Effect of early rhythm control on diabetes complications in subjects with diabetes and AF : a nationwide population study

JungMin Choi

Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea

Korean Heart Rhythm Society

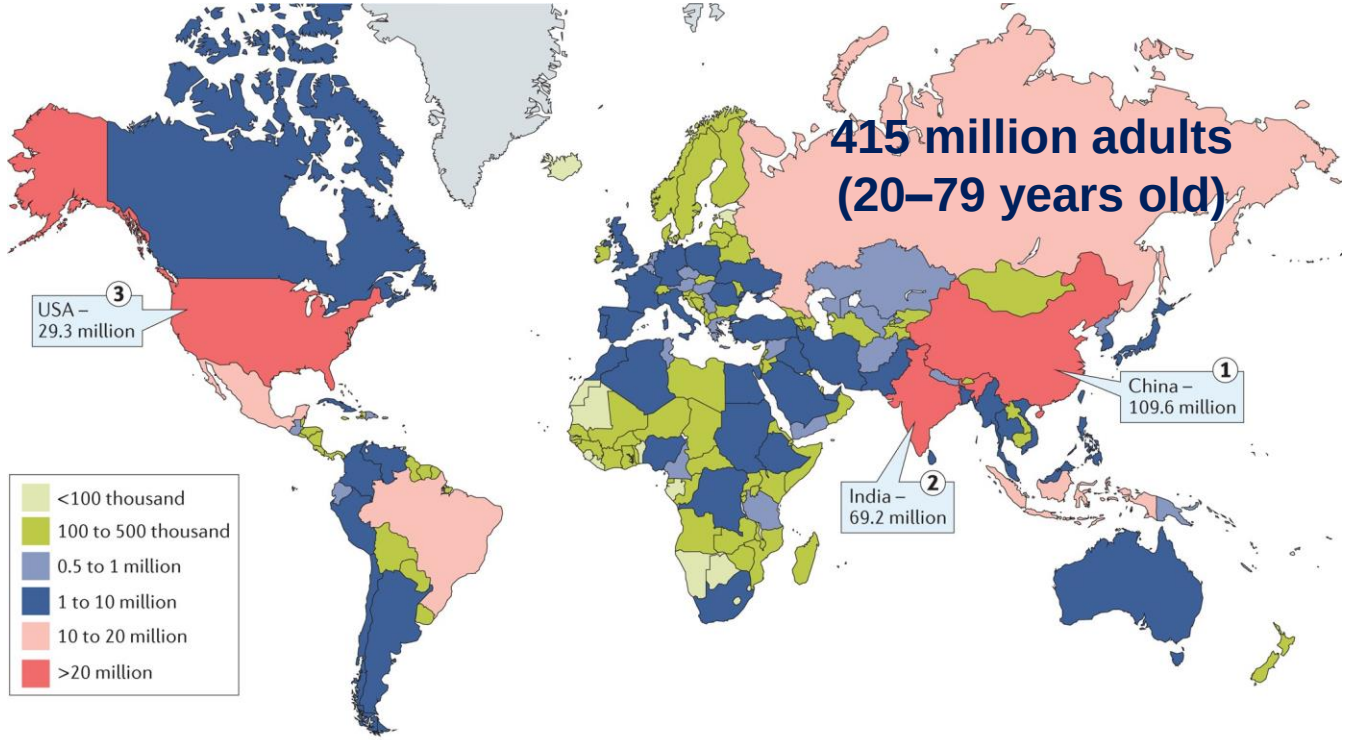
COI Disclosure

Name of First Author: JungMin Choi

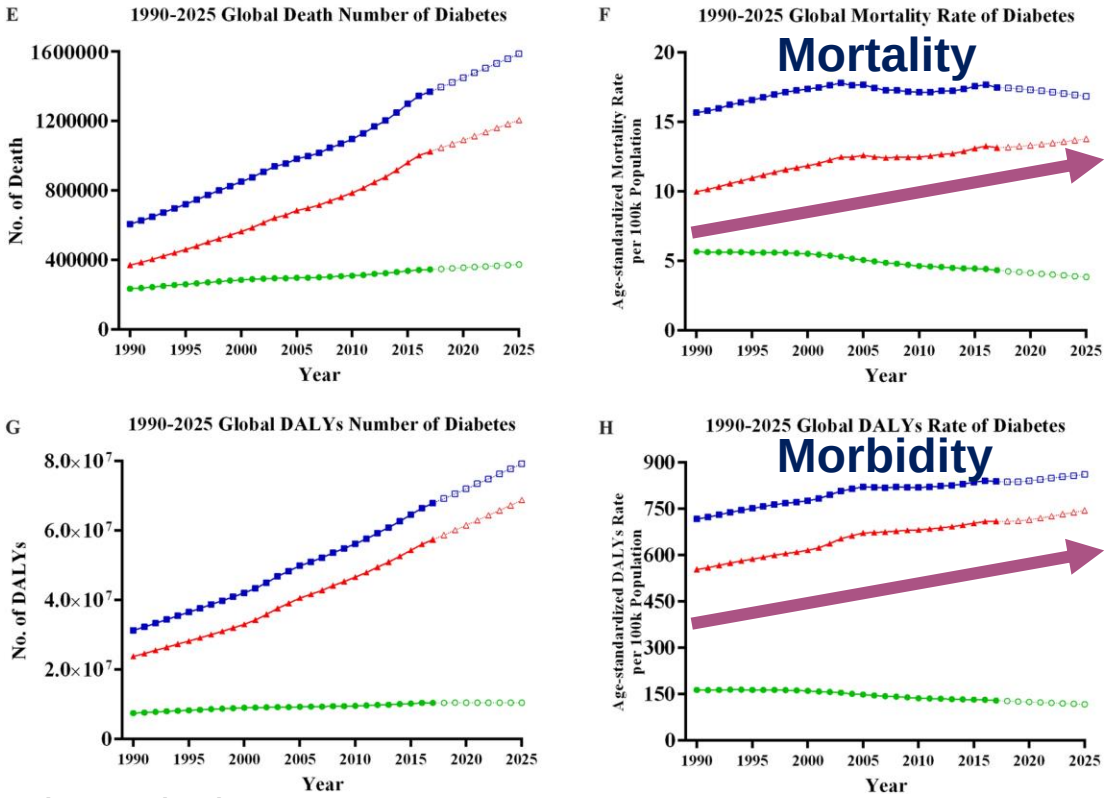
The authors have no financial conflicts of interest to disclose concerning the presentation

The prevalence of Diabetes Mellitus

- **One in 11 adults** have **diabetes mellitus (DM)**.
- The **burden of Type 2 DM is continuously increasing**.



