2019 Hot Topics in Cardiology

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Conflict of Disclosure

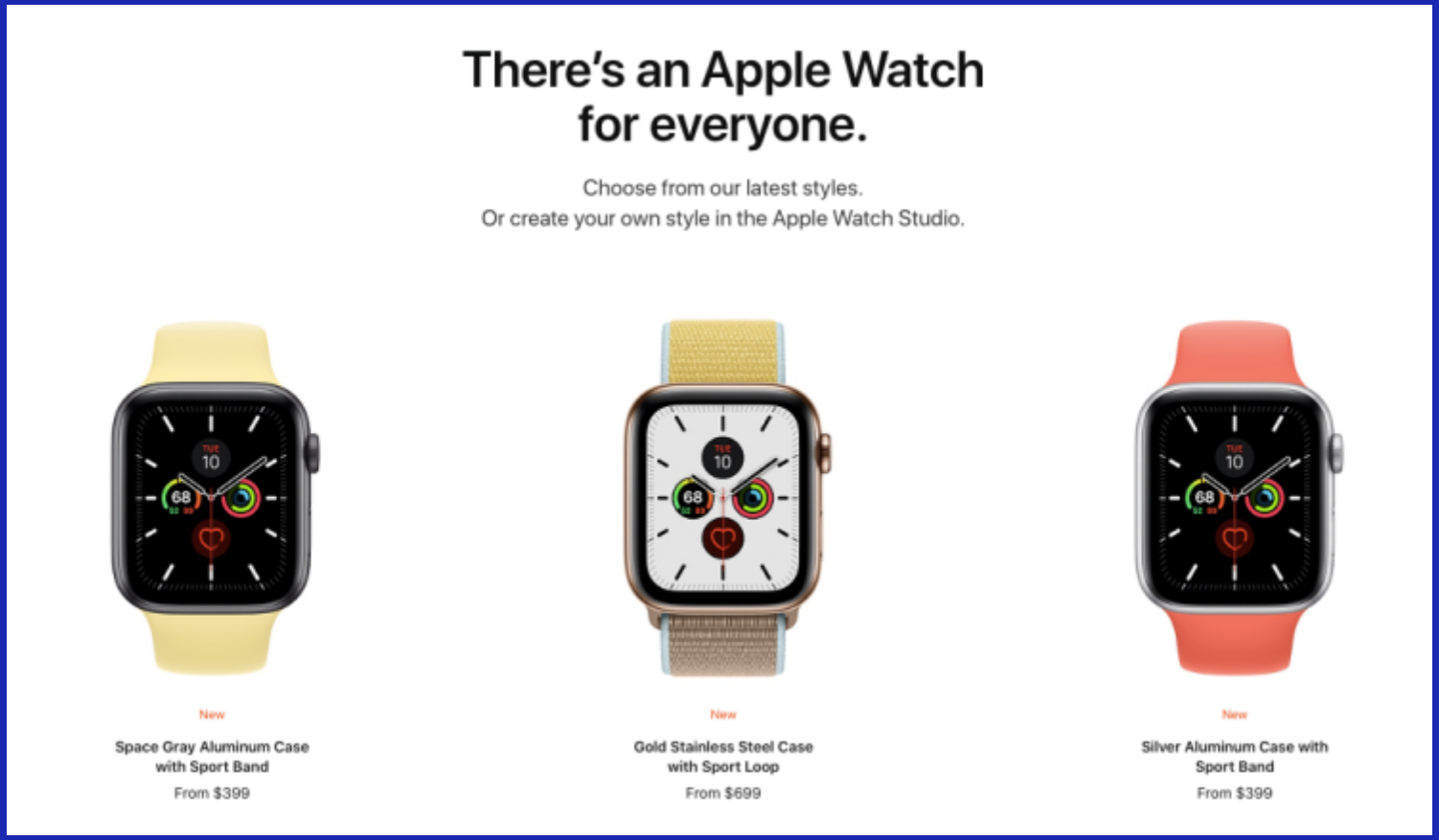
Speaker has no conflict of interest

Except bad jokes…

Objectives

- Update your knowledge on several key areas in cardiology
- Learn about new technologies that may be of use for your patients
- Understand the potential new treatments in heart failure patients with preserved ejection fraction

1. Apple Watch: the future of monitoring?
2. An old friend returns: Colchicine for myocardial infarction
3. SGLT2 blockers for nondiabetics?
4. Patients with HF with preserved EF: anything new?
5. How low can you get your LDL? PCSK9 inhibition
6. Not too much, not too little, just enough sleep will prevent an Mi
7. Subcutaneous ICDs: let's spare the vein!



"Using the ECG only takes about 30 seconds and it could save your life"

(Website: Cult of mac)

But is it worth the $399-$699 for the EKG monitoring alone?

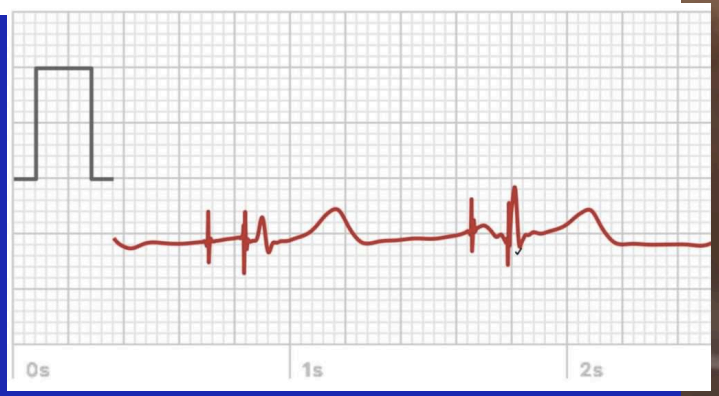
1.

The NEW ENGLAND JOURNAL of MEDICINE

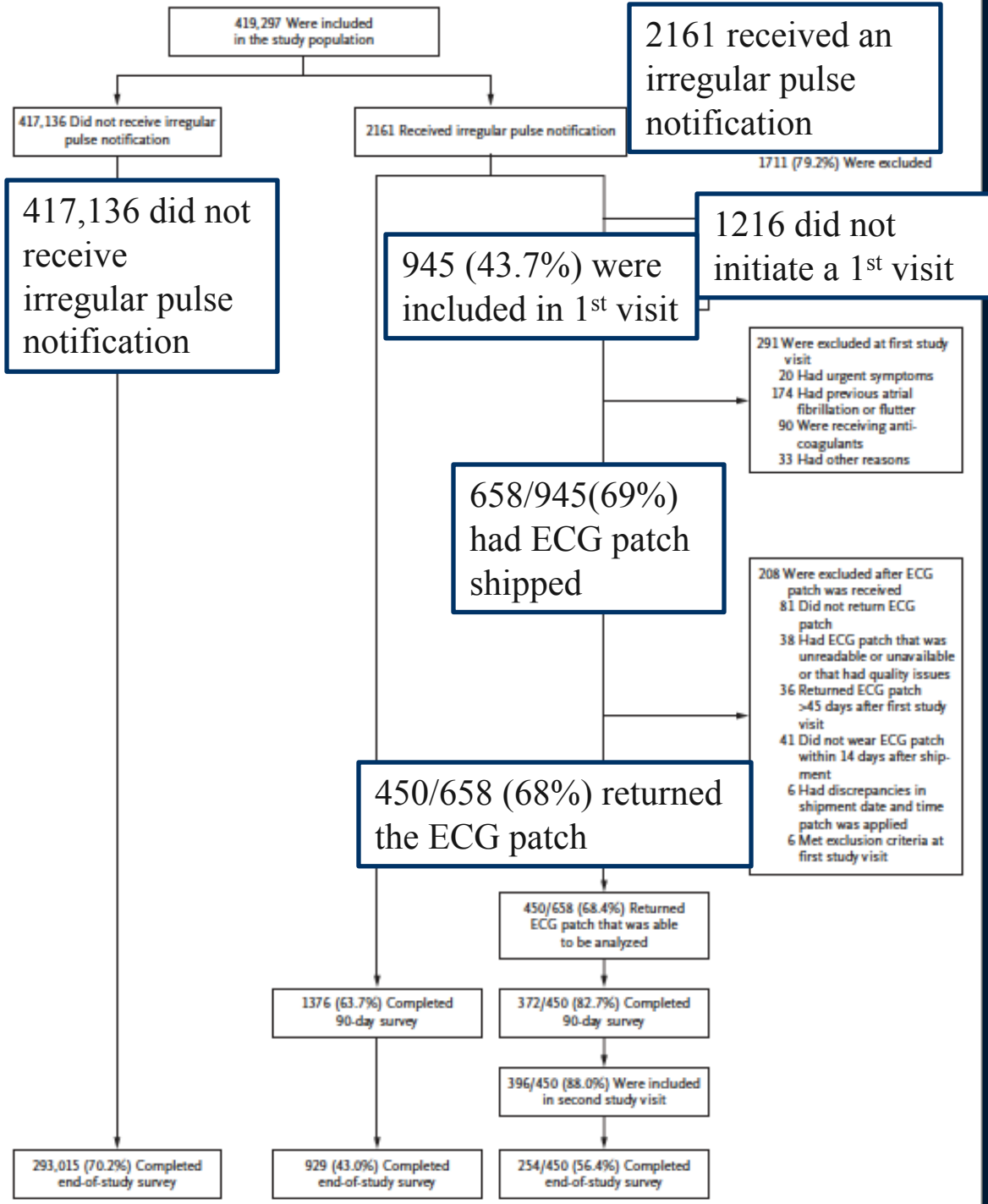
ORIGINAL ARTICLE

Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation

Marco V. Perez, M.D., Kenneth W. Mahaffey, M.D., Haley Hedlin, Ph.D., John S. Rumsfeld, M.D., Ph.D., Ariadna Garcia, M.S., Todd Ferris, M.D., Vidhya Balasubramanian, M.S., Andrea M. Russo, M.D., Amol Rajmane, M.D., Lauren Cheung, M.D., Grace Hung, M.S., Justin Lee, M.P.H., Peter Kowey, M.D., Nisha Talati, M.B.A., Divya Nag, Santosh E. Gummidipundi, M.S., Alexis Beatty, M.D., M.A.S., Mellanie True Hills, B.S., Sumbul Desai, M.D., Christopher B. Granger, M.D., Manisha Desai, Ph.D., and Mintu P. Turakhia, M.D., M.A.S., for the Apple Heart Study Investigators*



NEJM 2019;281:1909



- 419,297 participants over 8 months (not known for AF)
- Series 1 with OS version 4 later paired with iPhone 5S or later
- If the algorithm identified possible AF, a telemedicine visit was initiated (video chat) and an ECG patch was mailed to the participant, worn for up to 7 days
- Median 117 days of monitoring

NEJM

Irregular pulse notifications were received by 2161 participants **(0.52%):**

-3.1% of those ≥ 65 and 0.16% of those 22-40 years old

-more likely to be older, male, white, and CHADS-Vasc ≥2

Of 2161 who received a notification, 450 (20.8%) returned the ECG patch

Atrial fibrillation was diagnosed in 153 of 450 returned ECG patches =

34% diagnostic yield of AF
PPV 0.84 (84% notifications also had an ECG showing AF)

-the absence of AF on a subsequent ECG patch does not imply that the initial notification was a false positive – but that the AF may have been paroxysmal and infrequent. And the 34% suggests a high burden of AF – AF that lasted more than an hour

NEJM 2019;281:1909

Other monitoring devices

AliveCor® KardiaMobile EKG Monitor | FDA-Cleared | Wireless Personal EKG | Works with Smartphone | Detects AFib in 30 seconds

by AliveCor

4.4 out of 5 stars 359 ratings | 85 answered questions

Amazon's Choice for "alivecor ekg"

Price: CDN$ 129.00 prime

2 new from CDN$ 129.00

- EKG ON THE GO: Take unlimited medical-grade EKGs anytime, anywhere. No subscription required.
- EKG HISTORY: Store your EKGs on your phone, and email to your doctor with the press of a button.
- TRUSTED BY DOCTORS: FDA-cleared to detect Atrial Fibrillation, Bradycardia, Tachycardia or Normal Heart Rhythm in 30 seconds.
- EASY TO USE: Simply place your fingers on the sensors—no wires, patches or gels required.
- Works with most smartphones & tablets. See compatible devices below. Not recommended for use

Report incorrect product information.

