SHORT COMMUNICATION

Cardiovascular Therapeutics

Anticoagulation in Patients with Dilated Cardiomyopathy, Low Ejection Fraction, and Sinus Rhythm: Back to the Drawing Board

Alexandru Nicolae Mischie,[1,*] Valentin Chioncel,[1] Ionel Droc[2] & Crina Sinescu[1]

1 Cardiology Department, "Bagdasar Arseni" Emergency Hospital, Bucharest, Romania
2 Army's Center for Cardiovascular Diseases, Bucharest, Romania

Keywords
Apixaban; Dabigatran; Dilated cardiomyopathy; Heart failure; Low ejection fraction <35%; Rivaroxaban; Sinus rhythm.

Correspondence
Dr. Alexandru Nicolae Mischie, "Bagdasar Arseni" Emergency Hospital, 12 Berceni Street, 041915 Bucharest, Romania.
Tel.: 0040723708050;
Fax: 0040213353025;
E-mail: alexandru_mischie@yahoo.com

SUMMARY

Heart failure patients present an important thrombo-embolic risk, including symptomatic or silent peripheral arterial embolism, pulmonary embolism, and stroke. Patients in sinus rhythm who have concomitant depressed (<35%) left ventricular ejection fraction have a 4% rate of embolic events. Several prospective randomized trials of anticoagulation in this group of patients were either underpowered or had a short period of follow-up. Even though in two studies warfarin had a slight advantage over aspirin (in the WATCH and WARCEF trials), it was at the cost of an increased risk in major hemorrhage. To decrease bleeding rates and to improve anticoagulant effect, new treatment strategies have to be tested. Novel anticoagulants (dabigatran, rivaroxaban, and apixaban) seem to be a promising alternative.

doi: 10.1111/1755-5922.12019

Background

Heart failure patients present an important thrombo-embolic risk, including symptomatic or silent peripheral arterial embolism, pulmonary embolism, and stroke [1,2]. Even though anticoagulation proved to be useful and even life-saving in patients with atrial fibrillation, there are few reports regarding the efficacy of anticoagulant treatment in patients with sinus rhythm. Patients in sinus rhythm who have concomitant depressed (<35%) left ventricular (LV) ejection fraction (EF) have a 4% rate of embolic events [3–5]. Embolic events in the same category of patients but treated with warfarin are around 1.2%, if we count strokes, pulmonary, and systemic embolism [6]. Dilated cardiomyopathy (DCM) in sinus rhythm and LVEF <40% offer a suitable terrain for thrombus formation, according to a very recent study (LV thrombus was found in 13% of patients and left atrial appendage thrombus in 68% of patients) [7].

Increased embolic events provide the foundation for using oral anticoagulants in these patients. Unfortunately, all relevant studies relating this issue either did not reach statistical significance or were underpowered to show benefit of warfarin versus aspirin, clopidogrel, or placebo, as detailed below. Even though in 2 studies warfarin had a slight advantage over aspirin (in the WATCH and WARCEF trials- [6,8]), it was at the cost of an increased risk in major hemorrhage. To decrease bleeding rates and to improve the antithrombotic effect, new treatment strategies such as novel anticoagulants (dabigatran, rivaroxaban, or apixaban) have to be tested. Dabigatran seems to be a promising alternative especially because it proved the highest decrease in stroke/systemic embolism rates versus warfarin in patients with atrial fibrillation [9], in comparison with rivaroxaban or apixaban.

