

SUPPLEMENTAL MATERIAL

List of Swiss-AF investigators

University Hospital Basel and Basel University: Stefanie Aeschbacher, Chloé Auberson, Steffen Blum, Leo Bonati, Selinda Ceylan, David Conen, Simone Doerpfeld, Ceylan Eken, Marc Girod, Elisa Hennings, Philipp Krisai, Michael Kühne, Christine Meyer-Zürn, Pascal Meyre, Andreas U. Monsch, Christian Müller, Stefan Osswald, Anne Springer, Christian Sticherling, Thomas Szucs, Gian Voellmin, Leon Zwimpfer.
Principal Investigator: Stefan Osswald; Local Principal Investigator: Michael Kühne

University Hospital Bern: Faculty: Drahomir Aujesky, Urs Fischer, Juerg Fuhrer, Laurent Roten, Simon Jung, Heinrich Mattle; Research fellows: Luise Adam, Carole Elodie Aubert, Martin Feller, Axel Loewe, Elisavet Moutzouri, Claudio Schneider; Study nurses: Tanja Flückiger, Cindy Groen, Lukas Ehram, Sven Hellrigl, Alexandra Nuoffer, Damiana Rakovic, Nathalie Schwab, Rylana Wenger. Local Principal Investigator: Nicolas Rodondi

Stadtspital Triemli Zurich: Christopher Beynon, Roger Dillier, Michèle Deubelbeiss, Franz Eberli, Christine Franzini, Isabel Juchli, Claudia Liedtke, Jacqueline Nadler, Thayze Obst, Jasmin Roth, Fiona Schломowitsch, Xiaoye Schneider, Katrin Studerus, Noreen Tynan, Dominik Weishaupt. Local Principal Investigator: Andreas Müller

Kantonsspital Baden: Simone Fontana, Silke Kuest, Karin Scheuch, Denise Hischier, Nicole Bonetti, Alexandra Grau, Jonas Villinger, Eva Laube, Philipp Baumgartner, Mark Filipovic, Marcel Frick, Giulia Montrasio, Stefanie Leuenberger, Franziska Rutz. Local Principal Investigator: Jürg-Hans Beer

Cardiocentro Lugano: Angelo Auricchio, Adriana Anesini, Cristina Camporini, Giulio Conte, Maria Luce Caputo, Francois Regoli. Local Principal Investigator: Tiziano Moccetti

Kantonsspital St. Gallen: Roman Brenner, David Altmann, Michaela Gemperle. Local Principal Investigator: Peter Ammann

Hôpital Cantonal Fribourg: Mathieu Firmann, Sandrine Foucras, Martine Rime. Local Principal Investigator: Daniel Hayoz

Luzerner Kantonsspital: Benjamin Berte, Virginia Justi, Frauke Kellner-Weldon, Brigitta Mehmman, Sonja Meier, Myriam Roth, Andrea Ruckli-Kaeppli, Ian Russi, Kai Schmidt, Mabelle Young, Melanie Zbinden. Local Principal Investigator: Richard Kobza

Ente Ospedaliero Cantonale Lugano: Jane Frangi-Kultalahti, Anica Pin, Luisa Vicari Local Principal Investigator: Giorgio Moschovitis

University Hospital Geneva: Georg Ehret, Hervé Gallet, Elise Guillermet, Francois Lazeyras, Karl-Olof Lovblad, Patrick Perret, Philippe Tavel, Cheryl Teres. Local Principal Investigator: Dipen Shah

University Hospital Lausanne: Nathalie Lauriers, Marie Méan, Sandrine Salzmman. Local Principal Investigator: Jürg Schläpfer

Bürgerspital Solothurn: Andrea Grêt, Jan Novak, Sandra Vitelli. Local Principal Investigator: Frank-Peter Stephan

Ente Ospedaliero Cantonale Bellinzona: Jane Frangi-Kultalahti, Augusto Gallino. Local Principal Investigator: Marcello Di Valentino

University of Zurich/University Hospital Zurich: Fabienne Witassek, Matthias Schwenkglens.

Medical Image Analysis Center AG Basel: Jens Würfel (Head), Anna Altermatt, Michael Amann, Petra Huber, Esther Ruberte, Tim Sinnecker, Vanessa Zuber.