ECG/EKG Heart Health Tracker with PC Software, Home Use Heart Rate Monitor for Fitness, General Wellness Use

2.5 out of 5 stars 1 | CDN$ 135.99 prime

Shop now ›

Why I believe that monitoring benefits outweigh the negatives:

6011 pts with new dx of AF < 3 months, and CHADS-VASc score ≥ 1
Mean age 72; chads-vasc 3.3

-70% asymptomatic or minimally symptomatic, 30% symptomatic
-Incidence of prior stroke was more than 2x higher in the asymptomatic/minimally symptomatic (14.7%) vs the symptomatic group (6%).
-The higher incidence of embolic events is explained by a delay in diagnosing AF in less symptomatic patients, despite similar age and risk

EurObservation Research Programme AF registry: 2-fold higher mortality in asymptomatic vs symptomatic AF pts
Mayo clinic/Olmstead County registry: 3x increase mortality and 2x increase stroke

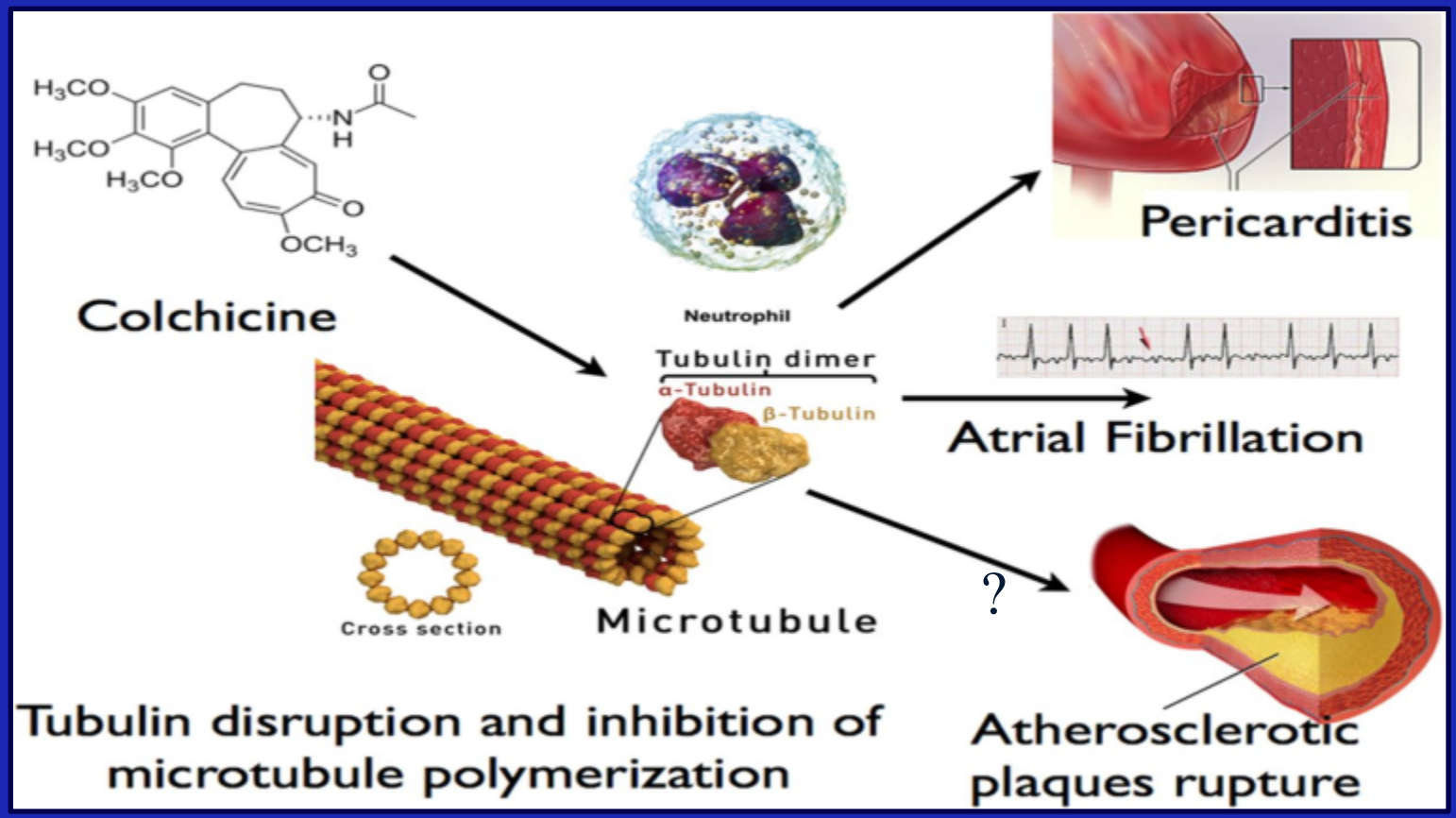
Technology can only take us so far…

2. Autumn Crocus

Mentioned in an old Egyptian medical papyrus dating back to 1550 BC

Introduced into North America by Benjamin Franklin who used them to treat his gout

1820: colchicine was isolated by French chemists Pelletier and Caventou



2.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Low-Dose Colchicine after Myocardial Infarction

Jean-Claude Tardif, M.D., Simon Kouz, M.D., David D. Waters, M.D., Olivier F. Bertrand, M.D., Ph.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., Fausto J. Pinto, M.D., Ph.D., Reda Ibrahim, M.D., Habib Gamra, M.D., Ghassan S. Kiwan, M.D., Colin Berry, M.D., Ph.D., José López-Sendón, M.D., Petr Ostadal, M.D., Ph.D., Wolfgang Koenig, M.D., Denis Angoulvant, M.D., Jean C. Grégoire, M.D., Marc-André Lavoie, M.D., Marie-Pierre Dubé, Ph.D., David Rhainds, Ph.D., Mylène Provencher, Ph.D., Lucie Blondeau, M.Sc., Andreas Orfanos, M.B., B.Ch., Philippe L. L'Allier, M.D., Marie-Claude Guertin, Ph.D., and François Roubille, M.D., Ph.D.

Randomized double-blind trial in patients recruited within 30 days post Mi
-Randomized to low-dose colchicine (0.5mg Qdaily) vs placebo
-Primary efficacy endpoint: composite of death from CV causes, resuscitated cardiac arrest, Mi, stroke, or urgent hospitalization for angina leading to coronary revascularization.
-Median follow up 22.6 months

Table 1. Characteristics of the Patients.*

Characteristic	Colchicine (N=2366)	Placebo (N=2379)
Age — yr	60.6±10.7	60.5±10.6
Female sex — no. (%)	472 (19.9)	437 (18.4)
White race — no./total no. (%)†	1350/1850 (73.0)	1329/1844 (72.1)
Body-mass index	28.2±4.8	28.4±4.7
Current smoking — no./total no. (%)	708/2366 (29.9)	708/2377 (29.8)
Hypertension — no. (%)	1185 (50.1)	1236 (52.0)
Diabetes — no. (%)	462 (19.5)	497 (20.9)
History of myocardial infarction — no. (%)	370 (15.6)	397 (16.7)
History of PCI — no. (%)	392 (16.6)	406 (17.1)
History of CABG — no. (%)	69 (2.9)	81 (3.4)
History of heart failure — no. (%)	48 (2.0)	42 (1.8)
History of stroke or TIA — no. (%)	55 (2.3)	67 (2.8)
Time from index myocardial infarction to randomization — days	13.4±10.2	13.5±10.1
PCI for index myocardial infarction — no./total no. (%)	2192/2364 (92.7)	2216/2375 (93.3)
Medication use — no. (%)		
Aspirin	2334 (98.6)	2352 (98.9)
Other antiplatelet agent	2310 (97.6)	2337 (98.2)
Statin	2339 (98.9)	2357 (99.1)
Beta-blocker	2116 (89.4)	2101 (88.3)

PCI for Mi in 93% and use of DAPT and statins in 98% and 99% resp.

Table 2. Major Clinical End Points (Intention-to-Treat Population).*

End Point	Colchicine (N = 2366)	Placebo (N = 2379)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary composite end point	131 (5.5)	170 (7.1)	0.77 (0.61–0.96)	0.02†
Components of primary end point				
Death from cardiovascular causes	20 (0.8)	24 (1.0)	0.84 (0.46–1.52)	
Resuscitated cardiac arrest	5 (0.2)	6 (0.3)	0.83 (0.25–2.73)	
Myocardial infarction	89 (3.8)	98 (4.1)	0.91 (0.68–1.21)	
Stroke	5 (0.2)	19 (0.8)	0.26 (0.10–0.70)	
Urgent hospitalization for angina leading to revascularization	25 (1.1)	50 (2.1)	0.50 (0.31–0.81)	
Secondary composite end point‡	111 (4.7)	130 (5.5)	0.85 (0.66–1.10)	NS
Death	43 (1.8)	44 (1.8)	0.98 (0.64–1.49)	NS
Deep venous thrombosis or pulmonary embolus	10 (0.4)	7 (0.3)	1.43 (0.54–3.75)	
Atrial fibrillation	36 (1.5)	40 (1.7)	0.93 (0.59–1.46)	

Endpoint driven by reduced stroke and angina hospitalization

High sensitivity C-Reactive Protein was measured in only a subgroup of 207 pts at randomization and at 6 months: median 4.28 mg/L declined by 70% in colchicine group vs 67% in the placebo: not significant. No significant decline in WBC either

Inflammation as a target post Mi: Conclusions

Proven secondary prevention treatments (aspirin and statins) have some effect on inflammation, but the identification of a specific target against inflammation post Mi has not been studied

CANTOS: canakinumab reduced hs CRP and resulted in a modest lower risk of death from cv cause/Mi/or stroke vs placebo. Higher risk of infections

CIRT: Methotrexate showed no reduction in hs CRP and no benefit with regard to CV outcomes

COLCOT: The modest benefit driven by a soft endpoint of hospitalization for angina and revascularization does not support the routine use of colchicine for secondary prevention without a better understanding of the absence of effect on death or Mi.

