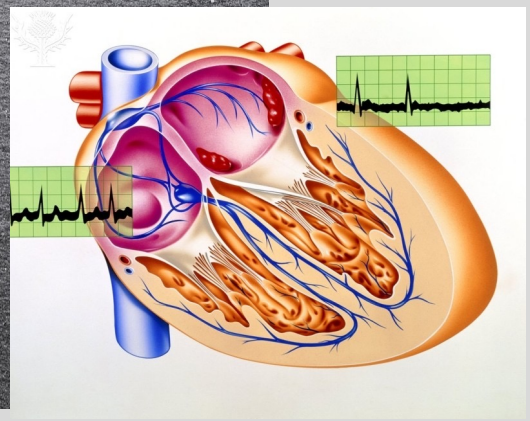

Diabetes and atrial fibrillation

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Centrum för diabetes, Akademiskt Specialistcentrum

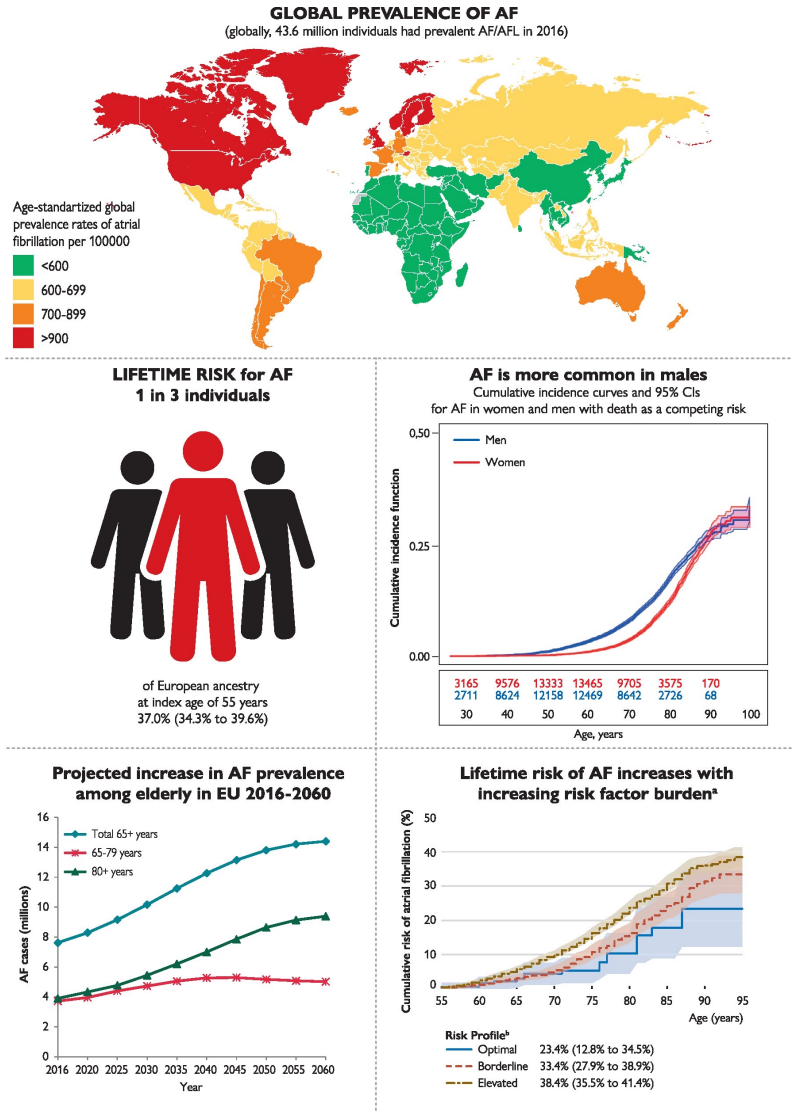
Karolinska Institutet

Region Stockholm

What I am going to talk about?

- Risk of atrial fibrillation in diabetes and prediabetes
- Pathophysiology linking diabetes and atrial fibrillation
- Why should we care if diabetes and AF coexist?
- What can we do to improve the prognosis in these patients?

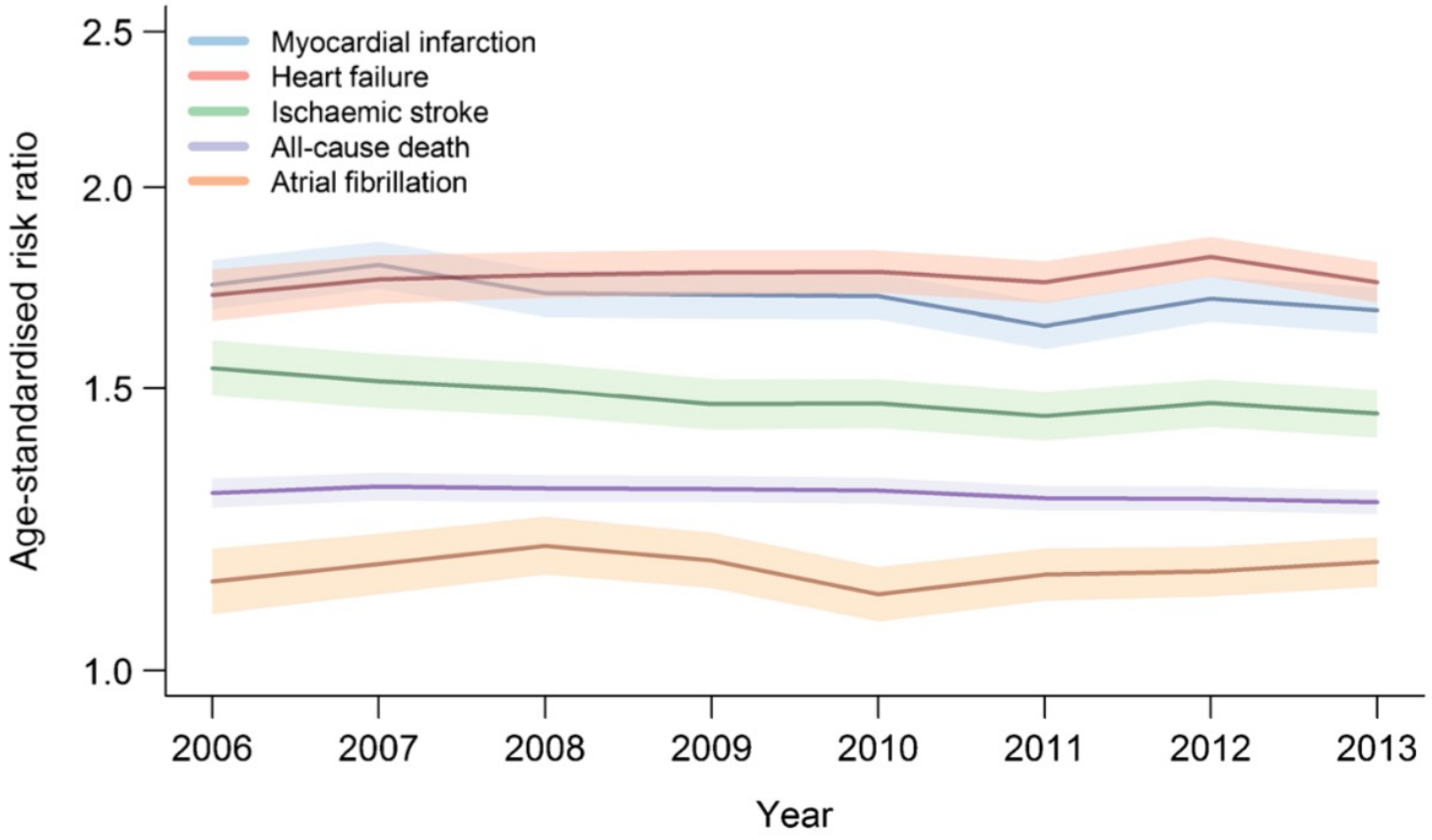
Epidemiology of atrial fibrillation (AF)



- **AF is the most common arrhythmia.**
- **Affects 3% of the adult population.**
- **Increasing prevalence with age.**
- **More common in men than women.**