Incidence of Stroke in Patients with DCM, Low EF, and Sinus Rhythm

There is a variable incidence in stroke; however, the mean incidence seems to be superior to 4–5% at 30 months or more. In patients treated with dronedarone, the incidence of stroke at 2 months was 5.6% versus 6% in the placebo groups, even though 30% of patients were in atrial fibrillation (from which 70% had anticoagulant treatment) [3]. In the placebo arm of another study that included 70% patients with ischemic DCM, stroke rate was 4.8% at 37-month follow-up [4]. In another ischemic cohort with severe heart failure treated with antiplatelet or anticoagulant therapy in a proportion of 90%, stroke was found in 4% for the placebo versus 3.5% for the rosuvastatin group at 32.8 months; a pulmonary embolism rate of 0.3% was found in the placebo group [5]. Other studies reveal slightly lower incidence in stroke, but patients had either combined antiaggregant or anticoagulant treatment or a shorter period of follow-up [10–13]. In patients with atrial fibrillation, the presence of chronic heart failure or LVEF<25% is responsible for 5.7% (4.4–7.0% range) of strokes per 100 patient/years and is considered high-risk factor for embolic disease [14].

Trials of Oral Anticoagulants or Antiaggregants in Patients with DCM in Sinus Rhythm and Low EF

There is an ongoing controversy regarding the role of oral anticoagulants as compared with aspirin in patients with heart failure with reduced EF [15–17]. Anticoagulant treatment seemed to reduce embolic rates even since the 1950s [18–20]. Retrospective nonrandomized studies that included patients with a low LVEF did not translate into clear treatment strategies [21–25]. The SAVE trial [22] found that for every decrease of 5% points in the EF, there was an 18% increase in the risk of stroke in patients who survived a MI; anticoagulant therapy was present in 38% of stroke patients and in 28% of patients without stroke; aspirin use was 46% versus 59% for the same groups. Another trial showed that there is an increasing risk of thrombo-embolic events for LVEF <20% [24]. In 630 cases of heart failure, those with stroke after heart failure had a 2.3-fold increase in death rate compared with those without stroke [25].

Several prospective randomized trials were either underpowered or had a short period of follow-up. The Heart Failure Long-Term Antithrombotic Study (HELAS) enrolled 197 patients with EF<35% of ischemic and idiopathic etiology, randomized to receive warfarin, aspirin, or placebo; no overall significant difference among the groups was noted regarding the embolic events [26]. In the WASH trial [27], 279 patients were randomized to warfarin, aspirin, or placebo with no significant difference regarding death, stroke, or myocardial infarction (MI). However, the highest rate of rehospitalization was among those receiving aspirin [27]. The WATCH trial (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) randomized 1587 patients with low EF to warfarin (target I.N.R of 2.5 to 3), aspirin (162 mg), or clopidogrel (75 mg) [6]. Warfarin was not superior to aspirin, and clopidogrel was not superior to aspirin; however, warfarin lowered the percentage of stroke, at the cost of an increased hemorrhage rate. The WARCEF trial (Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction) randomized 2305 patients with low EF and in sinus rhythm to warfarin (target I.N.R of 2 to 3.5) or aspirin (325 mg) [8]. Even though underpowered (69% power to test the primary null hypothesis and 83% power for the main secondary null hypothesis), it showed that there was no significant difference in stroke and death from any cause between treatment with warfarin and aspirin. A reduced risk of ischemic stroke with warfarin was offset by an increased risk of major hemorrhage. However, in multivariate analysis, age was the only significant parameter that interacted with treatment (treatment interaction with age: $P = 0.003$). Patients below 60 years might benefit the most from warfarin therapy, with a 37% decrease in the composite endpoint (death/ischemic stroke/intracerebral hemorrhage) (0.63 [0.48–0.84]; 0.001 vs. 1.09 [0.88–1.35]; 0.442) and important decrease in major bleedings (1.30 [0.56–3.07]; 0.636 vs. 2.73 [1.56–4.97]; 0.0002) at the cost of a slight increase in minor bleedings (1.95 [1.41–2.71]; <0.0001 vs. 1.43 [1.08–1.92]; 0.014)-for patients <60 years versus patients $\geq$60 years, HR (95% CI). Future studies will have to clarify which clinical/biological or echocardiography parameters are correlated with this decrease in mortality.