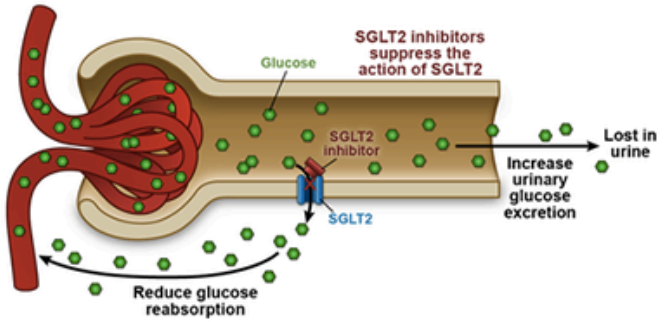
Future directions: Inflammation is important in atherosclerosis, but need to revisit whether it is inflammation itself that is the best treatment target, or the upfront mediators that incite inflammation and drive atherosclerosis


We will always be
friends til we are
old and senile..
then we can be
new friends

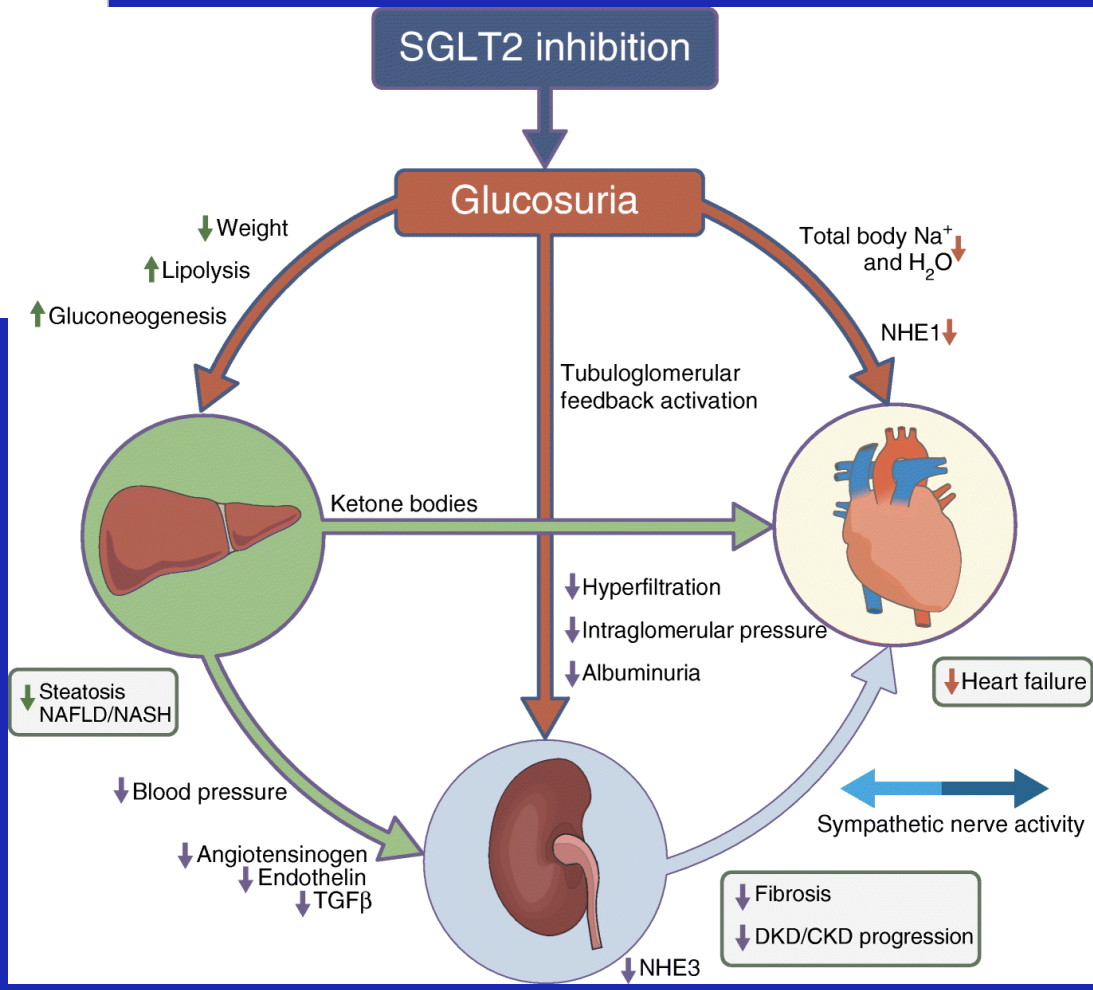
3. Sodium-glucose cotransporter 2 inhibitors

SGLT2 Inhibitor Mechanism of Action

- SGLT2 inhibitors work in the proximal tubules of the kidney to block the reabsorption of glucose back into the blood system, thus reducing blood glucose levels



In 4 large-scale clinical trials involving >36,000 pts with DM2 followed for 2-5 yrs who largely did not have a dx of HF at study entry, pts treated with SGLT2 inhibitor experienced a 25-35% lower risk of hospitalization for HF



ORIGINAL ARTICLE

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

J.J.V. McMurray, S.D. Solomon, S.E. Inzucchi, L. Køber, M.N. Kosiborod, F.A. Martinez, P. Ponikowski, M.S. Sabatine, I.S. Anand, J. Bělohlávek, M. Böhm, C.-E. Chiang, V.K. Chopra, R.A. de Boer, A.S. Desai, M. Diez, J. Drozdz, A. Dukát, J. Ge, J.G. Howlett, T. Katova, M. Kitakaze, C.E.A. Ljungman, B. Merkely, J.C. Nicolau, E. O'Meara, M.C. Petrie, P.N. Vinh, M. Schou, S. Tereshchenko, S. Verma, C. Held, D.L. DeMets, K.F. Docherty, P.S. Jhund, O. Bengtsson, M. Sjöstrand, and A.-M. Langkilde, for the DAPA-HF Trial Committees and Investigators*

4744 pts with NYHA II,III,IV and EF ≤40% randomized to dapagliflozin (10mg Qdaily) or placebo in addition to optimal HF meds

-Primary endpoint: composite of worsening HF (hospitalization or urgent visit resulting in IV therapy for HF) or cardiovascular death

Dapagliflozin is contraindicated in patients with symptomatic hypotension or systolic BP <95mmHg, eGFR <30ml/min, or rapidly declining renal function

DAPA-HF: NEJM Sept 19, 2019

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Age — yr	66.2±11.0	66.5±10.8
Female sex — no. (%)	564 (23.8)	545 (23.0)
Body-mass index†	28.2±6.0	28.1±5.9
Race — no. (%)‡		
White	1662 (70.0)	1671 (70.5)
Black	122 (5.1)	104 (4.4)
Asian	552 (23.3)	564 (23.8)
Other	37 (1.6)	32 (1.3)
Region — no. (%)		
North America	335 (14.1)	342 (14.4)
South America	401 (16.9)	416 (17.5)
Europe	1094 (46.1)	1060 (44.7)
Asia–Pacific	543 (22.9)	553 (23.3)
NYHA functional classification — no. (%)		
II	1606 (67.7)	1597 (67.4)
III	747 (31.5)	751 (31.7)
IV	20 (0.8)	23 (1.0)
Heart rate — beats/min	71.5±11.6	71.5±11.8
Systolic blood pressure — mm Hg	122.0±16.3	121.6±16.3
Left ventricular ejection fraction — %	31.2±6.7	30.9±6.9
Median NT-proBNP (IQR) — pg/ml	1428 (857–2655)	1446 (857–2641)
Principal cause of heart failure — no. (%)		
Ischemic	1316 (55.5)	1358 (57.3)
Nonischemic	857 (36.1)	830 (35.0)
Unknown	200 (8.4)	183 (7.7)
Medical history — no. (%)		
Hospitalization for heart failure	1124 (47.4)	1127 (47.5)
Atrial fibrillation	916 (38.6)	902 (38.0)
Diabetes mellitus§	993 (41.8)	990 (41.8)
Estimated GFR		
Mean — ml/min/1.73 m^2	66.0±19.6	65.5±19.3
Rate of <60 ml/min/1.73 m^2 — no./total no. (%)	962/2372 (40.6)	964/2371 (40.7)
Device therapy — no. (%)		
Implantable cardioverter–defibrillator¶	622 (26.2)	620 (26.1)
Cardiac resynchronization therapy‖	190 (8.0)	164 (6.9)

Age 66
23% female
70% white
44-46% European
NYHA II 67%
NYHA III 31%
NYHA IV 1%
LVEF 31%
HR 71bpm
Systolic BP 122mmHg
39% Afib
Mean GFR 66
26% ICDs

DAPA-HF: NEJM Sept 19, 2019

Table 1. (Continued.)

Characteristic	Dapagliflozin (N=2373)	Placebo (N=2371)
Heart failure medication — no. (%)		
Diuretic	2216 (93.4)	2217 (93.5)
ACE inhibitor	1332 (56.1)	1329 (56.1)
ARB	675 (28.4)	632 (26.7)
Sacubitril–valsartan	250 (10.5)	258 (10.9)
Beta-blocker	2278 (96.0)	2280 (96.2)
Mineralocorticoid receptor antagonist	1696 (71.5)	1674 (70.6)
Digitalis	445 (18.8)	442 (18.6)
Glucose-lowering medication — no./total no. (%)**		
Biguanide	504/993 (50.8)	512/990 (51.7)
Sulfonylurea	228/993 (23.0)	210/990 (21.2)
DPP-4 inhibitor	161/993 (16.2)	149/990 (15.1)
GLP-1 receptor agonist	11/993 (1.1)	10/990 (1.0)
Insulin	274/993 (27.6)	266/990 (26.9)