Clinical Trial Unit Basel: Michael Coslovsky (Head), Pascal Benkert, Gilles Dutilh, Milica Markovic, Pia Neuschwander, Patrick Simon

Schiller AG Baar: Ramun Schmid

Table S1. Association of antidiabetic medication with specific AF symptoms (n, 2411)[†]

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Palpitations		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	0.78 (0.59; 1.02)	0.76 (0.57; 1.00)
<i>Insulin-requiring diabetes</i>	0.41 (0.26; 0.66)	0.40 (0.25; 0.64)
Dizziness		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	1.15 (0.81; 1.63)	1.15 (0.80; 1.63)
<i>Insulin-requiring diabetes</i>	1.08 (0.64; 1.81)	1.08 (0.64; 1.81)
Chest pain		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	1.27 (0.84; 1.90)	1.22 (0.81; 1.84)
<i>Insulin-requiring diabetes</i>	1.50 (0.86; 2.61)	1.46 (0.84; 2.54)
Exercise intolerance		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	0.85 (0.62; 1.16)	0.86 (0.62; 1.17)
<i>Insulin-requiring diabetes</i>	0.57 (0.34; 0.96)	0.57 (0.34; 0.96)
Dyspnea		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	1.16 (0.87; 1.55)	1.13 (0.85; 1.51)
<i>Insulin-requiring diabetes</i>	0.88 (0.56; 1.36)	0.84 (0.54; 1.31)
Tiredness		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	0.96 (0.68; 1.37)	0.98 (0.69; 1.40)
<i>Insulin-requiring diabetes</i>	1.12 (0.69; 1.83)	1.12 (0.68; 1.83)
Syncope		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	1.25 (0.65; 2.42)	1.22 (0.63; 2.36)
<i>Insulin-requiring diabetes</i>	0.50 (0.12; 2.09)	0.49 (0.12; 2.05)
Other symptoms		
<i>No diabetes</i>	1 (Reference)	1 (Reference)
<i>Non-insulin-requiring diabetes</i>	0.70 (0.46; 1.05)	0.69 (0.46; 1.04)
<i>Insulin-requiring diabetes</i>	0.72 (0.39; 1.30)	0.71 (0.39; 1.28)

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, use of beta-blockers, and use of antiarrhythmic medications.

[†] For this analysis, participants were classified into patients without diabetes (reference), patients with non-insulin-requiring diabetes, and patients with insulin-requiring diabetes. Abbreviations: AF, atrial fibrillation; OR, odds ratio; CI, confidence interval.

Table S2. Association of diabetes with the domains of quality of life score† (n, 2411)

	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Impaired mobility	2.28 (1.82; 2.87)	1.59 (1.25; 2.02)
Impaired self-care	3.90 (2.57; 5.93)	3.20 (2.06; 4.95)
Impaired usual activities	2.49 (1.91; 3.25)	2.05 (1.55; 2.70)
Pain/discomfort	1.44 (1.16; 1.79)	1.14 (0.91; 1.43)
Anxiety/depression	1.02 (0.78; 1.34)	0.95 (0.72; 1.26)

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, smoking status, body mass index, and prevalent hypertension.

† The quality of life score was based on European Quality of life-5 Dimensions questionnaire (EQ-5D). EQ-5D was composed of five domains, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

Abbreviations: OR, odds ratio; CI, confidence interval.

Table S3. Baseline characteristics of participants with and without data available on left atrial size and ejection fraction†

	All (n, 2411)	LA measure available (n, 476)	Without LA measure available (n, 1935)	EF measure available (n, 711)	Without EF measure available (n, 1700)
Age, years	73.2 (8.4)	73.2 (8.4)	73.2 (8.4)	72.5 (8.6)	73.5 (8.3)
Women, n (%)	661 (27.4)	132 (27.7)	529 (27.4)	193 (27.1)	468 (27.6)
Smoking, n (%)					
<i>Current</i>	175 (7.3)	31 (6.5)	144 (7.4)	47 (6.6)	128 (7.5)
<i>Former</i>	1180 (48.9)	233 (48.9)	947 (48.9)	355 (49.9)	825 (48.5)
<i>Never</i>	1056 (43.8)	212 (44.5)	844 (43.7)	309 (43.5)	747 (43.9)
Body mass index, kg/m ²	27.7 (4.7)	27.6 (4.5)	27.6 (4.8)	27.6 (4.7)	27.6 (4.8)
Systolic blood pressure, mm Hg	133.8 (18.7)	134.9 (19.1)	133.5 (18.6)	133.9 (18.9)	133.8 (18.6)
Diastolic blood pressure, mm Hg	77.3 (11.8)	78.1 (11.8)	77.2 (11.8)	78.1 (11.9)	77 (11.8)
Diabetes mellitus, n (%)	420 (17.4)	74 (15.5)	346 (17.9)	115 (16.2)	305 (18)
History of hypertension, n (%)	1684 (69.8)	314 (66)	1370 (70.8)	472 (66.4)	1212 (71.3)
History of myocardial infarction, n (%)	390 (16.2)	78 (16.4)	312 (16.1)	114 (16)	276 (16.2)
History of heart failure, n (%)	625 (25.9)	113 (23.7)	512 (26.5)	175 (24.6)	450 (26.5)
History of stroke, n (%)	318 (13.2)	62 (13)	256 (13.2)	90 (12.7)	228 (13.4)
Quality of life	72.1 (17.4)	72.04 (18.4)	72.23 (17.2)	72.79 (17.6)	71.95 (17.4)

