AF Burden reduction vs. 30-second recurrence:

Is there any light at the end of the 30-second tunnel?

Rhythm 2022, Marseille, Jerome Kalifa, M.D; PhD

Volta Medical

18-21 MAY 2022

Golden Tulip Villa Massalia
Marseille, France

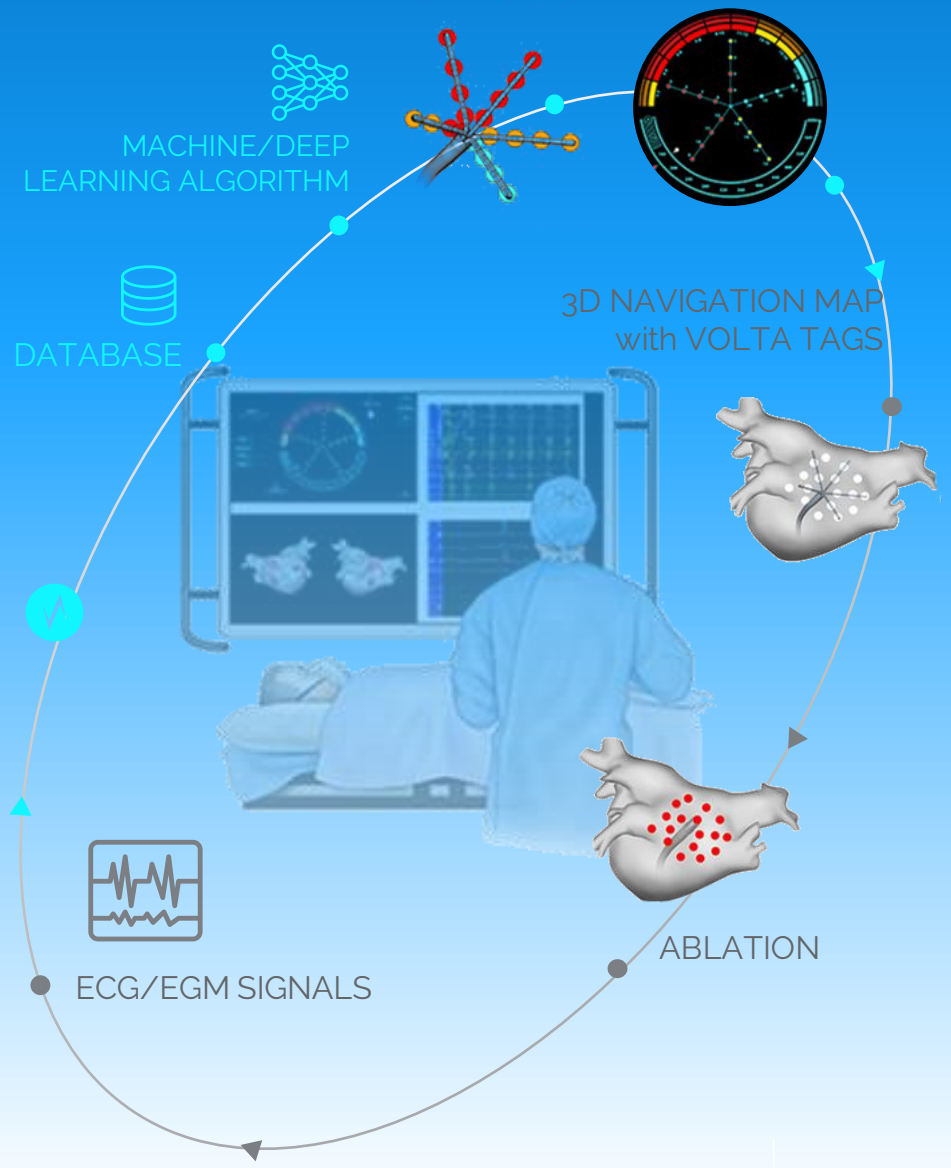
Volta Medical

Transforming EP Data Into AI Solutions

50+ employees- France-USA

VX1 by VOLTA

AI Decision Support System



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Agenda
The Start-up Management Perspective

1. The 30-second definition
2. Clinical relevance, pitfalls, real-life consequences
3. Alternatives
4. Proposals

AF Management: Catheter Ablation Trials The Start-up Management Perspective

- New technologies: energies, catheters, mapping
- The means of assessing such technologies are increasingly complicated and expensive
- Results of single-arm observational trials are challenging to interpret
- RCTs have become the gold standard to evaluating novel technologies

AF Management: Catheter Ablation Trials The Start-up Management Perspective

- Large budgets: $20M+
- Duration of follow-up critical- Time-to-value-generating events
- Multiple Stakeholders: investors, regulatory, physicians
- Massive opportunity costs

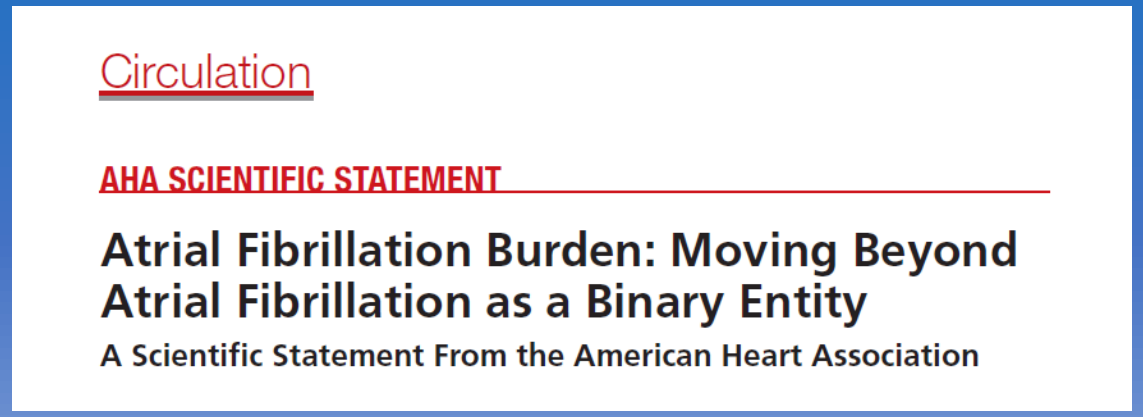
AF Management: Catheter Ablation Trials
The Start-up Management Perspective
RCT is like going to war

Choice
Of RCT
Success Criteria

RCTs for PsAF Ablation Clinical Trials

- Patient population— % of long-standing persistent
- Stringency of the follow-up: Methods, length of the blanking period
- Definition of atrial fibrillation relapse, censoring events
- Need for adapted Success/Failure evaluation criteria

30-second definition


Circulation

AHA SCIENTIFIC STATEMENT

Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity

A Scientific Statement From the American Heart Association

Chen, Turakhia et al. Circulation 2018

Electrocardiographic documentation of absolutely irregular RR intervals and no discernible, distinct P waves lasting for at least 30 seconds.

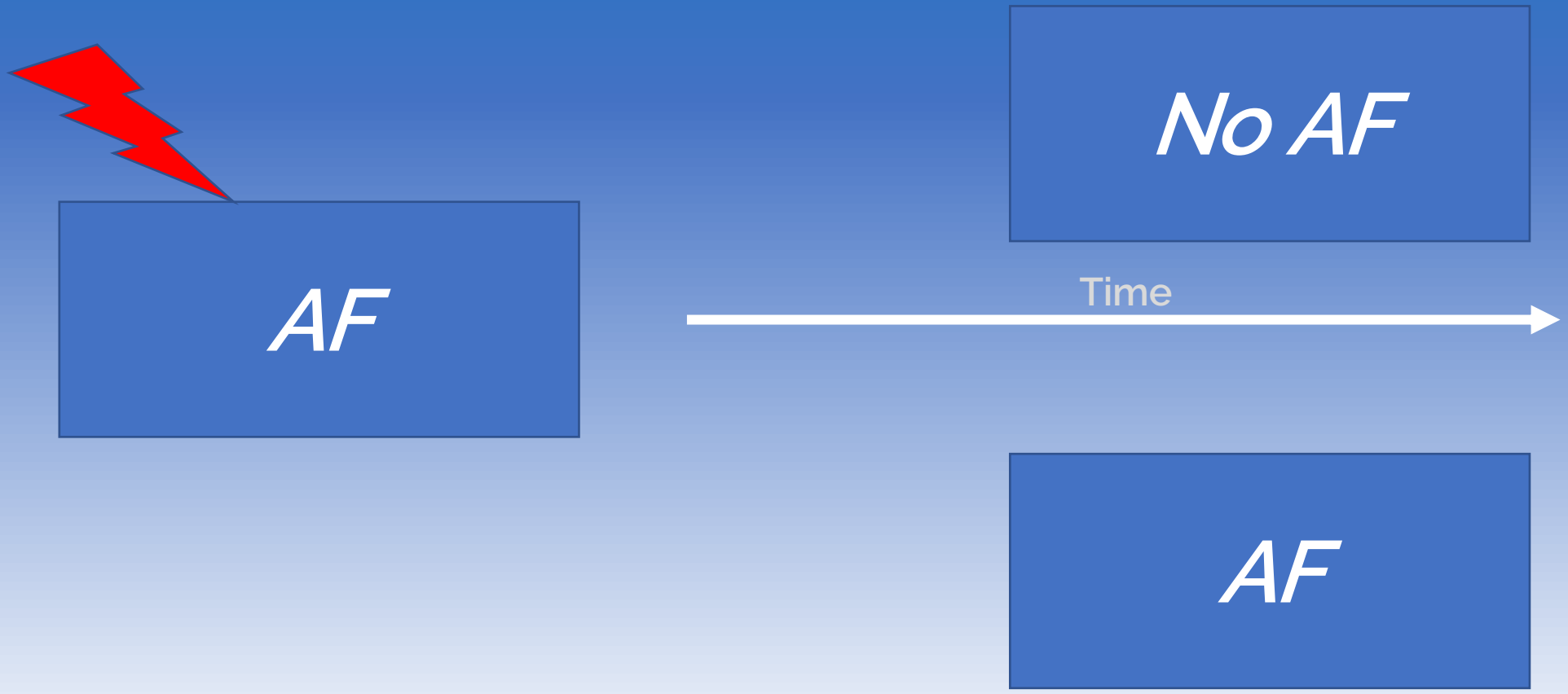
2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J.* 2016;37:2893–2962. doi: 10.1093/eurheartj/ehw210

The 30-second definition: Limitations

- Binary state of the disease
- Is poorly adapted to the persistent AF population
- Poor, non-linear predictability of first episode on future episodes
- Does not address AF density