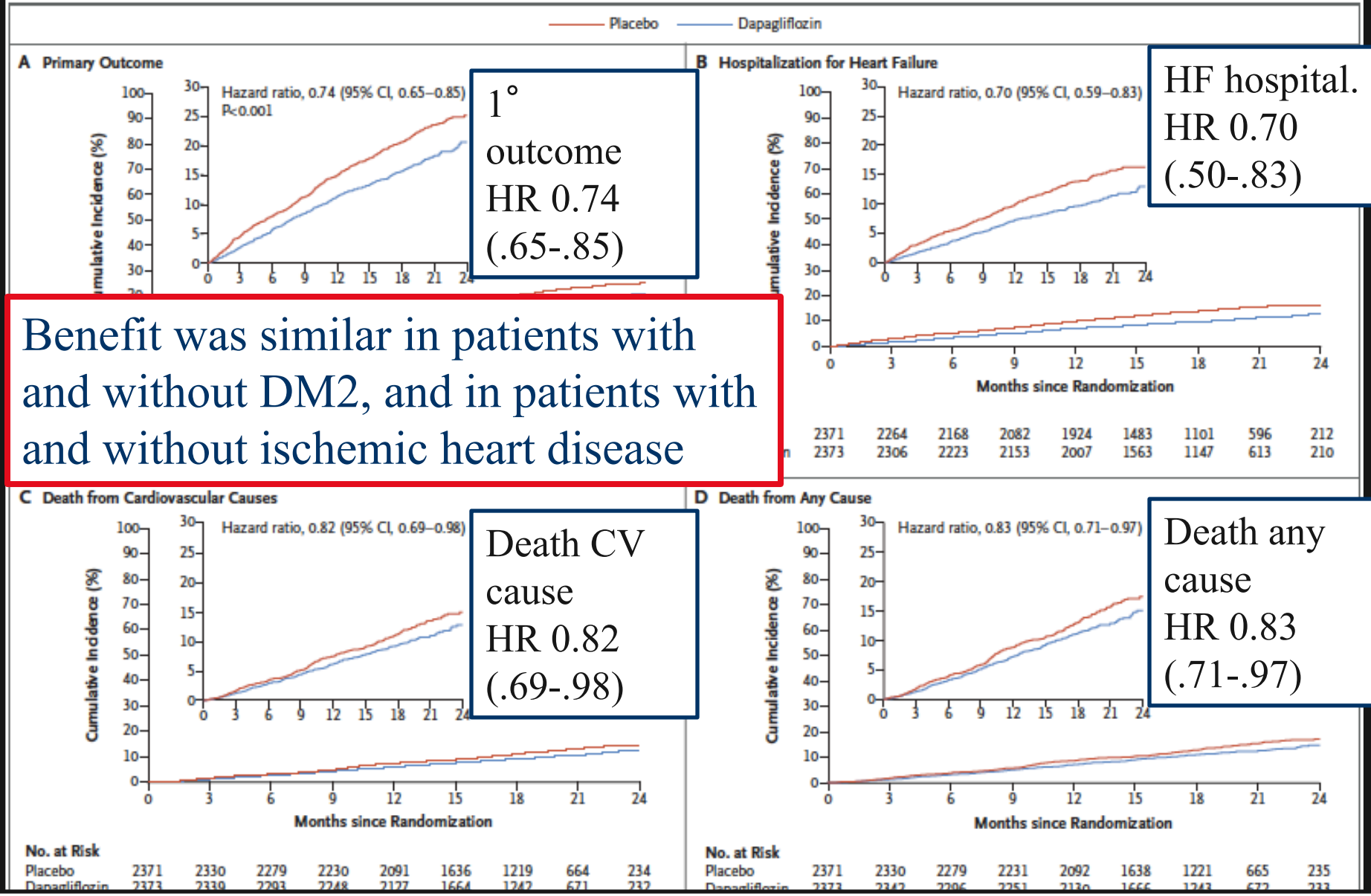
>90% on inhibitors of the renin angiotensin system and BB's

>70% on a mineralocorticoid receptor antagonist

≈50% had DM2 at baseline

>40% did not have underlying ischemic heart d.

DAPA-HF: NEJM Sept 19, 2019



1° outcome HR 0.74 (.65-.85)

HF hospital. HR 0.70 (.50-.83)

Benefit was similar in patients with and without DM2, and in patients with and without ischemic heart disease

Death CV cause HR 0.82 (.69-.98)

Death any cause HR 0.83 (.71-.97)

Primary composite outcome of worsening HF or death from CV cause occurred in 386 pts (16.3%) in the dapagliflozin group and in 501 patients (21.2%) in placebo

tus, with a history of hospitalization for heart failure and treatment-group assignment as explanatory variables. Included in these analyses are all the patients who had undergone randomization. The graphs are truncated at 24 months (the point at which less than 10% of patients remained at risk). The inset in each panel shows the same data on an enlarged y axis.

Explanations of the mechanism

Benefits go beyond glucose lowering : benefits in both diabetics and non-diabetics

Benefits were seen in pts receiving loop diuretics; dapagliflozin only produced a 10-15% decline in NT proBNP and use of the drug did not alter the dosing of diuretics. Therefore, this does not support a benefit of these drugs that is mediated by action on renal Na excretion (natiuresis)

Although increased ketones are favourable in pts with HF (increase cardiac contractility and inotropy), these effects are seen in pts with DM2. Because the magnitude of benefit was in both diabetics and non-diabetics, enhanced ketogenesis is unlikely the mechanism by which SGLT-2 inh improves HF

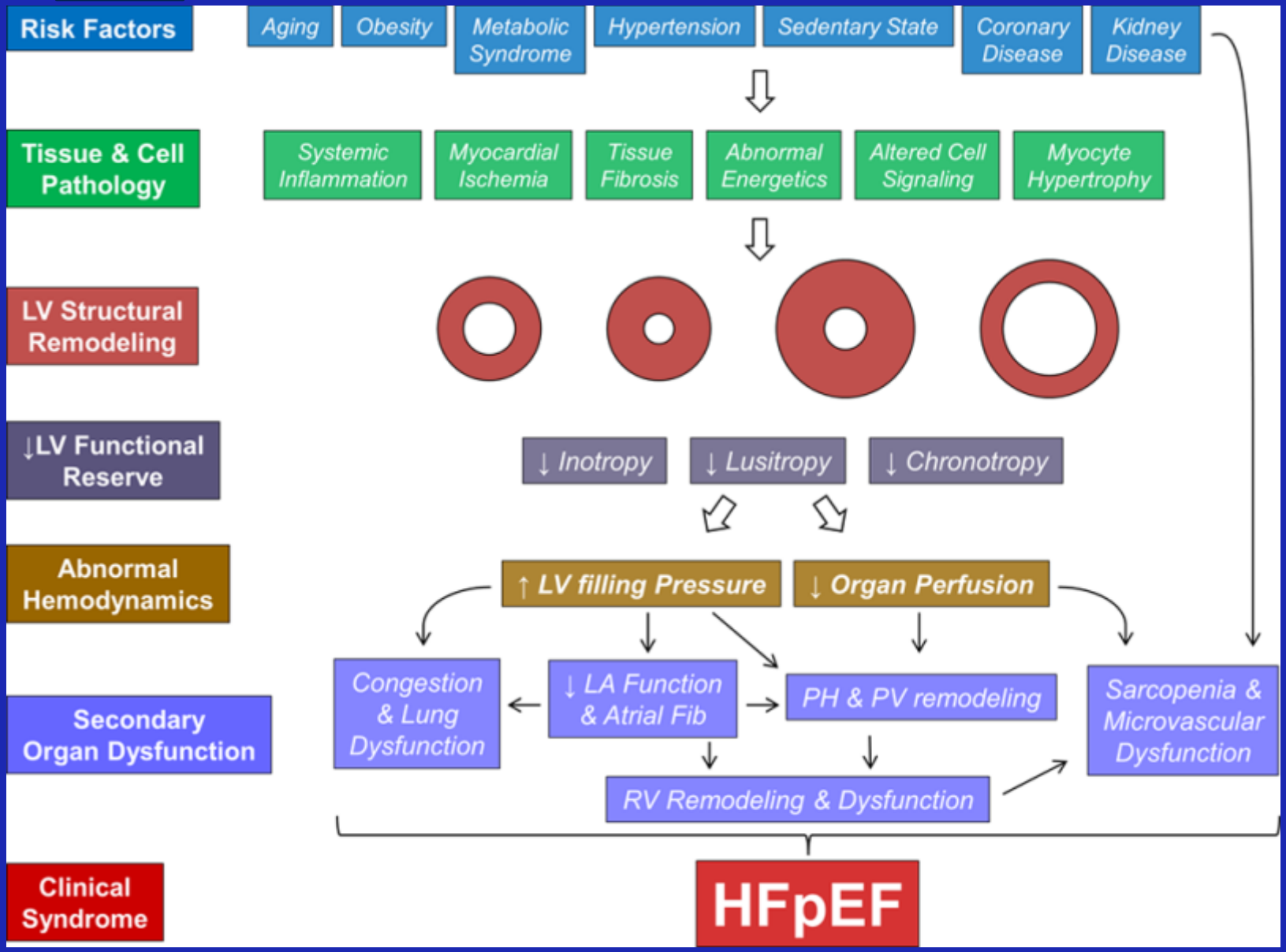
Benefits of SGLT2 inhibitors are likely related to promotion of cardiomyocyte viability.

SGLT2 inhibitor	Abbreviated study title	Full study title	Diabetes status	Trial identification number
Dapagliflozin	DEFINE-HF	Dapagliflozin Effect on Symptoms and Biomarkers in Diabetes Patients With Heart Failure	All T2DM	NCT0265348 2
Dapagliflozin	PRESERVED HF	Dapagliflozin in Type 2 Diabetes or Pre-diabetes, and Preserved Ejection Fraction Heart Failure	T2DM or prediabetes	NCT03 5
Dapagliflozin	DAPA-HF	Study to Evaluate the Effect of Dapagliflozin on Incidence of Worsening Heart failure or Cardiovascular Death in Patients with CHF	Nondiabetic and T2DM (T1DM excluded)	NCT03 4
Empagliflozin	EMPEROR-Preserved	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction	Nondiabetic, T1DM, and T2DM eligible	NCT03 1
Empagliflozin	EMPEROR-Reduced	Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction	Nondiabetic, T1DM, and T2DM eligible	NCT0305797 7
Empagliflozin	EMBRACE-F	Empagliflozin Impact on Hemodynamics in Patients With Diabetes and Heart Failure	All T2DM	NCT0303022 2

Stay tuned…

Just a few of the SGLT2 inhibitor trials that are now ongoing in heart failure populations..

4. HF with preserved EF



Pfeffer et al. Circ Res. 2019;124:1598

The Major Trials in HF with preserved EF

CHARM-PRESERVED: Candesartan vs placebo	3023 patients NYHA II-IV LVEF >40% F/up 36 months	Composite CV death or HF hospitalization: Non-significant impact on CV death**, but possible signal for HF hospitalization**	**class IIb to consider ARBs to decrease hospitalizations in HFpEF)**
PEP-CHF Trial: Perindopril vs placebo in elderly people	850 pts ≥ 70 LVEF >40 + diastolic dysfunction on echo 26 months	Composite all-cause mortality and HF hospitalization. No difference	Substantial study drug discontinuation
I-PRESERVE: Irbesartan vs placebo	4128 pts ≥ 60, NYHA II-IV LVEF ≥ 45%	Composite all cause mortality or CV hospitalization.	No difference
TOPCAT: spironolactone vs placebo	LVEF ≥45% and prior HF hospitalization or increased BNP. 3445 pts; 50% from Russia or Georgia	No significant reduction in CV death/HF hospitalization or aborted cardiac arrest	Major concerns regarding appropriateness of pts enrolled in Russia and Georgia
PARAMOUNT	-Phase 2: sacubitril-vals. vs valsartan	Significant reduction in BNP at 12 weeks -baseline BNP levels were 77% higher than in PARAGON-HF	HFpEF pts have lower neprilysin levels, so sacubitril-valsartan may not be effective