Novel Anticoagulants

Rivaroxaban inhibits factor Xa in a concentration-dependent manner via a rapid and reversible binding, having a 60–80% bioavailability, half-time of 5–13 h, 66% hepatic, and 33% renal excretion. It proved its noninferiority to warfarin for stroke/systemic embolism in the ROCKET-AF trial [28] at a dose of 20 mg o.d. (15 mg o.d. if creatinine clearance of 30–49 mL/min) (relative risk reduction of 21%, $P = 0.015$). In the setting of acute MI (the ATLAS ACS 2-TIMI 51 trial- [29]), rivaroxaban 2.5 and 5 mg b.i.d in addition to double antiaggregation therapy reduced significantly the primary endpoint (a composite of death from cardiovascular causes, myocardial infarction, or stroke) in comparison with double antiaggregation therapy alone (8.9% vs. 10.7%). Only the rivaroxaban 2.5 mg b.i.d group (but not the 5 mg group) reduced the death from cardiovascular causes (2.7% vs. 4.1%, $P = 0.002$) and from any cause (2.9% vs. 4.5%, $P = 0.002$). Safety outcomes referred to major bleedings not associated with coronary artery bypass graft (1.8%/2.4% vs. 0.6%, $P < 0.001$), intracranial hemorrhage (0.4%/0.7% vs. 0.2%, $P = 0.009$), and fatal bleeding (0.1%/0.4% vs. 0.2%, $P = 0.66$) for the 2.5 mg, 5 mg, and the "placebo" groups, respectively. Of note, the 2.5 mg b.i.d group had fewer fatal bleeding events than the 5 mg b.i.d group (0.1% vs. 0.4%, $P = 0.04$). Overall, rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding.

Apixaban is a reversible oral direct inhibitor of factor Xa with a bioavailability of 50%, half-time of 9–14 h, 75% fecal, and 25% renal excretion. It was better than aspirin in preventing strokes/systemic embolisms (55% reduction in primary endpoint) in the atrial fibrillation population from the AVERROES trial [30]. Compared with warfarin, it reduced the stroke/systemic embolic rate by 21%, reduced the major bleeding rates by 31%, and the all-cause mortality by 11%, at a dose of 5 mg b.i.d, adjusted to 2.5 mg b.i.d in patients $\geq$80 years, $\leq$60 kg or with a serum creatinine of $\geq$1.5 mg/dL. It has no role in acute MI (APPRAISE-2 trial) [31].

Dabigatran etexilate is a competitive reversible oral anticoagulant that inhibits thrombin directly and has a bioavailabity of 6%, half-time of 12–17 h, and 80% renal excretion. Compared with warfarin, in atrial fibrillation patients, dabigatran treatment (150 mg b.i.d.) induced lower rates of embolic events with similar rates of major hemorrhage as warfarin in the RE-LY study [9]. A lower dose (110 mg b.i.d.) was noninferior to warfarin for embolic event prevention, with lower rates of major bleeding. A relative risk reduction of 58% for the stroke/systemic embolic events was observed for the high dose. The Food and Drug Administration also approved the 75 mg b.i.d. in severe renal failure patients. Even though the high-dose dabigatran reduced significantly the embolic rates (relative risk of 0.66, 0.53–0.83, P for superiority<0.001) and decreased all-cause mortality by 11%, there is, however, a concern regarding an increased rate of MI, which is nonsignificant (relative risk of 1.27, 0.94–1.71 HR; $P = 0.12$; 0.81% for the high-dose dabigatran vs. 0.64% in patients treated with warfarin). Dabigatran has no role in the setting of acute MI [32].

Endoxaban is also a Xa oral inhibitor undergoing a phase III trial at this moment; results will be available perhaps in 2013.

None of the novel anticoagulants has a specific antidote. Dabigatran prolongs the activated partial thromboplastin time (at high concentrations, the correlation is not linear), and rivaroxaban prolongs the prothrombin time. For a rough evaluation of the anticoagulation effect of the anti-Xa oral inhibitors, an anti-Xa assay could be used.