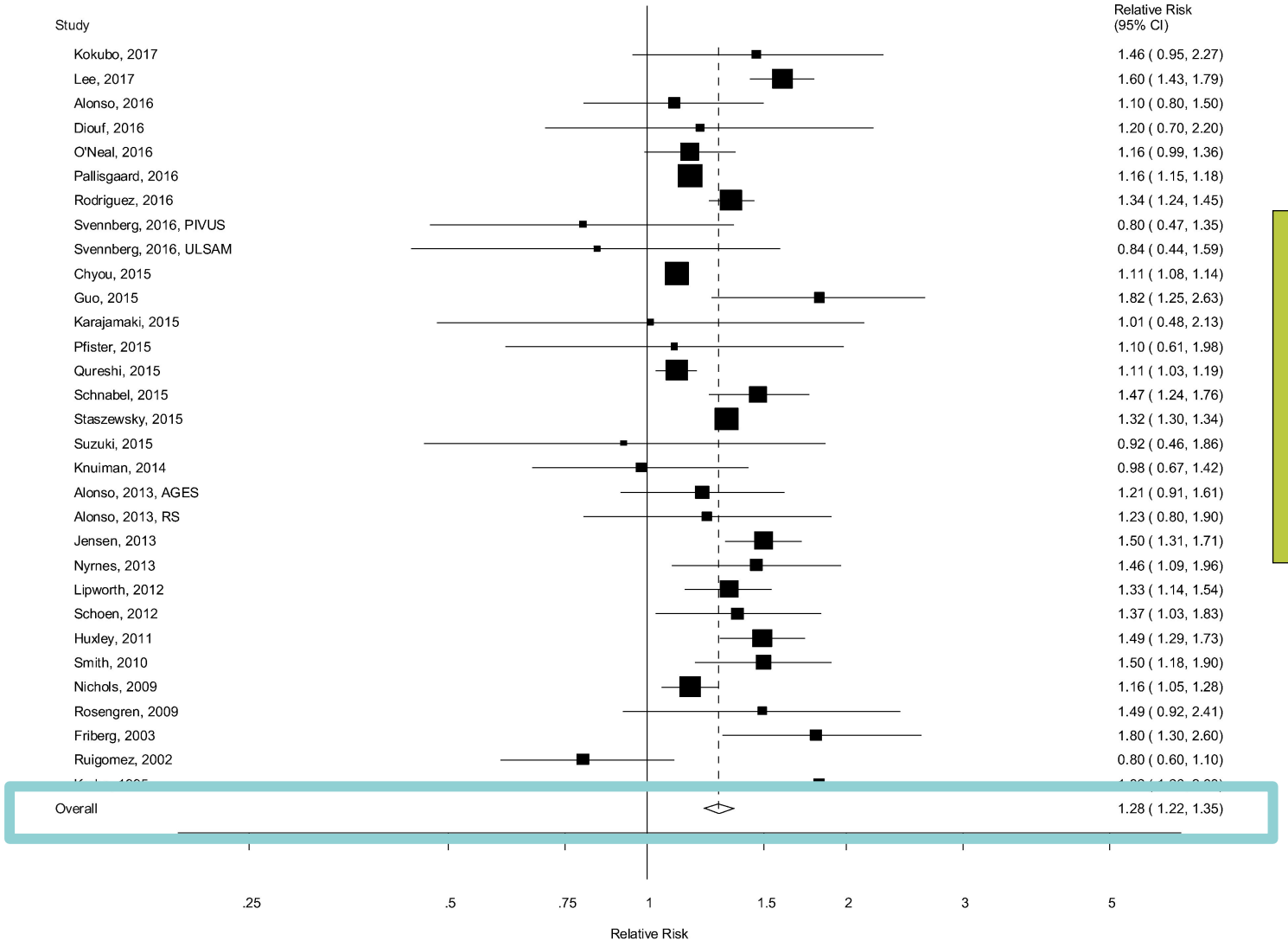
Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. Eur Heart J. 2020;ehaa612.

Higher risk for CVD complications including AF in patients with DM type 2



Compared to the general Swedish population patients with medication-treated type 2 diabetes had around 20% increased risk for AF.

Higher risk for AF in type 2 diabetes



Metaanalysis of 31 studies showed a 30% increased risk for AF in type 2 diabetes compared to those without diabetes.

Aune D, Feng T, Schlesinger S, Janszky I, Norat T, Riboli E. Diabetes mellitus, blood glucose and the risk of atrial fibrillation: A systematic review and meta-analysis of cohort studies. J Diabetes Complicat. 2018;32(5):501–11.

Higher risk for AF in type 2 diabetes

Atrial fibrillation, any position	All		Men		Women	
	Type 2 diabetes	Controls	Type 2 diabetes	Controls	Type 2 diabetes	Controls
All						
N	421,855	2,131,223	233,548	1,155,283	188,307	975,940
n (%)	37,590 (8.9%)	149,231 (7.0%)	21,808 (9.3%)	86,178 (7.5%)	15,782 (8.4%)	63,053 (6.5%)
Cases per 1000 years (95% CI)	15.99 (15.83–16.15)	11.89 (11.83–11.95)	16.95 (16.73–17.18)	12.66 (12.58–12.75)	14.83 (14.60–15.07)	10.97 (10.88–11.05)
Unadjusted IRR (95% CI)	1.35 (1.33–1.36)		1.34 (1.32–1.36)		1.35 (1.33–1.38)	
< 55 years						
N	83,356	424,662	50,094	255,240	33,262	169,422
n (%)	1569 (1.9%)	4356 (1.0%)	1175 (2.3%)	3478 (1.4%)	394 (1.2%)	878 (0.5%)
Cases per 1000 years (95% CI)	3.18 (3.02–3.34)	1.67 (1.62–1.72)	3.96 (3.74–4.20)	2.23 (2.15–2.30)	1.99 (1.80–2.20)	0.84 (0.79–0.90)
Unadjusted IRR (95% CI)	1.90 (1.79–2.01)		1.78 (1.67–1.90)		2.36 (2.10–2.66)	
55–64 years						
N	118,424	606,294	72,337	371,480	46,087	234,814
n (%)	6819 (5.8%)	22,332 (3.7%)	4901 (6.8%)	16,729 (4.5%)	1918 (4.2%)	5603 (2.4%)
Cases per 1000 years (95% CI)	9.50 (9.28–9.73)	5.84 (5.77–5.92)	11.30 (10.99–11.62)	7.20 (7.09–7.31)	6.75 (6.46–7.06)	3.74 (3.64–3.84)
Unadjusted IRR (95% CI)	1.63 (1.58–1.67)		1.57 (1.52–1.62)		1.81 (1.71–1.90)	
65–74 years						
N	122,848	623,184	67,666	335,590	55,182	287,594
n (%)	12,973 (10.6%)	50,919 (8.2%)	8011 (11.8%)	32,223 (9.6%)	4962 (9.0%)	18,696 (6.5%)
Cases per 1000 years (95% CI)	18.99 (18.67–19.32)	13.75 (13.63–13.87)	22.10 (21.62–22.59)	16.54 (16.36–16.72)	15.47 (15.05–15.91)	10.65 (10.50–10.80)
Unadjusted IRR (95% CI)	1.38 (1.36–1.41)		1.34 (1.30–1.37)		1.45 (1.41–1.50)	
75 + years						
N	97,227	477,083	43,451	192,973	53,776	284,110
n (%)	16,229 (16.7%)	71,624 (15.0%)	7721 (17.8%)	33,748 (17.5%)	8508 (15.8%)	37,876 (13.3%)
Cases per 1000 years (95% CI)	35.62 (35.08–36.17)	29.54 (29.33–29.76)	39.76 38.88–40.66)	34.82 (34.45–35.20)	32.54 (31.86–33.24)	26.02 (25.76–26.29)
Unadjusted IRR (95% CI)	1.21 (1.19–1.23)		1.14 (1.11–1.17)		1.25 (1.22–1.28)	

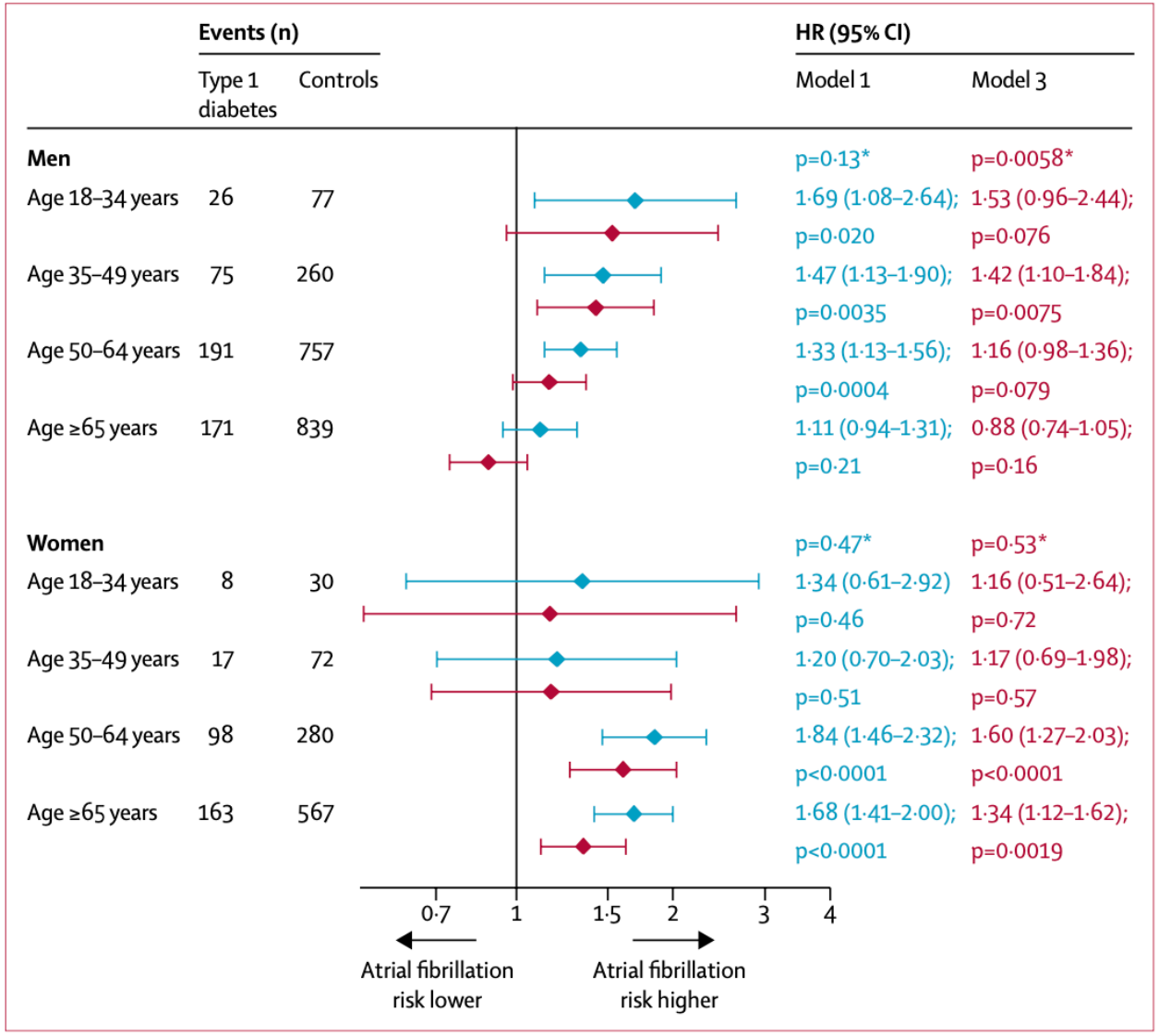
Swedish study from NDR.