The 30-second definition: Limitations

- Binary state of the disease

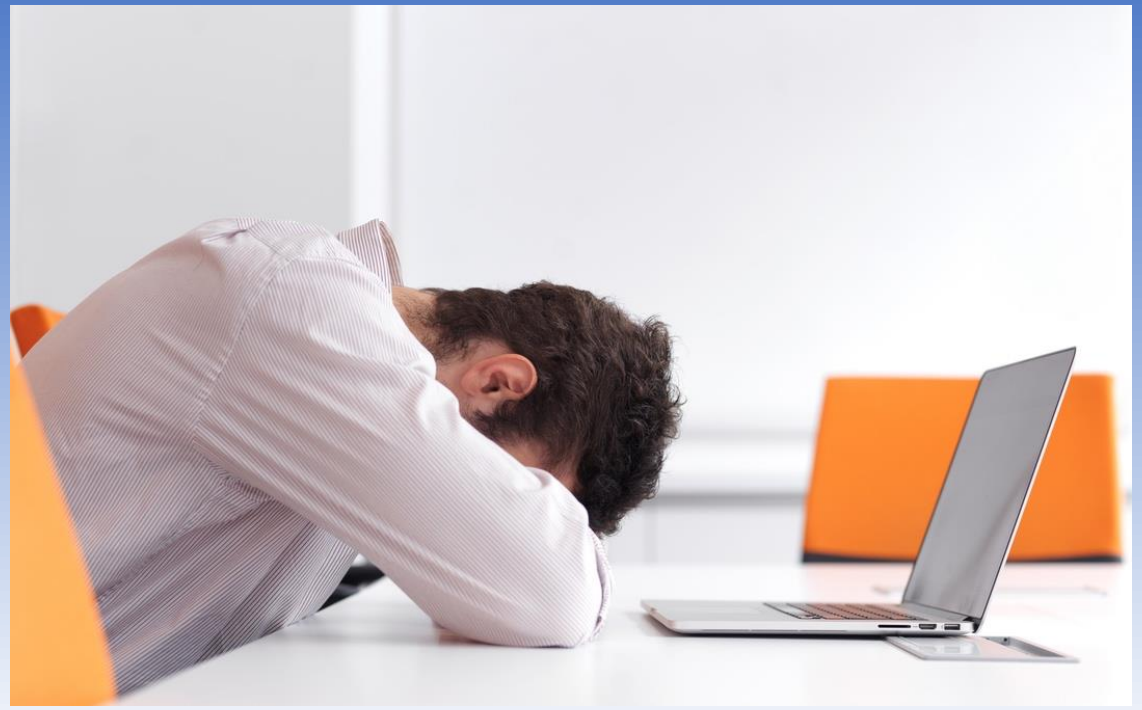


72-yo patient in symptomatic permanent AF- Ablation—6-month post ablation: 3 one-minute episodes over two weeks

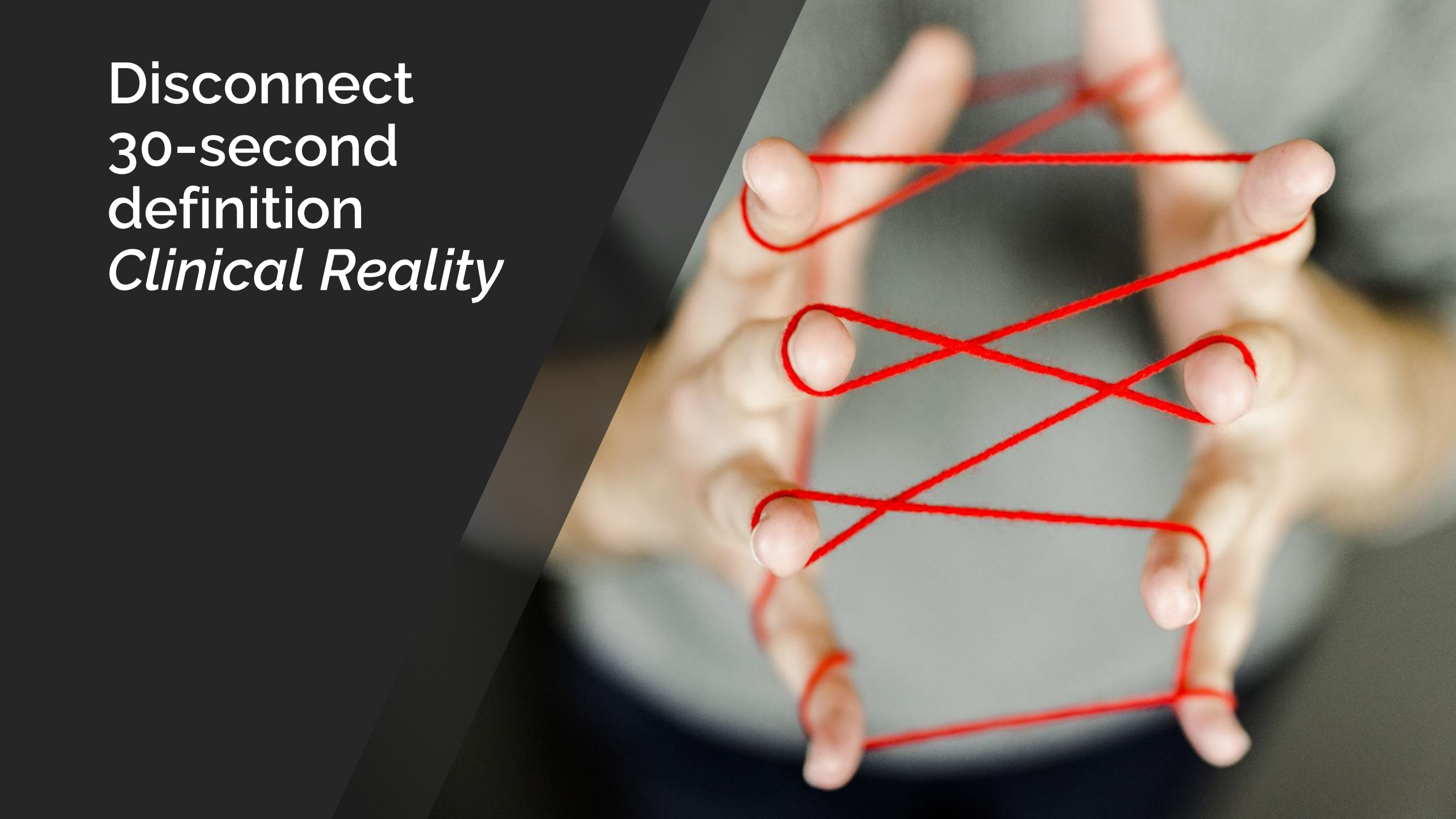
- 30-second definition

Management Failure

- Any physician: Success
- Patient: Success



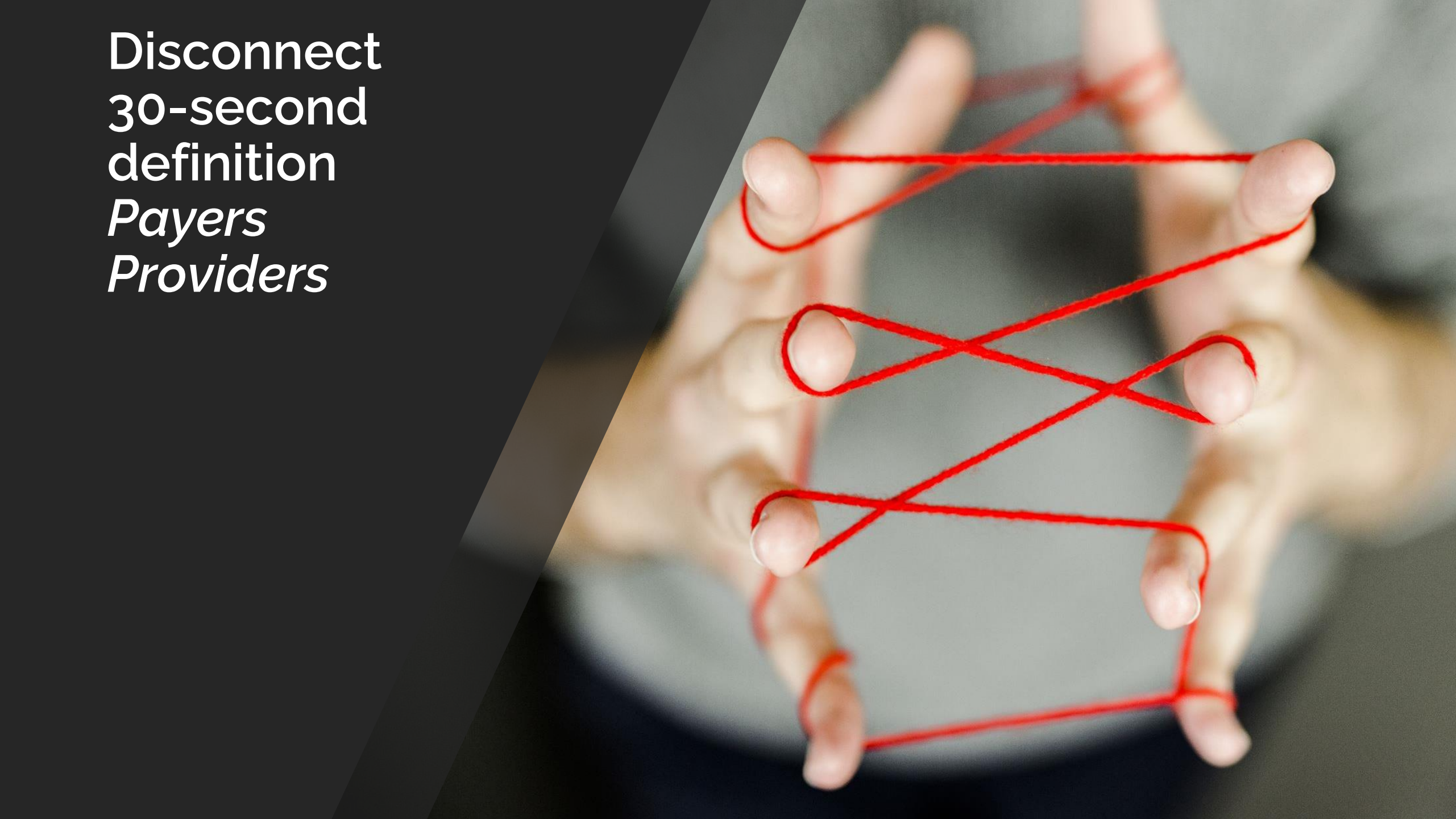
Disconnect 30-second definition *Clinical Reality*



