who also underwent transesophageal echo had concordant findings, with echogenic masses on the aortic aspect of the leaflets preventing normal motion.

None of the eight patients who received therapeutic warfarin were found to have reduced leaflet motion, as opposed to more than half of patients on no anticoagulation or antiplatelet agents alone. Moreover, all 11 of the patients who were subsequently placed on therapeutic warfarin recovered normal leaflet motion on follow-up CT, while this was true of only one of 10 patients who did not receive warfarin but had follow-up imaging.

Among the registry patients, the numbers were lower but still significant. Reduced leaflet motion occurred in 17 of 132 patients studied, including 15 of 105 with transcatheter valves and two of 27 with surgical valves. As in the PORTICO patients, none of the 13 patients who happened to be on therapeutic anticoagulation with warfarin had subsequent leaflet motion abnormalities.

The authors concluded that abnormal leaflet motion is reliably detected in a significant proportion of both surgical and transcatheter bioprosthetic aortic valves by volume-rendered CT scans. This phenomenon appears to be effectively prevented and treated by warfarin but not by antiplatelet drugs. These observations, in concert with the imaging findings on the leaflets themselves, suggest a thrombotic cause.

■ COMMENTARY

One important term in the title of this work is "subclinical." Both transcatheter and surgical aortic bioprostheses are routinely followed by transthoracic echocardiogram, which fails to detect the noted phenomenon in most cases. Despite the finding of often-severe restriction of leaflet motion, the mean gradients measured across these valves were not significantly different than those from unaffected valves. Clinically evident bioprosthetic valve thrombosis remains rare with currently available valves and periprocedural care, occurring in less than 1% of cases.

The potential link of subclinical valve thrombosis to stroke is tenuous at best, as the number of events in the combined studies was quite small. However, this clearly deserves more study.

Overall, the clinical data on these valves have not changed — for the most part they remain both effective and safe. The study paper itself, as well as two accompanying editorials, calls for more data to answer a host of questions brought up by these findings. Although it is clearly premature to change practice, I would be surprised if there were not a move to expand the use of warfarin in TAVR patients, at least in patients with higher risk profiles. Ultimately, the meaning and appropriate response to these findings will be answered by further rigorous study. ■

ABSTRACT & COMMENTARY

Beta-blocker Dose More Important Than Heart Rate in Systolic Heart Failure

By Van Selby, MD

Assistant Professor of Medicine, UCSF Cardiology Division, Advanced Heart Failure Section,

San Francisco

Dr. Selby reports no financial relationships relevant to this field of study.

SOURCE: Fiuzat M, et al. Heart rate or beta-blocker dose? Association with outcomes in ambulatory heart failure patients with systolic dysfunction: Results from the HF-ACTION trial. *JACC: Heart Failure* 2015. doi:10.1016/j.jchf.2015.09.002.

Beta-blockers reduce both morbidity and mortality in chronic heart failure with reduced ejection fraction (HFrEF). More recently, heart rate (HR) reduction has been associated with better outcomes in HFrEF. Fiuzat et al aimed to determine whether higher beta-blocker doses or reduced HR has a greater impact on outcomes in chronic HFrEF.

To compare the relative effects of HR reduction and higher beta-blocker dose, they performed a secondary analysis of the HF-ACTION trial. HF-ACTION randomized 2331 patients with ambulatory NYHA functional class II-IV heart failure and left ventricular ejection fraction < 35% to exercise training vs usual care. Patients were on stable doses of heart failure therapies for at least 6 weeks prior to study enrollment, with 94.5% receiving beta-blockers. Secondary analysis patients were categorized as either high (≥ 25 mg/day of carvedilol equivalent) or low beta-blocker dose and high (≥ 70 bpm) or low HR. The primary endpoint was the composite of death or all-cause hospitalization, and median follow-up was 2.5 years.

In unadjusted analyses, both higher beta-blocker dose and lower HR were associated with reduced risk of death or hospitalization. However, after adjusting for other predictors, only higher beta-blocker dose was significantly associated with the primary outcome (hazard ratio 0.77; $P = 0.03$). Higher beta-blocker dose was associated with improved outcomes regardless of the achieved HR. There was no increased risk of bradycardia among patients on higher doses of beta-blockers. The authors concluded that in HFrEF, titrating beta-blocker doses may confer a greater benefit than reducing HR.