30% increased risk of AF in patients with type 2 diabetes compared to matched controls from the general population.

Excess risk associated with grade of renal complications and glycemic control.

Ahmadi SS, Svensson AM, Pivodic A, Rosengren A, Lind M. Risk of atrial fibrillation in persons with type 2 diabetes and the excess risk in relation to glycaemic control and renal function: a Swedish cohort study. Cardiovasc Diabetol. 2020;19(1):9.

Higher risk for AF in type 1 diabetes



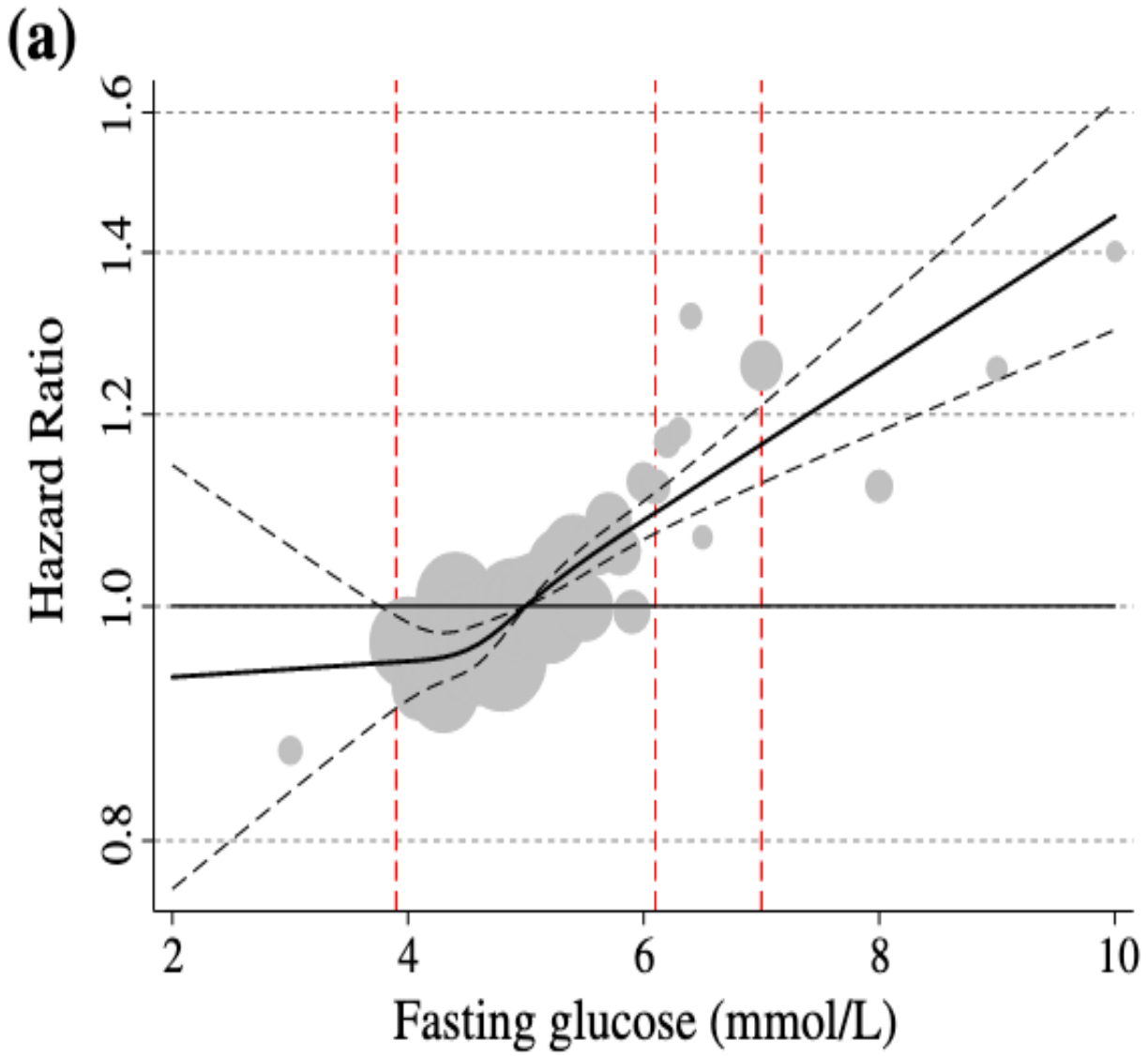
Swedish study from NDR.

Increased risk of AF in patients with type 1 diabetes (13% higher in men, 50% higher in women) compared to matched controls from the general population.

Excess risk associated with grade of renal complications and glycemic control.

Dahlqvist S, Rosengren A, Gudbjörnsdottir S, Pivodic A, Wedel H, Kosiborod M, et al. Risk of atrial fibrillation in people with type 1 diabetes compared with matched controls from the general population: a prospective case-control study. Lancet Diabetes Endocrinol. 2017;5(10):799–807.