Zheng Y, et. al. Nat Rev Endocrinol. 2018

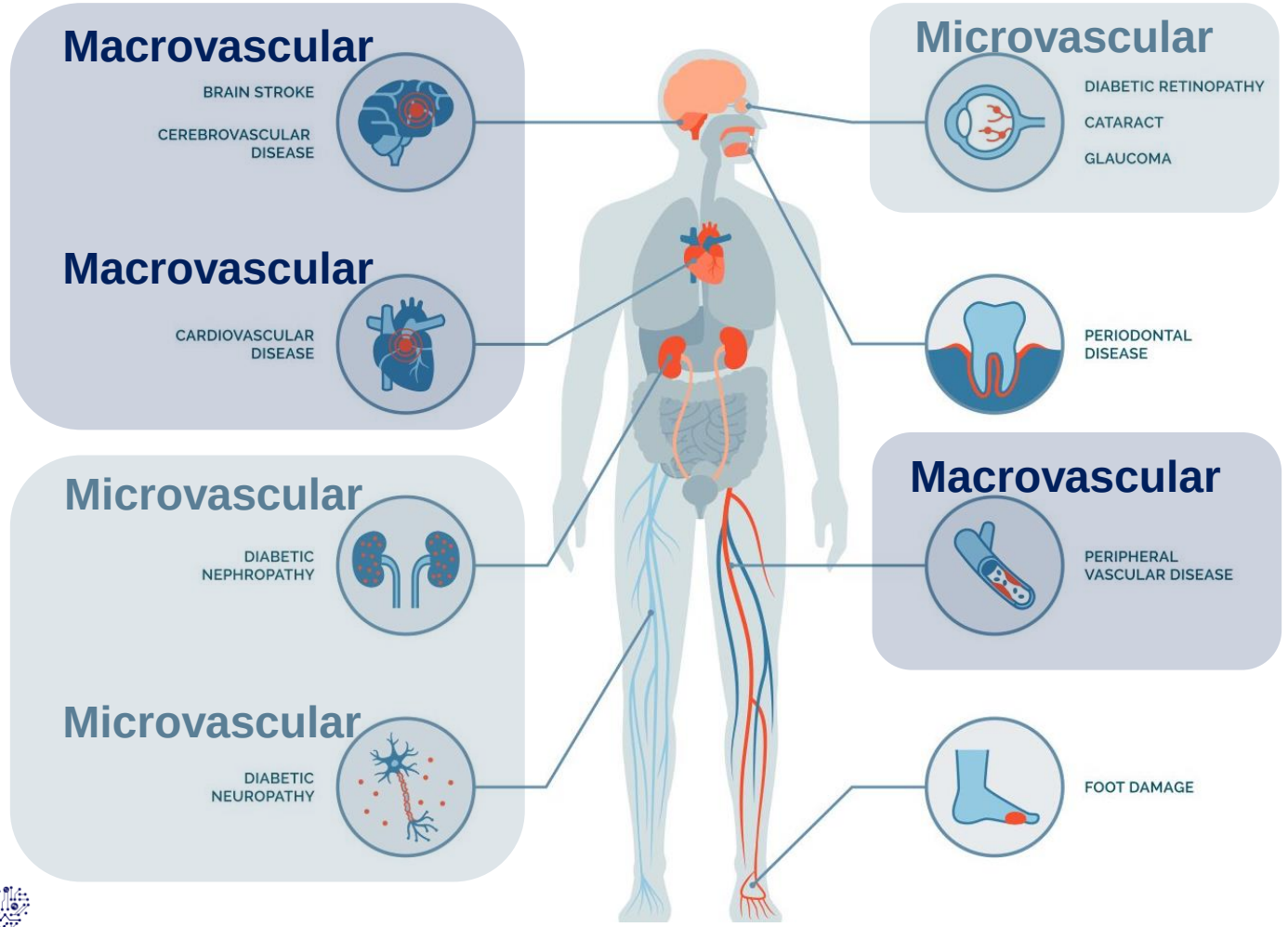


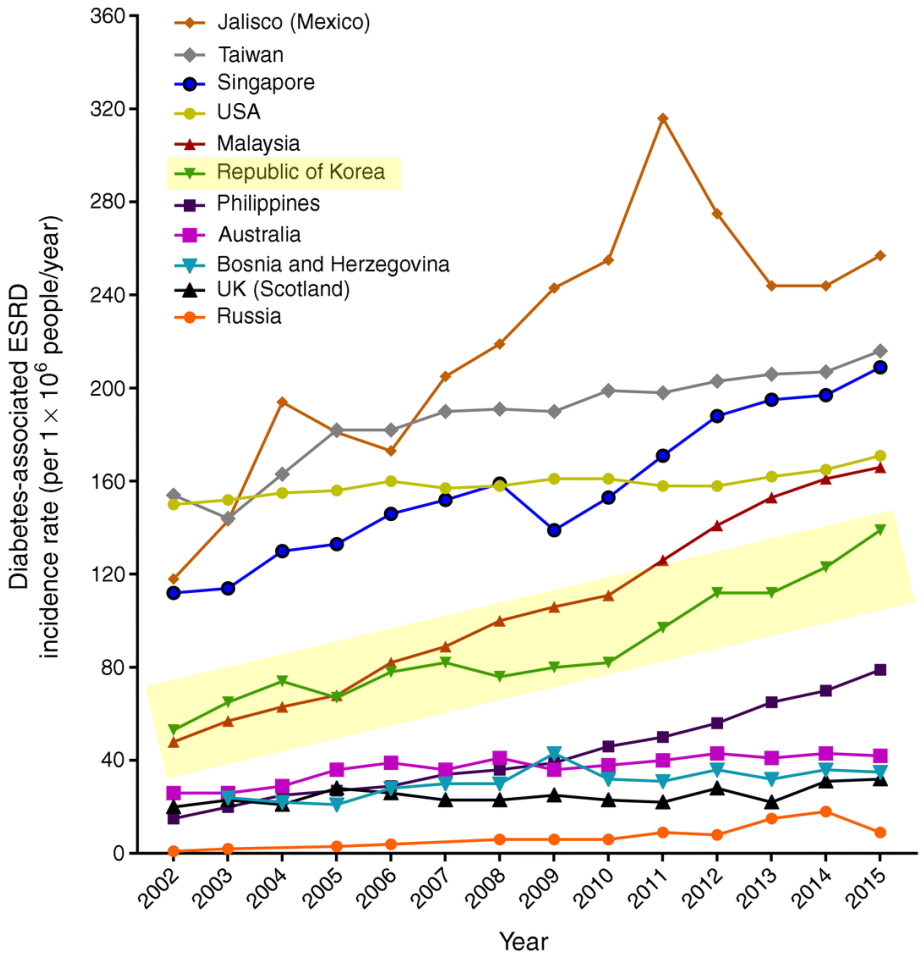
Lin X, et. al. Sci Rep. 2020

KHRS 2023

Diabetes-related complications

- The **diabetes-related complications are very common and increasing.**

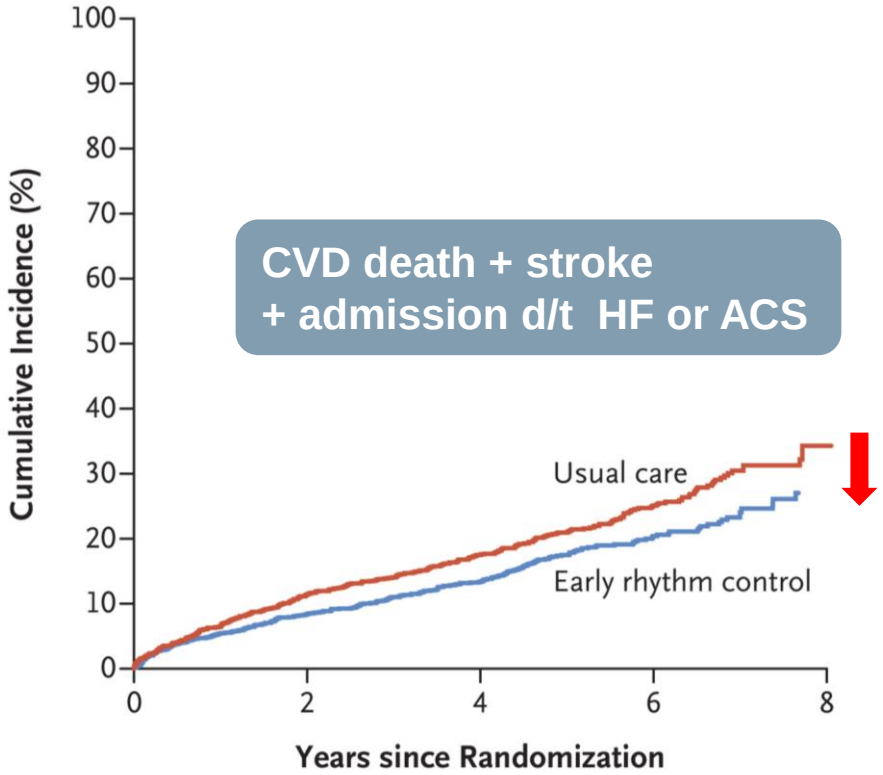




Harding JI, et. al. Diabetologia. 2019

Early rhythm control in AF patients

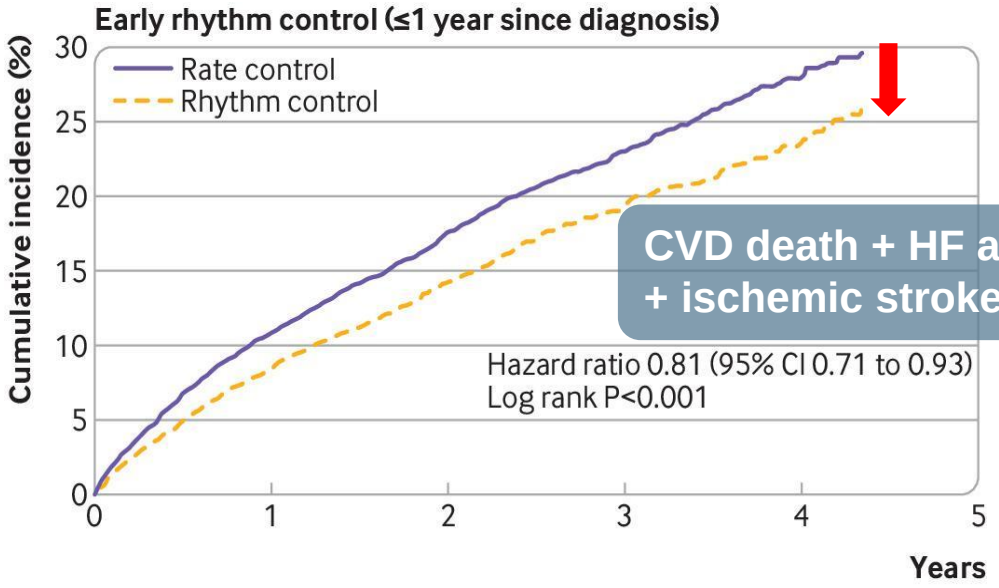
- **Early rhythm control (ERC) within 1 year after AF diagnosis** significantly **reduces the risk of major adverse cardiovascular outcomes (MACE)** in general patients.



CVD death + stroke
+ admission d/t HF or ACS

No. at Risk					
Usual care	1394	1169	888	405	34
Early rhythm control	1395	1193	913	404	26

Kirchhof P, et al. N Engl J Med. 2020



CVD death + HF admission
+ ischemic stroke + MI

No at risk (weighted cumulative incidence)