Disconnect 30-second definition

Payers

Providers



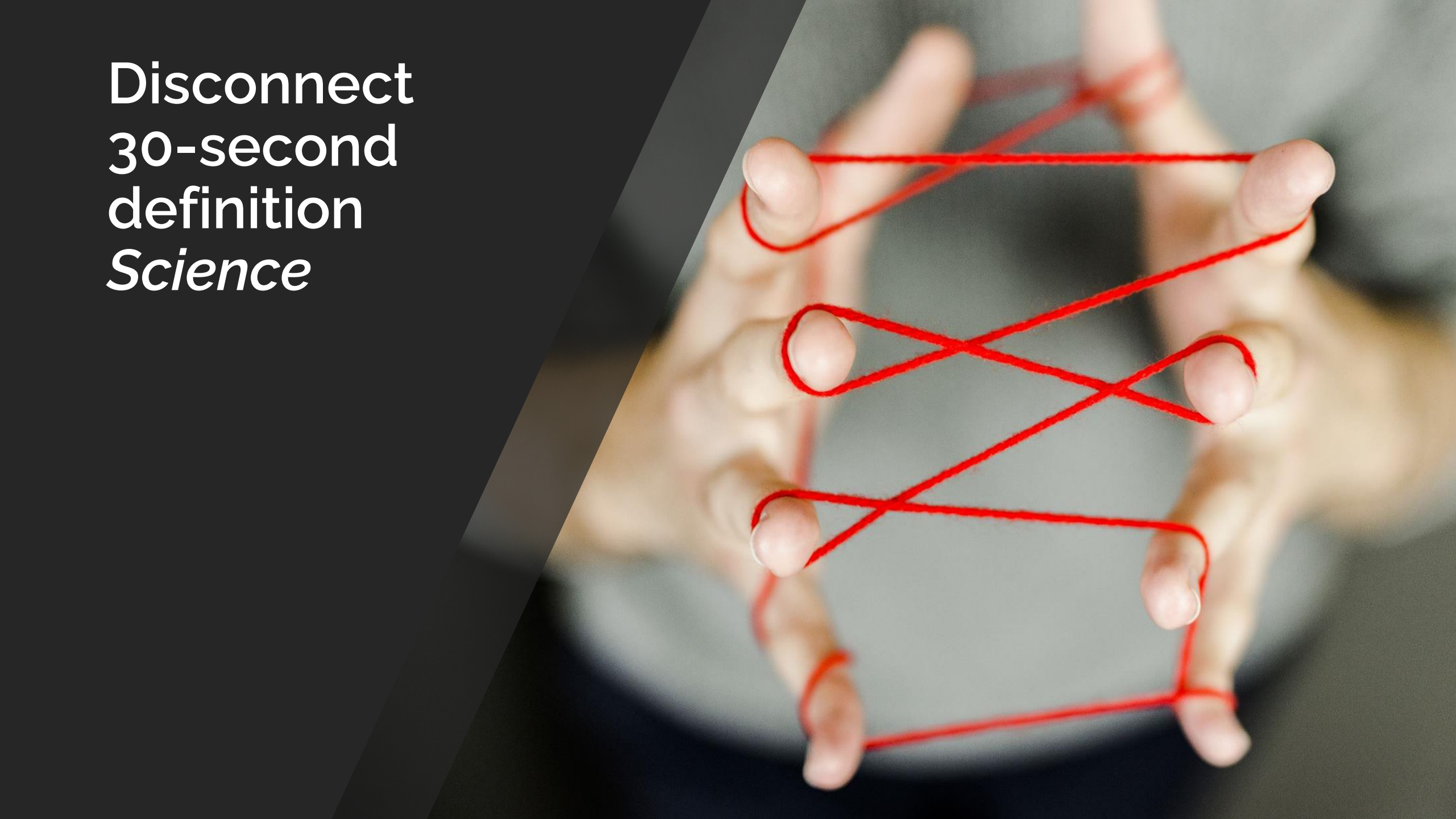
Real-life consequences Providers/Payers Reluctancy

2021 Medicare Average Fees vs. 2022 Medicare Final Fees*				
CPT Codes	**Code Descriptors**	**2021 Medicare Average Fees**	**2022 Medicare Final Fees**	**% Reduced**
93653 + 93613 + 93621	SVT Ablation (+ 3D Mapping & LA Pacing)	$1,283	$847.5	- 34%
93656 + 93613 + 93622	AF Ablation (+ 3D Mapping & ICE)	$1,574	$1,137	- 28%
93657	Treat AF additional Foci Add-On	$438	$316	- 28%
93655	Ablate Arrhythmia Add-On	$439	$317	- 28%
93654	VT Ablation	$1,152	$1,134	- 2%

**Congress boosted the final rule CF by 3% on December 10, 2021, in order to delay what would have been a 3.75 CF cut effective on January 1, 2022.*

https://www.hrsonline.org/CMS22

Disconnect 30-second definition *Science*



Circulation: Arrhythmia and Electrophysiology

ORIGINAL ARTICLE

Thirty-Second Gold Standard Definition of Atrial Fibrillation and Its Relationship With Subsequent Arrhythmia Patterns

Analysis of a Large Prospective Device Database

See Editorial by Terricabras et al

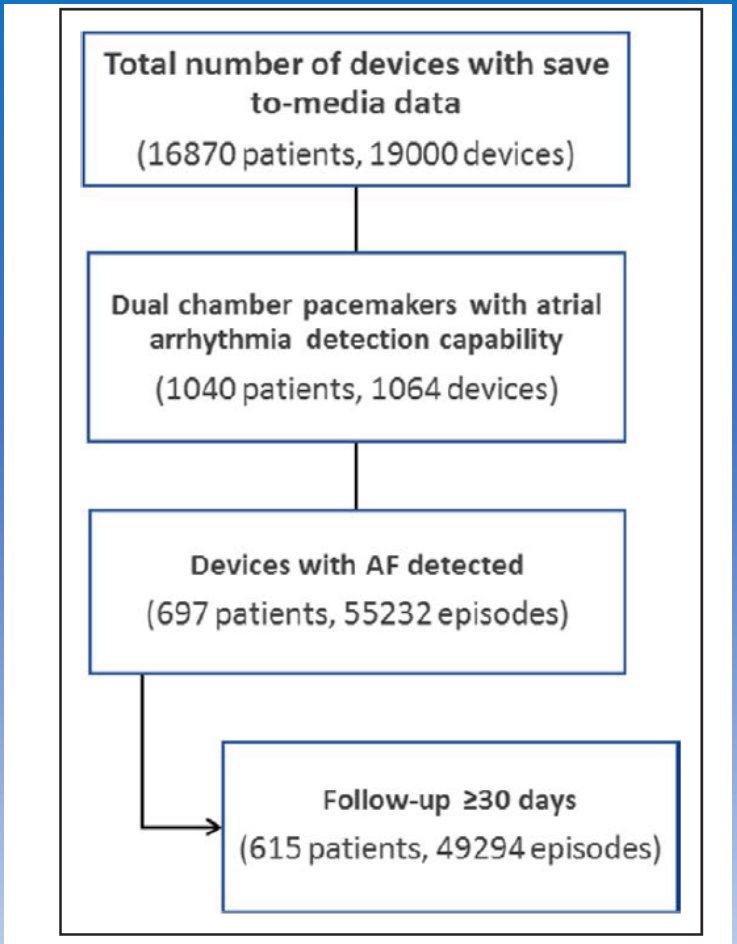
Jonathan S. Steinberg, MD
Heather O'Connell, MS
Shelby Li, MD, MS
Paul D. Ziegler, MS

BACKGROUND: The Heart Rhythm Society consensus statement arbitrarily defines atrial fibrillation (AF) ablation failure as any episode ≥30 seconds. However, if brief AF events are not correlated to longer events, the rationale for this end point is questionable. We determined the impact

The 30-second definition: How does that predict future episodes

615 patients with pacemaker with device-detected AF

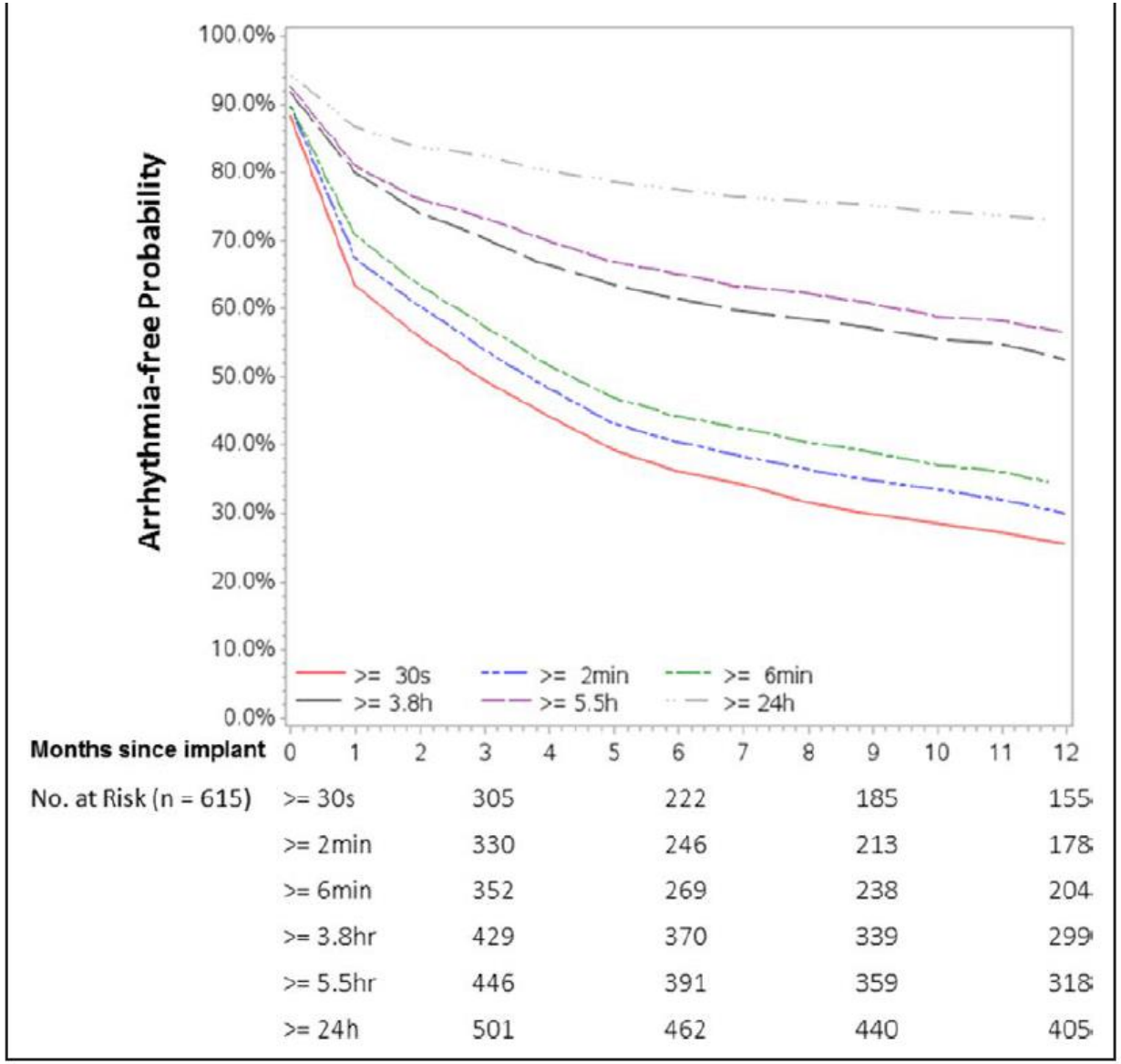
Data from dual chamber PM with atrial sensing capabilities



Steinberg et al. Circ Arrhythmia 2018
At least one episode of AF during a follow-up of 3.7 years.

