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Authors

Pullicino, Patrick M
Qian, Min
Sacco, Ralph L
et al.

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RECURRENT STROKE IN THE WARFARIN VERSUS ASPIRIN IN REDUCED EJECTION FRACTION (WARCEF) TRIAL

Patrick M. Pullicino[a], **Min Qian**[b], **Ralph L. Sacco**[c], **Ron Freudenberger**[d], **Susan Graham**[e], **John R. Teerlink**[f], **Douglas Mann**[g], **Marco R. Di Tullio**[h], **Piotr Ponikowski**[i], **Dirk J. Lok**[j], **Stefan D. Anker**[k], **Gregory Y.H. Lip**[p], **Conrado J. Estol**[q], **Bruce Levin**[l], **J.P. Mohr**[m], **John L. P. Thompson**[n], and **Shunichi Homma**[o] **for the WARCEF Investigators***

[a]University of Kent, Canterbury, UK [b,h,l,m,n,o]Columbia University, New York, NY [c]University of Miami, Miami, FL [d]LeHigh Valley Hospital, Allentown, PA [e]SUNY Buffalo, Buffalo, NY [f]University of California at San Fancisco and San Francisco VA Medical Center, San Francisco, CA [g]Washington University, St Louis, MO [i]Medical University, Wroclaw, Poland [j]Hospital Deventer, Deventer, The Netherlands [k]Charité Universitätsmedizin, Campus-Virchow-Klinikum, Berlin, Germany [p]the University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK [q]Centro Neurológico de Tratamiento y Rehabilitación, Buenos Aires, Argentina.(see supplementary on-line investigator list)

Abstract

Background and Purpose—WARCEF randomized 2305 patients in sinus rhythm with ejection fraction (EF) ≤35% to warfarin (INR 2.0–3.5) or aspirin 325 mg. Warfarin reduced the incident ischemic stroke (IIS) hazard rate by 48% over aspirin in a secondary analysis. The IIS rate in heart failure (HF) is too low to warrant routine anticoagulation but epidemiologic studies show that prior stroke increases the stroke risk in HF. We here explore IIS rates in WARCEF patients with and without baseline stroke to look for risk factors for IIS and determine if a subgroup with an IIS rate high enough to give a clinically relevant stroke risk reduction can be identified.

Methods—We compared potential stroke risk factors between patients with baseline stroke and those without using the exact conditional score test for Poisson variables. We looked for risk factors for IIS, by comparing IIS rates between different risk factors. For EF we tried cutoff points of 10%, 15% and 20%. 15% was used as it was the highest EF that was associated with a significant increase in IIS rate. IIS and EF strata were balanced as to warfarin/aspirin assignment by the stratified randomized design. A multiple Poisson regression examined the simultaneous effects of all risk factors on IIS rate. IIS rates per hundred patient years (/100PY) were calculated in patient groups with significant risk factors. Missing values were assigned the modal value.

Results—Twenty of 248 (8.1%) patients with baseline stroke and 64 of 2048 (3.1%) without had IIS. IIS rate in patients with baseline stroke (2.37/100PY) was greater than patients without (0.89/100PY)(rate ratio 2.68, p<0.001). Fourteen of 219 (6.4%) patients with ejection fraction

Corresponding author: Patrick Pullicino, KentHealth,: Rutherford Building, University of Kent, Canterbury, CT2 7PD, UK. Telephone/Fax:01227 827204. P.Pullicino@kent.ac.uk.

(EF)<15% and 70 of 2079 (3.4%) with EF ≥15% had IIS. In the multiple regression analysis stroke at baseline (p<0.001) and EF<15% vs. ≥15% (p=.005) remained significant predictors of IIS. IIS rate was 2.04/100PY in patients with EF<15% and 0.95/100PY in patients with EF ≥15% (p=0.009). IIS rate in patients with baseline stroke and reduced EF was 5.88/100PY with EF<15% decreasing to 2.62/100PY with EF<30%.

Conclusions—In a WARCEF exploratory analysis, prior stroke and EF<15% were risk factors for IIS. Further research is needed to determine if a clinically relevant stroke risk reduction is obtainable with warfarin in HF patients with prior stroke and reduced EF.

