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Case Reports

Spontaneous subdural hematoma and antiplatelet therapy: Does efficacy of Ticagrelor come with added risk?

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ABSTRACT

Antiplatelet therapy has established clinical benefit on cardiovascular outcome and has reduced the rates of re-infarction/in stent thrombosis following percutaneous coronary intervention in acute coronary syndromes. Major bleeding episodes can occur with antiplatelet therapy and intracranial hemorrhage (ICH) is one of the most feared complications resulting in significant morbidity and mortality. Identification of high risk groups and judicious use of antiplatelet therapy reduces the bleeding risk. Ticagrelor is a newer P2Y12 receptor antagonist with established clinical benefit. However, risks of having an ICH with these newer molecules cannot be ignored. Here, we report a case of spontaneous acute subdural hematoma developing in a patient on antiplatelet therapy with aspirin and ticagrelor. Early recognition, discontinuation of the medication and appropriate management resulted in resolution of hematoma and good clinical outcome. Authors have reviewed the antithrombotic drugs and their tendencies in causing intracranial bleeds from a neurophysicians perspective.

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1. Introduction

In the recent times, early intervention strategies and advances in antiplatelet therapy have reduced the risk of recurrent coronary events and mortality in patients with acute coronary syndromes (ACS). Antiplatelet therapy has been proven of major clinical benefit in cardiovascular clinical trials and is routinely prescribed in secondary prevention. However, major bleeding is a life threatening complication of triple antiplatelet therapy, and it can increase the risk of in-hospital death by 60%.[1] Also, major bleeding episodes can adversely affect long-term prognosis by increasing the 1-year mortality and re-infarction rates by five-fold.[2] Some patient subsets are at increased risk of having a major bleed. Ticagrelor is a newer reversible P2Y12 receptor antagonist, reported to be more effective than existing antiplatelet therapies with a similar safety profile.[3] However, long-term safety data are still awaited. Here, we report a 58-year-old male who developed spontaneous acute subdural hematoma (SDH) on antiplatelet therapy with Aspirin and ticagrelor following percutaneous coronary intervention (PCI) for a cardiac event and placing a drug eluting stent.

2. Case report

This 58-year-old male without any previous history of ischemic heart disease was admitted to the cardiology services with history of retrosternal burning pain of 4 h duration. He was a diabetic, and was on oral hypoglycemic agents for 16 years. He denied smoking and was normotensive.

He was hemodynamically stable with a heart rate of 92 beats per minute and blood pressure of 150/80 mmHg. Cardiovascular examination was unremarkable. His electrocardiogram showed sinus rhythm without any acute ST-T wave changes and features of left ventricular hypertrophy. Serial cardiac biomarkers were negative, (Troponin T – 0.019 ng/ml (0 h), <0.010 ng/ml (6 h) respectively). Transthoracic echocardiography was normal. He was diagnosed to have unstable angina and was started on glycoprotein IIb/IIIa inhibitors, antiplatelets, statins, and insulin. Coronary angiogram done subsequently revealed single vessel coronary artery occlusive disease. Left main coronary artery was normal. Left anterior descending artery was a type III vessel with 40% occlusive lesion in mid D1 segment. Left circumflex artery (LCX) was non-dominant with 80% lesion after major OM1. Right coronary artery was dominant without any disease. Successful Percutaneous Transluminal Coronary Angioplasty (PTCA) and stenting were done to mid LCX with Supraflex® (Cobalt Chromium Sirolimus eluting Stent system) stent of a caliber 3.0 mm × 16 mm. Patient had uneventful recovery following the procedure, and he was discharged on day 5 with a multitude of drugs including Aspirin, Ticagrelor, Statins, Angiotensin Converting Enzyme inhibitors, Ranolazine, Nikorandil, Insulin, and Proton pump inhibitors. He was advised a periodic follow-up.