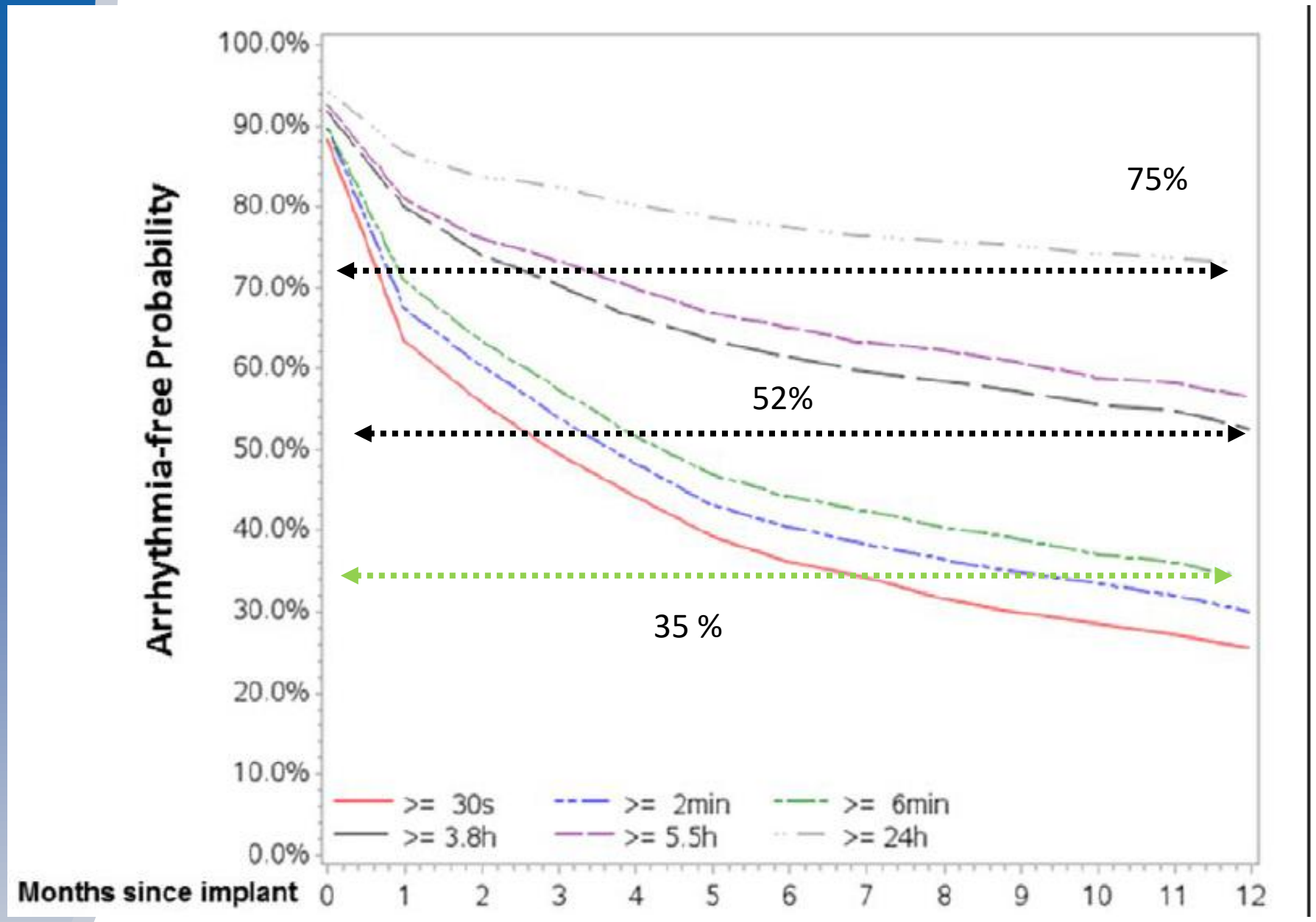
Astonishing!!

From 30% to 80%

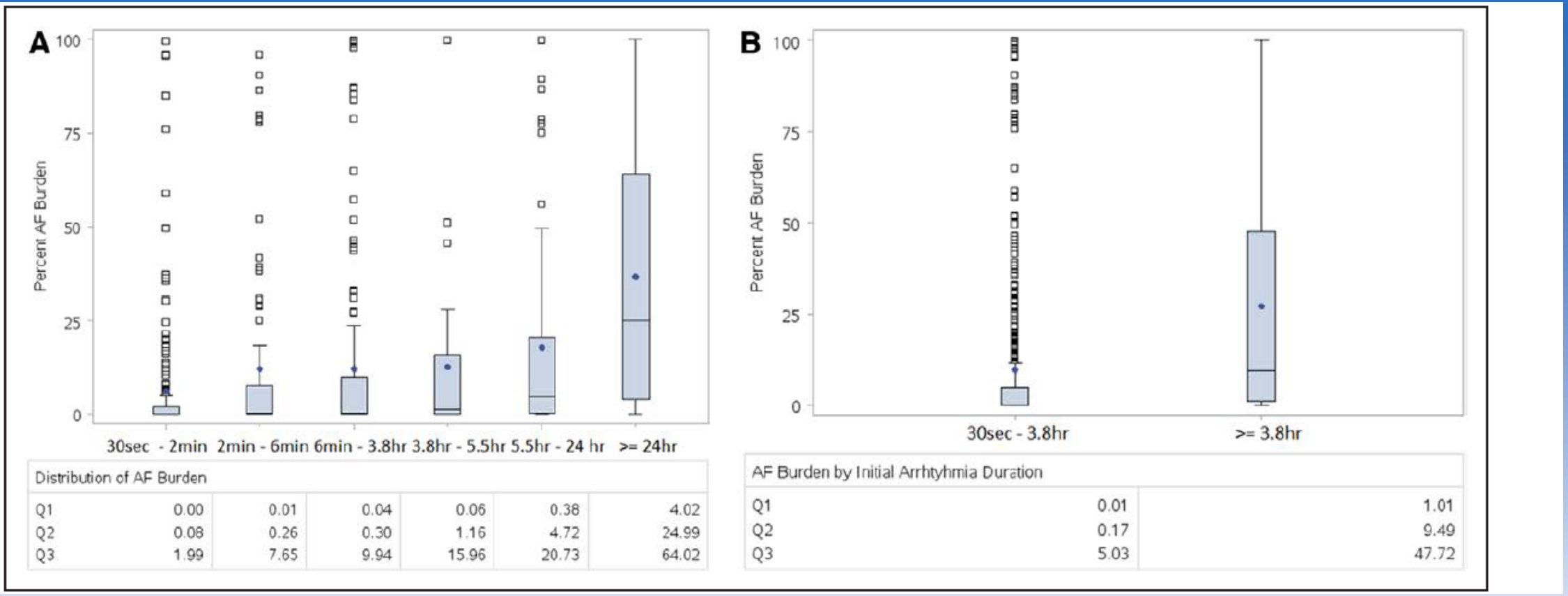


Terrifying!!

From 35% to 52% at 12-month



How is the threshold associated with the average burden? Non-linear relationship



Distribution of AF Burden						
Q1	0.00	0.01	0.04	0.06	0.38	4.02
Q2	0.08	0.26	0.30	1.16	4.72	24.99
Q3	1.99	7.65	9.94	15.96	20.73	64.02

AF Burden by Initial Arrhtyhmia Duration		
Q1	0.01	1.01
Q2	0.17	9.49
Q3	5.03	47.72

Alternatives

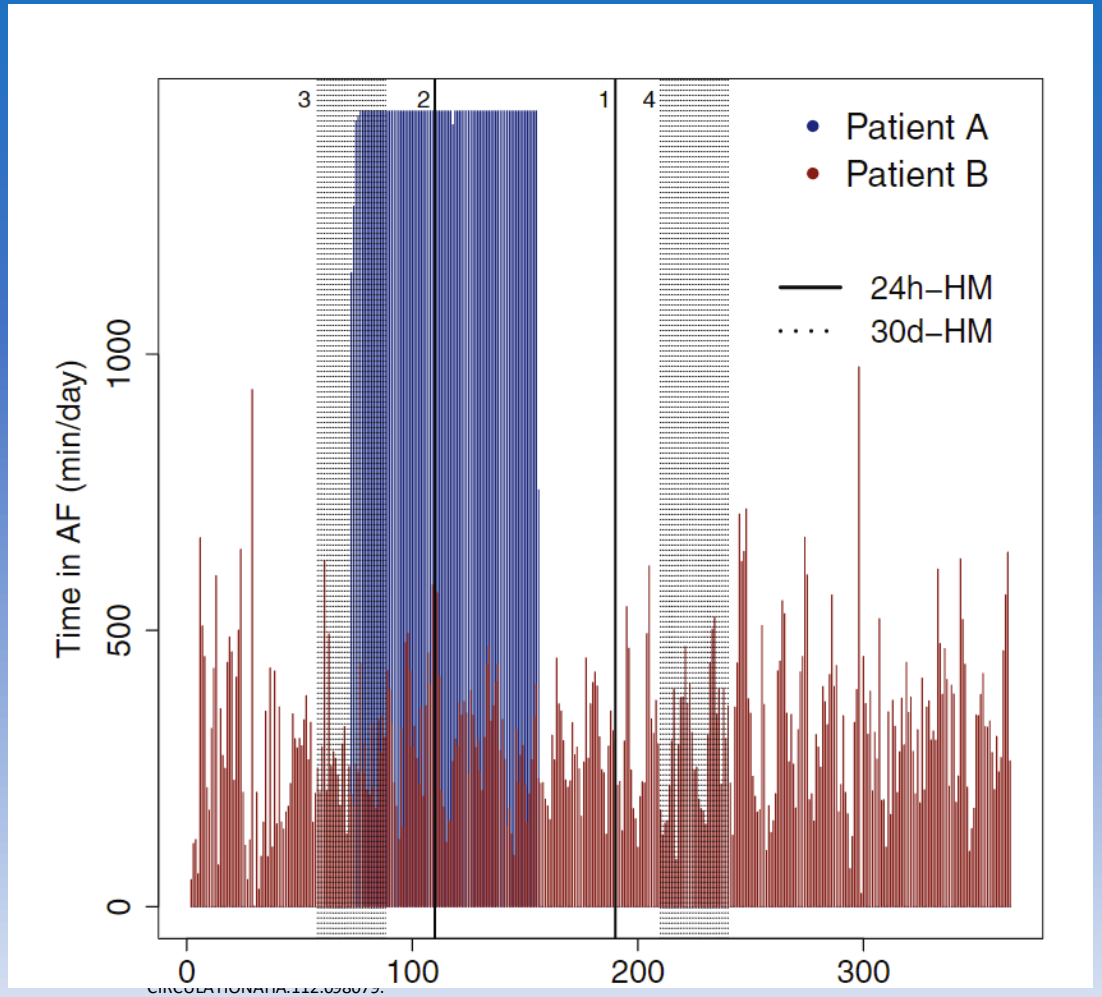
AF Burden

Amount of time spent in AF divided by the total amount of time a patient is monitored