Keywords

Heart Failure; Stroke; Ejection fraction

INTRODUCTION

The Warfarin versus aspirin in reduced cardiac ejection fraction (WARCEF) randomized 2305 patients in sinus rhythm with ejection fraction (EF) ≤35% to warfarin (INR 2.0–3.5) or aspirin 325 mg. Warfarin reduced the incident ischemic stroke (IIS) hazard rate by 48% over aspirin in a secondary analysis in terms of time to IIS, (HR 0.52; 95% CI 0.33 to 0.82; P = 0.005 in a stratified cause-specific Cox model).[1] Although this important finding is supported by a recent study,[2] its clinical significance is difficult to assess for several reasons: Firstly because it is the result of a subgroup analysis, the primary combined endpoint (death, stroke and intracerebral hemorrhage) of WARCEF having been negative. Secondly because the reduction in IIS rate with warfarin over aspirin in WARCEF has been said to be offset by an increase in major systemic hemorrhages.[3] Thirdly, we have found that the effect of warfarin on stroke in WARCEF is not homogenous and warfarin has a greater risk reduction effect in the cardio-embolic stroke subgroup.[4]

The situation in atrial fibrillation (AF) bears similarities to that in HF in sinus rhythm.[5] The stroke risk reduction effect of warfarin is similar[6] but subgroups with stroke risk high enough have to be identified in whom the benefits of warfarin give a net clinical advantage. In AF, these subgroups have been defined by use of scores such as CHADS2,[7] for which there is no counterpart in HF. A recent study[8] using decision analysis methodology showed that patients require at least an 0.8% absolute risk reduction (number needed to treat 125) in order to agree to initiate anticoagulation treatment. A 0.52 hazard rate with warfarin would not achieve this absolute risk reduction in patients with heart failure (HF) in sinus rhythm, who have stroke rates of 0.8%–1.5% per year.[2, 9] Although prior stroke also appears to increase the stroke rate in HF[10] it is unclear whether patients with recurrent stroke or some subgroup of them, would have a rate high enough to warrant routine anticoagulation. This study was initiated to look for risk factors for IIS and at the rate of IIS in patients with prior stroke in WARCEF to determine if a subgroup with a higher stroke rate can be identified.

METHODS

The primary outcome of this post-hoc analysis was onset of IIS, previously defined.[1] We investigated risk factors for IIS, comparing the IIS rates between patients with and without

different potential stroke risk factors in the WARCEF baseline data (see Table 1) using Poisson regression. For EF we assessed cut-off points of 10%, 15% and 20%. 15% was used as it was the highest EF showing a significant increase in IIS rate. IIS and EF strata were balanced as to warfarin/aspirin assignment by the stratified randomized design. A multiple Poisson regression examined the simultaneous effects of all risk factors on IIS rate. We also compared the IIS rate per hundred patient years (/100 PY) between the group with EF<15% vs. the group with EF≥15% in patients with and without baseline stroke. P-values and 95% CI were calculated based on the Wald test. Missing values were assigned the modal value. IIS rates were calculated for different EF levels in patients with baseline stroke.

RESULTS

Twenty of 248 (8.1%) patients with baseline stroke and 64 of 2048 (3.1%) without had IIS. Descriptive statistics (according to onset of IIS) for the demographic and clinical covariates are shown in table 1. Results from univariable and multivariable Poisson regression are presented in Table 2. For EF, 15% was the highest EF that was associated with a significant increase in IIS rate (p=0.064 at cutoff point 10%, p=0.009 at 15%, and p=0.261 at 20%). Only baseline stroke and EF<15% were significant risk factors for IIS in the univariable and multivariable models. IIS rates in patients with baseline stroke (2.37/100PY) were greater compared to patients without baseline stroke (0.89/100PY): unadjusted RR =2.68, p<0.001; adjusted RR=2.66, p<0.001. Fourteen of 219 (6.4%) patients with EF<15% and 70 of 2079 (3.4%) with EF ≥15% had IIS. IIS rates were 2.04/100PY in patients with EF<15% and 0.95/100PY in patients with EF ≥15% (unadjusted RR=2.15, p=0.009; adjusted RR=2.33, p=0.005). Comparison of IIS rate between groups with EF<15% vs. EF≥15% in patients with and without baseline stroke are presented in Table 3. IIS rate among the 21 patients with baseline stroke and EF<15% was 5.88/100PY and in patients without baseline stroke and EF<15% was 1.73/100PY. Table 4 shows warfarin/aspirin effect by presence of prior ischemic stroke. Table 5 shows warfarin/aspirin effect by EF categories.

DISCUSSION

We found that EF <15% is a risk factor for IIS in HF in sinus rhythm. This is a new finding but previous studies have suggested that EF <20% is a risk factor for stroke.[11] We have also confirmed previous studies[9, 10] showing prior stroke to be a risk factor for stroke in HF. Unlike previous studies, we did not find age,[9] diabetes[9, 10] or hypertension,[12] to be risk factors for IIS in HF. Apart from prior stroke (and HF), risk factors for stroke in HF in sinus rhythm are therefore different from those in AF.

A warfarin stroke risk reduction effect was not apparent in the WARCEF primary endpoint because it included a large number of deaths not reduced by warfarin. Stroke in HF can be fatal however and is disabling[4] and should be assessed for treatment in its own right. Although there were more major hemorrhages in the wafarin than aspirin arms in WARCEF, it is only intracerebral, not major systemic hemorrhage that offsets a risk reduction effect of warfarin since nonfatal systemic hemorrhage is treatable.[4] A recent study has shown that patients are willing to sustain 4.4 major systemic hemorrhages to prevent one stroke.[8] The rate of major systemic hemorrhage in WARCEF was well below this rate.