4.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 24, 2019 VOL. 381 NO. 17

Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

PARAGON-HF

S.D. Solomon, J.J.V. McMurray, I.S. Anand, J. Ge, C.S.P. Lam, A.P. Maggioni, F. Martinez, M. Packer, M.A. Pfeffer, B. Pieske, M.M. Redfield, J.L. Rouleau, D.J. van Veldhuisen, F. Zannad, M.R. Zile, A.S. Desai, B. Claggett, P.S. Jhund, S.A. Boytsov, J. Comin-Colet, J. Cleland, H.-D. Düngen, E. Goncalvesova, T. Katova, J.F. Kerr Saraiva, M. Lelonek, B. Merkely, M. Senni, S.J. Shah, J. Zhou, A.R. Rizkala, J. Gong, V.C. Shi, and M.P. Lefkowitz, for the PARAGON-HF Investigators and Committees*

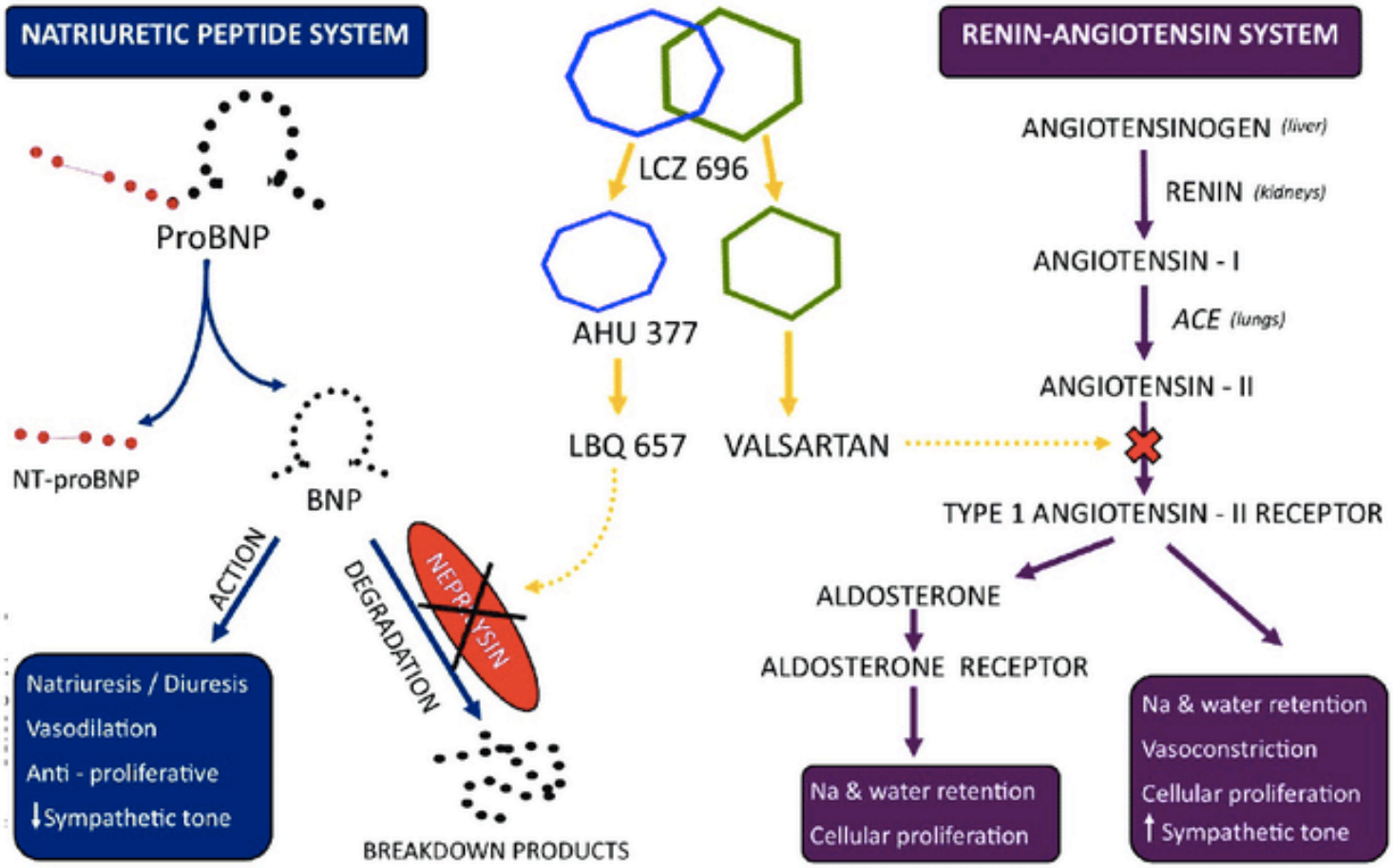
Sacubitril-valsartan vs valsartan alone in pts ≥ 50, with signs and symptoms of HF, an EF ≥ 45% and elevated natriuretic peptide levels

4822 pts (51% women) in 43 countries. Median 35 months

Primary outcome: composite of hospitalizations for HF and deaths from CV causes

2019. NEJM 381;15

Sacubitril-Valsartan: mechanism of action



PARADIGM-HF: sacubitril-valsartan vs enalapril in pts with HF with reduced EF, 20% lower risk of hospitalizaiton for HF or death from CV causes

53(10):545 · October 2017

Table 2. Primary and Secondary Outcomes.*

Outcome	Sacubitril–Valsartan (N=2407)	Valsartan (N=2389)	Ratio or Difference (95% CI)
Primary composite outcome and components			
Total hospitalizations for heart failure and death from cardiovascular causes†			RR, 0.87 (0.75–1.01)
Total no. of events	894	1009	
Rate per 100 patient-yr	12.8	14.6	
Total no. of hospitalizations for heart failure	690	797	RR, 0.85 (0.72–1.00)
Death from cardiovascular causes — no. (%)	204 (8.5)	212 (8.9)	HR, 0.95 (0.79–1.16)
Secondary outcomes			
Change in NYHA class from baseline to 8 mo — no./total no. (%)			OR, 1.45 (1.13–1.86)
Improved	347/2316 (15.0)	289/2302 (12.6)	
Unchanged	1767/2316 (76.3)	1792/2302 (77.8)	
Worsened	202/2316 (8.7)	221/2302 (9.6)	
Change in KCCQ clinical summary score at 8 mo‡	−1.6±0.4	−2.6±0.4	Difference, 1.0 (0.0–2.1)
Renal composite outcome — no. (%)§	33 (1.4)	64 (2.7)	HR, 0.50 (0.33–0.77)
Death from any cause — no. (%)	342 (14.2)	349 (14.6)	HR, 0.97 (0.84–1.13)

QOL and NYHA class were improved

This reduction was just short of statistical significance and was driven by a decline in heart failure hospitalization with no effect on cardiovascular death or all-cause mortality.

Among prespecified subgroups, there were interactions suggesting benefit in pts with lower EF and in women

-data from biomarker and proteomic profiling provide support for clinical phenotypic overlap as a continuum between HF with reduced EF and HFpEF.

2019. NEJM 381;15

What treatment then for HF with preserved EF?

Lifestyle modification: weight reduction, dietary consumption, cardiorespiratory fitness which reduce important HF risk factors (hypertension, diabetes mellitus, and atherosclerotic disease)

-limited RCT data, but robust epidemiological data support

Hypertension management reduces incidence of HF:

-SHEP trial: >60 years old

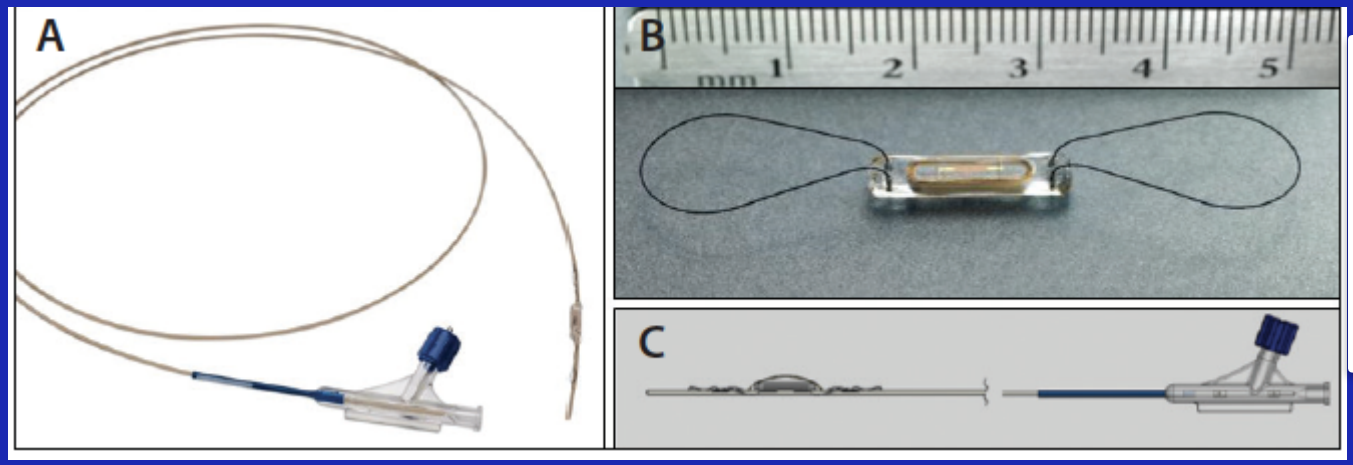
-HYVET: ≥ 80 years old

-SPRINT: targeting <120mmHg vs <140mmHg in 9361 nondiabetics with elevated CV risk. HF incidence was reduced by 37% with separation of HF event curves after 6 months.

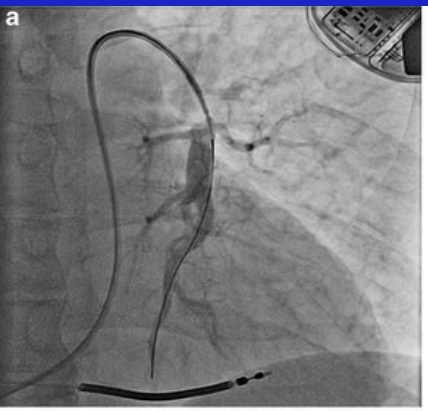
? Left ventricular pacing to improve dyssynchrony ???