AF Density

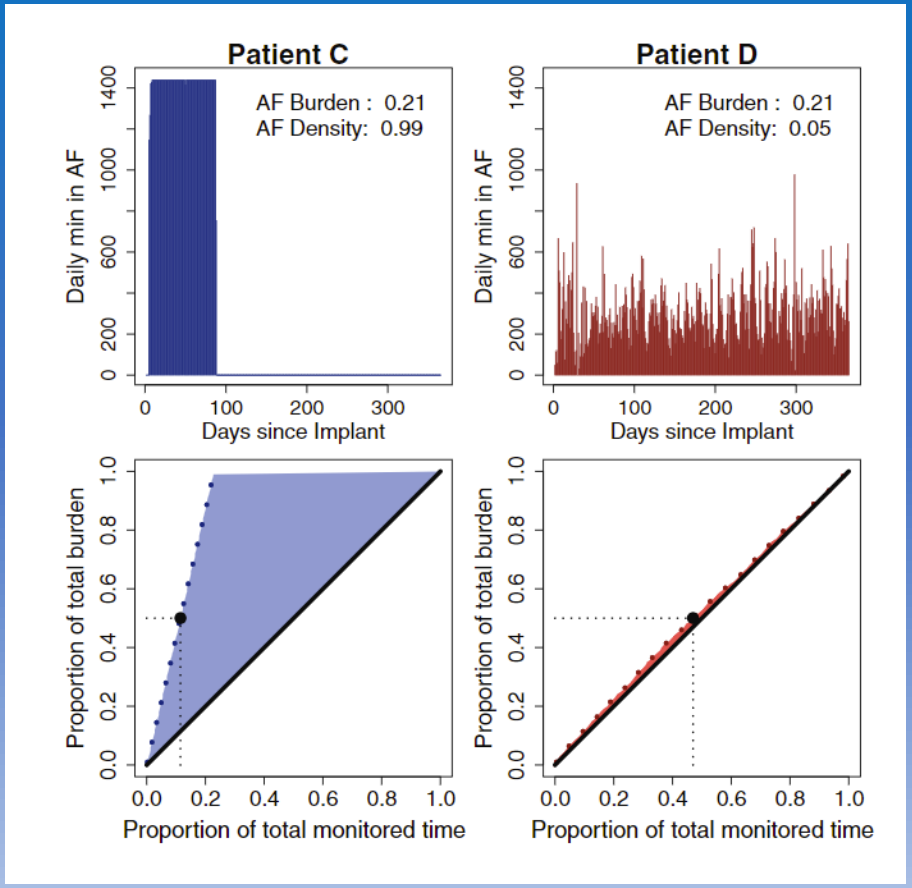
Measure of the concentration of AF episodes.
Absolute cumulative deviation of the patient's actual burden development from the hypothetical uniform burden development divided by the minimum time required for development of all AF episodes.

AF Density



$$\text{AF density} = 2 * \frac{\int_0^1 |F(p;b) - p| dp}{1 - b}.$$

AF Density



$$\text{AF density} = 2 * \frac{\int_0^1 |F(p;b) - p| dp}{1 - b}.$$

HH, Hanke T. A comprehensive evaluation of rhythm monitoring strategies for the detection of atrial fibrillation recurrence: insights from 647 continuously monitored patients and implications for monitoring after therapeutic interventions. *Circulation*. 2012;126:806–814. doi: 10.1161/CIRCULATIONAHA.112.098079.

Roadmap to implementation in clinical trials
Examples

- DECAAF 2: atrial fibrillation, atrial flutter, or atrial tachycardia demonstrated by at least one valid 12-lead ECG tracing, two consecutive smartphone ECG device tracings separated by at least 6h to a maximum of 7 days
- CONVERGE:

Primary endpoint: any AF/ AFL/AT episode of at least 30 seconds by Holter monitor or for full 10 seconds recording on a standard 12 lead electrogram

Secondary endpoint: at least 90% reduction in AF burden at 12 months when compared with baseline, absent an increased dose or new class I/III AADs

Roadmap to implementation in clinical trials

- Dedicated single-arm investigations using both the 30-second definition and various other measures of AF burden
- Progressive integration into primary and secondary endpoints of RCTs
- Non-censored, innovative composite-endpoint RCT approaches

Conclusions
The Start-up Industry Perspective

1. RCTs are major endeavors requiring extensive ressources
2. 30-second: Artificial binary classification-Poorly fits the needs to the persistent AF population
3. Poor predictability on future episodes
4. Time for a progressive transition to some measure of AF burden

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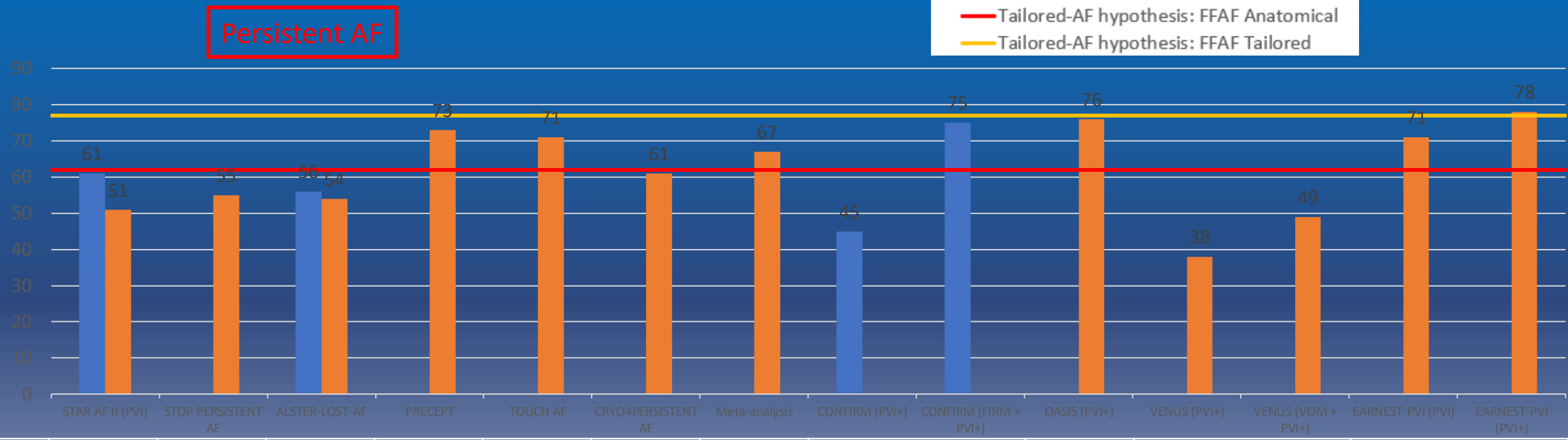
Thank You

Rules for Interpretation of PsAF Ablation Clinical Trials

- Any trial results must be interpreted based upon:
  - the patient population— % of long-standing persistent
  - The stringency of the follow-up: Methods, length of the blanking period
  - **Definition of a relapse**

7. Learnings from past trials (CONFIRM, OASIS, STARAF2 etc.)



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Patients	549	165	61	348	124	101	956	65	27	113	158	185	249	248
Persistent AF	100%	100%	100%	100%	100%	100%	100%	52%	63%	100%	100%	100%	100%	100%
AF duration	72-79% > 6 mo	100% < 6 mo	43% LsPeAF	100% < 12 mo	26% LsPeAF Max duration ~7mo	LsPeAF excluded	Minority of LsPeAF	15% LsPeAF	15% LsPeAF	29-31% LsPeAF	52% LsPeAF	54% LsPeAF	24% LsPeAF	28% LsPeAF
Ablation technology	Non-CF RF	Cryo	Non-CF RF	CF RF	CF RF	Cryo	45% Non-CF or CF RF 55% Cryo	Non-CF RF		Non-CF RF			93% CF RF	92% CF RF
Ablation protocol	PVI PVI+CFE PVI+lines	PVI	PVI	55% PVI 45% PVI+	Wide antral PVI + roof line	PVI	PVI only	PVI + roof line (PsAF)	FIRM + PVI + roof line (PsAF)	FIRM only FIRM+PVI PVI+	PVI+	VOM + PVI+	PVI	PVI + lines/CFAE
12-lead ECG	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Reveal (23%) or PM/ICD or quarterly for remaining pts	Reveal (85%) or PM/ICD or quarterly for remaining pts	Yes	Yes		Yes	
Holter Monitor	24-hr	24-hr	24-hr	24-hr	48-hr	48-hr	Mostly 24-hr			7-day	1-mo		24-hr	
TTM	Stringent	Stringent	None	None (in this analysis)	Limited (symptoms)	None	Mostly none			Limited (5 mo)	None		None	
Follow-up	3-18 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	Mostly 3-12 mo	from 3 mo to > 3 yrs		2-12 mo	3-12 mo		3-12 mo	