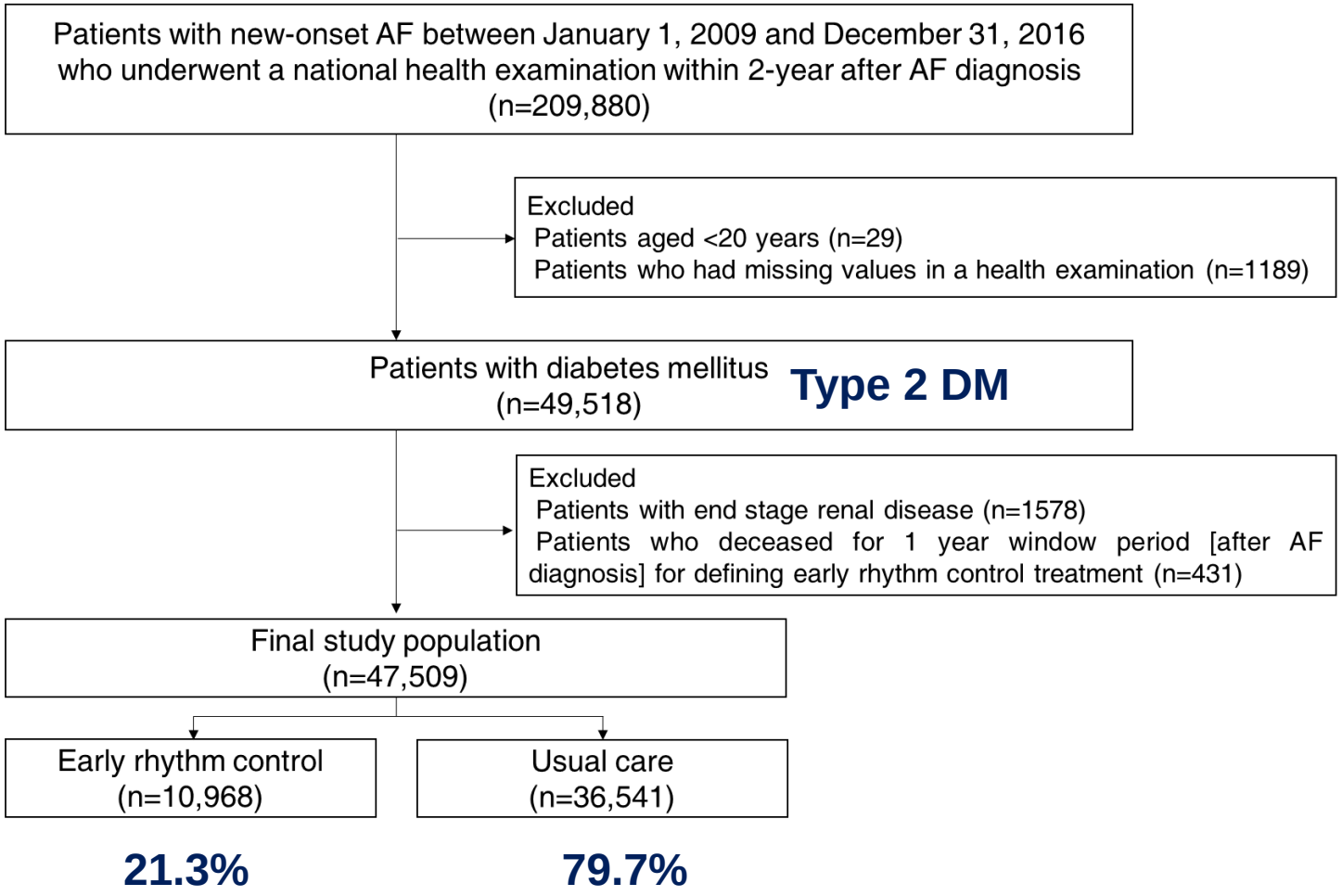
Rate control					
	7077 (0%)	5084 (10.8%)	3248 (17.5%)	1841 (22.9%)	728 (27.8%)
Rhythm control					
	9246 (0%)	6885 (8.3%)	4361 (14.2%)	2466 (19.3%)	1033 (23.4%)

Kim D, et al. BMJ. 2021

Study Aim

- To assess the **impact of ERC on ischemic stroke, diabetes-related co mplications, and all-cause death in patients with DM and newly diag nosed AF** using a **nationwide population-based cohort.**

Study Flow



- **ERC**: any of the following ≤ 1 year of AF diagnosis
  1) Anti-arrhythmic drug (Ic or III)
  2) Direct current cardioversion
  3) AF catheter ablation

- Primary: **ischemic stroke**
- Secondary:

1) Composite of **macrovascular complications** (ischemic stroke + myocardial infarction + peripheral artery disease)
2) Composite of **microvascular complications** (diabetic retinopathy + diabetic neuropathy + end-stage renal disease)
3) **All-cause death**

- Survival analysis (adjusted Kaplan-Meier)
- Multivariable Cox regression

Results: *Baseline characteristics*

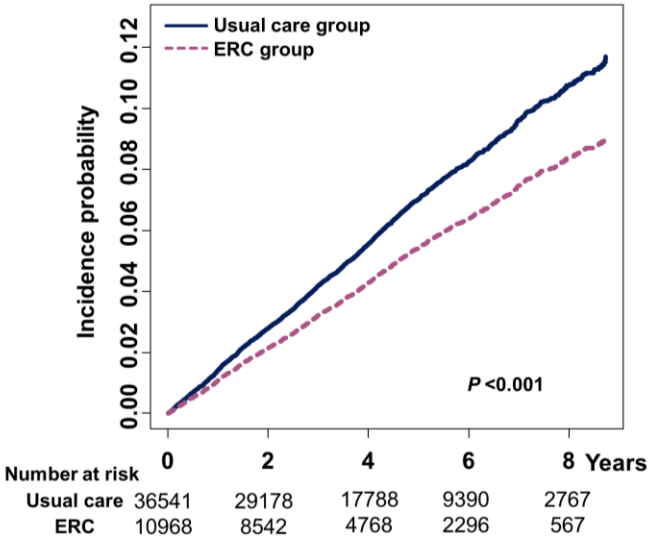
Category	Total (n=47,509)	Usual care (n=36,541)	Early rhythm control (n=10,968)	*P*-value
Demographics				
Age (years)	66.7±10.5	67.0±10.6	65.8±10.2	<0.001
Sex (men)	29,373 (61.8)	22,190 (60.7)	7183 (65.5)	<0.001
Body mass index (kg/m^2)	25.1±3.6	25.0±3.6	25.1±3.5	0.029
Duration of diabetes mellitus (years)	5.6±4.7	5.6±4.7	5.6±4.8	0.924
CHA_2DS_2-VASc score	4.6±1.8	4.6±1.9	4.5±1.8	<0.001
Charlson Comorbidity Index	4.5±2.3	4.5±2.3	4.5±2.4	0.098
AF rhythm control				
Duration from AF diagnosis to rhythm control (days)	27.6±68.2	-	27.6±68.2	-
Rhythm control methods				
Antiarrhythmic agents	10,903 (22.9)	0 (0)	10,903 (99.4)	<0.001
Class Ic	5845 (12.3)	0 (0)	5845 (53.3)	<0.001
Class III	6301 (13.3)	0 (0)	6301 (57.5)	<0.001
DC cardioversion	823 (1.7)	0 (0)	823 (7.5)	<0.001
AF catheter ablation	309 (0.7)	0 (0)	309 (2.8)	<0.001
Oral anticoagulants	22,983 (48.4)	16,063 (44.0)	6920 (63.1)	<0.001
Warfarin	6973(14.7)	4999 (13.7)	1974 (18.0)	<0.001
NOAC	16,010(33.7)	11,064 (30.3)	4946 (45.1)	<0.001