■ COMMENTARY

Multiple large randomized trials have shown that treatment with beta-blockers leads to symptomatic improvement, reduced hospitalization, and increased survival in HFrEF. These trials generally targeted high doses, and as a result current guidelines recommend treatment with moderate to high doses of beta-blockers in HFrEF. However, evidence of a strong dose-response relationship for beta-blockers is somewhat limited, and one meta-analysis found no association between beta-blocker dose and outcome. The findings from the current analysis show that patients with higher beta-blocker doses have a lower risk of hospitalization or death, even after adjusting for other clinical predictors, and support the current recommendations.

Despite clear guideline recommendations, multiple studies have found that most patients with HFrEF are not titrated to target doses. There are many reasons for this, including concern for side effects, health system barriers that prevent easy medication titration, and possibly a lack of clear evidence that outcomes improve at higher doses. With the recent FDA approval of ivabradine, clinicians may be tempted to keep beta-blockers at lower doses and instead initiate ivabradine to achieve HR goals in patients with HFrEF. Ivabradine effectively lowers HR without many of the side effects associated with beta-blockers, and does not affect blood pressure. The findings of Fiuzat and others remind us that such practices are unacceptable for patients with HFrEF. Beta-blockers have beneficial effects in HFrEF beyond lowering HR, and titrating to target doses must be considered the first-line treatment.

This was a post-hoc analysis with several limitations. It is possible that patients on lower doses of beta-blockers were sicker, and therefore unable to tolerate target doses. The authors adjusted for many clinical characteristics, but residual confounders are a possibility. Furthermore, this study did not evaluate the strategy of using a non-beta-blocking medication such as ivabradine to lower HR; rather, it studied the association between baseline HR and outcomes.

Certain strategies can help reach target beta-blocker doses, and there are published guidelines to help increase the chance of successful up-titration. Always start with low doses (i.e., carvedilol 3.125 mg twice per day), and there should be minimal or no evidence of fluid retention when beta-blockers are initiated or up-titrated. Patients should be instructed to check their weight every morning after every dose increase to identify worsening fluid retention, and they should be advised that any initiation or dose increase may be associated with mild worsening of heart failure symptoms that often resolves after several weeks. A growing body of literature shows the importance of reaching target doses of beta-blockers in HFrEF. It can be difficult at times, and may require close monitoring. Nevertheless, given the clear benefit this must be the goal for all HFrEF patients. The approval of ivabradine will be a useful addition for a small portion of HFrEF patients, but absolutely cannot substitute for higher beta-blocker doses in those patients who can tolerate it. ■

ABSTRACT & COMMENTARY

Slow Down, Save Lives? Rate Control in Atrial Fibrillation

By Cara Pellegrini, MD

Assistant Professor of Medicine, UCSF; Cardiology Division, Electrophysiology Section, San Francisco VA Medical Center

Dr. Pellegrini reports no financial relationships relevant to this field of study.

SOURCE: Chao TF, et al. Rate-control treatment and mortality in atrial fibrillation. *Circulation* 2015;132. [Epub ahead of print].

National guidelines emphasize the importance of rate control in the long-term management of atrial fibrillation (AF). Yet, there are limited data to support whether use of rate control agents impacts survival in AF patients, and there are no evidence-based data to guide choice of rate control agent. Chao et al have performed a large observational population study utilizing a Taiwanese nationwide AF cohort culled from a database that houses detailed healthcare information from > 99% of Taiwan's population. They compared mortality rates across AF patients who were receiving a single atrioventricular (AV) nodal blocking agent — 43,879 on beta-blockers (BBs), 18,466 taking calcium channel blockers (CCBs), and 38,898 receiving digoxin — with a 168,678 patient reference group who were not taking any rate control agents. Patients with combinations of AV nodal agents were excluded from the study. Propensity matching was performed to try to minimize confounding.