† Data are presented as mean (standard deviation), unless otherwise specified.

The quality of life score ranges from 0 to 100, with higher values indicating better quality of life.

Abbreviations: LA, left atrium; EF, ejection fraction.

Table S4. Association of diabetes and antidiabetic medication with echocardiographic parameters in AF patients[†]

	Model 1 β (95% CI)	Model 2 β (95% CI)
<u>Association of diabetes with echocardiographic parameters</u>		
Left atrial size (mm)	1.47 (-0.46; 3.40)	0.27 (-1.70; 2.23)
Left ventricular ejection fraction (%)	-1.63 (-3.90; 0.64)	-0.09 (-1.97; 1.79)
<u>Association of antidiabetic medication with echocardiographic parameters[‡]</u>		
Left atrial size (mm)		
<i>No diabetes</i>	0 (Reference)	0 (Reference)
<i>Non-insulin-requiring diabetes</i>	1.24 (-0.97; 3.46)	0.05 (-2.19; 2.29)
<i>Insulin-requiring diabetes</i>	2.07 (-1.42; 5.55)	0.85 (-2.61; 4.30)
Left ventricular ejection fraction (%)		
<i>No diabetes</i>	0 (Reference)	0 (Reference)
<i>Non-insulin-requiring diabetes</i>	-1.47 (-4.07; 1.14)	-1.56 (-4.26; 1.13)
<i>Insulin-requiring diabetes</i>	-2.07 (-6.16; 2.02)	-2.31 (-6.51; 1.88)

Model 1: adjusted for age and sex.

Model 2: adjusted for age, sex, smoking status, body mass index, and prevalent hypertension.

[†] Data on left atrial size and ejection fraction were available in a subsample of 476 and 711 participants, respectively. The beta regression coefficients indicate the predicted differences in mean echocardiographic parameters between categories of diabetes status.

[‡] For this analysis, participants were classified into patients without diabetes (reference), patients with non-insulin-requiring diabetes, and patients with insulin-requiring diabetes.

Abbreviations: AF, atrial fibrillation; β, beta regression coefficient; CI, confidence interval.

Table S5. Association of diabetes with AF phenotype, cardiac and neurological comorbidities, additionally adjusting for RCI and use of anticoagulation medication*