Results: *Baseline characteristics*

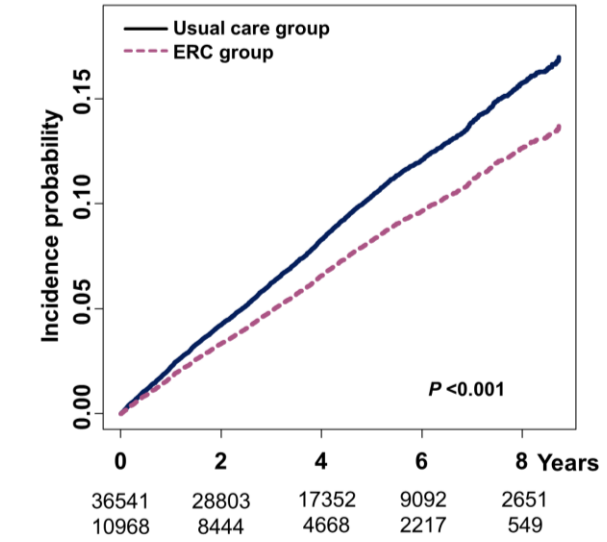
Category	Total (n=47,509)	Usual care (n=36,541)	Early rhythm control (n=10,968)	*P*-value
Diabetes medications				
Number				
Without medications	8143 (17.1)	6301 (17.2)	1842 (16.8)	<0.001
1 type	9925 (20.9)	7458 (20.4)	2467 (22.5)	
2 types	12,451 (26.2)	9652 (26.4)	2799 (25.5)	
≥3 types	**16,990 (35.8)**	13,130 (35.9)	3860 (35.2)	
Type				
Metformin	32113(67.59)	24735(67.69)	7378(67.27)	0.406
Sulfonylureas	22519(47.4)	17677(48.38)	4842(44.15)	<0.001
Meglitinides	1224(2.58)	955(2.61)	269(2.45)	0.350
α-glucosidase inhibitors	4867(10.24)	3880(10.62)	987(9)	<0.001
Thiazolidinediones	3433(7.23)	2693(7.37)	740(6.75)	0.027
DPP-4 inhibitors	14793(31.14)	11163(30.55)	3630(33.1)	<0.001
SGLT2 inhibitors	487(1.03)	360(0.99)	127(1.16)	0.115
GLP-1 agonists	16(0.03)	13(0.04)	3(0.03)	0.680
Insulin	**15058(31.7)**	11320(30.98)	**3738(34.08)**	<0.001

Results: *Outcomes*

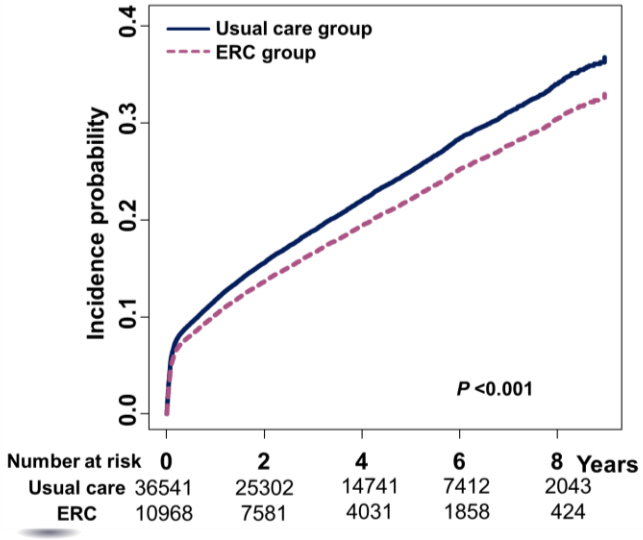
Primary outcome: Ischemic stroke



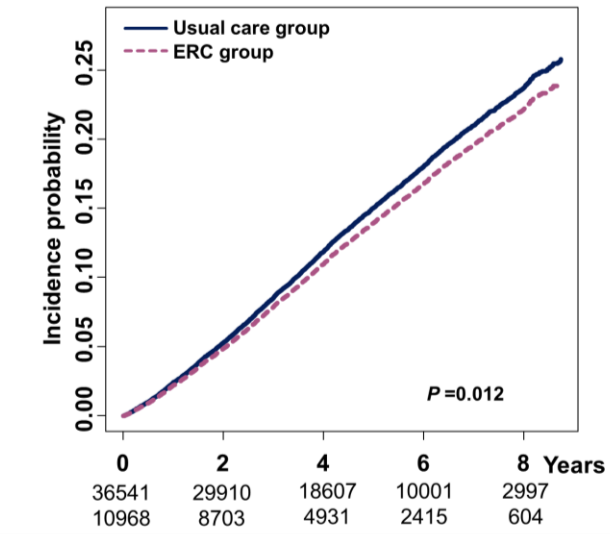
Composite of macrovascular complications



Composite of microvascular complications



All-cause death



- **Mean follow-up duration: 4.3±2.3 years**

	IR per 1000 PY	Adjusted HR (95% CI)	*P*-value
Primary outcome: ischemic stroke			
Usual care	13.7	1 (reference)	**<0.001**
Early rhythm control	11.2	**0.772 (0.699-0.854)**	
Secondary outcomes			
Composite of macrovascular complication*			
Usual care	20.5	1 (reference)	**<0.001**
Early rhythm control	17.4	**0.792 (0.730-0.859)**	
Composite of microvascular complication**			
Usual care	63.1	1 (reference)	**<0.001**
Early rhythm control	53.2	**0.861 (0.819-0.904)**	
All-cause death			
Usual care	33.0	1 (reference)	**0.012**
Early rhythm control	27.4	**0.922 (0.866-0.983)**	

* Composite of macrovascular complications
: ischemic stroke + myocardial infarction + peripheral artery disease
** Composite of microvascular complications
: diabetic retinopathy + diabetic neuropathy + ESRD

