



POSITION STATEMENT

Cerebrovascular mortality in Portugal: Are we overemphasizing hypertension and neglecting atrial fibrillation?

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Abstract

Cerebrovascular disease has long been the leading cause of death in Portugal. Despite improvements in the treatment of hypertension and the resulting decrease in associated mortality, the progressive aging of the population and increased prevalence of atrial fibrillation have prevented the incidence of stroke from falling as much as desired. The authors review the evidence on the situation in Portugal and propose an intervention plan.

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PALAVRAS-CHAVE

Fibrilhação auricular;
Hipertensão
auricular;
Acidente vascular
cerebral;
Mortalidade
cerebrovascular

Mortalidade cerebrovascular em Portugal: estaremos a colocar demasiada ênfase na hipertensão e a negligenciar a fibrilhação auricular?

Resumo A insuficiência cardíaca é uma patologia comum e uma causa importante de mortalidade, morbidade e deterioração da qualidade de vida. A anemia é uma comorbidade frequente na insuficiência cardíaca e agrava o seu prognóstico e capacidade funcional. Independentemente da presença ou não de anemia, a deficiência de ferro é um problema associado à insuficiência cardíaca muitas vezes não identificado. Este artigo revê os mecanismos, impacto prognóstico e tratamento da anemia e deficiência de ferro.

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Introduction

According to a 2008 report from the Portuguese Directorate-General for Health, diseases of the circulatory system remain the leading cause of death in Portugal,¹ accounting for 32.3% of all deaths. This is almost 40% more than the second cause of death, all forms of cancer, which account for 23.5%. However, unlike other European countries, in which ischemic heart disease is the most common form of cardiovascular disease, in Portugal cerebrovascular disease is more important, accounting for 13.9% of deaths.

For several decades particular attention has been paid to the diagnosis and treatment of hypertension. These efforts have been reasonably successful, with some improvements over time, although the problem is not completely resolved. However, partly as a result of this success, although cerebrovascular disease remains the leading cause of death in Portugal, the pattern of stroke has changed, with atrial fibrillation (AF) now being recognized as a major factor. AF is the most prevalent sustained cardiac arrhythmia,² occurring in up to 25% of individuals aged over 40 some point in their lives, and is associated with a marked increase in the incidence of cerebral and systemic thromboembolism.³ Stroke in patients with AF is also associated with higher mortality (50% at one year)⁴ and is usually more severe and incapacitating.⁵ Recent studies in Portugal show that the rate of diagnosis of AF is clearly unsatisfactory⁶ and that even when diagnosed, patients often do not receive appropriate treatment.⁷

Better understanding of the real situation concerning AF and stroke, together with a concerted effort on the part of the entire medical community – including cardiologists, neurologists, internists and family practitioners, as well as other healthcare workers – is urgently needed to put a halt to this train of events.

Hypertension in Portugal

Changes in diagnosis and control in recent years

The VALSIM study was a cross-sectional epidemiological study of the prevalence of the metabolic syndrome in the Portuguese population, supported by the National Cardiology Data Collection Center of the Portuguese Society of Cardiology, that ran between April 2006 and November 2007. It analyzed 16 856 participants aged over 18 assessed in a primary care setting, involving 719 general practitioners and representing all Portuguese regions. In this study the prevalence of hypertension adjusted for age and gender was 42.62%; with some regional variations in prevalence and treatment, some 10% of hypertensives were not receiving drug treatment (reaching over 50% in individuals aged under 30), and 47.6% were receiving monotherapy only. These figures are well above the European average, which shows that therapeutic inertia is all too common in Portugal.

In the AMALIA study, an epidemiological study assessing cardiovascular risk in Portugal based on direct interviews of 38 893 individuals aged 40 or over, the prevalence of self-reported hypertension was only 23.5%,⁹ considerably lower than in the above study, even though younger

age-groups were excluded. This may be explained by the sampling method (a questionnaire) and by the fact that people are frequently unaware that they have hypertension. In other words, these figures refer only to those individuals who had previously been diagnosed with hypertension and who wished to make this known, while excluding all those who were hypertensive but failed to report the fact or who were unaware of their condition through lack of blood pressure measurement.

The question of awareness of hypertension was analyzed by Pereira et al. in a sample of 2310 Portuguese individuals aged 18 or over randomly selected from the population of the city of Porto in 1999-2003. The prevalence of hypertension was 46.7% in men and 42.7% in women.¹⁰ Only 41.3% of the men and 58.9% of the women were aware of the diagnosis, while only 60.2% of women and 71.7% of men who were aware of their condition were medicated, and of these only 23.0% of women and 22.8% of men were controlled.