The mean age of patients was 70 ± 13 years and 56% were male. There were significant differences between groups with regard to age, sex, comorbidities, medications, degree of urbanization, and income level. Significantly more patients receiving digoxin had heart failure and there were fewer receiving antiarrhythmic medications in that group. Over a follow-up of 4.9 ± 3.7 years, about one-third of patients died. After adjustment for baseline characteristics, there were significant differences in mortality, with those receiving BBs having a 24% lower risk of death compared to no agent, those on CCBs having a 7% lower risk, and those taking digoxin displaying a 12% excess risk of mortality compared to those on no rate control agent. There appeared to be a dose effect, as risks were proportional to percentage of time using the drug; those receiving BBs more frequently had a lower mortality risk than those with less frequent usage, and the highest mortality was observed among those with the highest usage of digoxin. Propensity matching did not change results substantively. The authors concluded that AF patients receiving BBs or CCBs had lower risk of mortality compared to those not taking rate-control drugs, with the lowest mortality rate in the BB group, while digoxin use was associated with a higher risk of mortality.

■ COMMENTARY

The biggest limitation of this study is obviously its observational, non-randomized nature. As mentioned, the groups differed in multiple ways at baseline and very possibly these differences, which may have impacted the selection of rate control agents, played a much larger role than the agents themselves in the mortality differences observed. The authors attempted to control for this with the propensity analysis, which aims to account for the differences among participants that determine which treatment they receive, thereby making the groups more comparable. The similar findings after performing propensity matching are somewhat reassuring. Perhaps more convincing is the dose effect observed. If it were aspects of their heart failure that were poorly adjusted for in the analysis that made patients who happened to be receiving digoxin perform worse, why was there such a good match between digoxin exposure and severity of outcome? Was it really all mediated by an aspect of heart failure that both made more digoxin exposure more likely and the patient more likely to die sooner, or perhaps did the digoxin have something to do with it?

Additional limitations of this study include the absence of data on left ventricular ejection fractions, which could have helped adjust for heart failure differences more granularly, as well as data on type of AF — paroxysmal or persistent — which also could have impacted outcomes. The dosages of the rate control agents were not provided. Were higher doses of BBs needed to achieve the positive outcomes observed? Most notably, there was no indication of how well these agents did at controlling heart rates in the study population; it certainly would have been interesting to see how differences in heart rate might have related to

(or perhaps mediated) the mortality associations observed.

There is biologic plausibility for this study's findings. BBs were the most efficacious agent at heart rate lowering in AF patients in the large AFFIRM trial, and have many pleiotropic effects that could positively impact life expectancy. Another study, RATAF, sought to compare the heart rate control attained by various AV nodal blocking agents, and found diltiazem to be the most effective, giving support to the idea of CCBs' mortality impact via good heart rate control. Other studies have been quite mixed with regard to the potential harm or lack thereof in digoxin use for patients with AF. Clearly, a randomized trial would be most helpful. In its absence, I would still individualize treatment choice based on a patient's comorbidities, tolerances, and other factors. In the absence of other indications for digoxin, I would avoid it for AF rate control. ■

ABSTRACT & COMMENTARY

Finally, a Positive Outcomes Study for Platelet Function Testing

By Jeffrey Zimmet, MD, PhD

Associate Professor of Medicine, University of California, San Francisco; Director, Cardiac Catheterization Laboratory, San Francisco VA Medical Center

Dr. Zimmet reports no financial relationships relevant to this field of study.

SOURCE: Valenti R, et al. Prasugrel in clopidogrel nonresponders undergoing percutaneous coronary intervention: The RECLOSE (REsponsiveness to CLOpidogrel and StEnt Thrombosis) 3 Study. *JACC Cardiovasc Interv* 2015 Sept 9. pii:S1936-8798(15)01138-3.

For years, clopidogrel has been the mainstay of dual antiplatelet therapy following coronary stent implantation. Clopidogrel is a prodrug, however, and its conversion to the active drug is highly variable across patient populations. We have known for some time that patients who respond poorly to clopidogrel have higher event rates post-myocardial infarction and post stent. Despite this observation, as well as the ready availability of tests to determine which patients have high residual platelet reactivity on clopidogrel, no trial to date has been able to demonstrate a positive effect of platelet function testing-guided therapy on clinical outcomes. The recent availability of more potent antiplatelet agents, including prasugrel and ticagrelor, has improved the ability to treat clopidogrel nonresponders effectively.