In WARCEF, warfarin gave a hazard ratio of 0.52 for IIS versus aspirin and patients on warfarin had 0.07 intracerebral hemorrhage events/100PY more than aspirin. We found a rate of IIS of 5.88/100PY in patients with both prior stroke and EF<15% which is a rate similar to that of patients with AF with a moderate stroke risk,[7] who are routinely anticoagulated. This suggests that there are subgroups of patients with HF with a high enough stroke rate to have a clinically relevant benefit from anticoagulation. The rate of IIS in all patients with baseline stroke (2.37/100PY) is still however quite low, and we did not find a significant stroke risk reduction effect by warfarin over aspirin in this subgroup, so we cannot advise anticoagulation of all HF patients with prior stroke. Our findings are based on small numbers however, and do need confirmation in a separate population, preferably in patients who are not on antithrombotics. We are planning a similar analysis in the Warfarin versus Antiplatelet Therapy in Chronic Heart Failure (WATCH) Study.[2]

Since AF is a strong risk factor for stroke and paroxysmal AF gives a similar risk to overt AF, the question arises whether the increased stroke risk in HF in sinus rhythm could be totally or partly due to undiagnosed paroxysmal AF. Patients with a prior history of AF or AF on baseline electrocardiogram were excluded from WARCEF. None of the 84 patients with IIS in WARCEF had overt atrial fibrillation. Non-invasive cardiac monitoring in patients with acute stroke detects up to 7.7% of patients to have paroxysmal AF.[13] so about 6 of the IIS in WARCEF could have been due to paroxysmal AF on this basis. If paroxysmal AF accounted for more than a small proportion of patients with IIS we would have expected known risk factors for AF including hypertension, diabetes and particularly age, to become significant risk factors for IIS in HF too.

The major limitation of this study is that the numbers of patients with both prior stroke and EF<15% is very small and represents only 9% of patients with prior stroke. The group was too small to show a significant warfarin hazard ratio. We have recently reported that the warfarin effect is greatest in the cardioembolic stroke subtype in WARCEF[4] and strokes with EF <15% are likely to be cardioembolic. Mortality and intracerebral hemorrhage rates could however be greater in this subgroup. Although the overall impact of treating this small subgroup with warfarin would be small, our findings does establish the presence of a high stroke risk subgroup in patients with HF. Thrombin inhibitors need to be studied in HF in sinus rhythm since current guidelines[14] recommend their use in AF with a thromboembolic rate 2.5 [1.98–3.15]/100 PY. This rate is similar to the rate of IIS in all HF patients with baseline stroke in WARCEF and potentially gives a larger subgroup in which anticoagulation with these agents might be clinically indicated.

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Complete List of Contributors

Members of the Warfarin versus Aspirin in Patients with Low Ejection Fraction (WARCEF) Study Group are as follows: *Executive Committee:* S. Homma, J.L.P Thompson, P. Pullicino, R. Freudenberger, S. Graham, J. Teerlink, S. Ammon, D. Mann, J.P. Mohr, R.L. Sacco, B. Massie, S. Anker, A. Labovitz, and C. Moy; *National Institute of Neurological Disorders and Stroke:* C. Moy, P. Gilbert, L. Gutmann, and J. Marler; *Clinical Coordinating Center:* S. Homma, V. Mejia, A. Gabriel, S. Borden, E. Peña, C. Harris, R. Khadouri, D. Gohs, M. Brown, G. Berry, D. Disantis, M. Scullin, P. Smith, S. Kohsaka, W. Watson, and L. Guillory; *Statistical Coordinating Center:* J. L. P. Thompson, B. Levin, R. Buchsbaum, M. Del Valle, A. Sanford, G. Levy, K. Tea, J. Grier, L. Swydan, B. O'Hare, R. Prodhan, R. Arbing, E. Flanagan, E. Duverger, A. Peljto, W. Lo, A. Tierney, A. Henriquez, and J. Keen; *Data and Safety Monitoring Board:* G.J. del Zoppo, G.W. Albers, M. Eliasziw, J.A.