The PAP study of prevalence, awareness, treatment and control of hypertension in Portugal in 5023 adults representative of all Portuguese regions assessed between March 2003 and February 2004 showed similar results for prevalence and awareness of hypertension, although with even lower prevalence of treated and controlled hypertension than in Pereira et al. (39.0% and 11.2%, respectively).¹¹

Although the figures are still a cause for concern, developments at national level have been favorable. A recent systematic review shows that the prevalence of hypertension in Portugal fell in middle-aged individuals (from 58.3% to 49.1% in men and from 51.5% to 42.3% in women) and in the elderly (from 96.4% to 74.5% in men and from 89.6% to 67.6% in women) between 1990 and 2005.¹² The prevalence of awareness rose by 0.4% a year during the same period, while mean systolic and diastolic blood pressure decreased between 1975 and 2005, with mean systolic blood pressure in the elderly falling by 22 mmHg in men and by 32 mmHg in women. However, the authors noted that despite these favorable developments, the figures for Portugal were still above the average for countries in western Europe.

The problem of salt

Salt consumption in Portugal is high, as shown by a study by Polónio et al.¹³ that assessed 24-hour urinary sodium excretion while maintaining normal dietary habits in 426 individuals (mean age 50±22 years) in four groups: university students, factory workers, relatives of patients with recent stroke and hypertensives. The estimated daily salt intake was 12.3 g, double that recommended by international organizations,¹⁴ with no significant differences between the groups.

Following the publication of this study, in which the tertile with highest salt consumption also consumed the most bread, a review was undertaken of the salt content in Portuguese bread compared to six other European countries. The mean sodium content was 19.2 g per kg, 53% higher than that of bread in the other countries. A series of measures followed designed to educate the public concerning over-consumption of salt^{15,16} and approaches were made to

food producers, health authorities and government. The Portuguese Parliament passed a law in March 2009 imposing a limit of 1.4 g/100 g salt added to bread and obliging food manufacturers to show the relative and absolute quantities of salt, as a percentage of the product and per portion, on the labels of pre-packaged products.¹⁷

Another source of dietary sodium is carbonated mineral water, although in this case the ion bound to sodium is bicarbonate rather than chlorine, which is associated with different effects. However, a small unblinded cross-over study with 17 participants divided into two groups, drinking *Água das Pedras* (high sodium) or *Água Vitalis* (low sodium), with seven weeks in each arm and with six weeks of wash-out between them, showed that a daily consumption of 500 ml of *Água das Pedras* had no effect on blood pressure.¹⁸

As the measures to control salt consumption have only recently been implemented, it will be some years before their effects on the prevalence of hypertension and the number of strokes can be evaluated.

Stroke in Portugal: recent changes

Mortality from cerebrovascular disease has fallen in recent years, probably due to improved awareness and treatment of hypertension, together with general improvements in health care. In 1996 22.9% of deaths in individuals aged under 65 were due to stroke¹⁹; in 2008 the figure was 13.9% for the whole population, not only in those aged under 65.¹ Although the two figures are not directly comparable, they do illustrate a reduction.

At the same time, the type of stroke admitted to stroke units has changed. In a retrospective study of all patients admitted to a university hospital with a diagnosis of ischemic stroke in the first three months of 2011, Cunha found that 91 (37.3%) had a cardioembolic origin, as opposed to 15-20% in previous studies.²⁰ Of these, 86 (94.5%) were due to AF, which had been diagnosed in 72 (83.7%) patients, only 25 (34.7%) of whom were under anticoagulant therapy.

The prevalence of AF increases with age,² and so the global pattern of this arrhythmia has gradually changed as life expectancy increases. A recent analysis of causes of death in 187 countries between 1980 and 2010, part of the Global Burden of Disease Study 2010, showed an increase of 233.9% in mortality attributed to AF between 1990 and 2010.²¹

It is reasonable to assume that a paradigm shift is under way concerning the etiology of stroke, with fewer being attributable to untreated or uncontrolled hypertension and more being due to cardioembolism (Figure 1).

Atrial fibrillation in Portugal

Prevalence and comorbidities

The prevalence of AF (and atrial flutter) in Portugal was unknown until the publication of the FAMA study on the prevalence of AF in the Portuguese population aged 40 and over.⁶ This study, analyzing the results of an ECG and a questionnaire applied at home in 10 447 subjects

selected randomly from all regions of the country, showed a prevalence of 2.5% in this age-group. Since AF and atrial flutter frequently coexist, and as the thromboembolic risk and recommended treatment for the two conditions are the same, both conditions were screened. However, the number of cases of atrial flutter was very low (around 12), and removing them from the analysis reduced the prevalence by only 0.1%. The differences in AF prevalence according to age-group were similar to those in other series,² with a prevalence of 0.2% between 40 and 49, 1.0% between 50 and 59 and 1.6% between 60 and 69; it was significantly higher in older age-groups – 6.6% in those aged 70-79 and 10.4% in those aged 80 or more. Although overall there were no differences between the sexes, AF was more common in women aged over 80 and in men aged 70-79.