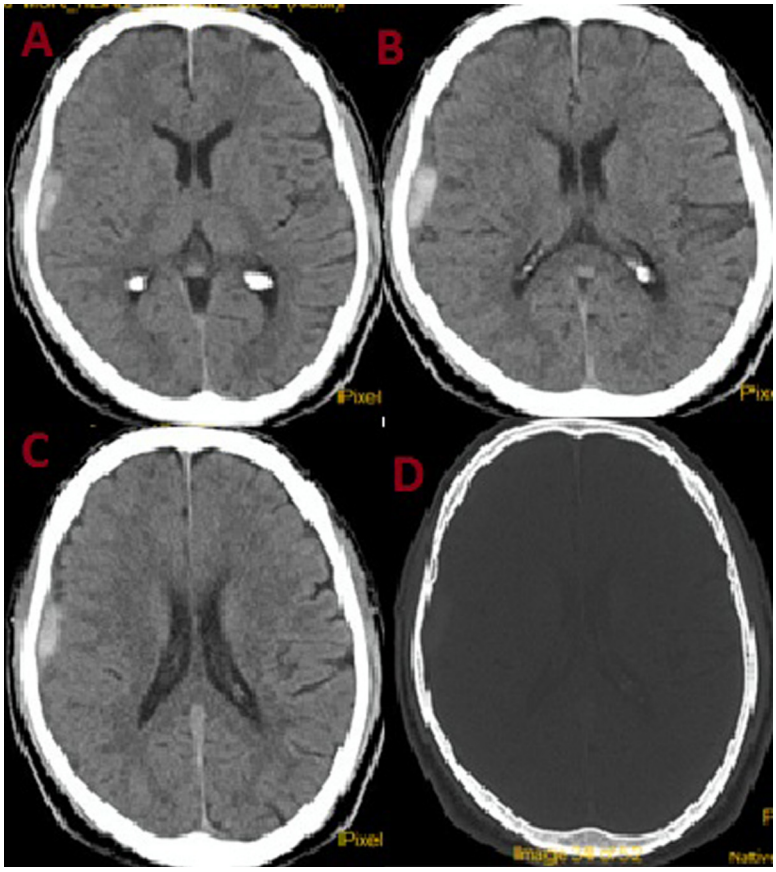

Fig. 1 – CT head plain axial view. (A–C) A right temporoparietal acute subdural hematoma, mild mass effect with effacement of sulci and (D) intact calvaria on bone windows.

Six weeks on antiplatelet therapy, the patient presented with progressively increasing right hemicranial headache of 10 days duration involving the right temporoparietal and frontal region. It was of throbbing type, present throughout the day and was associated with nausea and vomiting. He had no diplopia, blurring of vision, seizures, loss of consciousness, or limb weakness. He did not complain of hematemesis, hematuria, melena or bleeding per rectum. He denied any history of head trauma. He was evaluated by the neurology team and admitted for further management.

Clinical examination revealed a conscious, irritable patient with stable hemodynamic parameters. There was no papilloedema or cranial nerve involvement. He did not have any lateralizing neurodeficits. Routine blood investigations including hemogram, coagulation parameters, liver function, and renal function tests were normal. Cardiac evaluation including electrocardiogram, transthoracic echocardiography, and cardiac biomarker levels were normal. Noncontrast computed tomography (CT scan) on head revealed a right temporoparietal acute SDH (Fig. 1). There was no evidence of fracture or external contusion. Rest of the brain parenchyma was normal. This patient had a spontaneous acute right temporoparietal SDH.

A neurosurgical consultation was sought, and the patient was planned for conservative therapy and observation. He was monitored for progression of intracranial hematoma. As he was on antiplatelet therapy and developed an intracranial bleed, a decision was made to stop ticagrelor. He continued to receive aspirin and was added on clopidogrel, as cardiologists felt that stopping all of the antiplatelet drugs could have been too risky. He was started on analgesics, followed by short course of steroids and head end elevation. Headache reduced on day 4 of therapy, and he was discharged. Repeat CT brain on day 7 revealed a resolving hematoma as shown in Fig. 2. He remained asymptomatic at 90-day follow-up.