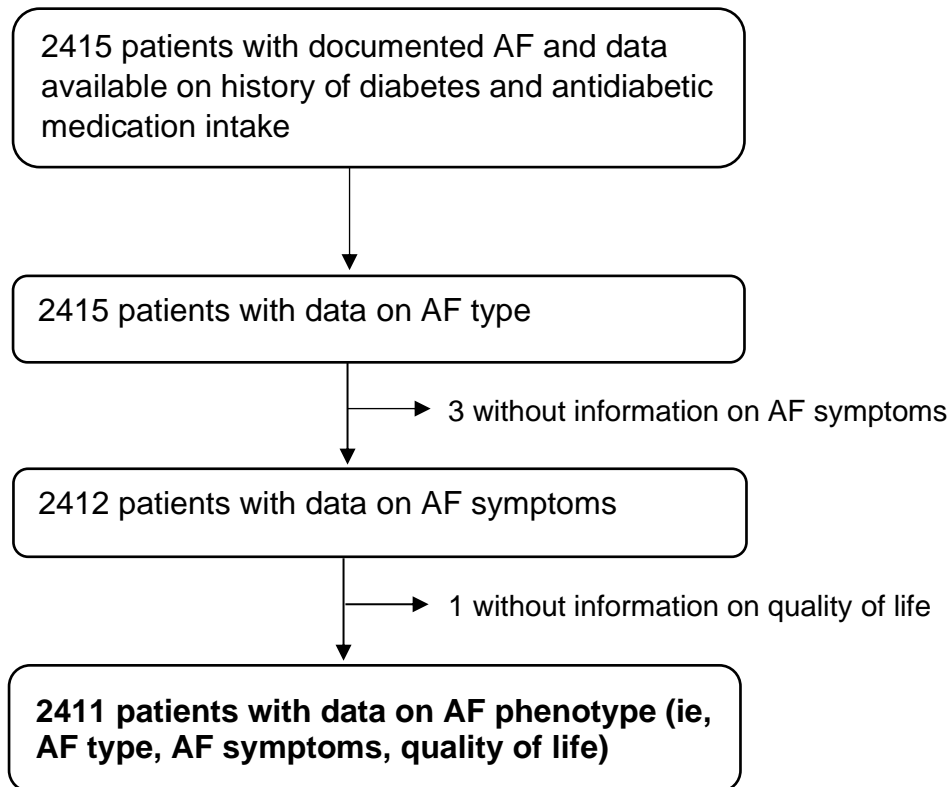
	Additionally adjusting for RCI	Additionally adjusting for use of anticoagulation medication
<u>Association of diabetes with AF phenotype</u>		
Non-paroxysmal AF, OR (95% CI)	1.04 (0.82; 1.30)	1.01 (0.80; 1.26)
Any AF symptoms, OR (95% CI)	0.75 (0.60; 0.92)	0.73 (0.59; 0.91)
Quality of life, β (95% CI)	-4.50 (-6.37; -2.64)	-4.53 (-6.39; -2.67)
<u>Association of diabetes with cardiac comorbidities</u>		
Hypertension, OR (95% CI)	2.98 (2.15; 4.14)	3.03 (2.18; 4.21)
Myocardial infarction, OR (95% CI)	1.53 (1.17; 2.01)	1.55 (1.18; 2.03)
Heart failure, OR (95% CI)	2.02 (1.59; 2.55)	1.99 (1.58; 2.52)
<u>Association of diabetes with neurological comorbidities</u>		
Stroke, OR (95% CI)	1.34 (1.00; 1.82)	1.38 (1.02; 1.86)
Cognitive impairment, OR (95% CI)	1.74 (1.38; 2.19)	1.76 (1.40; 2.21)

*Model 2 in the main analyses (reported in Table 2 and Table 3) was additionally adjusted for RCI and use of anticoagulation medication, respectively. Data on AF phenotype, history of hypertension and history of myocardial infarction were available in 2411 participants. Data on history of heart failure and data on history of stroke were available in 2409 and 2410 participants, respectively. Data on cognitive impairment were available in a 2398 participants. The quality of life score ranges from 0 to 100, with higher values indicating a better quality of life.

RCI was defined as either a history of pulmonary vein isolation and/or electrical cardioversion and/or use of antiarrhythmic medications, which altogether represent the most effective RCI currently available.