The FAMA study also provided important information on comorbidities in these patients. Hypertension was an independent predictor of AF and was found in 71.0% of patients with AF, demonstrating the close association between the two conditions.²³ As expected, stroke was nearly three times more prevalent in individuals with AF (14% vs. 5%; $p < 0.001$).⁶

Antithrombotic treatment in Portugal

Only 61.7% (161 of 261) of individuals with AF in the FAMA study said they had been diagnosed with AF. Of those with AF, given their age and their high prevalence of hypertension and other risk factors, one would assume that their CHADS₂ and CHA₂DS₂-VASc risk scores would be sufficient indication for oral anticoagulation. However, only 37.8% were in fact anticoagulated, which illustrates the low level of antithrombotic treatment for patients with AF in Portugal. Thus, according to the authors, “A possible explanation for this high rate of stroke could be a correspondingly high prevalence, diagnosed or not but frequently inadequately treated, of AF in the Portuguese population, and underuse of anticoagulant therapy.”

Some of the FAMA study's findings have since been validated in a hospital setting by an analysis of patients admitted consecutively to an internal medicine ward of a central hospital between October 2006 and October 2007 with a diagnosis of AF or atrial flutter at discharge. The mean age of the study population was 77±10 years, which even in the absence of any other risk factor in the CHADS₂ or CHA₂DS₂-VASc scores would be an indication for oral anticoagulation. According to the classification in the American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) 2006 guidelines for the management of patients with atrial fibrillation,²⁴ 126 (81.3%) of the patients assessed were at high thromboembolic risk, while the other 29 were at moderate risk (one moderate risk factor, all of which are now included in either the CHADS₂²⁵ or the CHA₂DS₂-VASc²⁶ score). Although the indication for oral anticoagulation was noted in 70.6% of the high-risk patients, only 51.6% were actually medicated accordingly.

This study highlights the fact that even in a hospital setting, the indication for oral anticoagulation was not noted in nearly 30% of AF patients at high thromboembolic risk, and even when identified, almost half did not receive appropriate treatment.

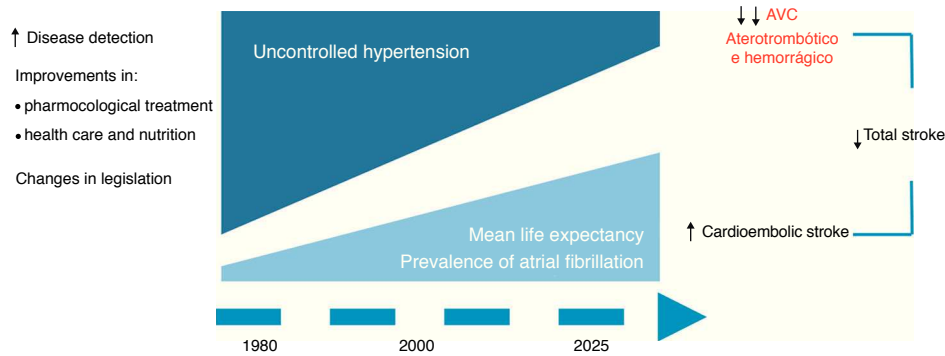


Figure 1 Diagram illustrating changes in the pattern of stroke in Portugal.

Importance of adequate antithrombotic treatment in patients with atrial fibrillation

Risk scores and European Society of Cardiology and other guidelines

Current guidelines recommend that decisions on thromboembolic prophylaxis in AF patients should be based on risk scores calculated on the basis of clinical risk factors that are easily identified in a brief patient history. The scores currently recommended in the European²⁷ and American²⁸ guidelines are CHA₂DS₂-VASc and CHADS₂, respectively (Table 1). The decision on whether to prescribe anticoagulation is based on the patient's thromboembolic risk (Table 2).

There is also a bleeding risk score, HAS-BLED, which should be used to support clinical decision-making.²⁹ However, since HAS-BLED shares several comorbidities with the CHA₂DS₂-VASc and CHADS₂ scores, patients with higher thromboembolic risk frequently are at greater bleeding risk. In such cases, a low bleeding risk strategy should be adopted, with one of the new anticoagulants or percutaneous left atrial appendage closure. It is now recognized that prescribing antiplatelet therapy rather than anticoagulation in the belief that the former carries a lower bleeding risk is incorrect, since antiplatelets confer 3-5 times lower protection against thromboembolic events and their bleeding risk is similar to that of the oral factor Xa inhibitor apixaban, as shown in the AVERROES study (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients,³⁰ and to that of warfarin in the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA).³¹

Anticoagulants

In the last few years three new anticoagulants (dabigatran, rivaroxaban and apixaban) have been developed for thromboembolic prevention in non-valvular AF that have certain advantages over warfarin. Since they are not the main focus of this article, they will only be briefly mentioned.