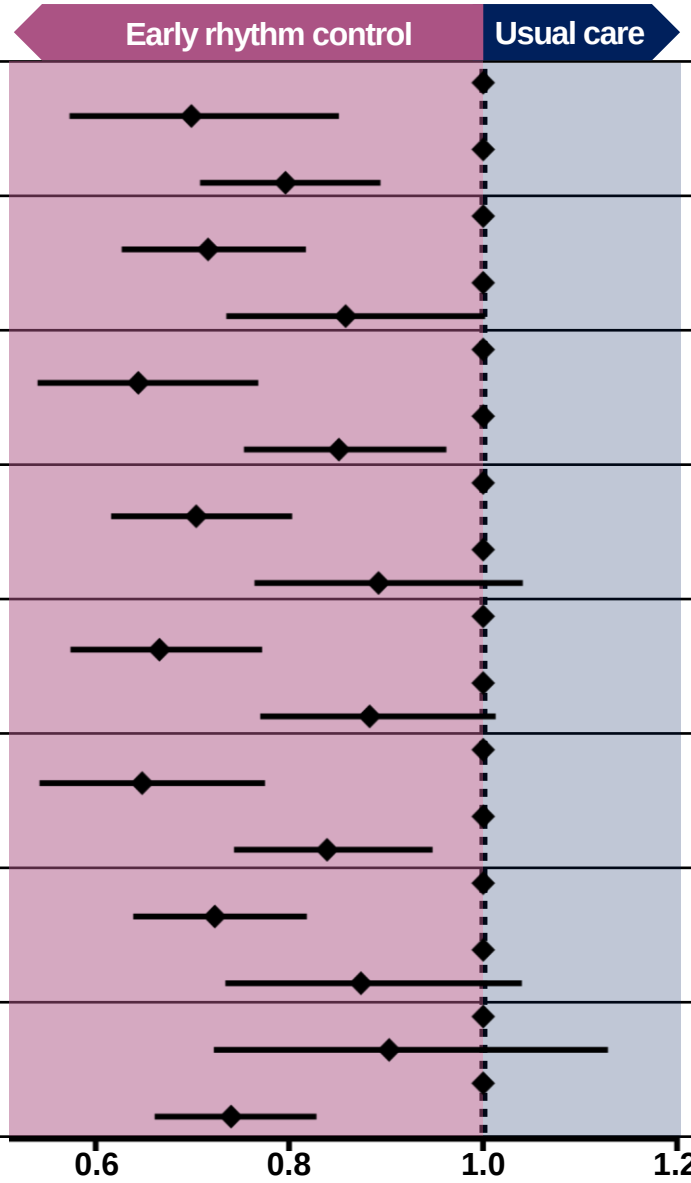
Results: *Competing risk analyses*

	Adjusted HR (95% CI)	*P*-value
Primary outcome: ischemic stroke		
Usual care	1 (reference)	**<0.001**
Early rhythm control	**0.769 (0.695-0.851)**	
Secondary outcomes		
Composite of macrovascular complication*		
Usual care	1 (reference)	**<0.001**
Early rhythm control	**0.788 (0.726-0.856)**	
Composite of microvascular complication**		
Usual care	1 (reference)	**<0.001**
Early rhythm control	**0.857 (0.816-0.901)**	

* Composite of macrovascular complications : ischemic stroke + myocardial infarction + peripheral artery disease
** Composite of microvascular complications: diabetic retinopathy + diabetic neuropathy + end-stage renal disease

Results: *Subgroup analyses for ischemic stroke*

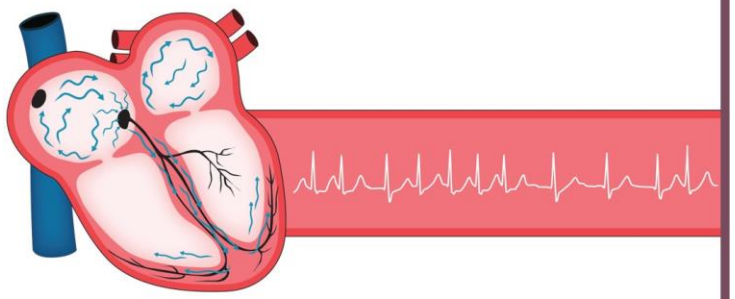
	Subgroup	Group	IR per 1000 PY	Model 3 HR (95% CI)	*P*-value	*P*-for-interaction
Age	<65 years	Usual care	7.9	1 (reference)		
		Early rhythm control	6.6	0.699 (0.573-0.851)	<0.001	0.304
	≥65 years	Usual care	17.9	1 (reference)		
		Early rhythm control	15.0	0.796 (0.708-0.894)	<0.001	
Sex	Male	Usual care	13.5	1 (reference)		
		Early rhythm control	9.7	0.716 (0.627-0.817)	<0.001	0.036
	Female	Usual care	14.0	1 (reference)		
		Early rhythm control	14.0	0.858 (0.735-1.002)	0.053	
Duration of DM	<3 years	Usual care	12.1	1 (reference)		
		Early rhythm control	8.4	0.644 (0.540-0.768)	<0.001	0.028
	≥3 years	Usual care	14.9	1 (reference)		
		Early rhythm control	13.2	0.851 (0.753-0.962)	0.010	
Number of DM medications	<3	Usual care	12.9	1 (reference)		
		Early rhythm control	9.5	0.704 (0.616-0.803)	<0.001	0.068
	≥3	Usual care	15.2	1(Ref.)		
		Early rhythm control	14.4	0.892 (0.764-1.041)	0.146	
CHA_2DS_2-VASc score	≤4	Usual care	8.4	1 (reference)		
		Early rhythm control	6.2	0.648 (0.542-0.775)	<0.001	0.011
	>4	Usual care	19.6	1 (reference)		
		Early rhythm control	17.6	0.839 (0.743-0.948)	0.004	
Charlson Comorbidity Index	≤4	Usual care	12.3	1 (reference)		
		Early rhythm control	8.7	0.666 (0.574-0.772)	<0.001	0.023
	>4	Usual care	15.6	1 (reference)		
		Early rhythm control	14.7	0.883 (0.770-1.013)	0.076	
Chronic kidney disease	No	Usual care	12.3	1 (reference)		
		Early rhythm control	9.5	0.723 (0.639-0.818)	<0.001	0.071
	Yes	Usual care	18.9	1 (reference)		
		Early rhythm control	17.1	0.874 (0.734-1.04)	0.128	
Use of oral anticoagulants	No	Usual care	6.6	1 (reference)		
		Early rhythm control	5.6	0.903 (0.722-1.129)	0.370	0.116
	Yes	Usual care	23.5	1 (reference)		
		Early rhythm control	14.5	0.740 (0.661-0.828)	<0.001	