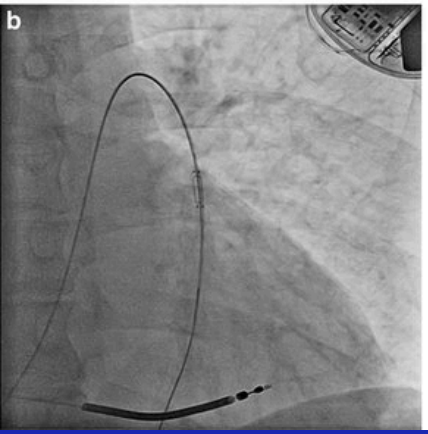
Interventions to reduce filling pressures

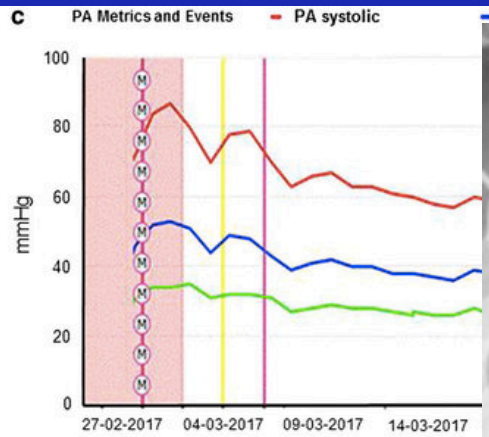
-CHAMPION trial (CardioMEMS) results confirmed in analyses restricted to patients with HFpEF

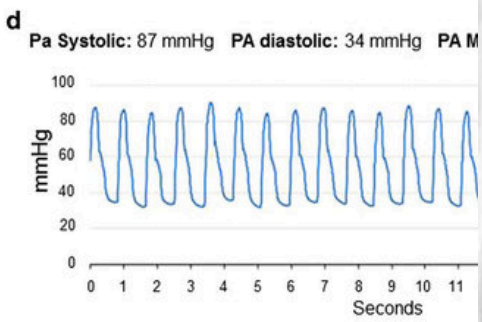


CardioMEMS -heart sensor in the pulmonary artery



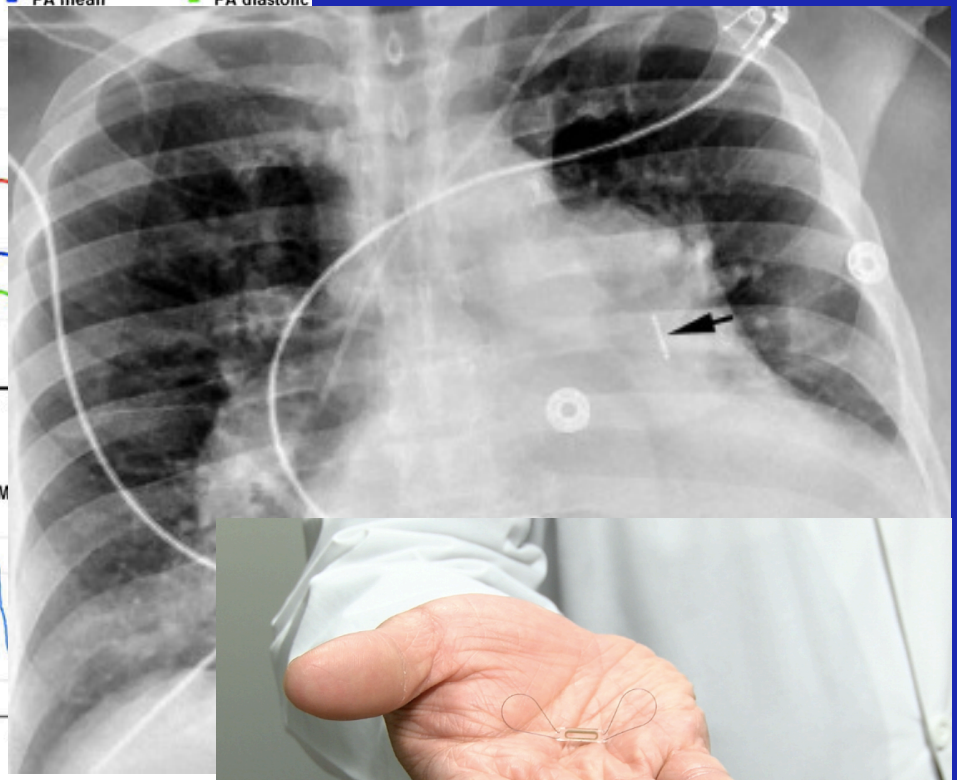






Exceeded Threshold:

- Exceeded the PA Systolic Pressure threshold by 52
- Exceeded the PA Diastolic Pressure threshold by 14
- Exceeded the PA Mean Pressure threshold by 28



5.

ELSEVIER

Journal of the American College of Cardiology

Volume 74, Issue 20, 19 November 2019, Pages 2452-2462

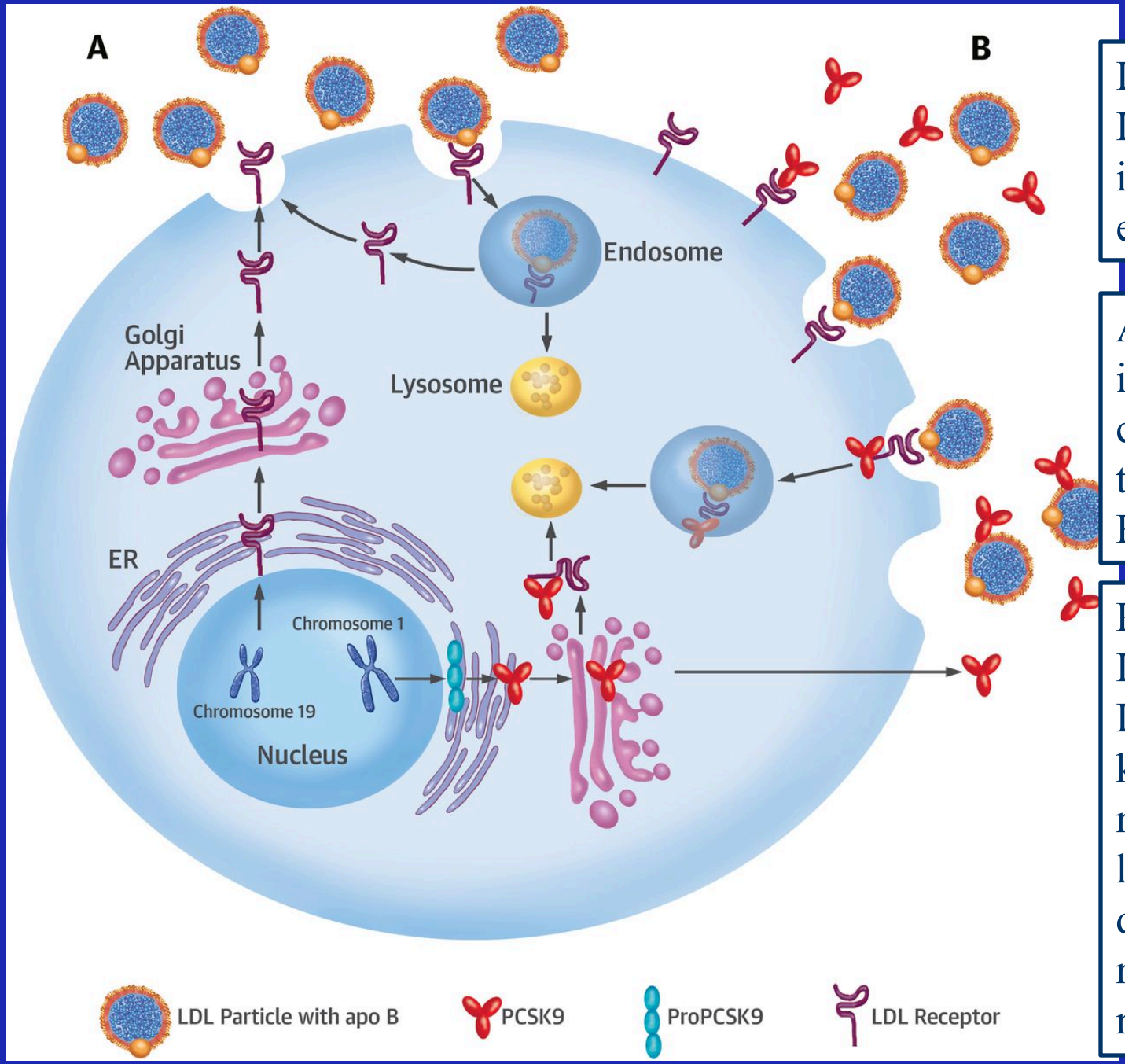
Original Investigation

Evolocumab for Early Reduction of LDL Cholesterol Levels in Patients With Acute Coronary Syndromes (EVOPACS)

Konstantinos C. Koskinas MD, MSc [a], Stephan Windecker MD [a], Giovanni Pedrazzini MD [b], Christian Mueller MD [c], Stéphane Cook MD [d], Christian M. Matter MD [e], Olivier Muller MD [f], Jonas Häner MD [a], Baris Gencer MD [g], Carmela Crljenica MD [b], Poorya Amini PhD [h], Olga Deckarm MD [a], Juan F. Iglesias MD [g], Lorenz Räber MD, PhD [a], Dik Heg PhD [h], François Mach MD [g]

Early initiation of a high-intensity statin to reduce LDL-C is recommended in all patients with an acute coronary syndrome (MIRACL)

The addition of a PCSK9 inhibitor to statin therapy during initial hospitalization (2 doses of evolocumab 420mg given 1 month apart); primary endpoint: a decrease in mean percentage change from baseline LDL-C at 8 weeks.



LDL receptor + LDL via apoB initiates rec-med endocytosis of LDL

A decrease in intracellular cholesterol activates transcription of PCSK9.

PCKS9 binds the LDL receptor and LDL particles, keeps the receptor retained in the lysosome and degrades both. LDL receptor cannot be recycled

Robert S. Rosenson et al. JACC 2018;72:314-329

TABLE 2 Efficacy Outcomes

	Evolocumab	Placebo	Mean Difference (95% CI)*	p Value
Calculated LDL-C				
Baseline, mmol/l	3.61 ± 1.00 (146)	3.42 ± 0.94 (148)	0.14 (−0.05 to 0.32)	
Week 8, mmol/l	0.79 ± 0.46 (141)	2.06 ± 0.63 (149)	−1.27 (−1.40 to −1.14)	<0.001
Absolute change from baseline, mmol/l	−2.83 ± 1.02 (132)	−1.35 ± 1.04 (145)	−1.43 (−1.63 to −1.22)	<0.001
% change from baseline (primary endpoint)	−77.1 ± 15.8 (132)	−35.4 ± 26.6 (145)	−40.7 (−45.2 to −36.2)	<0.001
Calculated LDL-C <1.8 mmol/l at week 8	141 (95.7)	149 (37.6)	57.8 (66.2 to 49.4)	<0.001
Other lipids, % change from baseline to week 8				
Cholesterol	−51.8 ± 14.6 (140)	−24.4 ± 19.3 (150)	−26.5 (−29.9 to −23.1)	<0.001
Apolipoprotein B	−63.6 ± 14.9 (137)	−28.8 ± 23.4 (149)	−34.2 (−38.2 to −30.2)	<0.001
Non-HDL-C	−67.3 ± 15.4 (140)	−31.7 ± 23.7 (150)	−34.6 (−38.5 to −30.6)	<0.001
Triglycerides	−16.4 ± 40.4 (140)	4.5 ± 98.4 (150)	−20.0 (−37.4 to −2.6)	0.024
HDL-C	9.5 ± 17.9 (140)	4.9 ± 19.7 (150)	4.8 (0.5 to 9.1)	0.03
Apolipoprotein A1	5.6 ± 15.5 (137)	3.5 ± 14.7 (148)	2.2 (−1.2 to 5.7)	0.21
Lipoprotein(a)	0.5 ± 67.6 (139)	10.4 ± 49.5 (150)	−10.4 (−38.3 to 17.6)	0.47