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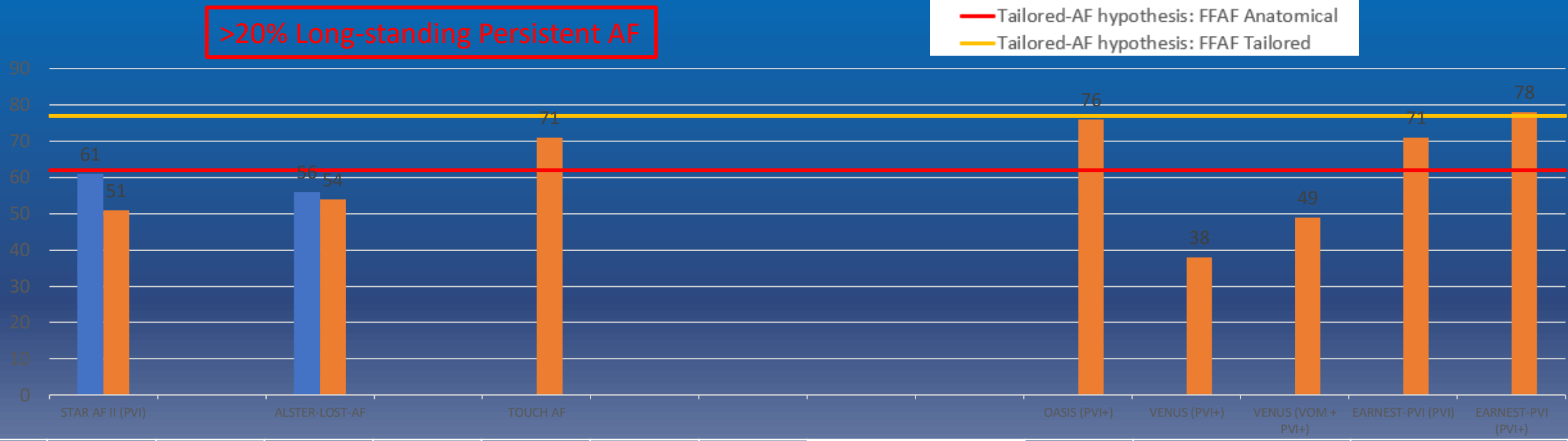

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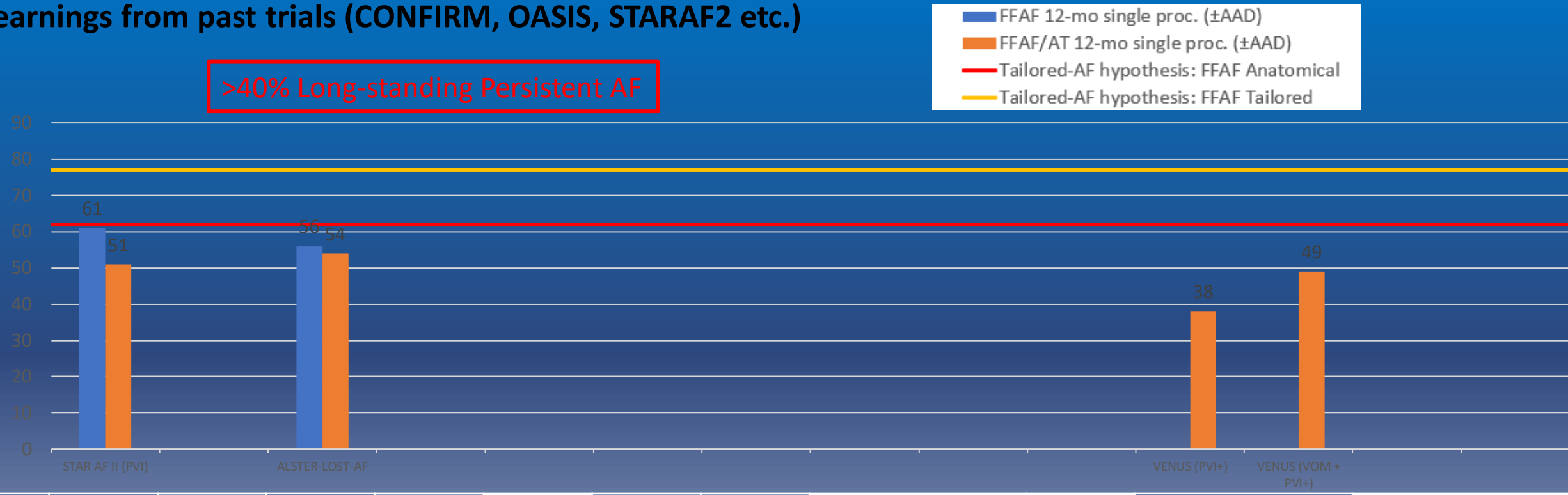
7. Learnings from past trials (CONFIRM, OASIS, STARAF2 etc.)

>40% Long-standing Persistent AF



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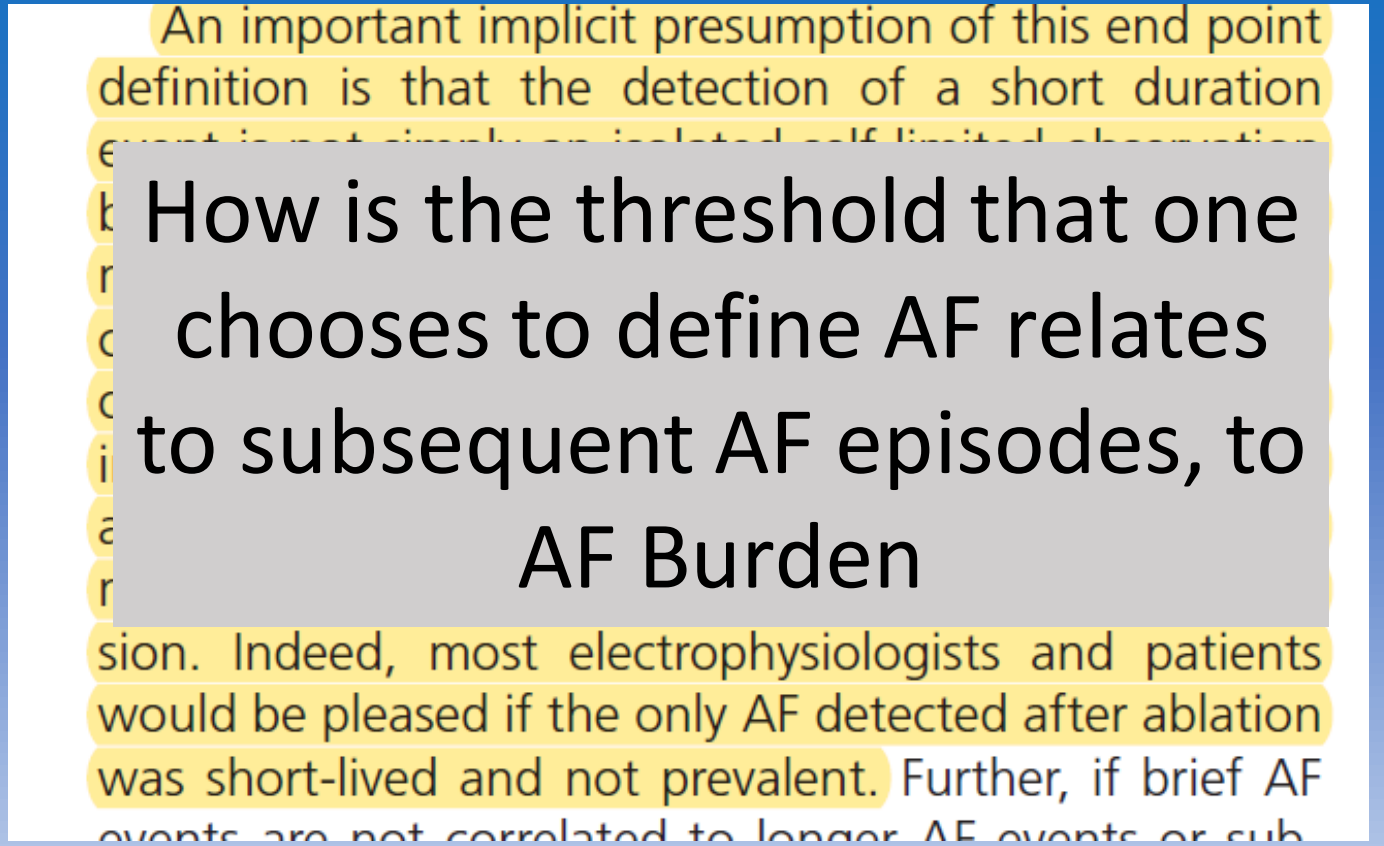
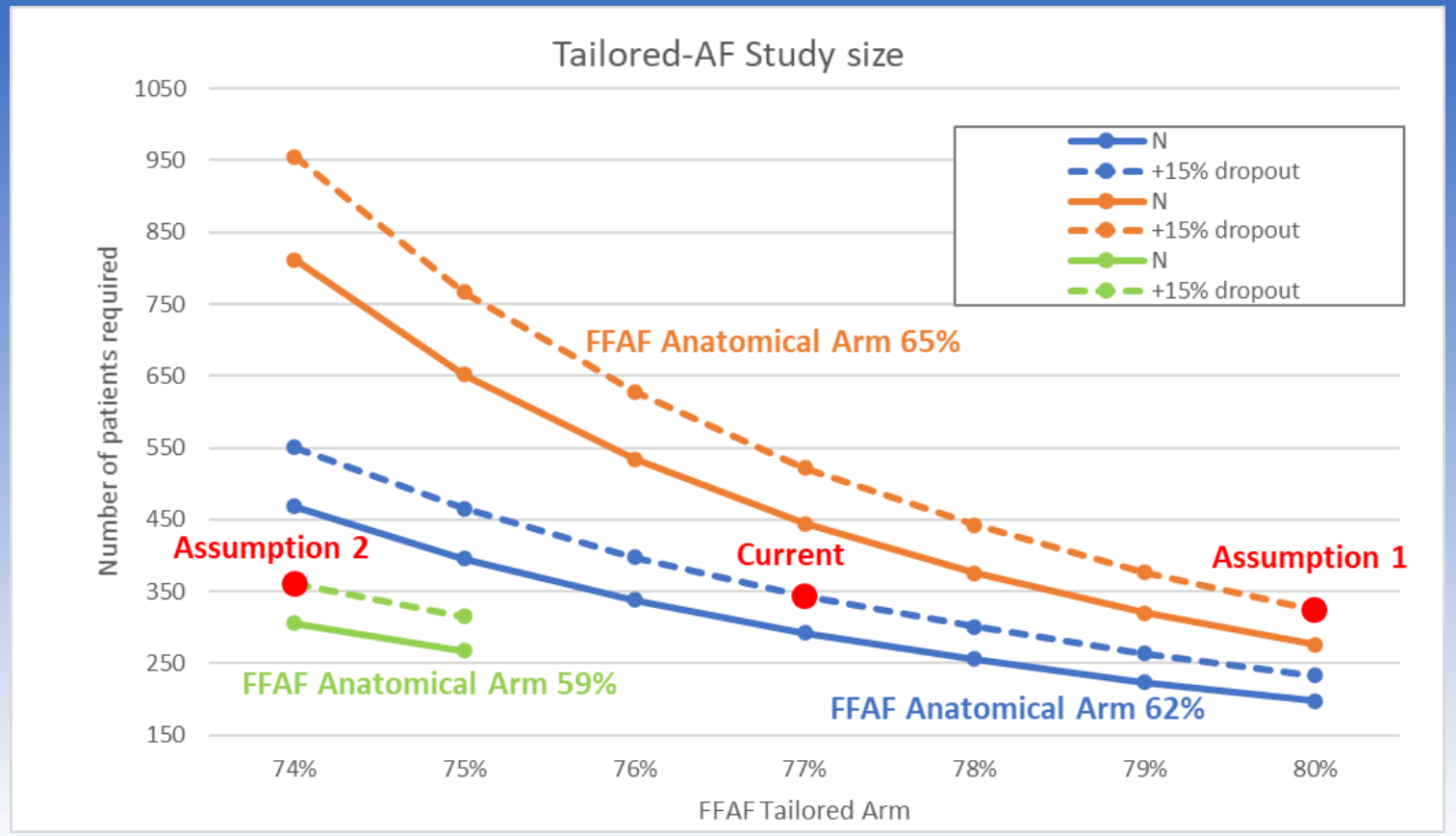
The 30 sec-definition