The main advantages of these new drugs – they do not require control of therapeutic levels by blood tests and have a much better profile for interactions with foods and

other drugs – raised expectations when they entered phase 3 trials using warfarin as comparator.³²⁻³⁴

Although there are specific issues with each of the new anticoagulants, meta-analyses³⁵⁻³⁸ of trials involving over 50 000 participants results show that they are superior to warfarin in almost all the endpoints assessed, with reductions in mortality, stroke and systemic embolism, hemorrhagic stroke, and intracranial and gastrointestinal bleeding.

Percutaneous left atrial appendage closure

The fact that most thrombi (up to 90%) in AF form in the left atrial appendage has prompted the development of another therapeutic option to prevent thromboembolism. The Watchman Left Atrial Appendage System for Embolic Protection in Patients With AF (PROTECT AF) trial demonstrated the non-inferiority of percutaneous left atrial appendage closure with the Watchman® device to warfarin in terms of efficacy.⁴⁰ It is thus a valid alternative for patients with contraindication to anticoagulation.²⁷

Some Portuguese centers are already using this technique. Faustino et al. presented their initial experience in a small group of 13 patients at high thromboembolic risk (CHADS₂ 3.5±0.9 and CHA₂DS₂-VASc 5.5±1.0), reporting a very low rate of procedural complications (two minor bleeds and one hematoma treated conservatively).⁴¹ One patient developed a thrombus on one of the device discs, which was resolved with a short course of medical therapy. None of the patients presented systemic embolism or stroke during a follow-up of 11±5 months, well below the rate predicted on the basis of their CHADS₂ score (7.3±2.3%).

Antithrombotic treatment: borderline decisions and unjustified fears

In a study by Dores et al., 19.0% of high-risk patients with indication were not prescribed oral anticoagulation due to contraindication: previous bleeding dyscrasia (26%), alcohol abuse (16%), renal disease (16%) and inability to control INR (13%).⁷ No reason was given for the failure to prescribe anticoagulation in the other 29.4%. Given the current state of knowledge and available treatments, almost all high-risk patients can be protected, surmounting contraindications by use of the new oral anticoagulants when INR is difficult

Table 1 Risk scores recommended by the European Society of Cardiology²⁷ and the American College of Cardiology/American Heart Association/Heart Rhythm Society²⁸ for prevention of thromboembolism in patients with non-valvular atrial fibrillation.

C	Congestive heart failure	C	Congestive heart failure or left ventricular ejection fraction $\leq 40\%$
H	Hypertension	H	Hypertension
A	Age ≥ 75	A ₂	Age 65-74 (1 point) or ≥ 75 (2 points)
D	Diabetes	D	Diabetes
S ₂	Prior stroke or TIA	S ₂	Prior stroke or TIA
		V A S c ^a	Vascular disease – defined as at least one of myocardial infarction, peripheral arterial disease or complex aortic plaque
			^a Female gender is also considered a risk factor.

In the ESC guidelines²⁷ oral anticoagulation is recommended with a CHADS₂ or CHA₂DS₂-VASc score of ≥ 2 unless contraindicated. With a score of 1, oral anticoagulation should be considered according to the patient's bleeding risk and preferences. No therapy is recommended for a score of 0. The ACC/AHA/HRS guidelines propose similar recommendations, although based on the more conservative CHADS₂ score. Two points should be noted. The decision whether to prescribe anticoagulation for a patient with non-valvular AF is based on these scores and not on the type of AF (paroxysmal, persistent or permanent); and antithrombotic therapy for atrial flutter should be the same as for AF.

Table 2 Estimated annual risk of stroke or systemic embolism without antithrombotic therapy in patients with non-valvular atrial fibrillation according to the CHADS₂ and CHA₂DS₂-VASc risk scores.

CHADS ₂	Estimated annual risk	CHA ₂ DS ₂ -VASc	Estimated annual risk
0	1.9%	0	0
1	2.8%	1	0.7%
2	4.0%	2	1.9%
3	5.9%	3	4.7%
4	8.5%	4	2.3%
5	12.5%	5	3.9%
6	18.2%	6	4.5%
		7	10.1%
		8	14.2%
		9	100% ^a

Data from the original articles validating the CHADS₂ and CHA₂DS₂-VASc scores.^{5,26} As these are annual rates, the patient's life expectancy should be taken into consideration when calculating the likelihood of an event without antithrombotic therapy. ^a The small number of subjects with a score of 9 in the validation study makes it impossible to establish a reliable figure for the predicted risk in this group.

to control or by percutaneous left atrial appendage closure in patients with too high a bleeding risk to be prescribed anticoagulation.