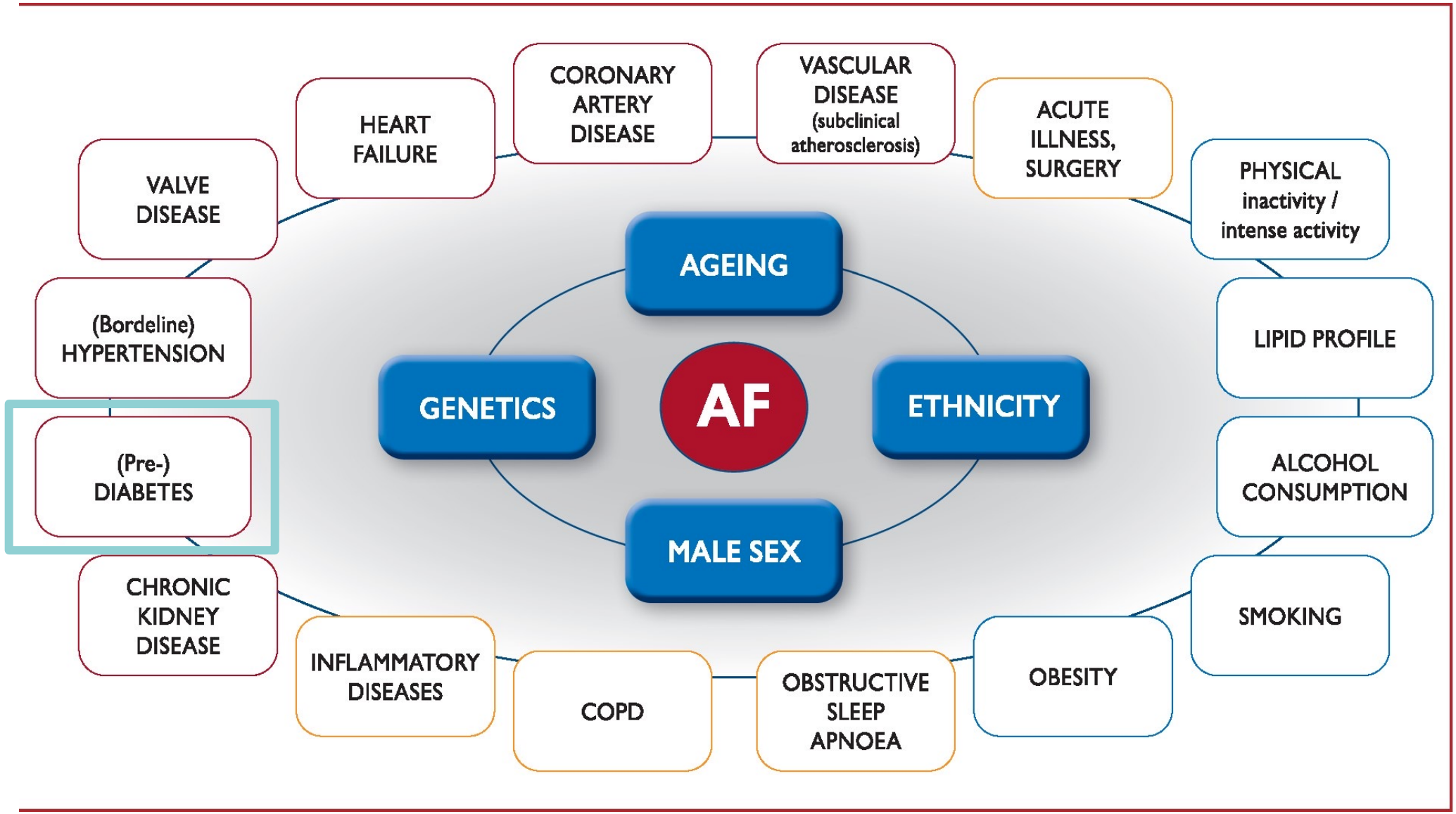
Higher risk for AF in prediabetes



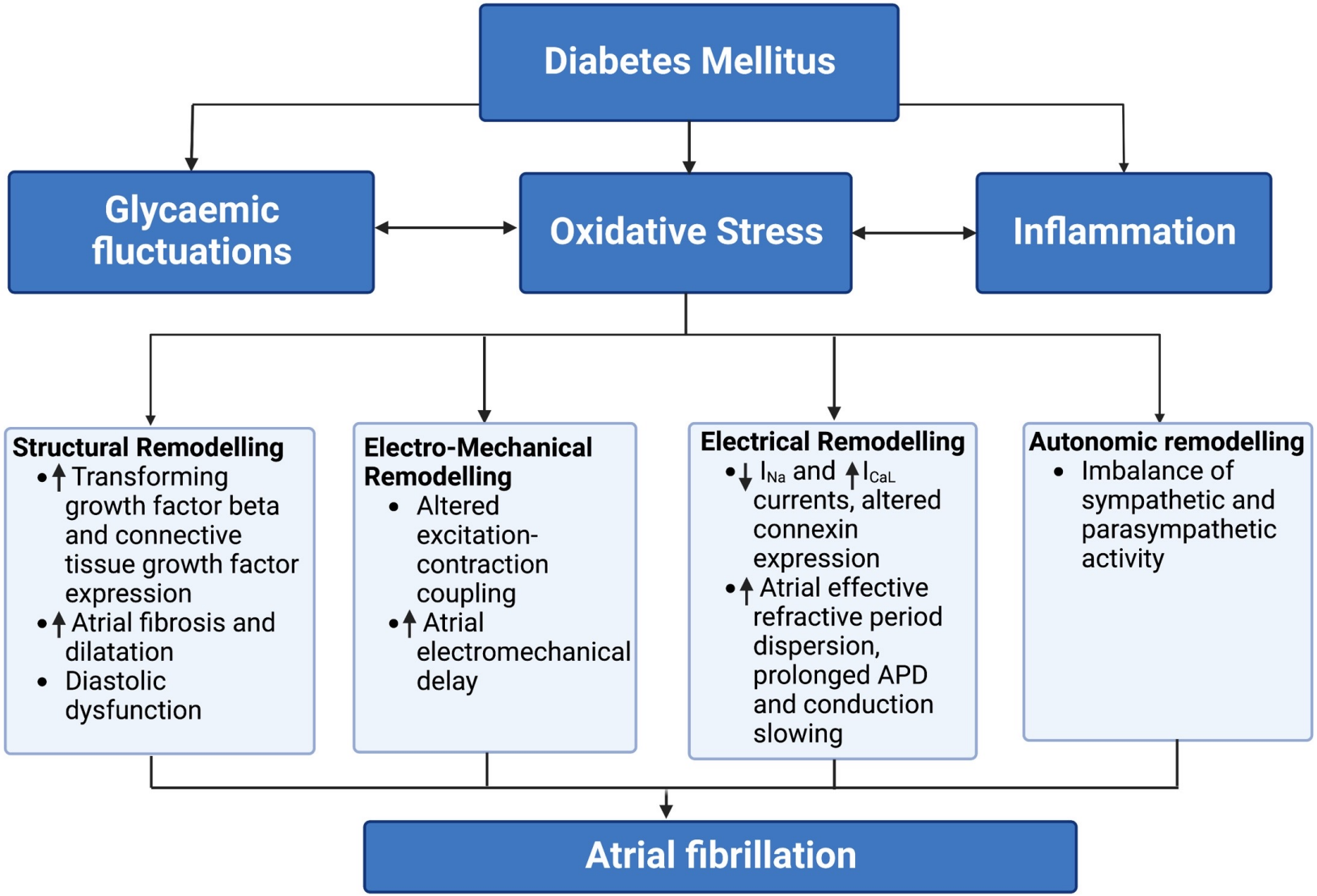
Impaired fasting glucose is associated with a 20% higher risk of incident AF.

Lind V, Hammar N, Lundman P, Friberg L, Talbäck M, Walldius G, et al. Impaired fasting glucose: a risk factor for atrial fibrillation and heart failure. Cardiovasc Diabetol. 2021;20(1):227.

Risk factors for atrial fibrillation



Pathophysiological mechanism linking diabetes and atrial fibrillation



Adapted from Allen Wang et al. *J Am Coll Cardiol* 2019; 74:1107-1115, with permission from Elsevier. Created with BioRender.com.

Prognosis in patients with concomitant diabetes and AF

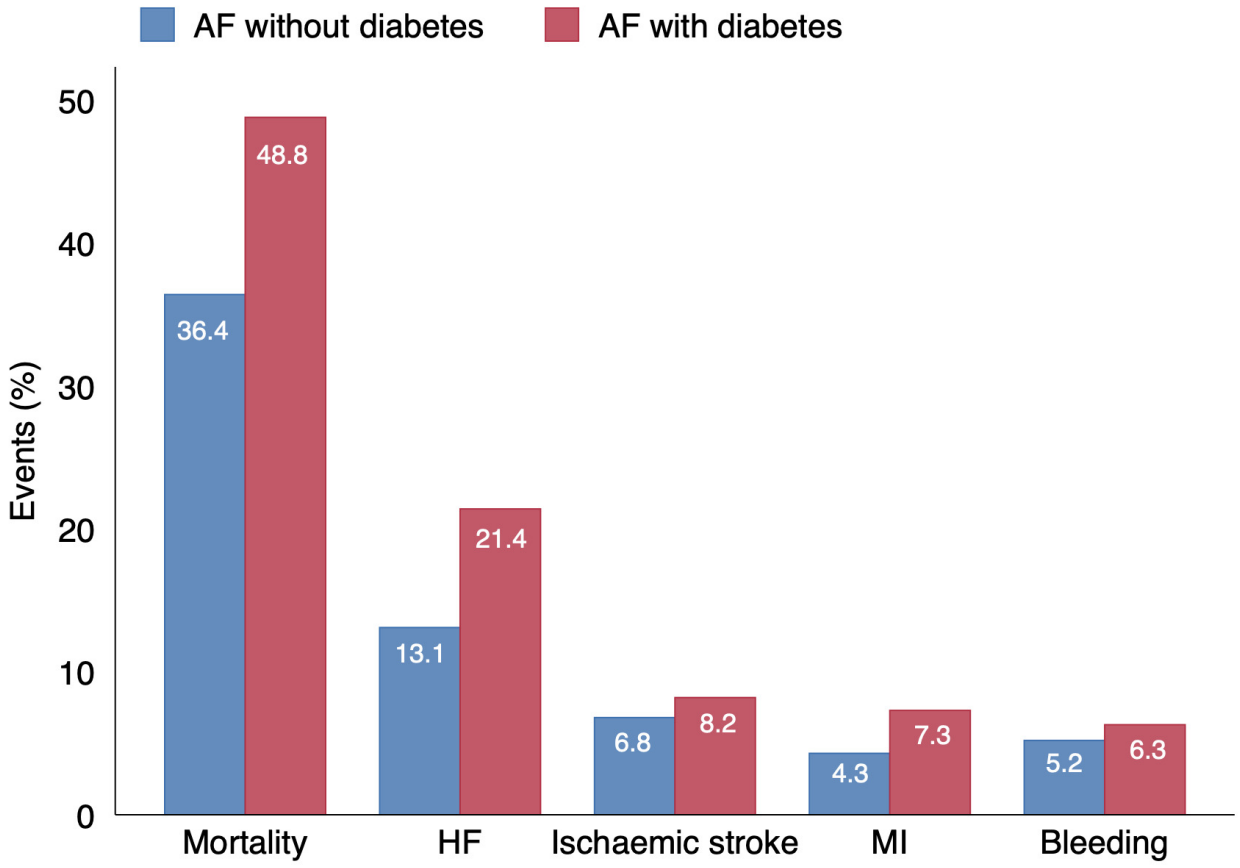
	No. of events (annual event rate, %)		Unadjusted		Multivariate-adjusted*		
	Patients with AF (n = 847)	Patients without AF (n = 10 293)	HR (95% CI)	P-value	HR (95% CI)	P-value	P-value for homogeneity
All deaths							
Male	83 (4.2)	517(2.0)	2.06 (1.63–2.60)	<0.0001	1.48 (1.15–1.91)	0.003	0.23
Female	53 (3.5)	226 (1.2)	2.93 (2.17–3.96)	<0.0001	1.86 (1.33–2.60)	0.0003	
Overall	136 (3.9)	743 (1.7)	2.33 (1.94–2.79)	<0.0001	1.61 (1.31–1.96)	<0.0001	
Cardiovascular deaths							
Male	46 (2.3)	273 (1.1)	2.16 (1.58–2.96)	<0.0001	1.49 (1.06–2.10)	0.02	0.04
Female	37 (2.4)	112 (0.6)	4.10 (2.83–5.95)	<0.0001	2.30 (1.51–3.49)	0.0001	
Overall	83 (2.4)	385 (0.9)	2.73 (2.15–3.46)	<0.0001	1.77 (1.36–2.30)	<0.0001	
Major coronary events							
Male	45 (2.3)	358 (1.4)	1.62 (1.19–2.21)	0.002	1.20 (0.87–1.68)	0.27	0.46
Female	24 (1.6)	132 (0.7)	2.25 (1.46–3.48)	0.0003	1.39 (0.86–2.26)	0.18	
Overall	69 (2.0)	490 (1.1)	1.78 (1.39–2.29)	<0.0001	1.27 (0.97–1.66)	0.09	
Major cerebrovascular events							
Male	31 (1.6)	229 (0.9)	1.75 (1.21–2.55)	0.003	1.57 (1.06–2.32)	0.03	0.75
Female	25 (1.7)	148 (0.8)	2.21 (1.39–3.24)	<0.0001	1.80 (1.13–2.88)	0.01	
Overall	56 (1.6)	377 (0.9)	1.90 (1.43–2.51)	<0.0001	1.68 (1.24–2.26)	0.0008	
Heart failure							
Male	46 (2.4)	190 (0.8)	3.18 (2.30–4.38)	<0.0001	1.76 (1.22–2.54)	0.002	0.92
Female	33 (2.3)	127 (0.7)	3.33 (2.27–4.88)	<0.0001	1.68 (1.10–2.55)	0.02	
Overall	79 (2.3)	317 (0.7)	3.23 (2.53–4.14)	<0.0001	1.68 (1.27–2.21)	0.0002	

Among patients with diabetes, those with AF had increased risk of all-cause mortality, CV mortality, major coronary events, major cerebrovascular events and heart failure.

Du X, Ninomiya T, Galan B de, Abadir E, Chalmers J, Pillai A, et al. Risks of cardiovascular events and effects of routine blood pressure lowering among patients with type 2 diabetes and atrial fibrillation: results of the ADVANCE study. Eur Heart J. 2009;30(9):1128–35.