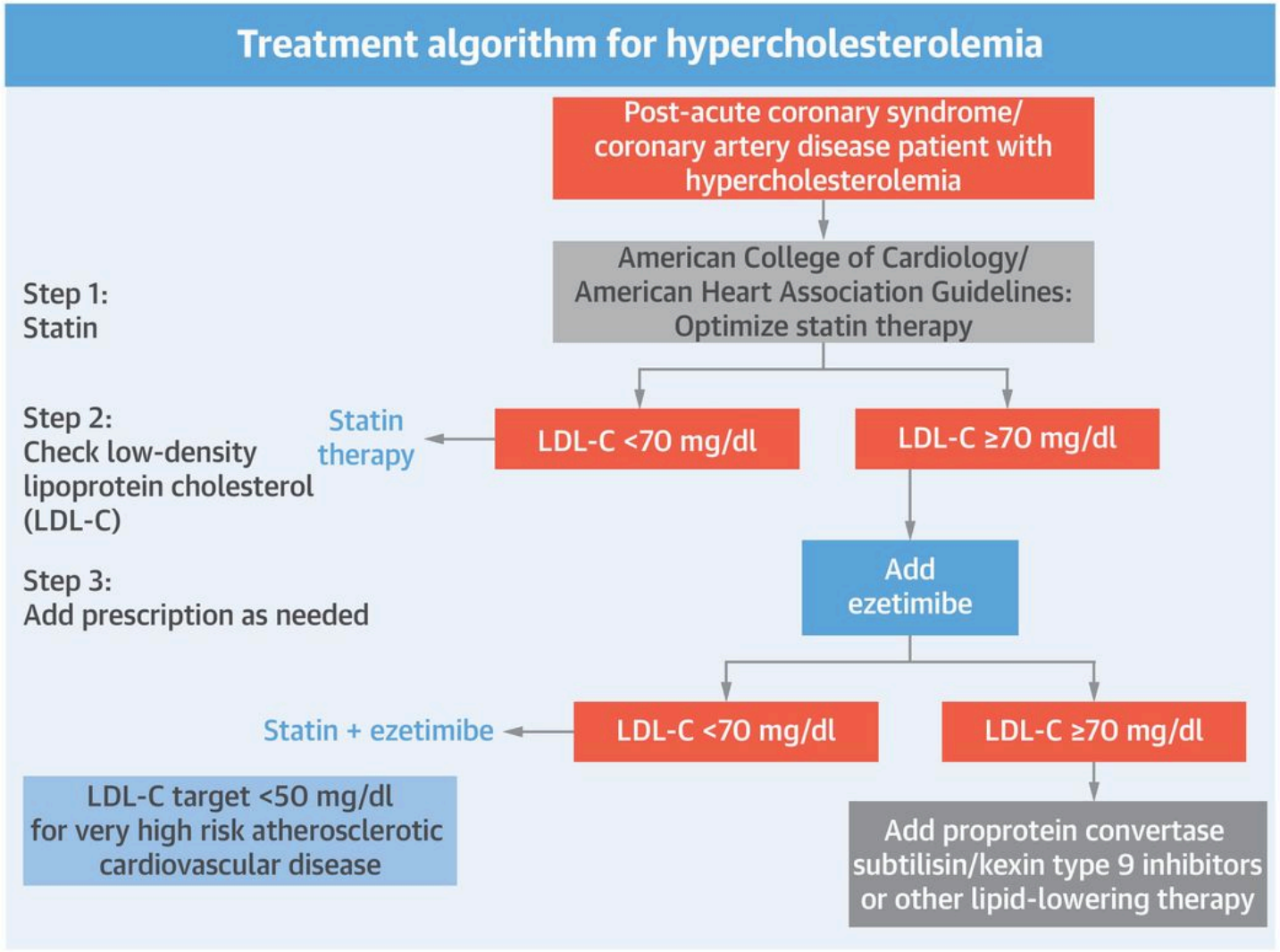
Pts had baseline LDL ≥ 70mg/dl (1.8mmol/L) on existing high-intensity statin treatment or were projected to have levels above that threshold.

3,581 screened patients, 308 (8.6%) were randomized -

Mean baseline LDL-C of 3.5 mmol/L, evolucumab reduced LDL-C by 77% vs 35%. hsCRP declined by 15% vs 35% respectively.

Additional studies evaluating clinical outcomes (death, Mi) are now needed

CENTRAL ILLUSTRATION: Clinical Algorithm for Managing Low-Density Lipoprotein Cholesterol



Rosenson, R.S. et al. J Am Coll Cardiol. 2018;72(3):314-29.

6. Sleep

Sleeping pills are counted among the best-selling drugs in the Western world

In 1900: average estimated sleep for an adult was 9 hours

In 1980: 7 hours

2000: 6.5 hours

35% of the general population sleep < 6 hours/night and 29.5% sleep 7 hours/night

JO HE AMERICAN COLLEGE OF CARDIOLOGY VOL. 74, NO. 10, 2019
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6.

Sleep Duration and Myocardial Infarction

Iyas Daghlas, BS,[a,b] Hassan S. Dashti, PhD, RD,[a,b] Jacqueline Lane, PhD,[a,b,c] Krishna G. Aragam, MD, MS,[a,b,d] Martin K. Rutter, MD,[e,f] Richa Saxena, PhD,[a,b,c] Céline Vetter, PhD[a,g]

461,347 UK Biobank participants who had never had an Mi, age 40-69
Authors measured adjusted HRs for myocardial infarction (5,128 cases)

Sleep duration was self reported: short (< 6 hours) and long (>9 hours); followed for 7 years for incident Mi.
-Secondary analysis: Assessed impact of sleep in people with genetic predisposition to heart disease

-Third analysis: Mendelian randomization analysis to look at a participant's genetic profile, to determine whether those who were genetically predisposed to short sleep were more likely to have Mi's (27 genetic variants have been assoc with short sleep)

TABLE 1 Association of Habitual Sleep Duration (in Hours) With Incident MI in the UK Biobank (N = 461,347)

	Habitual Sleep Duration (h)						
	4	5	6	7 to 8	9	10	11
Cases/person-yrs	82/28,496	310/138,902	1,058/621,416	3,248/2,205,231	375/182,263	129/42,441	16/3,948
Incidence rates per 1,000 person-yrs	2.88	2.23	1.70	1.47	2.06	3.04	4.05
Sample size, n	4,120	20,023	89,189	315,055	26,217	6,166	577
Unadjusted model	1.96 (1.57-2.43)	1.52 (1.35-1.70)	1.16 (1.08-1.24)	1.00 (ref)	1.40 (1.26-1.56)	2.07 (1.73-2.46)	2.78 (1.59-4.51)
Model 1: age- and sex-adjusted	2.12 (1.70-2.64)	1.58 (1.40-1.77)	1.18 (1.10-1.26)	1.00 (ref)	1.24 (1.10-1.37)	1.87 (1.57-2.24)	2.79 (1.71-4.56)
Model 2: model 1 + BMI and WHR	1.93 (1.55-2.41)	1.48 (1.32-1.66)	1.14 (1.06-1.22)	1.00 (ref)	1.18 (1.06-1.32)	1.69 (1.42-2.02)	2.45 (1.50-4.00)
Model 3: MV adjusted*	1.34 (1.07-1.68)	1.19 (1.06-1.35)	1.05 (0.98-1.13)	1.00 (ref)	1.07 (0.96-1.19)	1.32 (1.11-1.58)	1.87 (1.14-3.06)

Values are hazard ratios (95% confidence intervals) unless otherwise indicated. *Variables used for adjustment were age, sex, ethnicity, smoking status, frequency of alcohol consumption, history of heart disease in family, marital status, education, income, Townsend deprivation index, employment status, physical activity (metabolic equivalents/h-week), television watching, grip strength, BMI, WHR, history of seeing provider for mental health, snoring, use of sleep medications, self-reported or medical record-derived sleep apnea, and self-reported insomnia, probable type 2 diabetes, hypertension, use of blood pressure-lowering medication, history of high cholesterol, use of cholesterol-lowering medication, and use of aspirin.

BMI = body mass index; MI = myocardial infarction; MV = multivariable; ref = reference; WHR = waist-hip ratio.

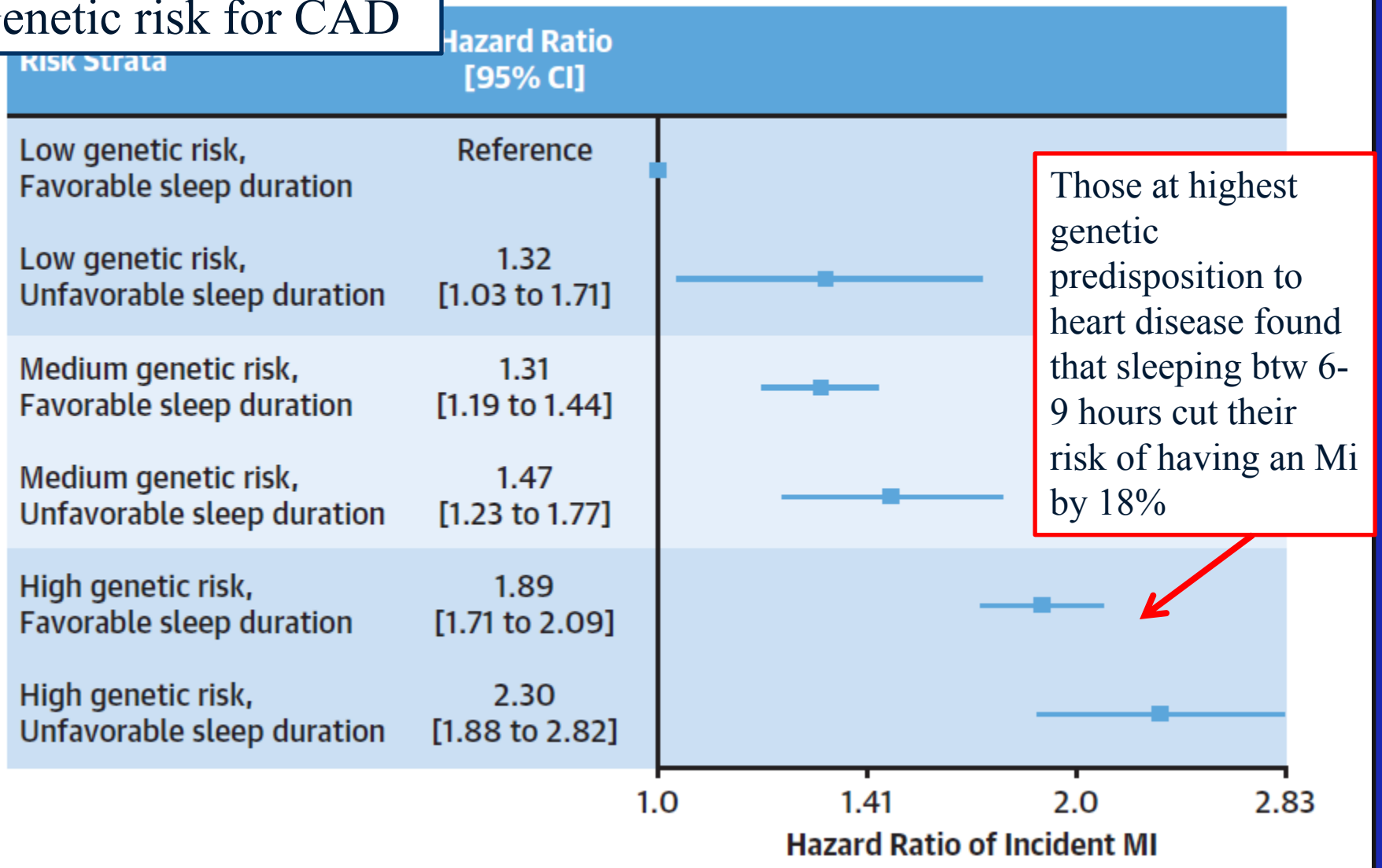
-Prospective observational analysis identified a dose-dependent contribution of short and long habitual sleep duration to the risk of incident Mi, independent of numerous confounders and sleep traits