Hinchey, K.C. Johnston, A.M. Lowe, I.L. Piña and J.A. Swain; *Endpoint Adjudication Committee:* J.R. Teerlink, S. Ammon, S. Slomiak, and L. Cape; *Neurology Adjudicators:* H.J.M. Barnett, A. Bruno, J.D. Easton, S. Levine, and D. Sahlas; *Cardiology Adjudicators:* F. Bleyer, P. Carson, A. Ellis, A. Miller, and S.T. Palmeri; *Core Echo Lab:* A. Labovitz, M. Di Tullio, M. Bierig, R. Liu, and C. Donato; *Hemorrhage adjudicator:* R. Hart. Clinical Research Organizations: *Clinsys (United States and Canada):* C. McKay, L. Wilson, E. Frey, K. Hayward, P. Stein-Beal and L. Konczarek; *Charite (Germany, Poland and Netherlands)*: M. Diek, M. Rohwedder, M. Bohdanowicz-Zazula, C.F. Peerenboom-Fey and M. Vissiennon; *Verum (Hungary and Ukraine)*: G. Rex, M. Varga, O. Kovtun and V. Orlyk; *FGK (Czech Republic and Slovakia):* P. Arenberger and J. Jaros. *STAT Research (Argentina):* A. Ruiz, M. Zimmermann and A. Ellenberg. The following institutions, investigators, and coordinators enrolled patients in the trial (shown in parenthesis is the number of patients randomized at the site): **United States,** *LSU Health Sciences Center (66):* A. Minagar, R. Kelley, J. McGee, P. Jinkins, and S. Bezucha; *Buffalo General Hospital (53):* S. Graham, V. Hart, M. Bonora, R. Sawyer, and K. Ammerman; *Detroit VA Medical Center (50):* P. Ramappa, V. Berchou, E. Jones, and E. Olgren; *Denver VA Medical Center (38):* B. Hattler, C. Anderson, B. Watson, and D. Wolf; *UMDNJ - New Brunswick (29):* J. Kosits, and L. Casazza; *Mayo Clinic - Transplant Center (28):* D. Yip, J. Meschia, A. McPhail, and K. Greenan; *LeBauer Cardiovascular Research (28):* R. Rothbart, J. Love, T. Schrader, and V. Garman; *Louisville VA Medical Center (27):* M. Stoddard, K. Remmel, and R. Longaker; *UMDNJ - Newark (26):* C. Gerula, M. Klapholz, J. Kirmani, and R. Mattessich; *Columbia University Medical Center (24):* M. Di Tullio, C. Rodriguez, and A. Gabriel; *Reno VA Medical Center (22):* W. Graettinger, A. Baker, and A. Valencia; *Madison VA Medical Center (22):* P. Kosolcharoen, and L. Williams; *University of Arizona Health Sciences Center (21):* V. Sorrell, B. Coull, and D. Bruck; *Morehouse School of Medicine (20):* E. Ofili, M. Frankel, and P. Jackson; *Cardiac Care and Vascular Medicine, PLLC (20):* M. Nanna, S. Sparr, and W. Almeida; *Long Island Jewish Medical Center (20):* R. Libman, B. Stephens, and C. DeMers; *Gulf Regional Research, LLC (20):* T. Giles, L. Roffidal, and D. Barratt; *Veterans Affairs Medical Center (19):* M. Liston, C. Lindsey, and L. Giron; *Virginia Commonwealth University (18):* W. Felton III, L. Joseph, and M. Lee; *University of Rochester Medical Center (16):* J. Bisognano, C. Benesch, and L. Caufield; *Santa Clara Medical Center (16):* E. Nishime, M. Moussavian, and E. Polland; *Black Hills Health Care System (16):* L. Fischer, K. Peterson, and B. McGinnis; *Lahey Clinic (15):* M. Tilem, G. Allam, and J. Beebe; *University of North Carolina at Chapel Hill (14):* P. Chang, S. Sen, and C. Schuler; *L.J. Chabert Medical Center (14):* L. Arcement, M. Charlet, and E. Falgout; *Sewickley Valley Medical Group, Cardiology (14):* M. Malkowski, T. Dugan, and J. Hobbs-Williams; *West Los Angeles VA Medical Center (14):* A. Warner, K. Panizzon, and J. Johnson; *Albert Einstein Medical Center (13):* J. Dissin, D. Karia, and N. Molakala; *Melbourne Internal Medicine Associates (11):* B. Dandapani, R. Vicari, and E. Anthony; *The Cleveland Clinic Foundation (11):* I. Katzan, R. Hobbs, and A. Richmond; *Denver Health Medical Center (11):* R. Hughes, W. Baker, and M Applegate; *Penn Presbyterian Medical Center (11):* B. Drachman, S. Khella, and S. Donovan; *Brooke Army Medical Center MCHE - MDC Cardiology Service (10):* A. Slim, and D. Pearce Moore; *Mount Sinai Medical Center (10):* B. Darrow, and A. Travis; *The Westchester Medical Group (10):* A. Mercando, and R. Pellegrino; *Salem VA Medical Center (10):* N. Jarmukli, and T. Ochalek;