3. Discussion

Intracranial hemorrhage (ICH) is the most feared bleeding complication known to occur in a patient on antiplatelet therapy following PCI. Here, we describe a case of spontaneous acute SDH in a patient with ischemic heart disease on antiplatelet therapy with Aspirin and Ticagrelor following PCI. He recovered with no residual neurological deficits. Timely withdrawal of ticagrelor resulted in resolution of hematoma and improvement in the patient symptoms. Early recognition of this complication with appropriate management resulted in a good outcome in this patient.

Bleeding complications after antiplatelet therapy have been long recognized and well-studied in large randomized trials. They constitute a key safety end point in all clinical trials assessing newer antiplatelet drugs in ACS.[4] In clinical trials, major bleeding is reported in 1–10% of all patients on antiplatelet therapy, and it is a cause of significant morbidity and mortality.[5] The factors predisposing to increased risk of

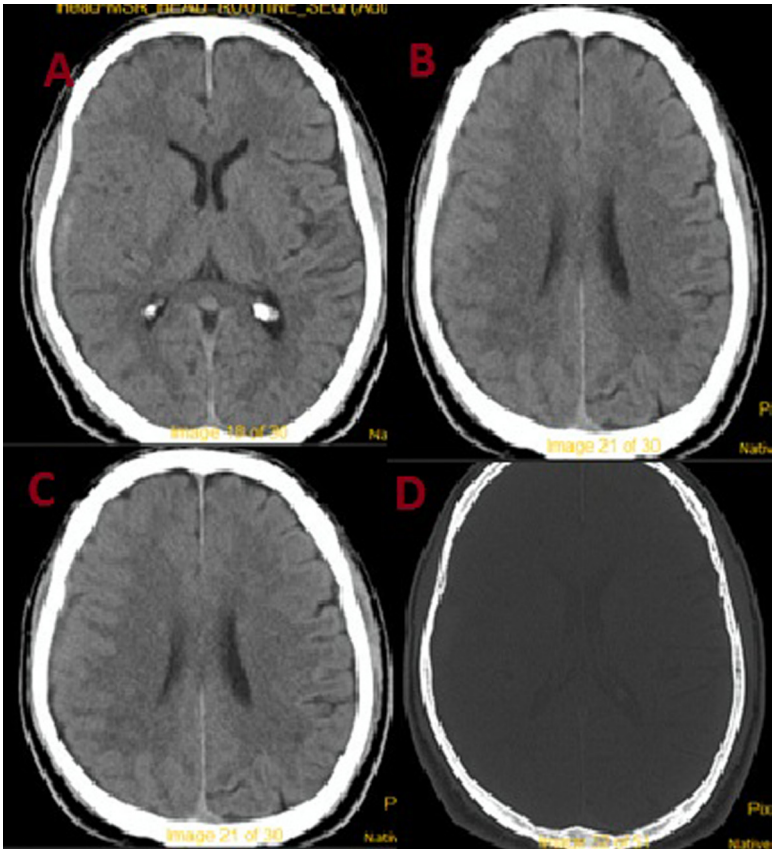

Fig. 2 – Repeated CT after a week. CT head plain axial view. (A–C) Resolving subdural hematoma and (D) intact calvaria on bone windows.

having a major bleed are elderly patients, female sex, low body weight, impaired renal function, base line anemia, and previous history of intracerebral haemorrhage.[6] It is interesting to note that ICH is uniformly classified as fatal/life threatening bleeding as per PLATO,[7] TIMI,[8] and GUSTO[9] trial definitions, though definition of a major bleed varies from trial-to-trial. Occurrence of ICH in turn is associated with increased risk of mortality and residual neurological deficit. Though a five-fold increase in risk of mortality/re-infarction rates at 1-year follow-up has been reported, causal link between bleeding and recurrent ischemic event is not proven.[2]

Connolly et al.[10] analyzed the risk of SDH in patients on aspirin therapy. In 4 published trials with 6565 participants, 8 cases of SDH were reported. Also in another 5 large unpublished series (90,689 participants), 18 cases of SDH were recognized. The published incidence of SDH was 0.02/1000 patient years on aspirin with pooled odds ratio of 1.6, suggesting that Aspirin was a safe antiplatelet therapy. Wong et al.[11] observed that incidence of lobar hematoma was more (32.8%) in aspirin users compared to control groups (10.3%), and this was statistically significant.