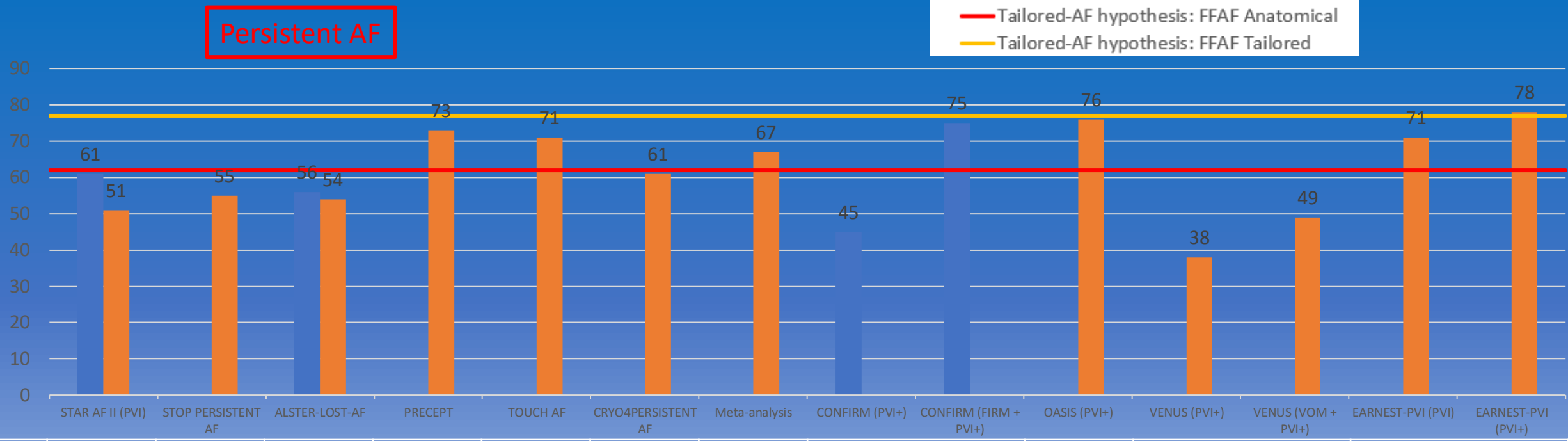
1. Study power
b. What is the impact on the study size if this is increased?

In keeping an hypothesized difference between arms at 15% and a 15% dropout rate, Log-Rank test for a one-sided superiority trial, significance level α=0.025, statistical power 80%, we present:

- **Assumption 1:** A 3% increase in the purported FFAF in the anatomical arm from 62% to 65%: **344 pts ⟶ 325 pts**
- **Assumption 2:** A 3% decrease in the purported FFAF in the anatomical arm from 62% to 59%: **344 pts ⟶ 360 pts**



Past trials (CONFIRM, OASIS, STARAF2 etc.)



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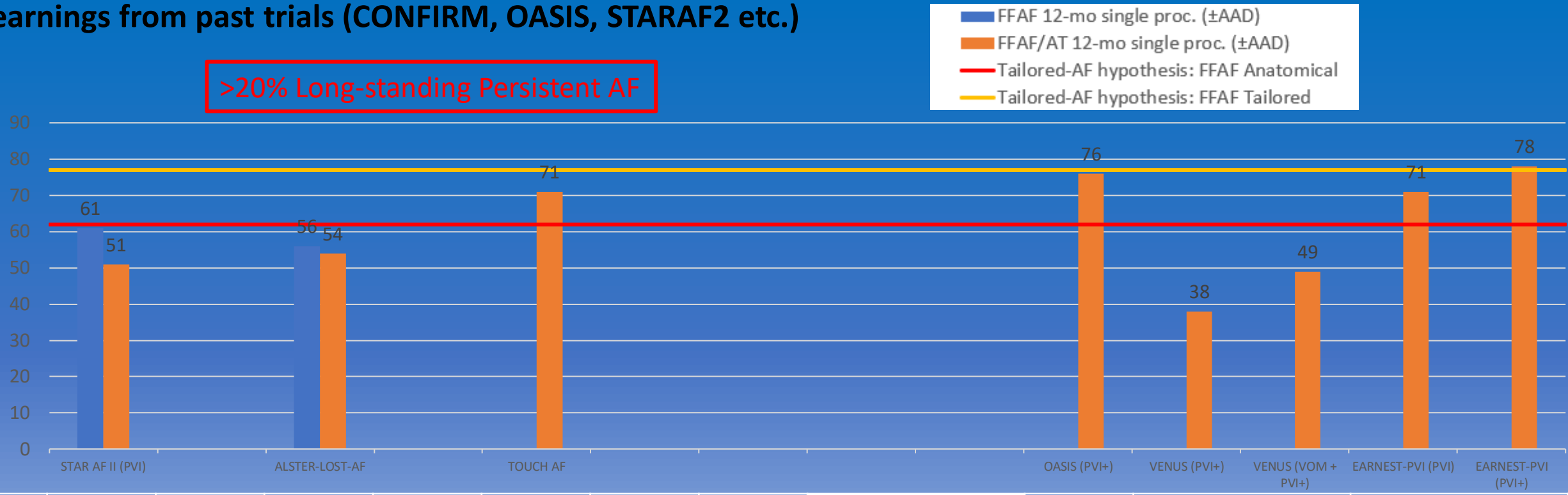

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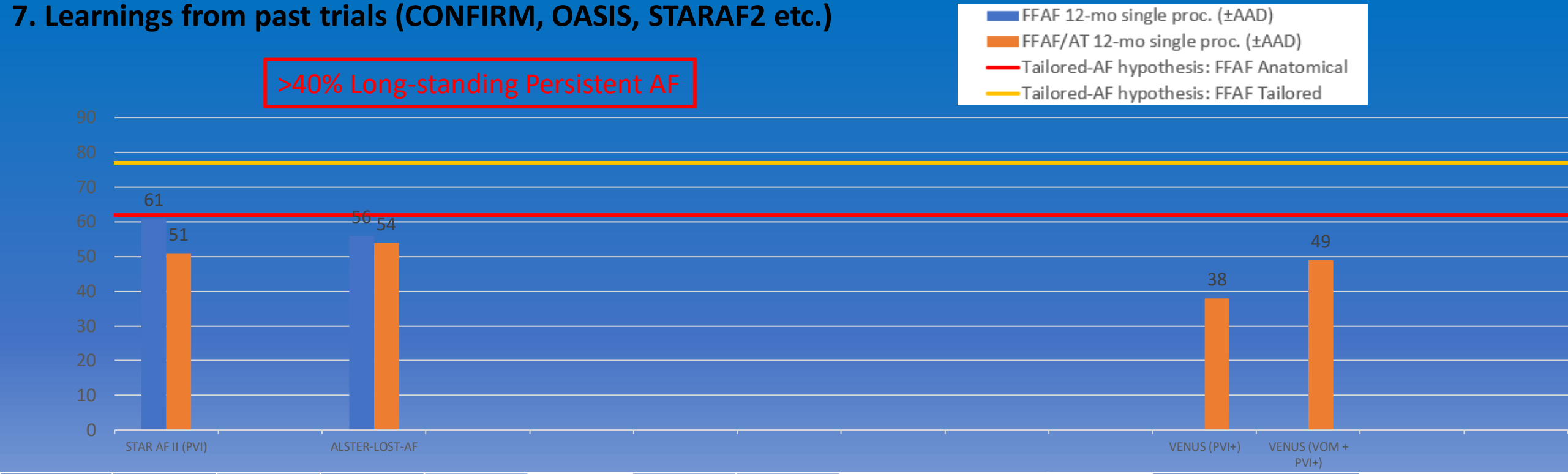
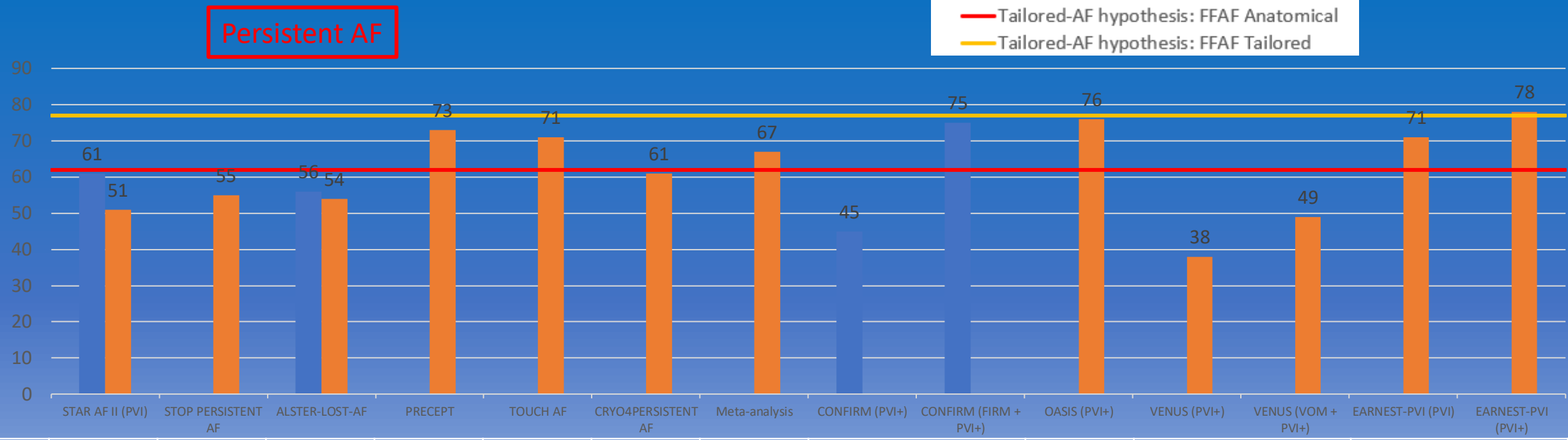