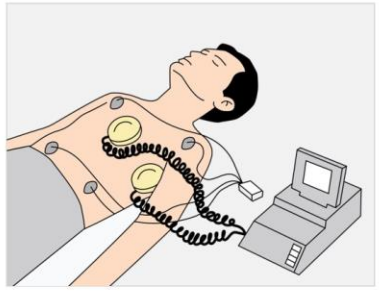
Summary of Results

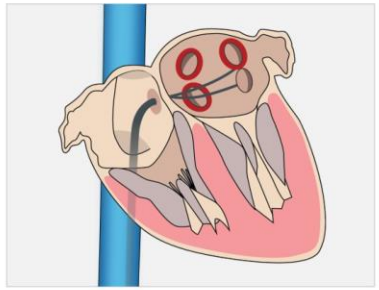
Diabetes mellitus

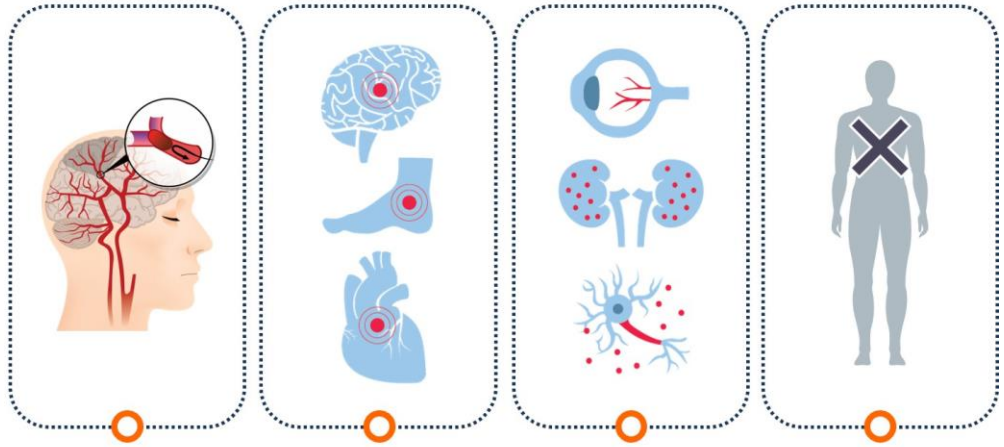
Atrial fibrillation



Early rhythm control







Stroke	Macrovascular complication	Microvascular complication	All-cause death
-23%	-21%	-14%	-8%

KHRS 2023

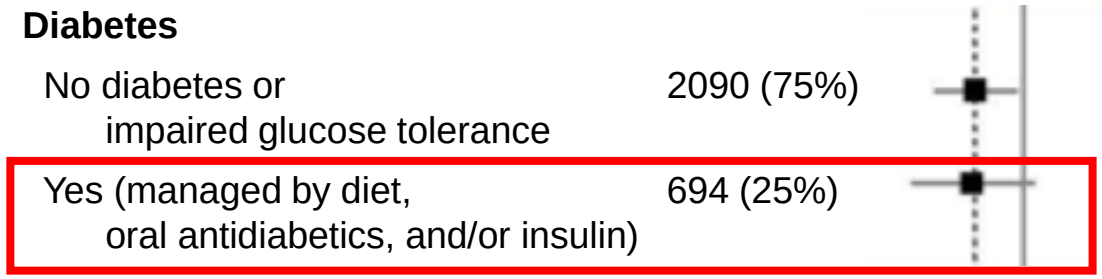
Discussion

- **AF in patients with DM** is associated with **significantly increased risk of cardiovascular events** (myocardial infarction, stroke, and heart failure), **chronic kidney disease, and death**.

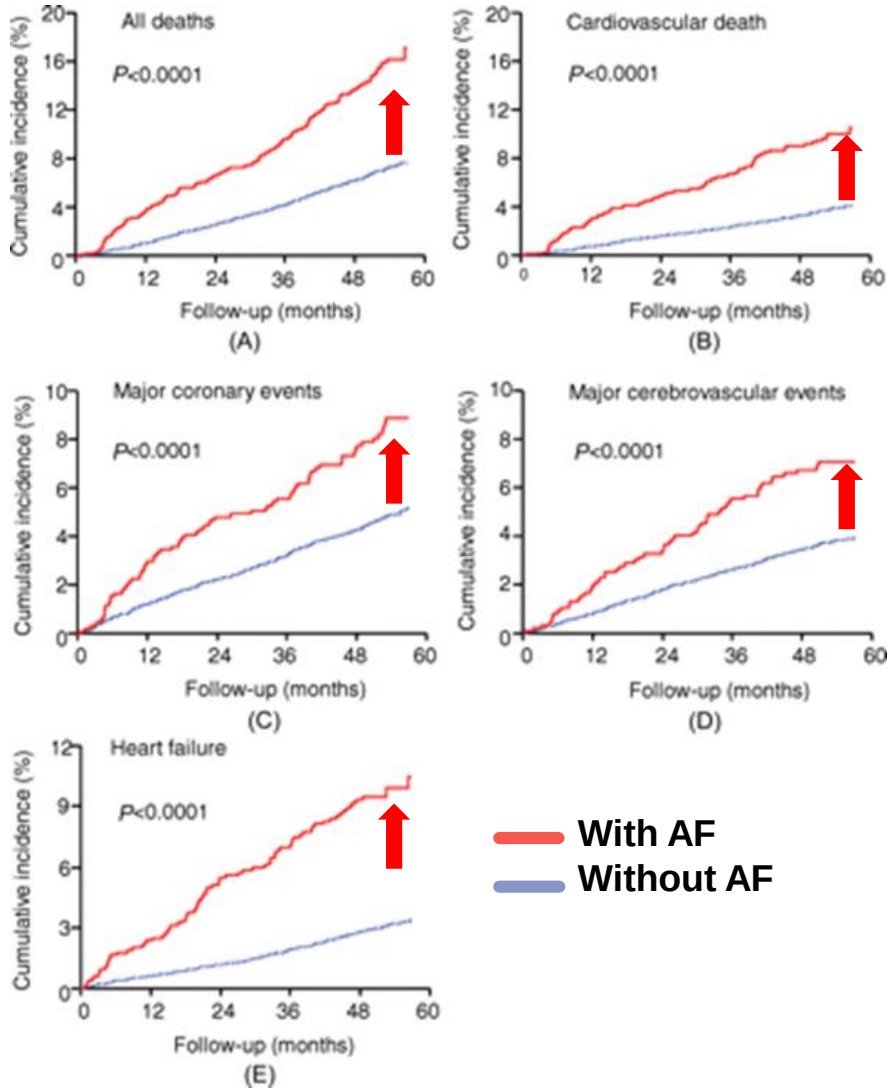
(Du X, et al. Eur Heart J. 2009, Geng T, et al. Diabetes Care. 2022)