Bakheet et al.[12] have reported on a meta-analysis of 11 randomized trials analyzing the incidence of SDH in patients on dual antiplatelet therapy (with Aspirin and Clopidogrel). Though 8 trials did not show any case of SDH, 3 trials involving 23,136 participants reported 39 cases of SDH. They concluded that there was no increased absolute risk of SDH in-patient on dual antiplatelet therapy. However, there was an increased risk noted in Aspirin and Clopidogrel sub-group compared to Aspirin alone group.

Ticagrelor is a newer reversible P2Y12 receptor antagonist which is reported to have good cardiovascular outcome in

Table 1 – Antiplatelet therapy in cardiovascular trials and risk of intracranial hemorrhage.

Drug & dose	Risk of ICH	Monitoring	Activity reversal in surgical emergency	Comments
Aspirin 81–325 mg	Absolute annual risk of 0.03%[19]	NA	DDAVP, platelets, cryoprecipitate, EACA, fresh frozen plasma	Increases the risk of ICH 1.65-fold. Association is not statistically significant
Prasugrel 60 mg bolus, 10 mg OD	0.4%[20]	NA	NA	Increased risk of intracranial bleed
Clopidogrel loading dose: 600 mg, 75 mg maintenance	0.33%[21]	NA	DDAVP, platelet transfusion	No effective tests to depict the drug level during acute bleeding
Aspirin + Clopidogrel 75 mg + 75 mg with placebo and aspirin 75 mg	Aspirin + clopidogrel 0.3% vs. aspirin[22] alone 0.3%. RR: 0.96	NA	DDAVP, cryoprecipitate, EACA, fresh frozen plasma	Dual therapy has no statistically increased risk of ICH
Aspirin + Clopidogrel + Tirofiban	RR similar to ASP + clopidogrel[23]	Platelet /ACT/aPTT	Compression over access site, platelet transfusion	ISARCOOL trial did not show any increase in ICH risk
Ticagrelor 90 mg, 180 mg	0.3%[13]	NA	NA	Fatal ICH in ticagrelor group was higher compared to clopidogrel group
Unfractionated heparin 5000 IU	0.7%[24]	aPTT	Protamine sulfate	Safe, long term use risks thrombocytopenia
Enoxaparin 40 mg	0.8%[24]	aPTT, PT, anti-Xa activity	Protamine sulfate	Caution while switching over from enoxaparin to oral anticoagulants
Abciximab 0.25 mg/kg IV bolus, later 0.125 μg/kg/min for 12 h	0.07%[25]	aPTT/ACT	Compression over arterial access site, fresh platelet transfusion	Safety profile similar to heparin
Warfarin 2.5–5 mg	1.8%/year (>75 years), 0.6%/year (<75 years)[26]	PT/INR	Vitamin K, FFP	Commonest cause of drug induced ICH in practice
Acenocoumarol 2 mg, 3 mg, 5 mg	ICH risk 0.2% per year[27]	PT/INR	Vitamin K, FFP	Concomitant use of antiplatelets with anticoagulation associated with increased risk of bleeding
Dabigatran 150 mg, 110 mg	0.31%[28]	NA	NA	Safer than warfarin in ICH risk. However, risk of major bleed higher than warfarin
Rivaroxaban 20 mg	0.5%[29]	NA	NA	Safer than warfarin (0.5% vs. 0.7%, $p = 0.02$)
Apixaban 5 mg	0.24%[30]	NA	NA	Safer than warfarin