Enter the RECLOSE-3 trial. In this study, Valenti et al screened 1550 patients undergoing percutaneous coronary intervention (PCI) with light transmittance aggregometry, of whom 302 were deemed to be clopidogrel nonresponders. This subset was subsequently switched to prasugrel 10 mg, after which all but 26 patients had a markedly improved antiplatelet response. The primary endpoint was a composite of cardiac death, myocardial infarction, urgent coronary revascularization, and stroke at 2-year follow-up. Stent thrombosis and the individual components of the composite were followed as secondary endpoints. Outcomes for patients from RECLOSE-3 were compared with those from the earlier RECLOSE 2-ACS trial, which had a similar design but included only acute coronary syndrome patients, and switched clopidogrel nonrespondeers to either high-dose clopidogrel or to ticlopidine (which are less effective than prasugrel at overcoming clopidogrel resistance).

Two-year mortality was lower in the RECLOSE-3 patients who took prasugrel compared with the RECLOSE 2-ACS nonresponders (4% in the RECLOSE-3 study vs 9.7% in nonresponders of the RECLOSE 2-ACS study, $P = 0.007$). This difference held true even when examining only the subset of patients with acute coronary syndromes (all of the RECLOSE 2-ACS patients, but only 42% of the RECLOSE-3 patients). Rates of cardiac death and of definite/probable stent thrombosis were also significantly lower in the prasugrel-treated RECLOSE-3 population. While major bleeding events were not different, minor bleeding was unsurprisingly higher in RECLOSE-3 than in RECLOSE 2-ACS nonresponders (5.3% vs 1.2%; $P = 0.009$).

The authors concluded that platelet function testing-defined clopidogrel nonresponsiveness can be overcome by prasugrel treatment, and that this is a modifiable risk factor whose treatment can improve outcomes.

■ COMMENTARY

Researchers have long known that clopidogrel is plagued by a significant number of patients with high on-treatment platelet reactivity, and that these patients have higher cardiac event rates compared with patients having a more robust clopidogrel response. Why, then, have previous trials failed to show a positive effect of platelet testing on cardiac outcomes? For older trials, the answer lies in the lack of good options for overcoming clopidogrel resistance. The randomized GRAVITAS trial, like RECLOSE 2-ACS, used high-dose clopidogrel in the treatment arm, and failed to show a treatment effect, compared with standard-dose clopidogrel. We know from pharmacodynamic studies, however, that simply doubling the dose of clopidogrel does not effectively overcome resistance in true clopidogrel nonresponders. The only large randomized platelet function testing trial to use prasugrel in the intervention arm was the TRIGGER PCI study, which enrolled only low-risk elective PCI patients, and had an event rate in both arms that was simply too low to show a treatment effect.

RECLOSE-3 was not a randomized trial, but rather compared 2-year outcomes in prasugrel-treated patients with those from the earlier RECLOSE 2-ACS trial in which clopidogrel nonresponders were treated with less-effective therapy. The potential problems with this approach are obvious and are acknowledged by the authors. Nonetheless, the outcome difference appears both robust and plausible. Concluding that clopidogrel resistance can be effectively overcome by switching to the more-potent drug seems quite reasonable.

Should we, then, invest in platelet function testing for all of our PCI patients? This is one interpretation of the data, but I believe most would say no. We already know that unselected ACS patients have lower event rates when treated with the more potent antiplatelet agents (prasugrel and ticagrelor, studied in the TRITON and PLATO trials, respectively) as compared with clopidogrel. Why not simply recommend, like the European Society of Cardiology, that the more-potent agents be preferred over clopidogrel in ACS? Platelet testing could alternatively be invoked in order to identify those higher-risk patients who respond well to clopidogrel, and could therefore be maintained on the less-expensive drug. We already know from TRIGGER and other studies that lower-risk elective PCI patients do well on clopidogrel, even among the so-called clopidogrel nonresponders. So in the end, while RECLOSE-3 is an important milestone, it is unlikely to change practice substantially. ■

ABSTRACT & COMMENTARY

Blood Pressure Targets in Flux Again

By Michael Crawford, MD, Editor

SOURCE: Press release from the National Institutes of Health (NIH). Landmark NIH study shows intensive blood pressure management may save lives. Available at http://www.nih.gov/news/health/sep2015/nhlbi-11.htm. Accessed on Sept. 11, 2015.