St. Louis University Hospital (9): D. Janosik, and J. Dizes; *University of Kentucky (9):* L.C. Pettigrew, and D. Taylor; *MetroHealth Medical Center (7):* J. Hanna, and S. Bailey; *Hackensack University Medical Center (7):* R. Berkowitz, and S. Mathus; *Huntington VA Medical Center (6):* V. Virkud, and S. Shaw; *Lehigh Valley Hospital (6):* R. Freudenberger, and S. Nabhan; *Winthrop University Hospital (5):* E. Wirkowski, and B. George; *Central Arkansas VA Medical Center (5):* E. Smith, and S. Locke*; Connecticut Heart and Vascular Center, PC (5):* C. Landau, and D. Ferguson; *University of Texas Medical School - Houston (5):* H.V. Anderson, and L. Westbrook; *Cincinnati VA Medical Center (5):* M. Apelian, and S. Khoury; *Berkshire Medical Center (5):* J. Leppo, and T. Bator; *Richmond VA Medical Center (4):* W. Felton III, and M. Lee; *University of Louisville (4):* M. Stoddard, and R. Longaker; *Oklahoma City VA Medical Center (4):* U. Thadani, and J. Turner; *Southern Arizona VA Health Care System (4):* S. Goldman, and S. Daugherty; *Methodist Heart, Lung and Vascular Institute (4):* A. Adler, and T. Rennie; *Tri-State Medical Group Cardiology (4):* M. Malkowski, and D. Chupka; *George Washington University (4):* R. Katz, and L. Witkin; *Rochester General Hospital (3):* W. S. Burgin, and C. Weber; *Penn State Milton S. Hershey Medical Center (3):* J. Boehmer, and P. Frey; *Kaleida Health Millard Fillmore Hospital (3):* M. Wilson, and H. Tworek; *Northport VA Medical Center (3):* G. Mallis, and D. Mauceri; *Holy Cross Medical Group (3):* R. Schneider, and W. Schneider; *Jackson Memorial Hospital (3):* G. Ortiz, and M. Lichtenberger; *Northeast Georgia Heart Center (3):* B. Hott, and D. Patrick; *Rush University Medical Center (2):* S. Dunlap, and S.J. Kim; *Fallon Clinic, Inc. (2):* S. Pezzella, and D. Aubin; *Temple University Hospital (2):* L. Nikolaidis, and J. Wong; *North Shore University Hospital (1):* D. Leifer, and M. Rossi; *Methodist Hospital - Physician Association (1):* G. Torre, and J. Arredondo; *Mayo Clinic Scottsdale (1):* J. Lynch, and A. Metcalf; *Watson Clinic Center for Research, Inc. (1):* J. Gonzalez, and B. Donley; *Hospital of the University of Pennsylvania (1):* T. Cappola, and K. Craig; *Houston VA Medical Center (1):* B. Bozkurt, and M. Bolos; *Blackstone Cardiology Associates (1):* T. Noonan, and C. Alteri; **Poland,** *Wroclaw Military Hospital (68):* P. Ponikowski, L. Kowalczyk, A. Cwynar, D. Drazek, and J. Biegus; *Specjalistyczny Szpital im dr A. Sokoloskiego (41):* R. Szelemej, M. Jurczok, R. Serafin, and A. Jurczyk; *Samodzielny Szpital Wojewodzki (33):* M. Ogorek, D. Kopcik, B. Metzkier-Wyrwa, and A. Szczepanska; *The Medical University of Warsaw (22):* M. Dluzniewski, W. Wicha, and M. Kuch; *SP ZOZ Szpital Wojewodzki (22):* K. Kuc, R. Piotrowski, and O. Lesniak; *Spzoz Szpital Miejski Nr 2 (15):* M. Krauze-Wielicka, J. Herman, and S. Nowakowska; *Miedzyleski Szpital Specjalistyczny (15):* T. Pasierski, B. Kozlowski, and K. Wolkowska; *NZOZ Poradnia Kardiologiczna Centrum-Serce (11):* A. Juszczak, J. Michalska, and I. Jedlinski; *SCBK Pro Cordis (8):* P. Miekus, and M. Konarzewski; *SP ZOZ Klodzko (8):* P. Berkowski, and N. Jacek; *Slaskie Centrum Chorob Serca (8):* Z. Kalarus, and A. Duszanska; *Szpital Zespolony (5):* J. Tarchalski, and P. Czaja; *Medical University of Warsaw (5):* Z. Gaciong, and J. Gora; *SP Szpital Wojewodzki im. Papieza Jana Pawla II (2):* A. Kleinrok, and G. Prokop-Lewicka; **Canada,** *Ottawa Heart Institute (41):* H. Haddad, R. Davies, L. Sitwell, and J. Donaldson; *Etobicoke Cardiac Research Centre (29):* T. To, R. Yufe, and B. Donelly; *Montreal General Hospital (21):* T. Huynh, R. Cote, and B. St. Jacques; *Brampton Research Associates (20):* D. Borts, G. Tullio, and A.M. Sindilar; *Center for Neurologic Research (19):* T. Winder, E. Janzen and C. Walker; *St. Michael's Hospital (19):* G. Moe, N. Bayer, and A. Konig; *London Health Sciences Centre (14):* M. Arnold, D. Spence, and J.