With regard to chronic renal disease, this has been shown to be a risk factor not only for bleeding but also for thromboembolism.⁴²⁻⁴⁴ The benefit of warfarin was demonstrated in a Danish cohort study linking data from national registries with over a hundred thousand patients with AF, in which aspirin, which is frequently prescribed for such patients, did not reduce the risk of stroke or thromboembolism and had a similar bleeding risk to warfarin.⁴² Trials with the new anticoagulants have been performed in patients with creatinine clearance of 25-30 ml/min, and these drugs may also be an option in patients with renal disease. However, below this level, the only drug for which there is evidence to support its use is warfarin.

Besides the question of renal failure, there are certain practices that are common but are not based on any evidence and which can actually be detrimental to the

patient. It is frequently thought that aspirin is safer than oral anticoagulants, but the AVERROES trial (apixaban vs. aspirin),³⁰ the Danish study⁴² and the BAFTA study (warfarin vs. aspirin)³¹ all showed that the incidence of bleeding was similar with the two treatments and that aspirin was less effective in preventing stroke and embolic events.

Another reason often put forward for failure to prescribe anticoagulants is the fear of bleeding complications associated with the high risk of falls in the elderly. However, it has been demonstrated that 295 falls per year would be required to negate the benefit of anticoagulation in a patient with a CHADS₂ score of 2-3.⁴⁵

Importance of early detection of atrial fibrillation

Given the range of therapeutic options available, it is reasonable to assume that we are now in an era in which

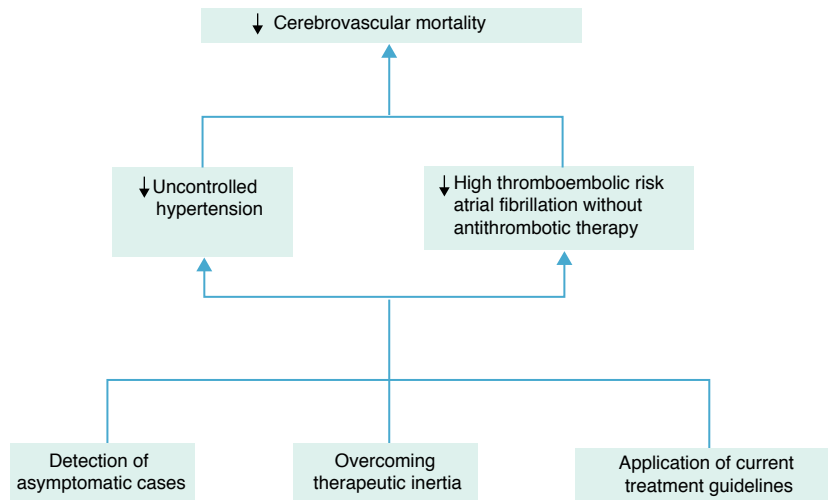


Figure 2 Main lines of action to reduce cerebrovascular mortality.

almost all AF patients can be appropriately treated whatever their individual characteristics.

The authors of the FAMA study stated that “In view of the high mortality from stroke in Portugal, and assuming that AF is the cause in 15% of cases, we considered that accurate knowledge of AF prevalence in different age-groups would be important not only to improve control of this arrhythmia but also to prevent such vascular complications”.⁶ More recent figures²⁰ further emphasize the importance of recognizing and treating high-risk patients.

One of the main obstacles to achieving this goal is lack of awareness of the presence of AF, as shown in the FAMA study, which also showed that older age, higher body mass index, hypertension and lack of exercise were all independent predictors of AF. Of particular relevance is the fact that besides having a greater prevalence of AF, older and hypertensive individuals are also at higher thromboembolic risk, and it is therefore these patients that derive the most benefit from early diagnosis.⁶

Considering that AF is often asymptomatic and that its first manifestation is frequently stroke, the best way to ensure that it is diagnosed is systematic screening, ideally for all individuals after a certain age, to be repeated regularly in high-risk groups. Such programs are currently under development in the UK; one option being studied is routine pulse checking by general practitioners in individuals aged over 65, those with an irregular pulse being referred for an ECG.⁴⁶ The efficacy of such screening is also currently being assessed in Spain.⁴⁷ However, since a significant proportion of the Portuguese population either have no access to or rarely see a general practitioner, other options should be considered, including universal ECG screening at particular ages (such as every five or 10 years from the age of 65) or installing automated pulse-measuring equipment that can detect irregular rhythms in pharmacies, health centers, and places where large numbers of people congregate such as shopping malls and sports centers. In a small German study, ECG showed high diagnostic capability, detecting previously unknown AF in seven out of 132 participants with a mean age of 64 and different risk factors such as hypertension and diabetes.⁴⁸

When there is a high probability that AF is present, 24-hour, or even longer, ECG monitoring may be considered.