multiple randomized trials. Platelet inhibition and patient outcome trial (PLATO)[7] was a randomized, double-blind parallel group, multicentric clinical study comparing efficacy of Ticagrelor and Clopidogrel in 18,624 participants with ACS. Rates of major bleeding in both the groups were similar. ICH was seen in 27 cases (0.3%) in the Ticagrelor arm and 14 cases (0.2%) in the Clopidogrel arm ($p = 0.08$). However, fatal outcomes secondary to bleed were more in Ticagrelor group (11 cases – 0.12%) when compared to Clopidogrel group (1 case – 0.0%) ($p = 0.02$).[13] Though risks of ICH were not statistically significant, mortality was higher in the Ticagrelor group (relative risk – 5.47). Bleeding events resulted in permanent discontinuation of ticagrelor compared to clopidogrel (2.4% vs. 1%, $p < 0.001$). However, this trial reported a net clinical benefit (a composite end point of cardiovascular death, myocardial infarction, stroke, and major bleeds) that favored Ticagrelor over Clopidogrel ($p = 0.026$). However, neurophysicians are cautious in patients on these medications as there is no reversal agent available[14] to counteract bleeding due to ticagrelor in life threatening bleeds and monitoring their activity is an uphill task.

Antiplatelet therapy is known to improve cardiovascular outcomes in ACS. Table 1 depicts the relative risks of having an ICH on the commonly used antiplatelet therapies. Strategies recommended[15] to reduce bleeding complications include use of low dose aspirin, restricting the use of theinopyridine therapy following PCI to 2 weeks for angioplasty, for 4 weeks in cases of bare metal stent insertion, and for 12 months if DES is placed. Peterson et al.[16] in their study noted that for every 10% increase in adherence to guidelines, there is a possible 10% reduction in mortality.

Unfortunately, there are no data on volume, location of hematoma, and different ICH subtypes in patients with antiplatelet therapy associated ICH. Volume of hematoma is the single-most important predictor of clinical outcome in patients with ICH.[17] Furthermore, elderly people have a higher risk of fall, with 30% of people older than 65 and 50% of people older than 80 falling at least once a year,[18] increasing the risk of traumatic brain injury. Patients on antiplatelet therapy may have higher risk of having a large volume ICH and thus indirectly contributing to the poorer outcome in such scenarios.

To the treating neurophysicians, newer antiplatelet therapies throw newer challenges. They are more potent, their actions are difficult to monitor and there are no reversal agents available if needed in case of neurosurgical emergencies. Stopping these drugs in a perioperative setting may be equally hazardous on one hand; achieving hemostasis during emergency neurosurgical intracranial interventions is more difficult on the other. Though it is advantageous to have an antiplatelet medication, which does not require regular monitoring of its effect, same can sum up as a disadvantage, when the patient develops an intracranial bleed requiring neurosurgical intervention and monitoring needs priority. Hence, caution needs to be exercised in prescribing these medications to optimize the therapeutic benefits.

4. Conclusion

This case depicts a possible association of spontaneous acute SDH and antiplatelet therapy with aspirin and ticagrelor. Though Ticagrelor is found to be superior to other ADP antagonists in reducing cardiovascular morbidity, it has increased risk of life threatening ICH compared to clopidogrel. Treating cardiologist must identify patient subsets with increased risk of bleeding while prescribing antiplatelet therapy and design appropriate treatment strategies to improve clinical outcome.