Smith; *Saint John Regional Hospital (13):* R. Bessoudo, P. Bailey, and A. McNulty; *Sudbury Cardiac Research (10):* S. Nawaz, and C. Dewar; *QE II Health Sciences Centre (10):* M. Rajda, and M. MacFarlane*; Jewish General Hospital (6):* J. Minuk, and C. Schanz; *Vancouver Island Health Research Center (6):* A. Penn, and L. Atkins; *Montreal Heart Institute (4):* A. Ducharme, and H. Brown; *St. Boniface General Hospital (4):* S. Zieroth, and A. Muñoz; **Netherlands,** *Deventer Ziekenhuis Cardiologie Research (73):* D. Lok, J.B.M. ten Holter, C. Huls, P. Bruggink- Andre, and A. van Bujisen-Nutters; *Jeroen Bosch Ziekenhuis (39):* M. Daniels, A. Coppes, M. van Zagten, and N. Elzebroek; *Tweesteden Ziekenhuis (22):* K. Hamroui, P. L. M. de Kort, and J. Vuijsters; *Elisabeth Ziekenhuis (16):* N. Holwerda, W. Hermans, and R. van der Loo; *Medisch Spectrum Twente (14):* E. Wajon, G. Hageman, and G. v. Buchem-Damming; *Reiner de Graaf Gasthuis (11):* E. Ronner, A. Wissenburg-van Lieshout, and H. Niekus; *Groene Hart Ziekenhuis (9):* M.W.J. van Hessen, and G.A.M. Verheul; *Twenteborg Ziekenhuis (2):* G. Linssen, and L. te Pas; *Ziekenhuis Hilversum (2):* J. Plomp, and P.A.R. de Milliano; *Medisch Centrum Leeuwarden (1):* R. Breedveld, and M.J. Bos; **Czech Republic,** *Kolin Hospital, Internal Dept. (44):* M. Houra, D. Beran, and R. Lebedova; *Trebic Kardiologicka Ambulance (20):* J. Carda, E. Bednarova, and J. Vosmerova; *Slany Municipal Hospital (17):* G. Marcinek, T. Drasnar, and O. Najmanova; *Litomysl Hospital, Internal Dept. (15):* M. Dunaj, E. Pechackova, and M. Kuchar; *Motol Faculty Hospital (14):* P. Jansky, J. Simon, and H. Dvorakova; *Prague Cardiological Clinic (13):* P. Gregor, M. Maruskova, and L. Svoboda; *Cardiology Outpatient Clinic Pilsen (13):* Z. Lorenc, and P. Kralicek; *Soukroma Kardiologická ambulance Opava (9):* L. Pollak, Z. and M. Krobot; *Brno Faculty Hospital, Internal and Cardiological Dept. (6):* J. Spinar, and M. Nemec; *St. Ann's Hospital Brno, (5):* L. Spinarova, and R. Kuba; *Prague Faculty Hospital Na Bulovce (3):* F. Padour, and I. Padourova; *Prague Homolka Hospital (3):* M. Padour, and M. Michalova; *The Charles University Hospital (3):* L. Golan, and M. Hajkova; *CARDIOMED s.r.o. (3):* J. Povolny, and L. Krizova; *Liberec District Hospital (2):* D. Horak, and P. Kucera; *IKEM Cardiological Clinic (2):* I. Malek, and B. Krizova; *Health Centre of Cardiology, Trutnov (1):* J. Svoboda, and R. Ferkl; **Hungary,** *Karolyi Hospital (44):* L. Regos, L. Csuros, O. Lovasz, and G. Kiss; *Bacs-Kiskun County Hospital (31):* S. Timar, N. Torok, and A. Hajnalne; *Uzsoki Hospital (30):* B. Palossy, A. Nagy, P. Fulop, and G. Jakab; *Peterfy Hospital (13):* A. Ronaszeki, M. Bodi, and M. Satori; *Medical and Health Science Center, Debrecen (5):* I. Edes, and I. Varga; *Dr. Bugyi Istvan Hospital (5):* A. Kovacs, and L. Berente; *DRC Gyógyszervizsgáló Központ Kft. (5):* E. Péterfai, and R. Pauer; *Ferenc Jahn Hospital (4):* K. Toth, and E. Nagy; *Hetenyi Hospital (4):* B. Benczur, and K Karsay; *Erzsebet County Hospital (3):* T. Végh, and R. Nagy; *St. Stephan Hospital (3):* P. Karpati, and Z. Davidovits; *National Institute of Cardiology (2):* J. Borbola, and J. Vanyi; *Toldy Ferenc Hospital (2):* B. Oze and A. Bujdoso; *Veszprem megyei Csolnoky Ferenc Kórház- Rendeőintézet (1):* I. Kosa, and L. Baliko; **Germany,** *Medical Practice Dr. Natour (46):* M. Natour, M. Morgil, E. Hartmann, and H. Morgil; *Ludwigshafen Clinic (18):* R. Winkler, S. Gass, and S. Baumann; *Medical Practice Dr. Jeserich (18):* M. Jeserich, J. Rodl, and M. Dzaiy; *Charité Berlin (16):* S. Anker, G. Turhan, and K. Wolf; *Johannes Gutenberg University (10):* S. Genth- Zotz, and T. Siebert; *Medical Practice Dr. Jakobs (9):* C. Jakobs, and M. Kiorwantsi; *Georg August University (7):* B. Pieske, and R. Wachter; *Leipzig Medical Network (4):* M. Schoenauer, and S. Voigt; *Schleswig-Holstein University Hospital (4):* H. Schunkert, and A.