Prognosis in patients with concomitant diabetes and AF

Event proportion (%)*



*p <0.001 for all comparisons

No diabetes

Mortality: 36.4%
HF: 13.1%
Ischaemic stroke: 6.8%
MI: 4.3%
Bleeding: 5.2%

Diabetes

Mortality: 48.8%
HF: 21.4%
Ischaemic stroke: 8.2%
MI: 7.3%
Bleeding: 6.3%

Karayiannides S, Lundman P, Friberg L, Norhammar A. High overall cardiovascular risk and mortality in patients with atrial fibrillation and diabetes: A nationwide report. Diabetes Vasc Dis Re. 2017;15(1):31–8.

Prognosis in patients with concomitant diabetes and AF

Hazard ratios and 95% confidence intervals for all events*

Diabetes

Combined event (CE)
1.22 (1.20-1.25)

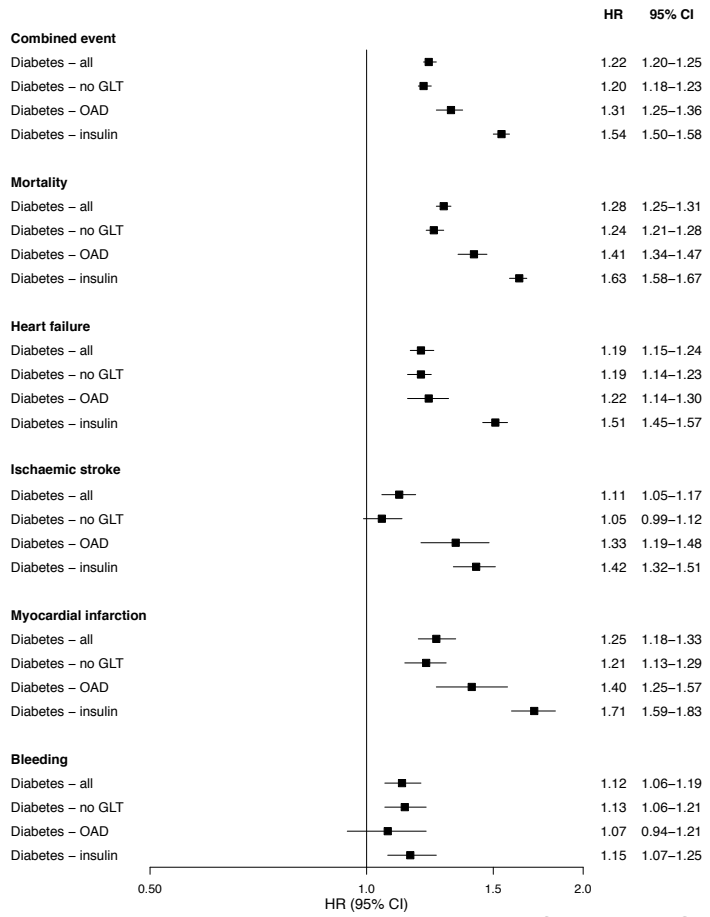
All-cause mortality
1.28 (1.25-1.31)

Heart failure
1.19 (1.15-1.24)

Ischaemic stroke
1.11 (1.05-1.17)

Myocardial infarction
1.25 (1.18-1.33)

Bleeding
1.12 (1.06-1.19)



Diabetes associated with an increased risk for all studied events.
Among individuals with diabetes worse prognosis in insulin-treated.

* Adjustments for: age, sex, comorbidities, medication use, socioeconomic factors; CE=first of mortality, HF, MI, ischaemic stroke

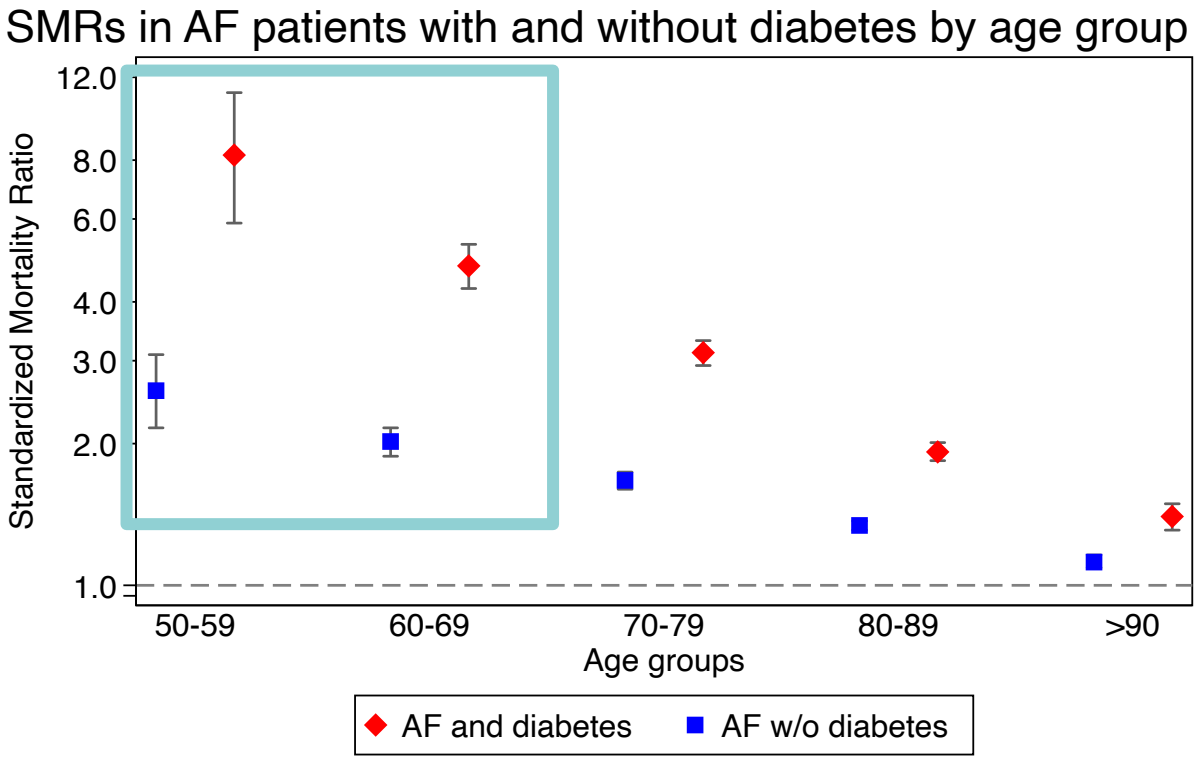
Karayiannides S, Lundman P, Friberg L, Norhammar A. High overall cardiovascular risk and mortality in patients with atrial fibrillation and diabetes: A nationwide report. Diabetes Vasc Dis Re. 2017;15(1):31–8.

Prognosis in patients with concomitant diabetes and AF

Standardised mortality ratios (SMR)

AF without diabetes

SMR
1.33 (1.31-1.35)



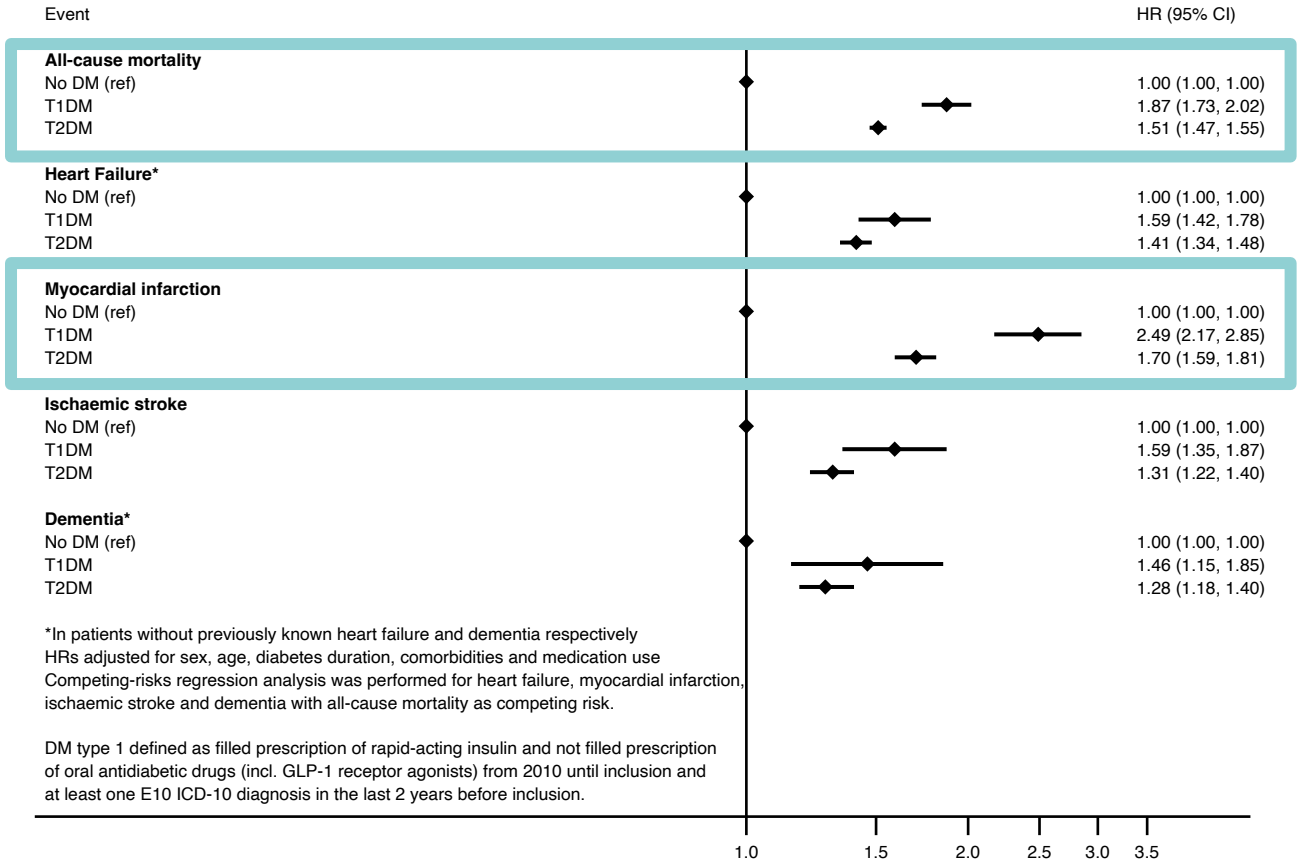
AF with diabetes

SMR
2.06 (2.00-2.12)

Karayiannides S, Lundman P, Friberg L, Norhammar A. High overall cardiovascular risk and mortality in patients with atrial fibrillation and diabetes: A nationwide report. Diabetes Vasc Dis Re. 2017;15(1):31–8.