Considerations Regarding Future Trials

Taking into account the superiority of all novel anticoagulants over warfarin [9,28–30], the fact that there is an increased risk of embolic events in the subgroup of patients in sinus rhythm who have concomitant depressed LVEF [3–5] and that this risk is reduced by warfarin treatment (with the cost of increased hemorrhage rates- 6, 8), the novel anticoagulants have to be tested in this population, as it could really be of benefit in decreasing embolic events.

What Patients Should Be Enrolled?

Ideally, a trial that could provide solutions for both ischemic and idiopathic cardiomyopathies would be the perfect solution, especially because ischemic cardiomyopathy is the main cause of heart failure worldwide. However, the need for aspirin or double antiplatelet treatment in ischemic cardiomyopathy could increase bleeding risk and provide unclear results if outcomes are mixed with those suffering from idiopathic cardiomyopathy; on the other hand, it is unethical to treat ischemic cardiomyopathy without aspirin or anticoagulant (in the case of a placebo arm). If only patients with idiopathic cardiomyopathy will be enrolled, problems like insufficient enrollment sites and longer enrollment period due to the very small incidence of these patients will make the trial difficult to conduct.

Another issue regards the phase of the heart failure in which the patient will be enrolled: acute or chronic versus first episode or advanced disease, as embolic risk is slightly different in each phase. In the Rotterdam Study, the risk of ischemic stroke was highly increased in the first month after diagnosis of heart failure (age- and sex-adjusted HR 5.79, 95% CI 2.15–15.62), but returned to normal within 6 months [33]. This is highly important, because this population could benefit most from anticoagulation therapy. In another study, patients diagnosed with heart failure had a 17.4-fold increased risk of stroke in the first 30 days after heart failure diagnosis, compared with patients in the general population [25].

What Should Be Compared?

A trial that compares newer antithrombotic therapies versus placebo (and eventually vs. warfarin) would be preferable. For example, in the WARCEF trial, we know that warfarin and aspirin have the same effect, but we do not know whether they are equally harmful or equally effective. Similarly, in patients <60 years, we know that warfarin does better than aspirin, but we do not know whether warfarin is ineffective and aspirin harmful or whether warfarin is effective and aspirin is ineffective/less effective.

Which of the Novel Anticoagulants Should Be Compared?

Either of the novel anticoagulants could be used. However, one issue is of increasing importance: does anticoagulant treatment, apart from decreasing stroke/systemic embolic rates, increase coronary plaque rupture and provoke increased myocardial events? Apparently yes, if we look at the RE-LY study. Rivaroxaban at a dose of 2.5 mg b.i.d in addition with double antiplatelet treatment has already been used in acute MI setting, with favorable results regarding death/thrombosis; however, the therapeutic doses of rivaroxaban are of least 15 mg b.i.d. In consideration should be taken also the profile of enrolled patients with regard to the anticoagulant's pharmacokinetic property. Dose adjustment for special populations (renal or hepatic disease, higher bleeding risk) is also important.

What Should Be the Outcomes?

We suggest that a future study, which would include as primary outcome the rate of any embolic event at 3 years (stroke, embolic MI, pulmonary, or peripheral embolism), with concomitant safety outcome that would include death and major bleeding, would be extremely helpful in deciding whether anticoagulant treatment is really of any help in this setting. Embolic events should be defined as any new lesion detected on computed tomography or magnetic resonance imaging (MRI) in comparison with the initial examination; major bleeding should be defined as intracerebral, epidural, subdural, subarachnoid, spinal intramedullary, retinal, or any other bleeding causing a decline in the hemoglobin level of more than 2 g per deciliter in 48 h or bleeding requiring transfusion of 2 or more units of whole blood, hospitalization, or surgical intervention.