Boguschewski; *Regensburg University Hospital (1):* M. Resch, and R. Wensel; *Gesellschaft fur Innovative Therapie (1):* V. Schumann and P. Heidrich; **Ukraine,** *National Medical University (27):* O. Girina, Y. Prokopovych, M. Lebedynska, and I. Sorokina; *City Clinical Hospital #1, Kiev (21):* O. Karpenko, N. Brodi, and S. Klochkov; *M.D. Stazhesko Institute of Cardiology (17):* L. Voronkov, Y. Besaga, and O. Novikova; *Kyiv Central Clinical Hospital (12):* K. Amosova, O. Yaremenko, and K. Balaban; *M.D. Strazhesko Institute of Cardiology of AMS (9):* V. Kovalenko, and N. Polenova; *Department Therapy of Stomatology faculty of National Medical University (9):* I. Sakharchuk, and A. Ogorodnichuk; *Kiev City Clinical Hosp of Ambulance (8):* L. Rudenko, and Y. Tutov; *M.D. Strazhesko Institute of Cardiology of AMS (6):* A. Parkhomenko, and S. Kozhukhov; *Odessa Municipal Clinical Hospital #9 (4):* E. Yakimenko, and S. Kolomiets; *Odessa State Medical University (2):* V. Yurlov, and S. Tikhonova; **Argentina,** *Centro Neurologico de Tratamiento y Rehabilitacion (25):* C. Estol, A. Elizalde, and B. Mangariello; *CIPREC (12):* C. Zaidman, and F. Guerlloy; *Hospital Fernandez (11):* P. Gitelman, K. Crotto, and S. Sassone; *Grupo Medico Alem (11):* J. Aiub, and F. Novoa; *CICLO/Instituto de Cardiologia La Plata (10):* R. Lopez Santi, and P. Romia; *CEDIMBA (Ramos Mejia) (8):* O. Montaña, and D. Malchik; *Instituto Medico Adrogue (Centro Adrogue) (6):* F. Sokn, and P. Schygiel; *UAI Hospital Universitario (5):* R. Porcile, and F. Soria Tito; *Instituto Cardiovascular de Buenos Aires (2):* J. Thierer, and P. Avellana; *Sanatorio Itoiz, Avellaneda (2):* C. Rapallo, and M. Calderon; **United Kingdom,** *City Hospital, Birmingham (41):* R. MacFadyen, R. Haynes, and J. Partridge; **Slovakia,** *III. Interna klinika, FNsP Nemocnica ak. L. Dérera (11):* M. Kokles, S. Mehešová, and A. Zachar; *KARDIOCENTRUM NITRA s.r.o. (11):* M. Hranai, T. Varadyova, and T. Göbö; *Kardiocentrum TN sro (5):* J. Litvinova, and P. Loviska.

Table 1

Baseline Characteristics of the Study Participants, According to onset of IIS

covariate	IIS (n=84)	No IIS (n=2221)	p-value*
Older patients (age ≥60)	46/ 84 (54.8)	1229/ 2221 (55.3)	0.917
Male	66/ 84 (78.6)	1774/ 2216 (80.1)	0.739
White non-hispanic	64/ 84 (76.2)	1669/ 2215 (75.3)	0.861
Continent			0.508
EU	36/ 84 (42.9)	1058/ 2221 (47.6)	
NA	43/ 84 (51.2)	1076/ 2221 (48.4)	
Systolic BP ≥119.5	51/ 84 (60.7)	1374/ 2215 (62.0)	0.807
Ejection fraction <15%	14/ 84 (16.7)	205/ 2214 (9.3)	0.023
NYHA Class III or IV	27/ 84 (32.1)	681/ 2206 (30.9)	0.804
Alcohol consumption			0.755
Current consumption, >2 oz/day	18/ 83 (21.7)	554/ 2215 (25.0)	
Previous consumption, >2 oz/day	18/ 83 (21.7)	488/ 2215 (22.0)	
Smoking status			0.989
Current smoker	15/ 83 (18.1)	393/ 2213 (17.8)	
Former smoker	42/ 83 (50.6)	1138/ 2213 (51.4)	
Already on warfarin	8/ 84 (9.5)	171/ 2221 (7.7)	0.540
Atrial Fibrillation	3/ 84 (3.6)	83/ 2211 (3.8)	0.931
Diabetes Mellitus	31/ 84 (36.9)	691/ 2210 (31.3)	0.275
Hypertension	49/ 81 (60.5)	1318/ 2151 (61.3)	0.888
Ischemic Cardiomyopathy	37/ 84 (44.0)	954/ 2209 (43.2)	0.876
Baseline stroke	20/ 84 (23.8)	228/ 2212 (10.3)	<0.001
Myocardial Infarction	47/ 84 (56.0)	1065/ 2210 (48.2)	0.162
Peripheral vascular disease	14/ 84 (16.7)	247/ 2221 (11.1)	0.115

* p-values were calculated using Chi-square test.