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Segev A, Strauss BH, Tan M, et al. Predictors and 1-year outcome of major bleeding in patients with non-ST-elevation acute coronary syndromes: insights from the Canadian Acute Coronary Syndrome Registries. *Am Heart J*. 2005;150:690–694.
2. Fitchett D. The impact of bleeding in patients with acute coronary syndromes: how to optimize the benefits of treatment and minimize the risk. *Can J Cardiol*. 2007;23:663–671.
3. US Food and Drug Administration. *The FDA ticagrelor review of complete response*. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000TOC.cfm [accessed 10.05.12].
4. Becker RC, Bassand JP, Budaj A, et al. Bleeding complications with the P2Y12 receptor antagonists clopidogrel and ticagrelor in the PLATelet inhibition and patient Outcomes (PLATO) trial. *Eur Heart J*. 2011;32:2933–2944.
5. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation*. 2011;123:2736–2747.
6. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. *Circulation*. 2006;114:774–782.
7. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
8. Antman EM, McCabe CH, Gurfinkel E, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593–1601.
9. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. The GUSTO investigators. *N Engl J Med*. 1993;329:673–682.
10. Connolly BJ, Pearce LA, Kurth T, Kase CS, Hart RG. Aspirin therapy and risk of subdural hematoma: meta-analysis of randomized clinical trials. *J Stroke Cerebrovasc Dis*. 2013;22:444–448.
11. Wong KS, Mok V, Lam WW, et al. Aspirin-associated intracerebral hemorrhage: clinical and radiologic features. *Neurology*. 2000;54:2298–2301.

12. Bakheet MF, Pearce LA, Hart RG. Effect of addition of clopidogrel to aspirin on subdural hematoma: meta-analysis of randomized clinical trials. *Int J Stroke*. 2014. http://dx.doi.org/10.1111/ijs.12419.
13. DiNicolantonio JJ, D'Ascenzo F, Tomek A, et al. Editorial. Clopidogrel is safer than ticagrelor in regard to bleeds: a closer look at the PLATO trial. *Int J Cardiol*. 2013;168:1739–1744.
14. *BRILINTA® Ticagrelor prescribing information*, USFDA approved. Astra Zeneca. 2013.
15. Manoria P, Manoria PC, Saha KK, Manoria P. Antiplatelet therapy in difficult clinical conditions. *Med Update*. 2012;188–192.
16. Peterson ED, Roe MT, Mulgund J, et al. Association between hospital process performance and outcomes among patients with acute coronary syndromes. *JAMA*. 2006;295:1912–1920.
17. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. *Stroke*. 1993;24:987–993.
18. *Falls: Assessment and Prevention of Falls in Older People*. *NICE Clinical Guideline*. 2013;1–33.
19. McQuaid KR, Laine L. Systematic review and meta-analysis of adverse events of low-dose aspirin and clopidogrel in randomized controlled trials. *Am J Med*. 2006;119:624–638 [Review].
20. Antman EM, Wiviott SD, Murphy SA, et al. Early and late benefits of prasugrel in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a TRITON-TIMI 38 (TRial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet InhibitioN with Prasugrel-Thrombolysis In Myocardial Infarction) analysis. *J Am Coll Cardiol*. 2008;51:2028–2033.
21. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329–1339.
22. Bhatt DL, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. *N Engl J Med*. 2006;354:1706–1717.
23. Neumann FJ, Kastrati A, Pogatsa-Murray G, et al. Evaluation of prolonged antiplatelet pretreatment (cooling off strategy) before intervention in patients with unstable coronary syndromes: a randomized controlled trial. *JAMA*. 2003;290:1593–1599.
24. Petersen JL, Mahaffey KW, Hasselblad V, et al. Efficacy and bleeding complications among patients randomized to enoxaparin or unfractionated heparin for antithrombin therapy in non-ST-segment elevation acute coronary syndromes: a systematic overview. *JAMA*. 2004;292:89–96.
25. Memon MA, Blankenship JC, Wood GC, et al. Incidence of intracranial hemorrhage complicating treatment with glycoprotein IIb/IIIa receptor inhibitors: a pooled analysis of major clinical trials. *Am J Med*. 2000;109:213–217.
26. Stroke Prevention in Atrial Fibrillation Investigators. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343:687–691.
27. Acar J, Iung B, Boissel JP, et al. AREVA: multicenter randomized comparison of low dose versus standard dose anticoagulation in patients with mechanical prosthetic heart valves. *Circulation*. 1996;94:2107–2112.
28. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
29. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
30. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.