Conclusions

Detection and control of hypertension is and should remain a priority; the levels of diagnosis and treatment in Portugal are still far from ideal and below those in most European countries.

However, atrial fibrillation may have been neglected as a cause of cerebrovascular mortality even though it is a significant factor in the high incidence of death from stroke in Portugal.

The expected rise in the mean age of the Portuguese population at least until 2025 is set to lead to an increase not only in AF but also in the number of strokes that can be attributed to this arrhythmia. To prevent this it will be necessary to develop an intervention plan with three main lines of action: detection of asymptomatic cases, overcoming therapeutic inertia, and application of the treatment guidelines for thromboembolic prophylaxis for high-risk patients (Figure 2).

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

- Portugal. Direcção-Geral da Saúde. Direcção de Serviços de Epidemiologia e Estatísticas de Saúde. Divisão de Estatísticas de Saúde. Elementos Estatísticos: Informação Geral: Saúde 2008 / Direcção-Geral da Saúde – Lisboa: Direcção-Geral da Saúde, 2008. Available at: www.dgs.pt/upload/membro.id/ficheiros/i013685.pdf, accessed January 6, 2013.
- Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, D'Agostino RB, Massaro JM, Beiser A, Wolf PA, Benjamin EJ. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004 Aug 31;110(9):1042-6.
- Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991 Aug;22(8):983-8.
- Marini C, De Santis F, Sacco S, Russo T, Olivieri L, Totaro R, Carolei A. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. *Stroke*. 2005 Jun;36(6):1115-9.
- Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, D'Agostino RB. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996 Oct;27(10):1760-4.
- Bonhorst D, Mendes M, Adragão P, De Sousa J, Primo J, Leiria E, Rocha P. Prevalence of atrial fibrillation in the Portuguese population aged 40 and over: the FAMA study. *Rev Port Cardiol*. 2010 Mar;29(3):331-50.
- Dores H, Cardiga R, Ferreira R, Araújo I, Gândara F, Abreu A, Marques F, Leitão A, Fonseca C, Ceia F. Atrial fibrillation and thromboembolic risk: what is the extent of adherence to guidelines in clinical practice? *Rev Port Cardiol*. 2011 Feb;30(2):171-80.
- Cortez-Dias N, Martins S, Belo A, Fiuza M; Investigadores do Estudo VALSIM. Prevalence and management of hypertension in primary care in Portugal. Insights from the VALSIM study. *Rev Port Cardiol*. 2009 May;28(5):499-523.
- Perdigão C, Rocha E, Duarte JS, Santos A, Macedo A. Prevalence and distribution of the main cardiovascular risk factors in Portugal-the AMALIA study. *Rev Port Cardiol*. 2011 Apr;30(4):393-432.
- Pereira M, Azevedo A, Barros H. Determinants of awareness, treatment and control of hypertension in a Portuguese population. *Rev Port Cardiol*. 2010;29(12):1779-92.
- Macedo ME, Lima MJ, Silva AO, Alcantara P, Ramalhinho V, Carmona J. Prevalence, awareness, treatment and control of hypertension in Portugal: the PAP study. *J Hypertens*. 2005 Sep;23(9):1661-6.
- Pereira M, Carreira H, Vales C, Rocha V, Azevedo A, Lunet N. Trends in hypertension prevalence (1990-2005) and mean blood pressure (1975-2005) in Portugal: a systematic review. *Blood Press*. 2012;21(4):220-6.
- Polónia J, Maldonado J, Ramos R, Bertoquini S, Duro M, Almeida C, Ferreira J, Barbosa L, Silva JA, Martins L. Estimation of salt intake by urinary sodium excretion in a Portuguese adult population and its relationship to arterial stiffness. *Rev Port Cardiol*. 2006;25(9):801-17.