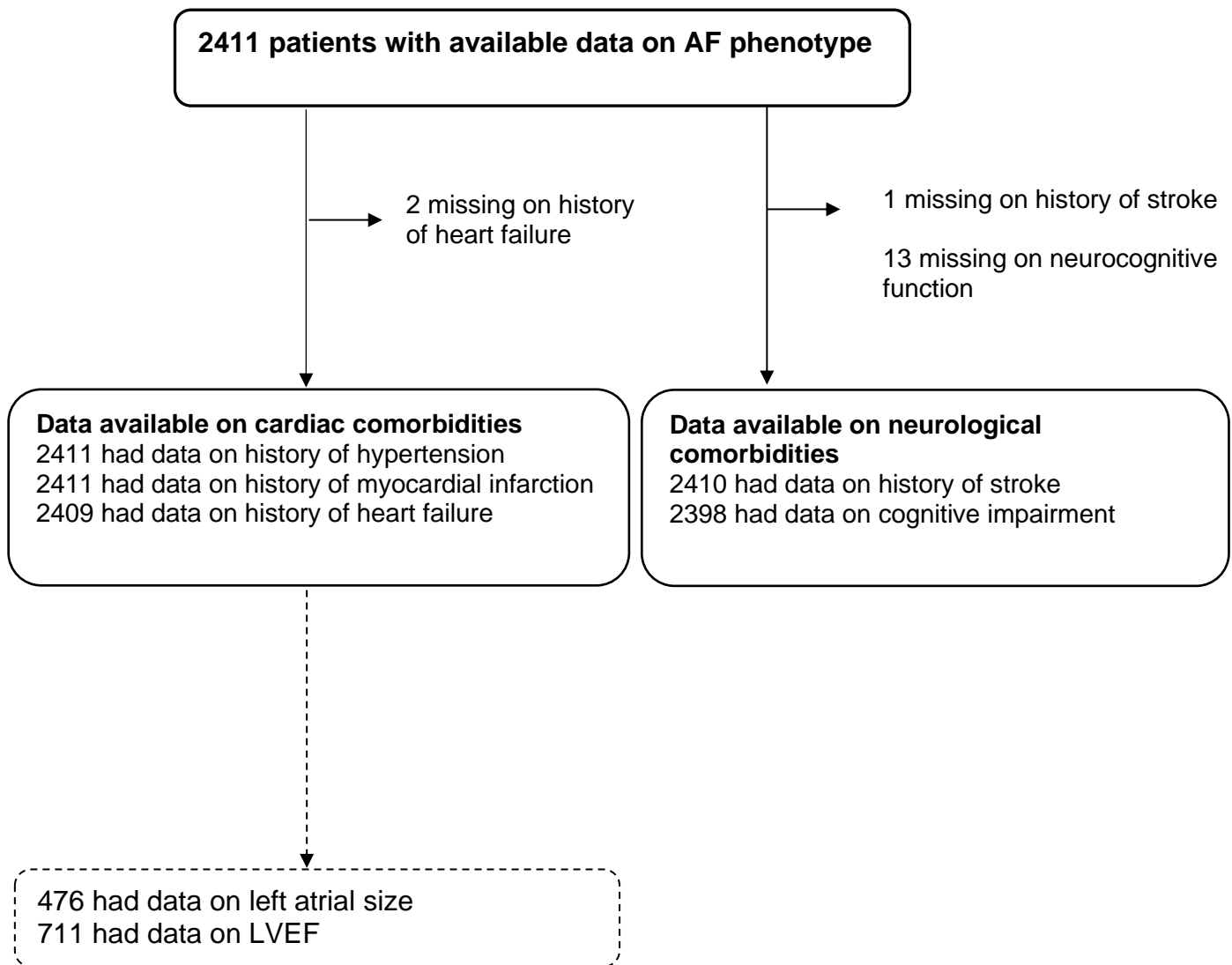
Abbreviations: AF, atrial fibrillation; RCI, rhythm control intervention; OR, odds ratio; CI, confidence interval; β , beta regression coefficient.

Figure S1. Flow chart for selection of study participants with data available on AF phenotype (primary analyses).