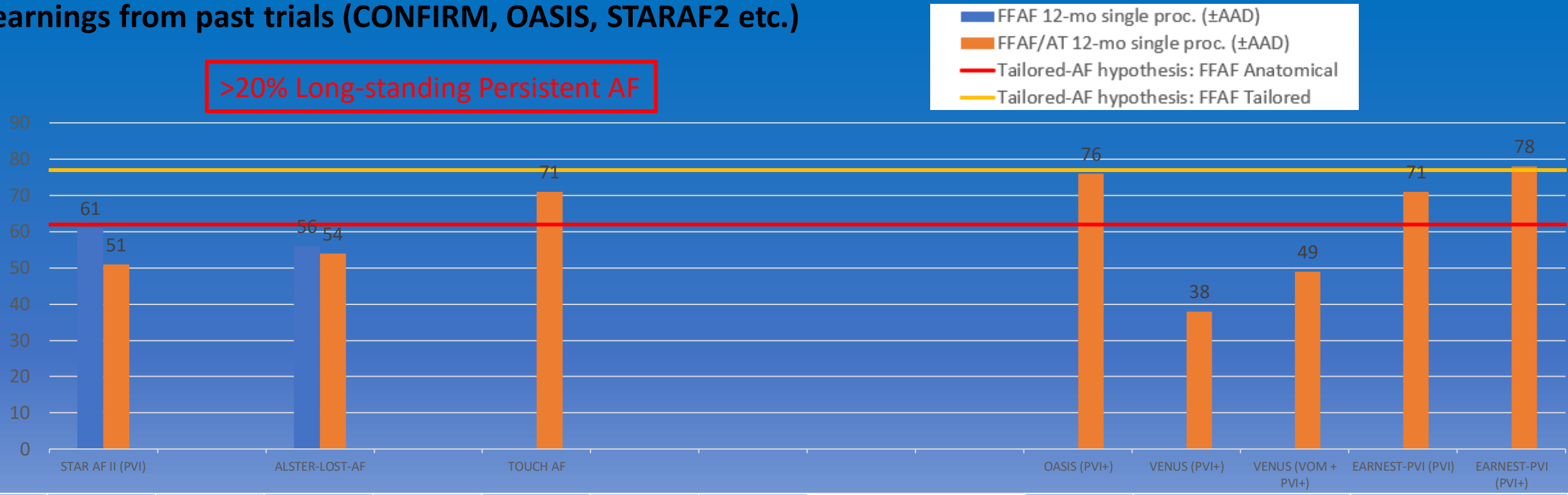
Reference	Verma et al. NEJM 2015	Calkins et al. AF symposium 2020	Fink et al. Circ Arrhythm Electrophysiol 2017	Mansour et al. JACC 2020	Boveda et al. JACC Clin Electrophysiol 2018	Voskonoinik et al. Heart Rhythm 2017	Miguel Valderrabano ACC 2020	
Patients	549	165	61	348	101	956	158	185
Persistent AF	100%	100%	100%	100%	100%	100%	100%	100%
AF duration	72-79% > 6 mo	100% < 6 mo	43% LsPeAF	100% < 12 mo	LsPeAF excluded	Minority of LsPeAF	52% LsPeAF	54% LsPeAF
Ablation technology	Non-CF RF	Cryo	Non-CF RF	CF RF	Cryo	45% Non-CF or CF RF 55% Cryo		
Ablation protocol	PVI PVI+CFE PVI+lines	PVI	PVI	55% PVI 45% PVI+	PVI	PVI only	PVI+	VOM + PVI+
12-lead ECG	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Holter Monitor	24-hr	24-hr	24-hr	24-hr	48-hr	Mostly 24-hr	1-mo	
TTM	Stringent	Stringent	None	None (in this analysis)	None	Mostly none	None	
Follow-up	3-18 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	Mostly 3-12 mo	3-12 mo	

Learnings from past trials (CONFIRM, OASIS, STARAF2 etc.)



Reference	Verma et al. NEJM 2015	Calkins et al. AF symposium 2020	Fink et al. Circ Arrhythm Electrophysiol 2017	Mansour et al. JACC 2020	Conti et al. Heart Rhythm 2018	Boveda et al. JACC Clin Electrophysiol 2018	Voskonoinik et al. Heart Rhythm 2017	Narayan et al. JACC 2012 JACC 2014		Mohanty et al. JACC 2016 (RETRACTED)	Miguel Valderrabano ACC 2020		Koichi Inoue ESC 2019	
Patients	549	165	61	348	124	101	956	65	27	113	158	185	249	248
Persistent AF	100%	100%	100%	100%	100%	100%	100%	52%	63%	100%	100%	100%	100%	100%
AF duration	72-79% > 6 mo	100% < 6 mo	43% LsPeAF	100% < 12 mo	26% LsPeAF Max duration ~7mo	LsPeAF excluded	Minority of LsPeAF	15% LsPeAF	15% LsPeAF	29-31% LsPeAF	52% LsPeAF	54% LsPeAF	24% LsPeAF	28% LsPeAF
Ablation technology	Non-CF RF	Cryo	Non-CF RF	CF RF	CF RF	Cryo	45% Non-CF or CF RF 55% Cryo	Non-CF RF		Non-CF RF			93% CF RF	92% CF RF
Ablation protocol	PVI PVI+CFE PVI+lines	PVI	PVI	55% PVI 45% PVI+	Wide antral PVI + roof line	PVI	PVI only	PVI + roof line (PsAF)	FIRM + PVI + roof line (PsAF)	FIRM only FIRM+PVI PVI+	PVI+	VOM + PVI+	PVI	PVI + lines/CFAE
12-lead ECG	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Reveal (23%) or PM/ICD or quarterly for remaining pts	Reveal (85%) or PM/ICD or quarterly for remaining pts	Yes	Yes		Yes	
Holter Monitor	24-hr	24-hr	24-hr	24-hr	48-hr	48-hr	Mostly 24-hr			7-day	1-mo		24-hr	
TTM	Stringent	Stringent	None	None (in this analysis)	Limited (symptoms)	None	Mostly none			Limited (5 mo)	None		None	
Follow-up	3-18 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	Mostly 3-12 mo	from 3 mo to > 3 yrs		2-12 mo	3-12 mo		3-12 mo	

7. Learnings from past trials (CONFIRM, OASIS, STARAF2 etc.)



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Persistent AF	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%	100%
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Ablation protocol	PVI PVI+CFE PVI+lines	PVI	PVI	55% PVI 45% PVI+	Wide antral PVI + roof line	PVI	PVI only	FIRM only FIRM+PVI PVI+	PVI+	VOM + PVI+	PVI	PVI + lines/CFAE
12-lead ECG	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes	
Holter Monitor	24-hr	24-hr	24-hr	24-hr	48-hr	48-hr	Mostly 24-hr	7-day	1-mo		24-hr	
TTM	Stringent	Stringent	None	None (in this analysis)	Limited (symptoms)	None	Mostly none	Limited (5 mo)	None		None	
Follow-up	3-18 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	Mostly 3-12 mo	2-12 mo	3-12 mo		3-12 mo	

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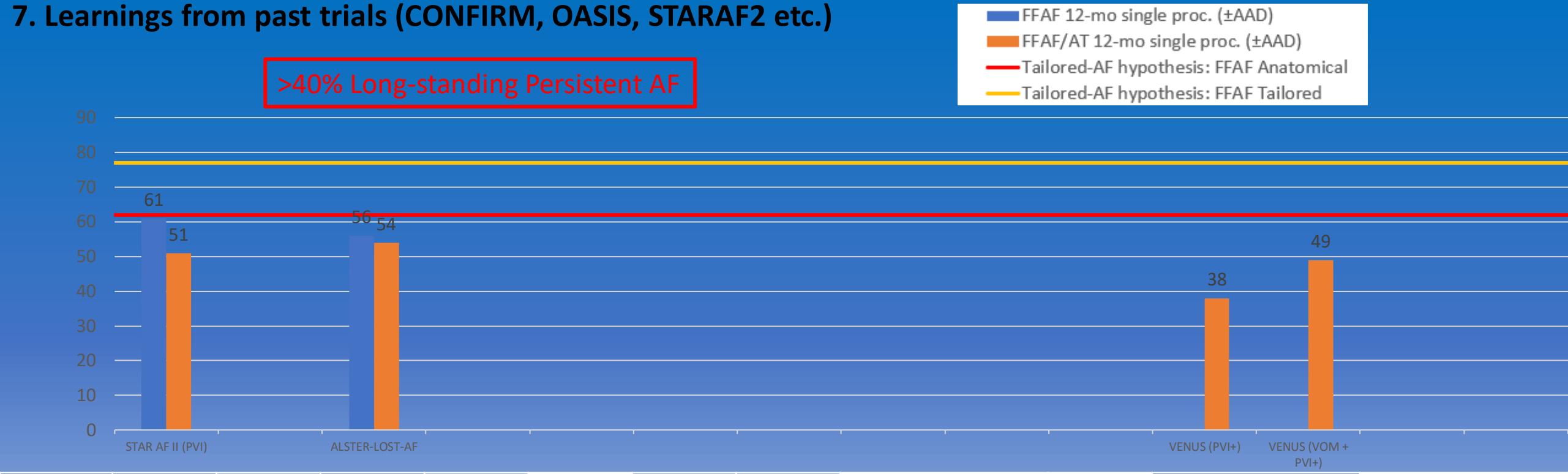

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12-lead ECG	Yes	Yes	Yes	Yes	Yes	Yes	Yes	
Holter Monitor	24-hr	24-hr	24-hr	24-hr	48-hr	Mostly 24-hr	1-mo	
TTM	Stringent	Stringent	None	None (in this analysis)	None	Mostly none	None	
Follow-up	3-18 mo	3-12 mo	3-12 mo	3-12 mo	3-12 mo	Mostly 3-12 mo	3-12 mo	

The 30 sec-limit

A **complicated** Reality