Prognosis in patients with concomitant diabetes and AF

Hazard ratios and 95% confidence intervals for all events in type 1 and type 2 diabetes*



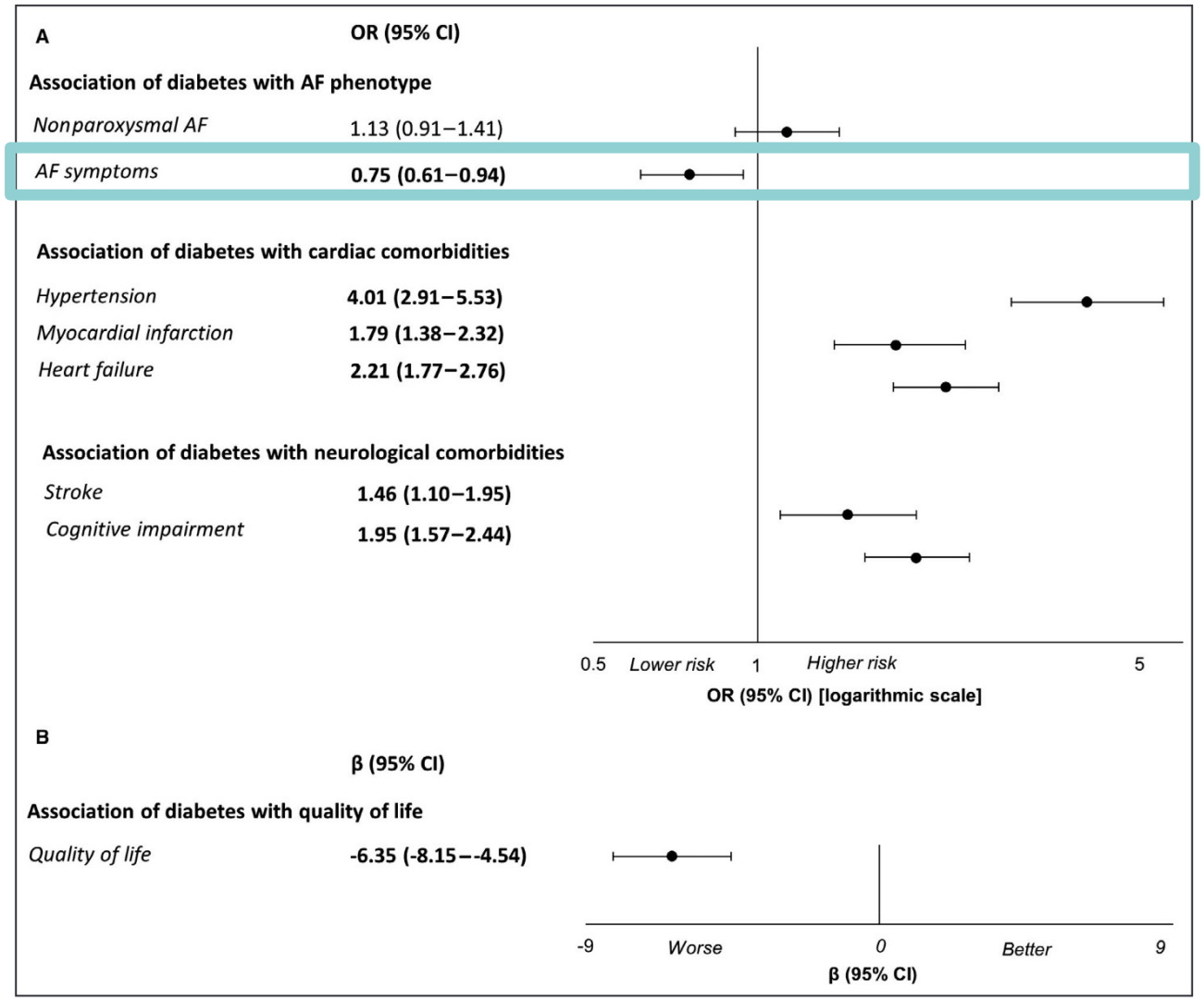
More pronounced increase in risk of all-cause mortality and myocardial infarction in type 1 diabetes than type 2 diabetes.

Observed risks similar for the other events.

* Adjustments for: age, sex, diabetes duration, comorbidities, medication use.

Karayiannides S, Norhammar A, Landstedt-Hallin L, Friberg L, Lundman P. Prognostic impact of type 1 and type 2 diabetes mellitus in atrial fibrillation and the effect of severe hypoglycaemia: a nationwide cohort study. Eur J Prev Cardiol. 2022;29(13):1759–69.

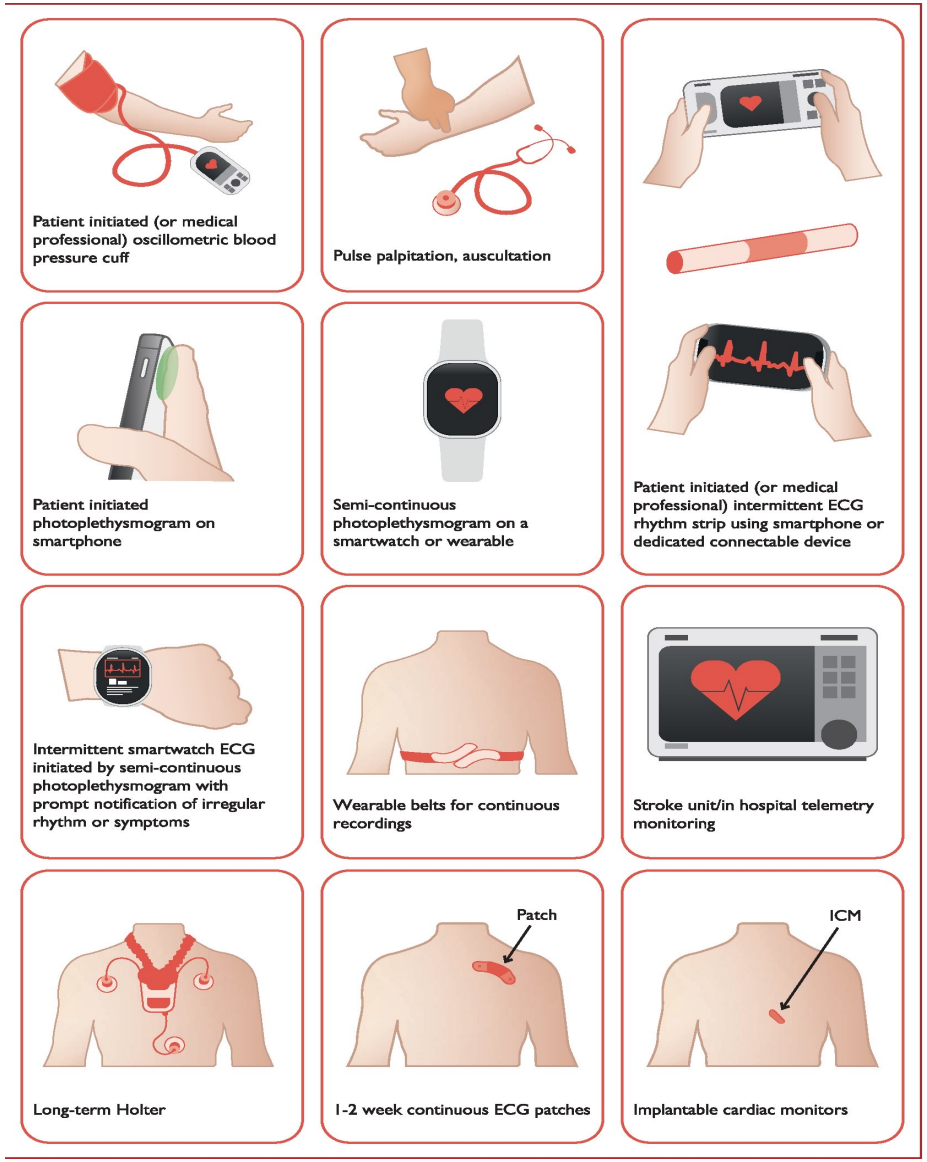
Association of diabetes with (AF) phenotype and cardiac and neurological comorbidities



Among patients with AF, those with diabetes were more likely to have cardiac and neurological comorbidities, less often perceived AF symptoms and had worse quality of life.

Bano A, Rodondi N, Beer JH, Moschovitis G, Kobza R, Aeschbacher S, et al. Association of Diabetes With Atrial Fibrillation Phenotype and Cardiac and Neurological Comorbidities: Insights From the Swiss-AF Study. J Am Heart Assoc. 2021;10(22):e021800.