Silent embolic event has been associated with poor outcomes that will be detailed below. The prevalence of silent cerebral infarcts in 226 elderly patients with first-ever stroke or transient ischemic attack was 20% in one study [34]. Silent strokes are correlated with increased risk of in-hospital mortality [35], overall mortality (OR=3.4; 95% CI, 1.4 to 8.5 [36] and OR = 1.95, 95% CI = 1.16–3.29 [37]), dementia [36], recurrent strokes [34,37], and progression of renal disease in patients with chronic kidney disease [38]. Silent lacunar infarcts due to cerebral small vessel disease also have an increased risk of vascular (HR 2.6; 95% CI, 1.4 to 4.9) and nonvascular death (HR 2.7; 95% CI, 1.3 to 5.3) [39]. Silent MI expressed as late gadolinium enhancement at cardiac MRI is found in 28% of patients with diabetes who had negative history of MI or absence of Q waves on ECG [40]. Increased major adverse cardiovascular events and death rates have been found in these patients (adjusted HR 4.13; 95% confidence interval, 1.74 to 9.79; $P = 0.001$). Silent MI–baseline Q waves outside the infarct-related artery territory in ST-elevated MI setting have a death rate of 6.7% versus 4.0% in STEMI patients without prior MI [41].

We would like to highlight the importance of finding those "silent" embolic events associated with poorer outcomes that may pass as "normal" if a detailed work-up is not done [the difference between the rates of embolic events without anticoagulant/antiaggregant treatment is 4–5% at 3 years [3–5] and 0.6–1.2% [6] in the same population treated with warfarin,

but those studies did not take into account the silent embolic events such as ministrokes or small peripheral/pulmonary embolism that do not necessarily translate into clinical symptomatology immediately].

What Should the Trial Design Look Like?

Probably an "intention to treat" design would be appropriate. The initial clinical, biological, and imaging (computer tomography/MRI) examination should be performed for these patients with idiopathic DCM in sinus rhythm and LVEF<35%. Coronary angiography should be performed. Patients should have full medical/interventional therapy according to the guidelines for the treatment of HF. Randomization to active placebo arm should be performed; if dabigatran should be used, for example, it should be titrated in function of the HAS-BLED [42] score: 110 mg b.i.d if high bleeding score>2, 150 mg b.i.d if bleeding score 0–2. However, the validation of prediction scores like HAS-BLED in heart failure patients in sinus rhythm should precede use of these scores as a tool to titrate anticoagulation in these patients. Biological follow-up for adverse effects of dabigatran should be carried out twice a week for the first week, then every week for 2 weeks, and then at each follow-up visit.

Sample size calculation is crucial, as none of the previous randomized trials [6,8,26,27] succeeded in having a sufficiently powered result. As previously stated, the incidence of stroke in severe heart failure is at least 4–5% [3–5], compared with a risk of less than 0.5% in those without heart failure [43,44] and also compared with a risk of 0.6% in patients with DCM with low EF and in sinus rhythm treated with warfarin [6]. Even though previous studies did not count silent embolic events and even though the incidence of those silent events is of at least 10–20% [34,40], we will be very drastic and suppose that the embolic rate will be of at least 5%, number clearly confirmed by the literature data [3–5]. If we consider 3 groups (placebo, warfarin, and novel anticoagulant), 954 patients per group should be enrolled to have a 95% chance of detecting, as significant at the 5% level, a decrease in the primary outcome measure from 5% in the control group to 1% in the novel anticoagulant group, allowing for a 15% crossover between groups (due to anticoagulant noncompliance or newly diagnosed atrial fibrillation). Thus, a total of 2862 patients should be enrolled.

Conclusions

We are looking forward in seeing real advances in antithrombotic therapies targeted at decreasing embolic events in special patient populations such as those with atrial fibrillation or those with dilated chambers in sinus rhythm and low EF. If proven effective, novel anticoagulants will decrease health-care costs, improve the QoL, increase the lifespan, and improve primary prevention for these patients.