- AHA Dietary Guidelines revision. A statement for healthcare professionals from the Nutrition Committee of the American Heart Association 2000. *Circulation* 2000;102:2284-99.
- Martins L, Nazare J, Pinto F, Polonia J. Portuguese action against salt and hypertension (PAASH). From research to a national policy and regulatory law on food salt content. *J Hypertens* 2009; 27(suppl 4): S326.
- Polonia J, Martins L. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens*. 2009 Nov;23(11):771-2.
- Diário da República, 1ª série, N.º 155, 12 de Agosto de 2009, Lei nº 75/2009.
- Santos A, Martins MJ, Guimarães JT, Severo M, Azevedo I. Sodium-rich carbonated natural mineral water ingestion and blood pressure. *Rev Port Cardiol*. 2010 Feb;29(2):159-72.
- MINISTÉRIO DA SAÚDE. DIRECÇÃO-GERAL DA SAÚDE. Programa Nacional de Prevenção e Controlo das Doenças Cardiovasculares. Despacho nº. 16415/2003 (II série) – D.R. nº. 193 de 22 de Agosto, com as alterações do Despacho nº. 266/2006 do Alto Comissário da Saúde, publicado no DR, II Série, número 9, de 12 de Janeiro, available at <http://www.portaldasaude.pt/NR/rdonlyres/9B01E25D-D16C-422C-B3E0-140D1B591198/0/circularnormativadgs03dpsps060206.pdf>, accessed January 6, 2012.
- Cunha L. Fibrilhação auricular de causa não valvular: perspectiva do neurologista. *Rev Port Cardiol*. 2012; 31(Supl.1) :27-31.
- Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Barker-Collo S, Bartels DH, Bell ML, Benjamin EJ, Bennett D, Bhalla K, Bikbov B, Bin Abdulhak A, Birbeck G, Blyth F, Bolliger I, Boufous S, Bucello C, Burch M, Burney P, Carapetis J, Chen H, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahodwala N, De Leo D, Degenhardt L, Delossantos A, Denenberg J, Des Jarlais DC, Dharmaratne SD, Dorsey ER, Driscoll T, Duber H, Ebel B, Erwin PJ, Espindola P, Ezzati M, Feigin V, Flaxman AD, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabriel SE, Gakidou E, Gaspari F, Gillum RF, Gonzalez-Medina D, Halasa YA, Haring D, Harrison JE, Havmoeller R, Hay RJ, Hoen B, Hotez PJ, Hoy D, Jacobsen KH, James SL, Jasrasaria R, Jayaraman S, Johns N, Karthikeyan G, Kassebaum N, Keren A, Khoo JP, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lipnick M, Lipshultz SE, Ohno SL, Mabweijano J, MacIntyre MF, Mallinger L, March L, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGrath J, Mensah GA, Merriman TR, Michaud C, Miller M, Miller TR, Mock C, Mocumbi AO, Mokdad AA, Moran A, Mulholland K, Nair MN, Naldi L, Narayan KM, Nasseri K, Norman P, O'Donnell M, Omer SB, Ortblad K, Osborne R, Ozgediz D, Pahari B, Pandian JD, Rivero AP, Padilla RP, Perez-Ruiz F, Perico N, Phillips D, Pierce K, Pope CA 3rd, Porrini E, Pourmalek F, Raju M, Ranganathan D, Rehm JT, Rein DB, Remuzzi G, Rivara FP, Roberts T, De León FR, Rosenfeld LC, Rushton L, Sacco RL, Salomon JA, Sampson U, Sanman E, Schwebel DC, Segui-Gomez M, Shepard DS, Singh D, Singleton J, Sliwa K, Smith E, Steer A, Taylor JA, Thomas B, Tleyjeh IM, Towbin JA, Truelsen T, Undurraga EA, Venketasubramanian N, Vijayakumar L, Vos T, Wagner GR, Wang M, Wang W, Watt K, Weinstock MA, Weintraub R, Wilkinson JD, Woolf AD, Wulf S, Yeh PH, Yip P, Zabetian A, Zheng ZJ, Lopez AD, Murray CJ. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012 Dec 15;380(9859):2095-128.
- Providência R. Thromboembolic risk in atrial flutter resembles non-valvular atrial fibrillation: insights from transesophageal echocardiography. *American Journal of Cardiology* 2012 Jun 1;109(11):1686-7.
- Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation*. 2003 Aug 12;108(6):711-6.