Table 2

Predictors of IIS rate in univariable and multivariable Poisson regression models.

Covariates	Unadjusted (univariable) model		Adjusted (multivariable) model	
	Rate ratio (95% CI)	p-value*	Rate ratio (95% CI)	p-value*
Older patients (age >=60)	1.11 (0.72,1.70)	0.641	1.02 (0.65,1.59)	0.946
Male	0.96 (0.57,1.61)	0.869	0.96 (0.55,1.66)	0.875
White, non-hispanic	1.03 (0.63,1.71)	0.893	0.99 (0.58,1.69)	0.981
Systolic BP >=119.5	0.95 (0.61,1.48)	0.827	0.96 (0.61,1.52)	0.874
Ejection fraction <15%	2.15 (1.21,3.82)	0.009	2.33 (1.30,4.18)	0.005
NYHA Class III or IV	1.14 (0.72,1.80)	0.570	1.04 (0.65,1.66)	0.882
Alcohol consumption		0.637		0.740
Current consumption, >2 oz/day	0.79 (0.46,1.35)		0.86 (0.49,1.51)	
Previous consumption, >2 oz/day	0.85 (0.49,1.45)		0.81 (0.45,1.45)	
Smoking status		0.992		0.977
Current smoker	0.98 (0.52,1.84)		0.93 (0.47,1.84)	
Former smoker	0.97 (0.60,1.58)		0.95 (0.57,1.60)	
Already on warfarin	1.20 (0.58,2.49)	0.620	1.03 (0.49,2.15)	0.937
Atrial Fibrillation	1.00 (0.32,3.17)	0.998	1.07 (0.34,3.42)	0.905
Diabetes Mellitus	1.34 (0.86,2.09)	0.193	1.19 (0.74,1.91)	0.471
Hypertension	1.01 (0.65,1.57)	0.965	0.91 (0.57,1.46)	0.694
Ischemic Cardiomyopathy	1.20 (0.78,1.84)	0.415	0.96 (0.58,1.60)	0.887
Myocardial Infarction	1.42 (0.92,2.18)	0.111	1.36 (0.81,2.28)	0.249
Peripheral vascular disease	1.74 (0.98,3.09)	0.058	1.59 (0.87,2.89)	0.132
Baseline stroke	2.68 (1.62,4.42)	<0.001	2.66 (1.59,4.45)	<0.001

* p-values were calculated using Wald test. Score tests for overdispersion were not significant.

Table 3

IIS rate by Baseline stroke and EF categories.

	EF<15%	EF≥15%	Rate Ratio	p-value*
With Baseline Stroke no. of events (no./100 pt-yr)	N=21, 51.0 pt-yrs	N=227, 793.4 pt-yrs		
	3 (5.88)	17 (2.14)	2.75	0.107
Without Baseline Stroke no. of events (no./100 pt-yr)	N=198, 635.7 pt-yrs	N=1859, 6597.4 pt-yrs		
	11 (1.73)	53 (0.80)	2.15	0.021

* p-values were calculated using Wald test.

Table 4

Warfarin/aspirin effect by presence of prior ischemic stroke.

	Warfarin	Aspirin	Rate Ratio	p-value*
With Baseline Stroke no. of events (no./100 pt-yr)	N=128, 444.7 pt-yrs	N=120, 399.7 pt-yrs		
	8 (1.80)	12 (3.00)	0.60	0.262
Without Baseline Stroke no. of events (no./100 pt-yr)	N=1014, 3600 pt-yrs	N=1043, 3633.1 pt-yrs		
	21 (0.58)	43 (1.18)	0.49	0.008

* p-values were calculated using Wald test.

Table 5

Warfarin/aspirin effect by EF categories

	Warfarin	Aspirin	Rate Ratio	p-value*
EF<15% no. of events (no./100 pt-yr)	N=110, 341.5 pt-yrs	N=109, 345.2 pt-yrs		
	8 (2.34)	6 (1.74)	1.35	0.580
EF≥15% no. of events (no./100 pt-yr)	N=1032, 3703.2 pt-yrs	N=1054, 3687.6 pt-yrs		
	21 (0.57)	49 (1.33)	0.43	0.001

* p-values were calculated using Wald test.