- In the **EAST-AFNET 4 trial, subgroup of DM showed decrease in MACE but without statistical significance.**

(Kirchhof P, et al. N Engl J Med. 2020



Kirchhof P, et al. N Engl J Med. 2020



Du X, et al. Eur Heart J. 2009

KHRS 2023

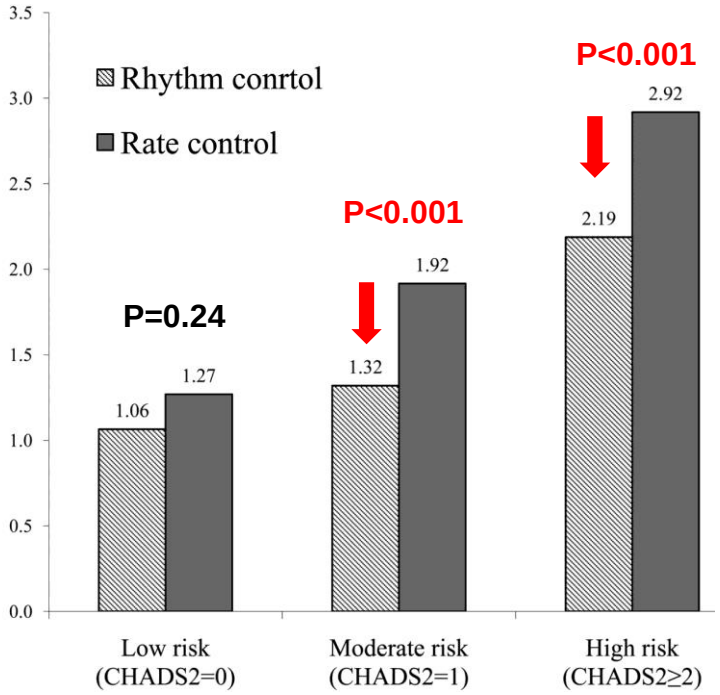
Discussion

- The **mechanism** that underlies the reduction of diabetes-related complications due to ERC may be attributed to the **restoration of sinus rhythm** resulting in reduced systemic inflammation.

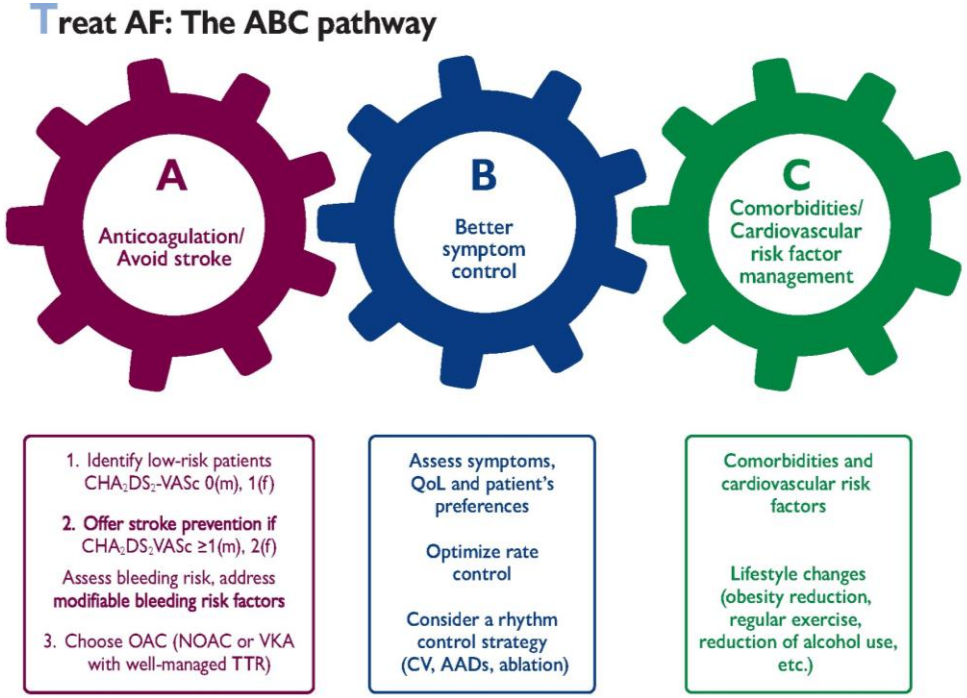
(Tsadok MA, et al. Circulation. 2012)

- As DM patients are commonly accompanied by various comorbidities, current paradigm of more **holistic AF management** based on the **ABC pathway would be beneficial.** *(Hindricks G, et al. Eur Heart J. 2021)*

Stroke incidence per 100PY



Tsadok MA, et al. Circulation. 2012



Hindricks G, et al. Eur Heart J. 2021

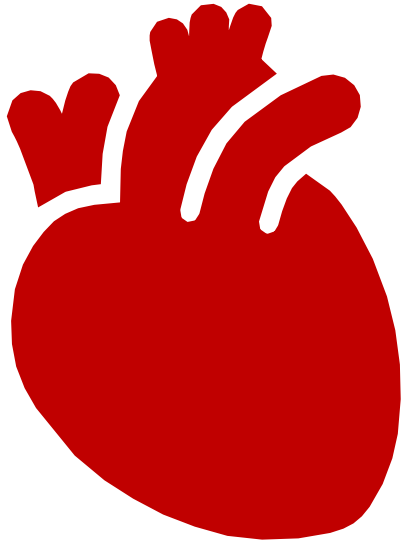
Study Limitations

- Observational study.
- No information on glycemic control during follow-up period.
- Specific type of AF not identified.
- Restoration and maintenance of sinus rhythm after ERC unknown.

Conclusion

- Early rhythm control was associated with **lower risks of ischemic stroke, composite of macrovascular complications, composite of microvascular complications, and all-cause death** compared to usual care.

- **Early rhythm control within 1 year of AF diagnosis should be considered** to prevent adverse outcomes in patients with diabetes and new-onset AF.



Thank you for your attention

JungMin Choi, MD

Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital,

Republic of Korea

jmlisachoi@gmail.com