24. Fuster V, Rydén LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: Circulation 2006;114:e257-e354.
25. 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 Jun 13;285(22):2864-70.
26. Lip GY, Nieuwlaet R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010 Feb;137(2):263-72.
27. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines-CPG; Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation-developed with the special contribution of the European Heart Rhythm Association. Europace. 2012 Oct;14(10):1385-413.
28. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, Halperin JL, Kay GN, Le Huez JY, Lowe JE, Olsson SB, Prystowsky EN, Tamargo JL, Wann LS, Smith SC Jr, Priori SG, Estes NA 3rd, Ezekowitz MD, Jackman WM, January CT, Lowe JE, Page RL, Slotwiner DJ, Stevenson WG, Tracy CM, Jacobs AK, Anderson JL, Albert N, Buller CE, Creager MA, Ettinger SM, Guyton RA, Halperin JL, Hochman JS, Kushner FG, Ohman EM, Stevenson WG, Tarkington LG, Yancy CW; American College of Cardiology Foundation/American Heart Association Task Force. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011 Mar 15;123(10):e269-367. doi: 10.1161/CIR.0b013e318214876d. Epub 2011 Mar 7.
29. Pisters R, Lane DA, Nieuwlaet 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 Nov;138(5):1093-100.
30. Connolly SJ, Eikelboom J, Joyner C, Diener HC, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim KH, Lewis BS, Van Mieghem W, Lip GY, Kim JH, Lanan-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, Afzal R, Yusuf S; AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. N Engl J Med. 2011 Mar 3;364(9):806-17. doi: 10.1056/NEJMoa1007432. Epub 2011 Feb 10.
31. Mant J, Hobbs FD, Fletcher K, Roalfe A, Fitzmaurice D, Lip GY, Murray E; BAFTA investigators; Midland Research Practices Network (MidReC). Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007 Aug 11;370(9586):493-503.
32. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009 Sep 17;361(12):1139-51.
33. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in non-valvular atrial fibrillation. N Engl J Med. 2011 Sep 8;365(10):883-91.
34. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011 Sep 15;365(11):981-92.
35. Rui Providência, Joana Providência, Maria João Ferreira, A.M. Leitão-Marques, Luís A. Providência. Novos anticoagulantes na fibrilhação auricular: meta-análise de três ensaios controlados com varfarina. Rev Port Cardiol. 2012;31(Espec Congr):23:CO-27.
36. Capodanno D, Capranzano P, Giacchi G, Calvi V, Tamburino C. Novel oral anticoagulants versus warfarin in non-valvular atrial fibrillation: A meta-analysis of 50,578 patients. Int J Cardiol. 2012 Apr 9. [Epub ahead of print]
37. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol. 2012 Aug 1;110(3):453-60.
38. Dentali F, Riva N, Crowther M, Turpie AG, Lip GY, Ageno W. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. Circulation. 2012 Nov 13;126(20):2381-91.
39. Johnson WD, Ganjoo AK, Stone CD, Srivivas RC, Howard M. The left atrial appendage: our most lethal human attachment! Surgical implications. Eur J Cardiothorac Surg. 2000;17:718-722.
40. Holmes DR, Reddy VY, Turi ZG, Doshi SK, Sievert H, Buchbinder M, Mullin CM, Sick P; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet. 2009;374:534-42.
41. Ana Faustino, Rui Providência, Luís Paiva, Romeu Cação, Marco Costa, António Leitão-Marques. Encerramento percutâneo do apêndice auricular esquerdo com dispositivo Amplatzer Cardiac Plug em doentes com fibrilhação auricular: experiência de um Serviço. Rev Port Cardiol 2012;31(Espec Congr):101:C88.
42. Olesen JB, Lip GY, Kamper AL, Hommel K, Køber L, Lane DA, Lindhardsen J, Gislason GH, Torp-Pedersen C. Stroke and bleeding in atrial fibrillation with chronic kidney disease. N Engl J Med. 2012 Aug 16;367(7):625-35.
43. Piccini JP, Stevens SR, Chang Y, Singer DE, Lokhnygina Y, Go AS, Patel MR, Mahaffey KW, Halperin JL, Breithardt G, Hankey GJ, Hacke W, Becker RC, Nessel CC, Fox KA, Califf RM. Renal Dysfunction as a predictor of stroke and systemic embolism in patients with nonvalvular atrial fibrillation: validation of the R2CHADS2 index in the ROCKET AF and ATRIA study cohorts. Circulation. 2012 Dec 3. [Epub ahead of print]
44. Providência R, Fernandes A, Paiva L, Faustino A, Barra S, Botelho A, Trigo J, Nascimento J, Leitão-Marques A. Decreased glomerular filtration rate and markers of left atrial stasis in patients with nonvalvular atrial fibrillation. Cardiology. 2012 Dec 13;124(1):3-10.
45. Man-Son-Hing M, Nichol G, Lau A, Laupacis A. Choosing antithrombotic therapy for elderly patients with atrial fibrillation who are at risk for falls. Arch Intern Med. 1999 Apr 12;159(7):677-85.
46. Christie B. People over 65 should be screened for atrial fibrillation, say stroke specialists. BMJ. 2012 Mar 5;344:e1644. doi: 10.1136/bmj.e1644.

47. de Torres LA, Adell MA, Blanco VG, Díez JM, Rioboó EM, Rejano JM, Lama JG, Alvarez RM, Moral RR, García JA, Díaz MP, de Castroviejo JR, de Torres CP, Martín AV, Villalobos AR, Larumbe MC, Joaquín EB, Solé MC, León MC, Costa LC, Collaborative Group Dofa-Ap. Opportunistic detection of atrial fibrillation in subjects aged 65 years or older in primary care: a randomised clinical trial of efficacy. DOFA-AP study protocol. *BMC Fam Pract.* 2012 Oct 30;13(1):106. [Epub ahead of print]
48. Samol A, Masin M, Gellner R, Otte B, Pavenstädt HJ, Ringelstein EB, Reinecke H, Waltenberger J, Kirchhof P. Prevalence of unknown atrial fibrillation in patients with risk factors. *Europace.* 2012 Dec 20. [Epub ahead of print]