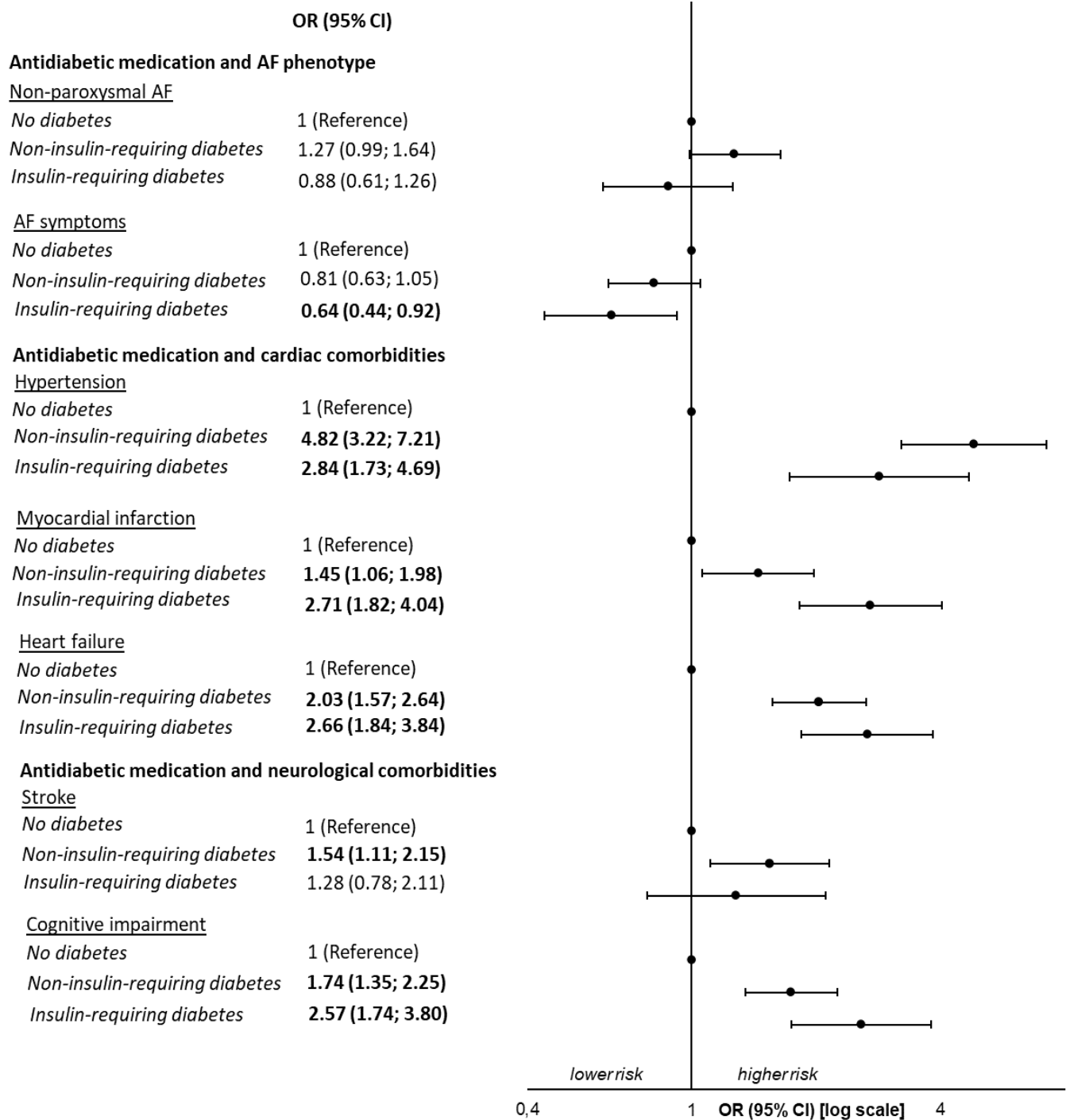
Abbreviation: AF, atrial fibrillation

Figure S2. Flow chart for selection of study participants with data available on cardiac and neurological comorbidities (secondary analyses).



Abbreviation: AF, atrial fibrillation; LVEF, left ventricular ejection fraction.

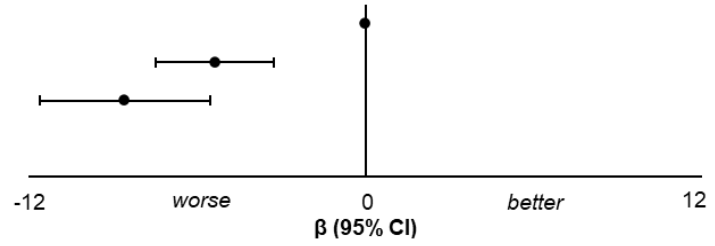
Figure S3. Association of antidiabetic medication with AF phenotype, cardiac and neurological comorbidities.



β (95% CI)

Association of antidiabetic medication with quality of life

<i>No diabetes</i>	0 (Reference)
<i>Non-insulin-requiring diabetes</i>	-5.36 (-7.46; -3.26)
<i>Insulin-requiring diabetes</i>	-8.59 (-11.6; -5.54)



For this analysis, participants were classified into: patients without diabetes, patients with non-insulin-requiring diabetes, and patients with insulin-requiring diabetes. **a.** Age- and sex- adjusted OR and 95% CI are derived based on logistic regression. The vertical line represents an odds ratio of 1. **b.** Age- and sex- adjusted β and 95% confidence intervals are derived based on linear regression. The vertical line represents a β of 0. The quality of life score ranges from 0 to 100, with higher values indicating better quality of life. Abbreviations: OR, odds ratio; CI, confidence interval; AF, atrial fibrillation; β , beta regression coefficient.