The Systolic Blood Pressure Intervention Trial (SPRINT) study compared pharmacologic systolic blood pressure lowering to < 120 vs 120-140 mmHg in more than 9300 subjects > 50 years of age with hypertension and at least one additional risk factor for heart disease or who have kidney disease.

The study population was diverse and included women, racial/ethnic minorities, and the elderly. The study excluded patients with diabetes, prior stroke, or polycystic kidney disease. The trial, which began in 2009, ended early due to the significant results that showed achieving a systolic blood pressure < 120 mmHg was associated with reduced rates of cardiovascular events, such as myocardial infarction, heart failure, and stroke, by almost one-third and the risk of death by almost one-quarter, as compared to the target systolic pressure of 120-140 mmHg.

The 120-140 group needed an average of two drugs to achieve this goal and the < 120 group required an average of three drugs. Lawrence Fine, MD, chief, Clinical Applications and Prevention Branch at the National Heart, Lung, and Blood Institute concluded on behalf of the investigators that, "Our results provide important evidence that treating blood pressure to a lower goal in older or high-risk patients can be beneficial and yield better health results overall."

■ COMMENTARY

At the time the trial began, the systolic blood pressure targets were < 140 mmHg for otherwise healthy adults and < 130 mmHg for those with diabetes or kidney disease. Also, when this study began, the results of the Hypertension in the Very Elderly (HYVET) trial had been released. This trial of patients > 80 years of age also ended early

because of the significant 21% reduction in all-cause mortality, 30% reduction in stroke, 64% reduction in heart failure, and 34% reduction in all cardiovascular events, when systolic blood pressure was treated to a goal of < 150/80 mmHg using a thiazide diuretic with the addition of an ACE inhibitor when necessary.[1] A meta-analysis of all the trials by Bangalore et al showed that reducing systolic blood pressure below 130 may be beneficial in stroke and kidney disease prevention, but not other cardiovascular endpoints.[2] Hence, the various guidelines published subsequently have not recommended aggressive systolic blood pressure lowering (< 120). Thus, this trial could be a game changer if the results are robust.

[Unfortunately, the trial has not yet been published in a peer-reviewed journal, we don't know the upper age cut off, and we don't know what the complications of lowering systolic blood pressure to < 120 were in high-risk patients.]

Unfortunately, at this time we only have the press release, as the trial has not been published in a peer-reviewed journal yet. Also, researchers provided no upper age cut off, so we don't know how many were > 80 years of age and what their results were. Additionally, we don't know what the complications of lowering systolic blood pressure to < 120 were in these high-risk patients. It is well known that excessively low blood pressure can precipitate strokes or myocardial infarctions in some patients with extensive atherosclerosis. Perhaps that is why Dr. Fine provided this caveat: "But patients should talk to their doctor to determine whether this lower goal is best for their individual care." Indeed. ■

REFERENCES

1. Beckett NS, et al. Treatment of hypertension in patients 80 years of age or older. *N Engl J Med* 2008 May 1;358:1887-98. doi:10.1056/NEJMoa0801369. Epub 2008 Mar 31.
2. Bangalore S, et al. Blood pressure targets in subjects with type 2 diabetes mellitus/impaired fasting glucose: Observations from traditional and bayesian random-effects meta-analyses of randomized trials. *Circulation* 2011;123:2799-2810.