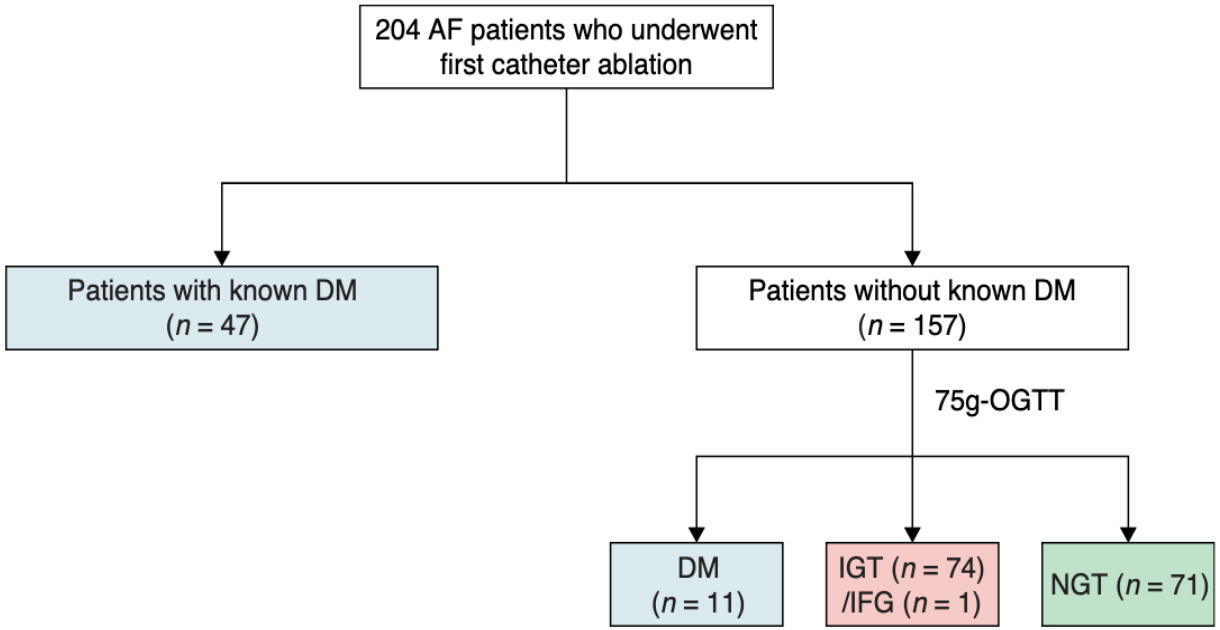
Screen patients with diabetes for AF?



Screen patients with diabetes ≥ 65 years old for atrial fibrillation, especially those with diabetic nephropathy and suboptimal glycemic control?

Picture from: Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, et al. Eur Heart J. 2020;ehaa612.

Screen patients with AF for diabetes?

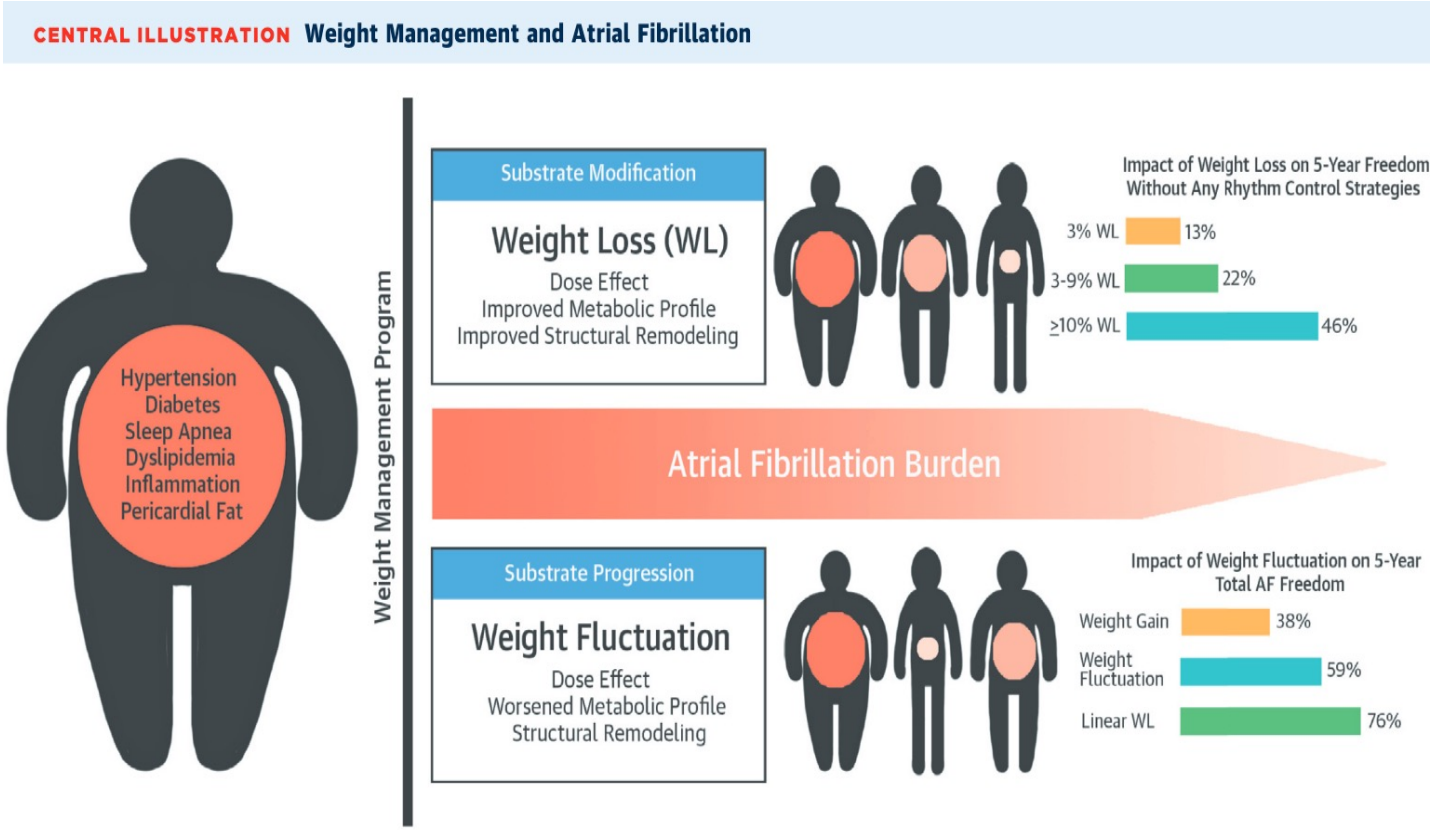


Individuals with AF undergoing catheter ablation screened with OGTT using WHO criteria.

55% (86/157) had undiagnosed glucose abnormalities

Nakanishi K, Daimon M, Fujiu K, Iwama K, Yoshida Y, Hirose K, et al. Prevalence of glucose metabolism disorders and its association with left atrial remodelling before and after catheter ablation in patients with atrial fibrillation. Europace. 2023;

Effects of weight loss in risk for AF in T2DM



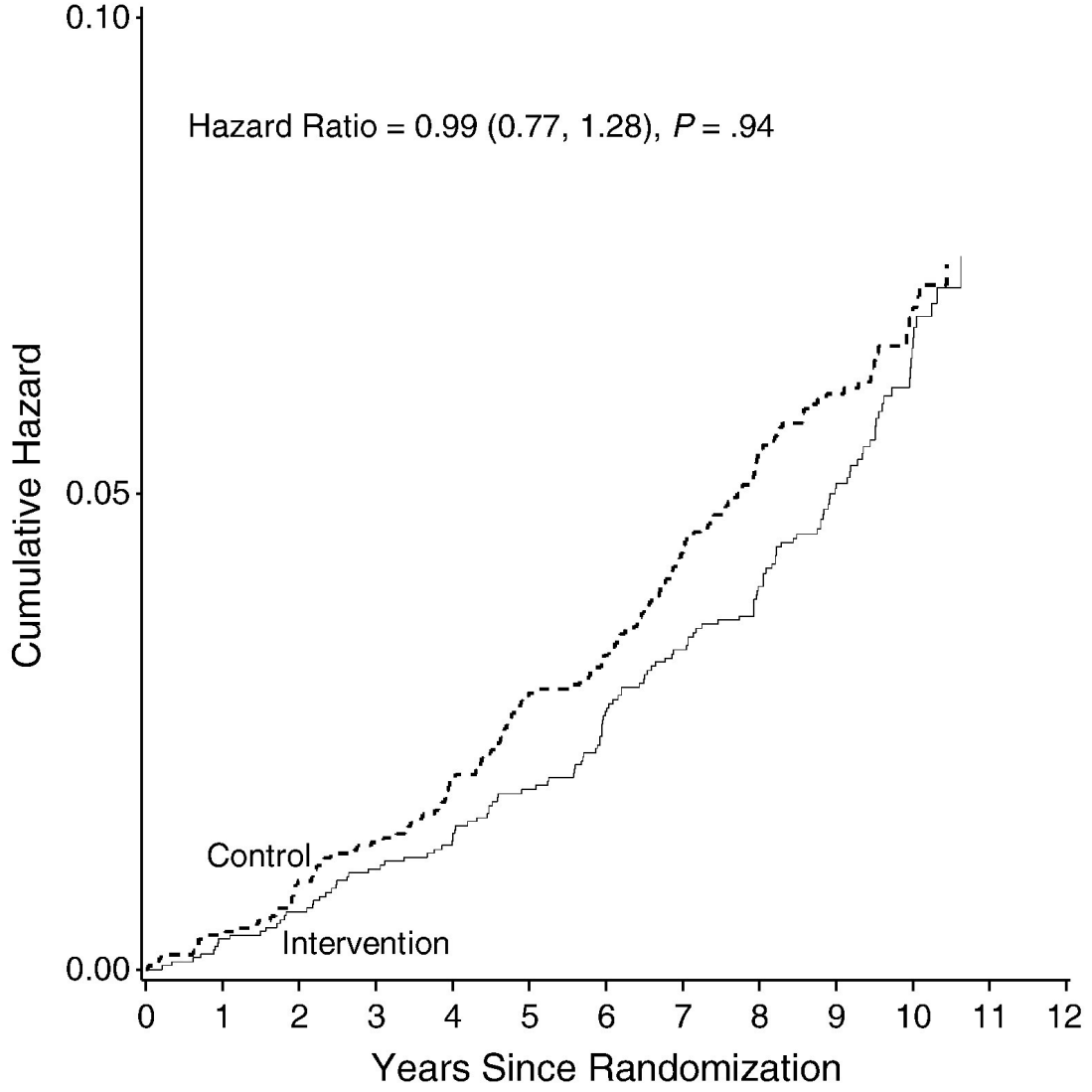
Pathak, R.K. et al. J Am Coll Cardiol. 2015; 65(20):2159-69.