Source of Funding

No source of funding was used for this review.

Author Contribution

Mischie Nicolae Alexandru contributed data collection, concept/design, interpretation, drafting article, critical revision of article, and approval of article. Chioncel Valentin contributed interpretation, critical revision of article. Droc Ionel contributed interpretation, critical revision of article. Sinescu Crina contributed interpretation, critical revision of article, approval of article.

Conflict of Interest

The authors declare no conflict of interest.

References

1. Kalaria VG, Passannante MR, Shah T, Modi K, Weisse AB. Effect of mitral regurgitation on left ventricular thrombus formation in dilated cardiomyopathy. *Am Heart J* 1998;**135**:215–220.
2. Lip GYH, Gibbs CR. Does heart failure confer a hypercoagulable state? Virchow's triad revisited. *J Am Coll Cardiol* 1999;**33**:1424–1426.
3. Kober L, Torp-Pedersen C, McMurray JJ, et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med* 2008;**358**:2678–2687.
4. Perry G, Brown E, Thornton R, et al. The effect of digoxin on mortality and morbidity in patients with heart failure. The Digitalis Investigation Group. *N Engl J Med* 1997;**336**:525–533.
5. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. *N Engl J Med* 2007;**357**:2248–2261.
6. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation* 2009;**119**:1616–1624.
7. Bakalli A, Georgievska-Ismail L, Koçinaj D, Musliu N, Krasniqi A, Pllana E. Prevalence of left chamber cardiac thrombi in patients with dilated left ventricle at sinus rhythm: the role of transesophageal echocardiography. *J Clin Ultrasound* 2013;**41**:38–45.
8. Homma S, Thompson JL, Pullicino PM, et al. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med* 2012;**366**:1859–1869.
9. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;**361**:1139–1151.
10. Zannad F, McMurray JJ, Krum H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *N Engl J Med* 2011;**364**:11–21.
11. Pitt B, Remme W, Zannad F, et al. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
12. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, doubleblind, placebo-controlled trial. *Lancet* 2008;**372**:1223–1230.
13. Pitt B, Zannad F, Remme WJ, et al. 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**:709–717.
14. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;**285**:2864–2870.
15. Freudenberger RS, Halperin JL. Should we use anticoagulation for patients with chronic heart failure? *Nat Clin Pract Cardiovasc Med* 2006;**3**:580–581.
16. Ezekowitz M. Antithrombotics for left ventricular impairment? *Lancet* 1998;**351**:1904.