United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Clinical Cardiology Alert	0 7 4 1 – 4 2 1 8	10/1/15
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$349.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*
950 East Paces Ferry Road NE, Ste. 2850, Atlanta
Fulton County, GA 30326-1180
Contact Person: Peter Balch
Telephone: 404-262-5434

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
950 East Paces Ferry Road NE, Ste. 2850, Atlanta, GA 30326-1180

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
AHC Media LLC, David Fournier, President and CEO
950 East Paces Ferry Road NE, Ste. 2850, Atlanta, GA 30326-1180

Editor *(Name and complete mailing address)*
Leslie Coplin, same as above

Managing Editor *(Name and complete mailing address)*
Jonathan Springston, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
AHC Media LLC	950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180
David Fournier	950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180
Bethany Schilling	950 East Paces Ferry Road NE, Ste 2850, Atlanta, GA 30326-1180
Lone Peak Capital Group, LLC	79 West Paces Ferry Road, Suite 200-A, Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☒ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526,** October 1999 *(See Instructions on Reverse)*

13. Publication Title: Clinical Cardiology Alert	14. Issue Date for Circulation Data Below: September 2015	
15. **Extent and Nature of Circulation**	**Average No. Copies Each Issue During Preceding 12 Months**	**No. Copies of Single Issue Published Nearest to Filing Date**
a. Total Number of Copies *(Net press run)*	357	332
b. Paid and/or Requested Circulation (1) Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	303	283
(2) Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
(3) Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	17	14
(4) Other Classes Mailed Through the USPS	8	4
c. Total Paid and/or Requested Circulation *[Sum of 15b. (1), (2),(3),and (4)]*	328	301
d. Free Distribution by Mail *(Samples, complimentary, and other free)* (1) Outside-County as Stated on Form 3541	9	11
(2) In-County as Stated on Form 3541	0	0
(3) Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or other means)*	5	5
f. Total Free Distribution *(Sum of 15d. and 15e.)*	14	16
g. Total Distribution *(Sum of 15c. and 15f)*	342	317
h. Copies not Distributed	15	15
i. Total *(Sum of 15g. and h.)*	357	332
j. Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*	96%	95%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2015 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: *David R. Fournier* Publisher & CEO — Date: 09/10/2015

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or, if the publication is not published during October, the first issue printed after October.
6. In item 16, indicate the date of the issue in which this Statement of Ownership will be published.
7. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of Periodicals authorization.

PS Form **3526,** October 1999 *(Reverse)*

QUESTIONS & COMMENTS:
Contact Jonathan Springston, Associate Managing Editor, at (404) 262-5416 or email at jonathan.springston@ahcmedia.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right, or log on to **AHCMedia.com** and click on My Account. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be emailed to you instantly.

CME QUESTIONS

1. **A large observational population study of patients with atrial fibrillation showed that which of the following was associated with higher mortality?**
   a. Digoxin
   b. Beta-blockers
   c. Rate-lowering calcium blockers
   d. No rate lowering drug use

2. **When clopidogrel non-responders by platelet aggregometry were switched to prasugrel in a recent post-PCI trial, compared to those who received double-dose clopidogrel or ticlopidine in a prior trial, which of the following was observed?**
   a. More major bleeding
   b. More minor bleeding
   c. Higher total mortality
   d. Higher cardiac mortality

3. **A secondary analysis of a recent trial of beta-blockers for heart failure with reduced ejection fraction showed that adjusted mortality and re-hospitalization were least when:**
   a. beta-blockers were titrated to heart rates < 70 bpm.
   b. high doses of beta-blockers were used.
   c. when heart rates < 55 bpm were avoided.
   d. vasodilator beta-blockers were used.

4. **CT scans of recently implanted bioprosthetic valves has shown:**
   a. commissural edge thickening.
   b. Lambl's excrescences.
   c. sinus of Valsalva thrombi.
   d. all of the above.

5. **A recent press release from the SPRINT announced that systolic blood pressure goals for all apparently healthy individuals > age 50 should be?**
   a. < 150 mmHg
   b. < 140 mmHg
   c. < 130 mmHg
   d. < 120 mmHg

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the most current information related to cardiac illness and the treatment of cardiac disease;
- explain the advantages and disadvantages, as well as possible complications of interventions to treat cardiac illness;
- discuss the advantages, disadvantages, and cost-effectiveness of new and traditional diagnostic tests in the treatment of cardiac illness; and
- discuss current data regarding outpatient care of cardiac patients.