(Left) Obesity is associated with a variety of associated comorbidities. These are all associated with progression of the atrial substrate and the development of atrial fibrillation (AF). **(Top)** A dedicated weight management program with weight loss (WL) is associated with reverse remodeling of the atrial substrate and a dose-dependent reduction in the AF burden, which is sustained in the long term. **(Bottom)** The consequence of weight fluctuation, which somewhat curtails the beneficial effects of WL.

Weight loss reduced burden of AF in this cohort of AF patients that had 29% diabetes and 10% IGT.

Pathak RK, Middeldorp ME, Meredith M, Mehta AB, Mahajan R, Wong CX, et al. Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort A Long-Term Follow-Up Study (LEGACY). J Am Coll Cardiol. 2015;65(20):2159–69.

Effects of weight loss in risk for AF in T2DM

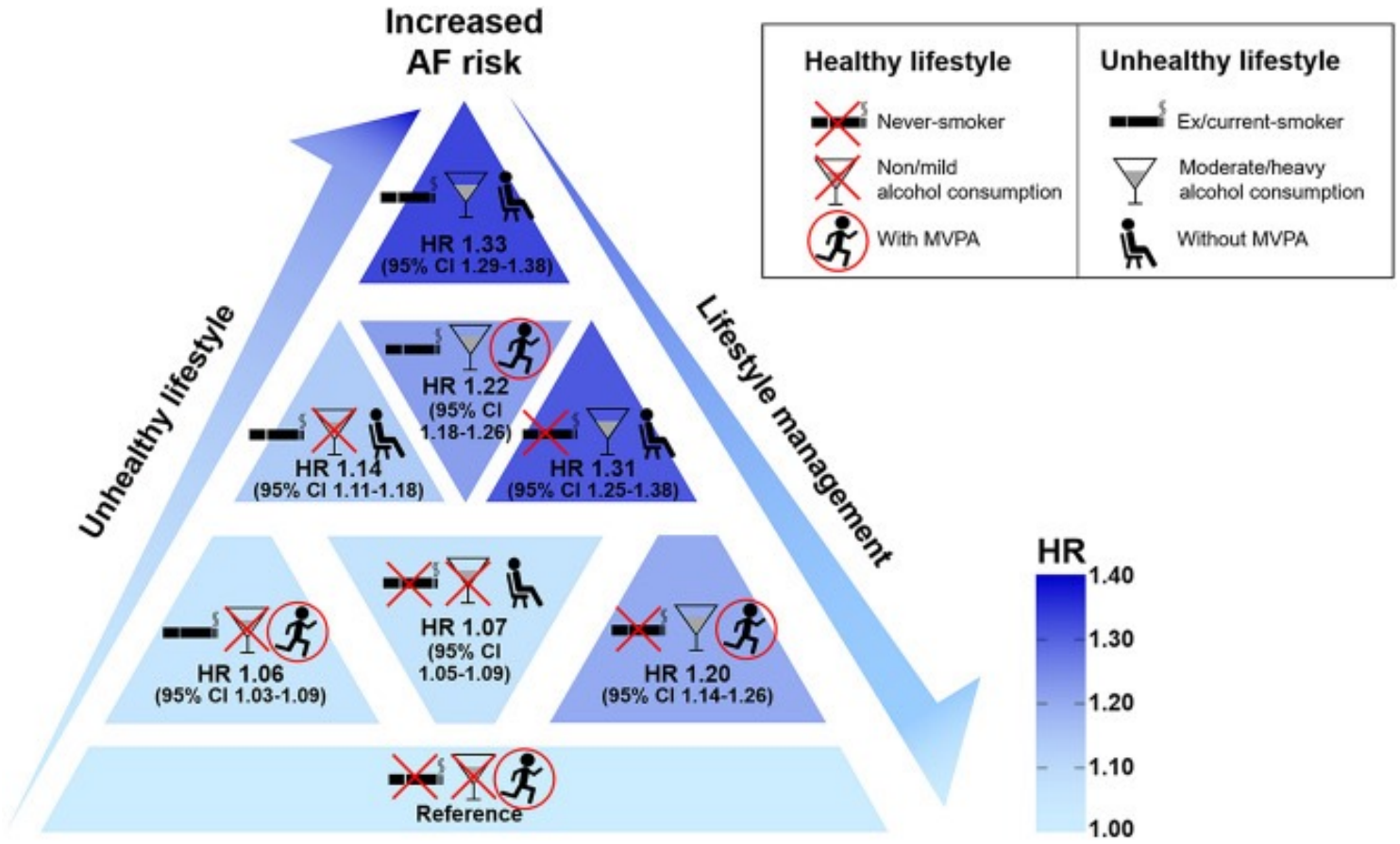


Modest weight loss in T2DM did not reduce the risk for AF in this RCT that included only patients with DM.

However, weight loss difference between intervention and control group reduced at the end of study and more use of cardioprotective medication in control group.

Alonso A, Bahnson JL, Gaussoin SA, Bertoni AG, Johnson. KC, Lewis CE, et al. Effect of an intensive lifestyle intervention on atrial fibrillation risk in individuals with type 2 diabetes: The Look AHEAD randomized trial. Am Heart J. 2015;170(4):770-777.e5.

Effects of lifestyle factors in risk for AF in T2DM

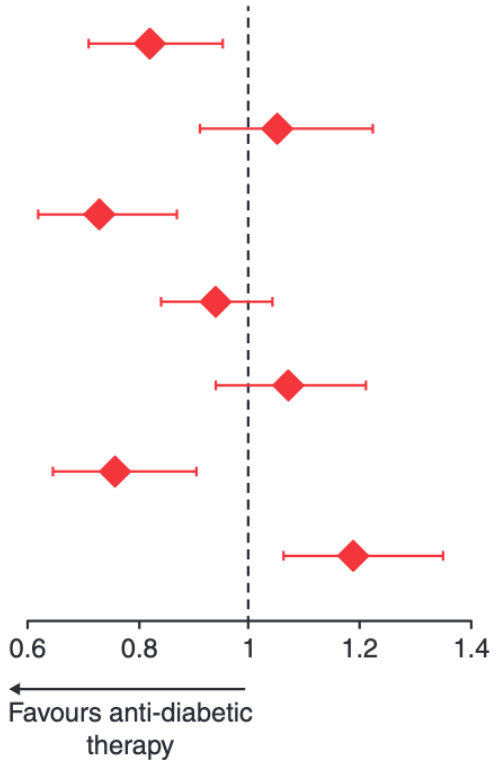


Risk for incident AF in individuals with T2DM is increased with smoking, alcohol consumption and decreased with physical activity.

Park CS, Han KD, Choi EK, Kim DH, Lee HJ, Lee SR, et al. Lifestyle is associated with atrial fibrillation development in patients with type 2 diabetes mellitus. Sci Rep-uk. 2021;11(1):4676.

Risk of AF with specific glucose lowering drugs in T2DM

Antidiabetic drug	Type of study	Number of patients	Odds or Hazard ratio (95% CI)	Ref
Metformin	Case-control, 1:4 matching	14 410	0.82 (0.71-0.95)	Liou, 2018
Sulfonylurea	Case-control, 1:4 matching	14 410	1.05 (0.91-1.22)	Liou, 2018
Thiazolidinediones	Meta-analysis. of RCTs and obs. studies	130 854	0.73 (0.62-0.87)	Zhang, 2017
GLP-1 agonists	Meta-analysis of RCTs	59 105	0.94 (0.84-1.04)	Nreu, 2020
DPP-4 inhibitors	Case-control, 1:4 matching	14 410	1.07 (0.94-1.21)	Liou, 2018
SGLT-2 inhibitors	Meta-analysis of RCTs	38 335	0.76 (0.65-0.9)	Li, 2020
Insulin	Case-control 1:4 matching,	14 410	1.19 (1.06-1.35)	Liou, 2018



The use of metformin, thiazolidinediones and SGLT-2 inhibitors is associated with lower risk for AF in T2DM.

Fauchier L, Boriani G, Groot JR de, Kreutz R, Rossing P, Camm AJ. Medical therapies for prevention of cardiovascular and renal events in patients with atrial fibrillation and diabetes mellitus. Ep Europace. 2021;23(12):1873–91.

Conclusions

- Diabetes mellitus is an established risk factor for AF. Both type 1 and type 2 diabetes as well as prediabetes are associated with an increased risk for AF.

- Coexisting diabetes and AF are associated with increased risks of all-cause mortality and cardiovascular complications as compared to the risks associated with either condition in isolation.

- Among individuals with AF, type 1 diabetes confers similar increase in cardiovascular risk as type 2 diabetes when compared to those without diabetes and even more pronounced increase in risk for myocardial infarction and all-cause mortality.

Conclusions (2)

- The introduction of targeted screening for AF in patients with diabetes and for diabetes in patients with AF in routine patient care could be considered.

- Lifestyle interventions such as weight loss, smoking cessation, minimized alcohol consumption, and increased physical activity, as well as the use of specific glucose-lowering drugs such as metformin, thiazolidinediones and SGLT-2 inhibitors, may help to reduce the burden of AF in patients with diabetes.