17. Sacco RL, Adams R, Albers G, et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Circulation* 2006;**113**:e409–e449.
18. Anderson GM, Hull E. The effects of dicumarol upon the mortality and incidence of thromboembolic complications in congestive heart failure. *Am Heart J* 1950;**39**:697–702.
19. Griffith GC, Stragnell R, Levinson DC, Moore FJ, Ware AG. A study of the beneficial effects of anticoagulant therapy in congestive heart failure. *Ann Intern Med* 1952;**37**:867–887.
20. Harvey WP, Finch CA. Dicumarol prophylaxis of thromboembolic disease in congestive heart failure. *N Engl J Med* 1950;**242**:208–211.
21. Al-Khadra AS, Salem DN, Rand WM, Udelson JE, Smith JJ, Konstam MA. Warfarin anticoagulation and survival: a cohort analysis from the Studies of Left Ventricular Dysfunction. *J Am Coll Cardiol* 1998;**31**:749–753.
22. Loh E, Sutton MS, Wun CC, et al. Ventricular dysfunction and the risk of stroke after myocardial infarction. *N Engl J Med* 1997; **336**:251–257.
23. Dunkman WB, Johnson GR, Carson PE, Bhat G, Farrell L, Cohn JN. Incidence of thromboembolic events in congestive heart failure. *Circulation* 1993;**87**:VI94–V101.
24. Freudenberger RS, Hellkamp AS, Halperin JL, et al. Risk of thromboembolism in heart failure: an analysis from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2007; **115**:2637–2641.
25. Witt BJ, Brown RD Jr, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, Roger VL. Ischemic stroke after heart failure: a community-based study. *Am Heart J* 2006;**152**:102–109.
26. Cokkinos DV, Haralabopoulos GC, Kostis JB, Toutozas PK. Efficacy of antithrombotic therapy in chronic heart failure: the HELAS study. *Eur J Heart Fail* 2006;**8**:428–432.
27. Cleland JGF, Findlay I, Jafri S, et al. The Warfarin/Aspirin Study in Heart Failure (WASH): a randomized trial comparing antithrombotic strategies for patients with heart failure. *Am Heart J* 2004;**148**:157–164.
28. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;**365**:883–891.
29. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med* 2012; **366**:9–19.
30. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;**364**:806–817.
31. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med* 2011;**365**: 699–708.
32. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J* 2011;**32**:2781–2789.
33. Alberts VP, Bos MJ, Koudstaal PJ, Hofman A, Witteman JC, Stricker BH, Breteler MM. Heart failure and the risk of stroke: the Rotterdam Study. *Eur J Epidemiol* 2010;**25**:807–812.
34. Ong CT, Sung KC, Sung SF, Wu CS, Hsu YC, Su YH. Impact of silent infarction on the outcome of stroke patients. *J Formos Med Assoc* 2009;**108**:224–230.
35. Corea F, Tambasco N, Luccioli R, Ciorba E, Parnetti L, Gallai V. Brain CT-scan in acute stroke patients: silent infarcts and relation to outcome. *Clin Exp Hypertens* 2002;**24**:669–676.
36. Liebetrau M, Steen B, Hamann GF, Skoog I. Silent and symptomatic infarcts on cranial computerized tomography in relation to dementia and mortality: a population-based study in 85-year-old subjects. *Stroke* 2004; **35**:1816–1820.
37. Bokura H, Kobayashi S, Yamaguchi S, et al. Silent brain infarction and subcortical white matter lesions increase the risk of stroke and mortality: a prospective cohort study. *J Stroke Cerebrovasc Dis* 2006;**15**:57–63.
38. Kobayashi M, Hirawa N, Morita S, et al. Silent brain infarction and rapid decline of kidney function in patients with CKD: a prospective cohort study. *Am J Kidney Dis* 2010;**56**:468–476.
39. Conijn MM, Kloppenborg RP, Algra A, et al. Cerebral small vessel disease and risk of death, ischemic stroke, and cardiac complications in patients with atherosclerotic disease: the Second Manifestations of ARTerial disease-Magnetic Resonance (SMART-MR) study. *Stroke* 2011;**42**: 3105–3109.
40. Kwong RY, Sattar H, Wu H, et al. Incidence and prognostic implication of unrecognized myocardial scar characterized by cardiac magnetic resonance in diabetic patients without clinical evidence of myocardial infarction. *Circulation* 2008;**118**:1011–1020.
41. Toma M, Fu Y, Ezekowitz JA, McAlister FA, Westerhout CM, Granger CB, Armstrong PW. Does silent myocardial infarction add prognostic value in ST-elevation myocardial infarction patients without a history of prior myocardial infarction? Insights from the Assessment of Pexelizumab in Acute Myocardial Infarction (APEX-AMI) Trial. *Am Heart J* 2010;**160**:671–677.
42. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;**138**: 1093–1100.
43. Dec GW, Fuster V. Idiopathic dilated cardiomyopathy. *N Engl J Med* 1994;**331**:1564–1575.
44. Manolio TA, Baughman KL, Rodeheffer R, et al. Prevalence and etiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung, and Blood Institute workshop. *Am J Cardiol* 1992;**69**:1458–1466.