-Concomitant insomnia symptoms and difficulty getting up exacerbated this risk

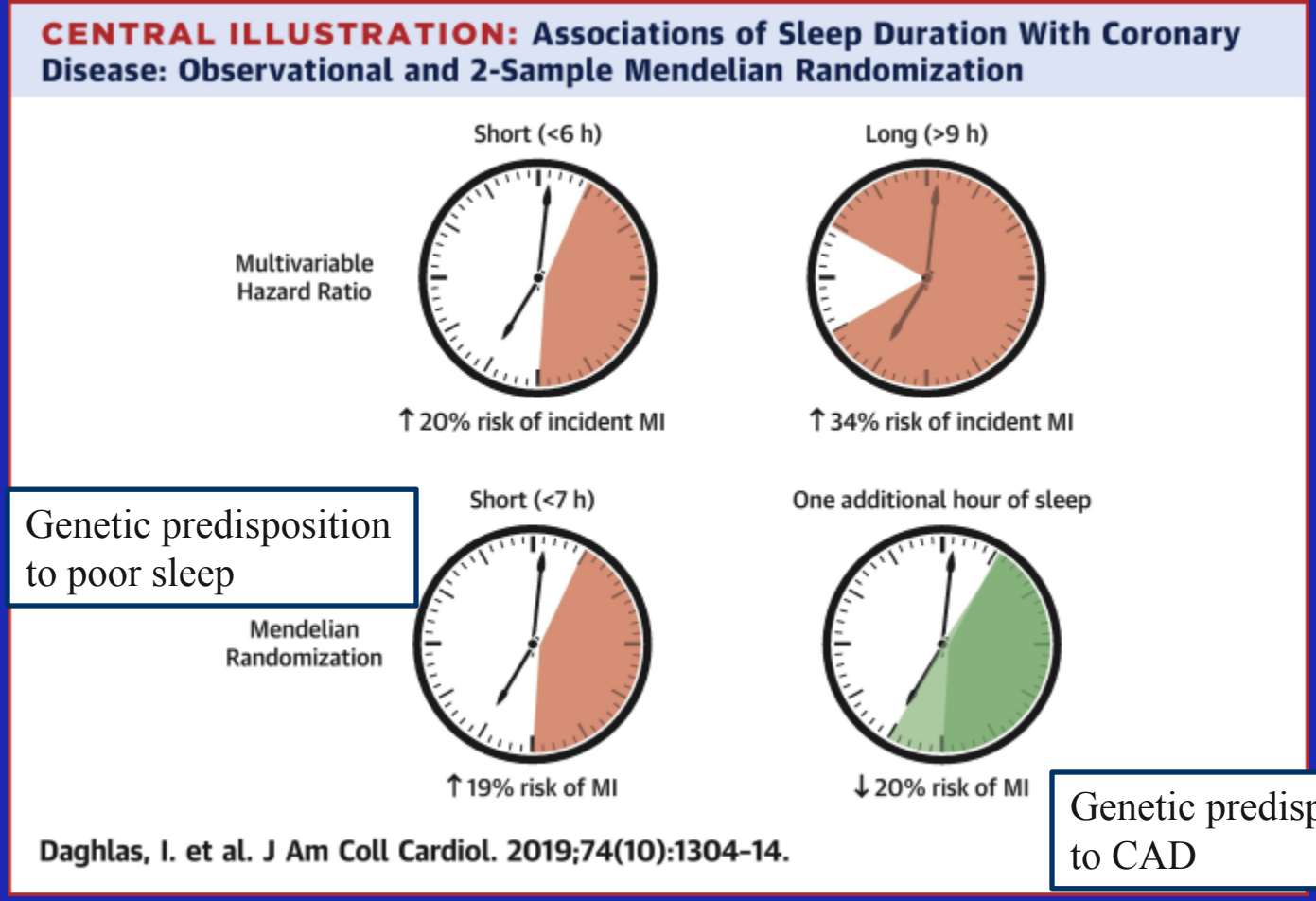
JACC vol. 74 No 10.2019

Genetic risk for CAD

FIGURE 2 Concomitant Associations of Sleep Duration and CAD GRS With Risk of Incident MI (N = 310,917)



Those at highest genetic predisposition to heart disease found that sleeping btw 6-9 hours cut their risk of having an Mi by 18%



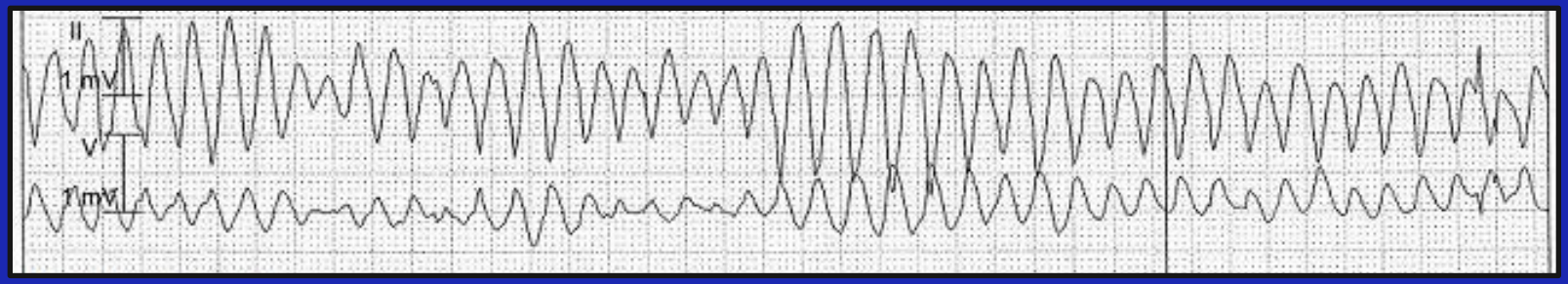
Those with < 6 hours sleep had a 20% higher risk of Mi than normal sleepers (HR 1.2, 95% CI 1.07-1.33); Longer sleepers had 34% higher risk (HR 1.34; 95% CI 1.13-1.58).

-In pts with a high genetic liability of Mi, those with healthy sleep duration (6-9 hrs) mitigated Mi risk (HR 0.82; 95% CI 0.68-0.998): **behavioural factors (such as sleep) may overcome the genotype that modifies one's personal risk profile**

7.

Case: 19M

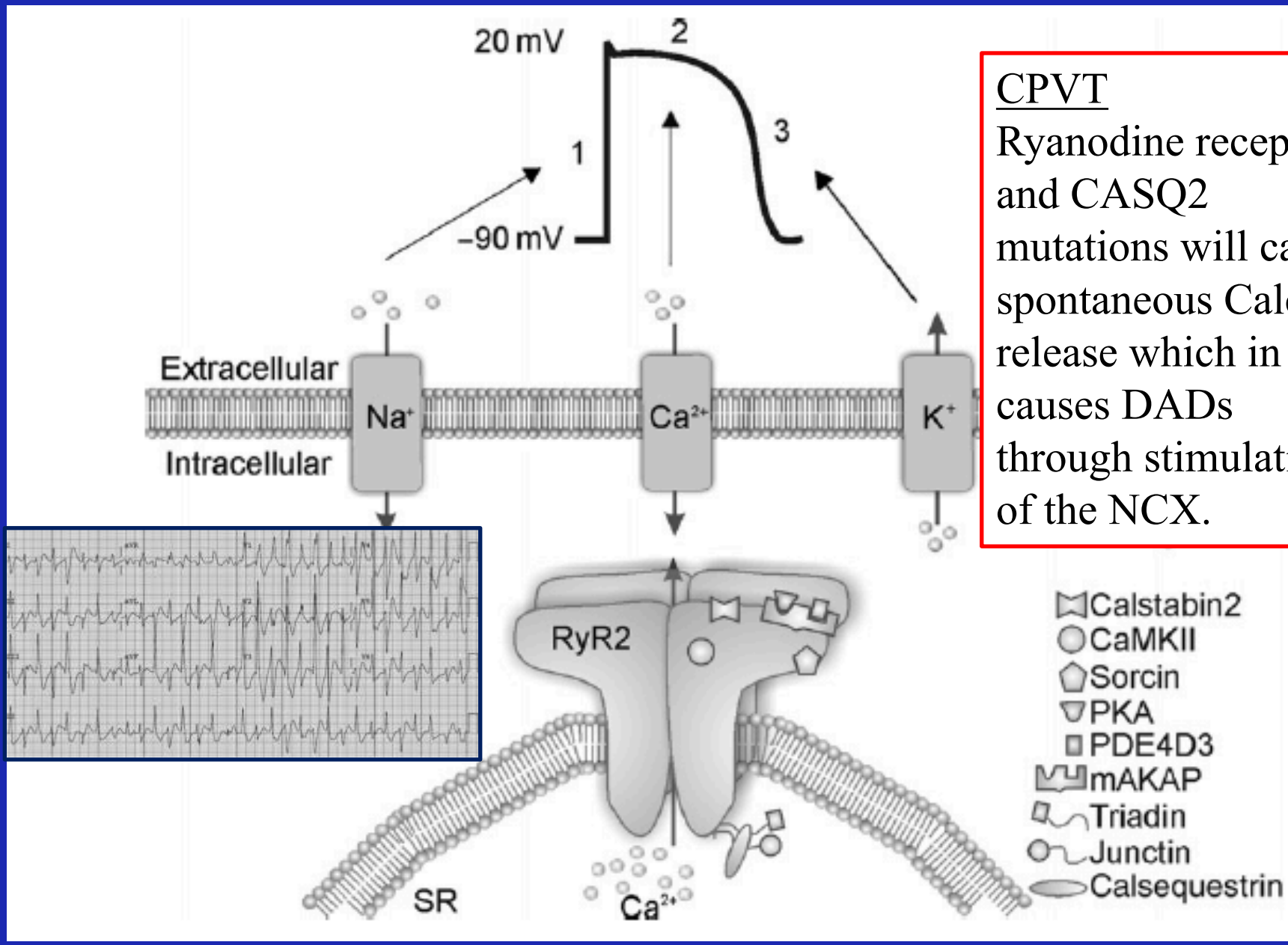
Rushing back to work at the grocery store, and suddenly collapsed



Resuscitated, CPR and 2 shocks delivered by EMS
Neurologically intact
Electrolytes normal; ECG normal; No coronary artery disease; echo and eventual cardiac MRI normal

Genetics results:

RYR2 NM_001035.2	Autosomal Dominant	c.12424G>A p.Ala4142Thr

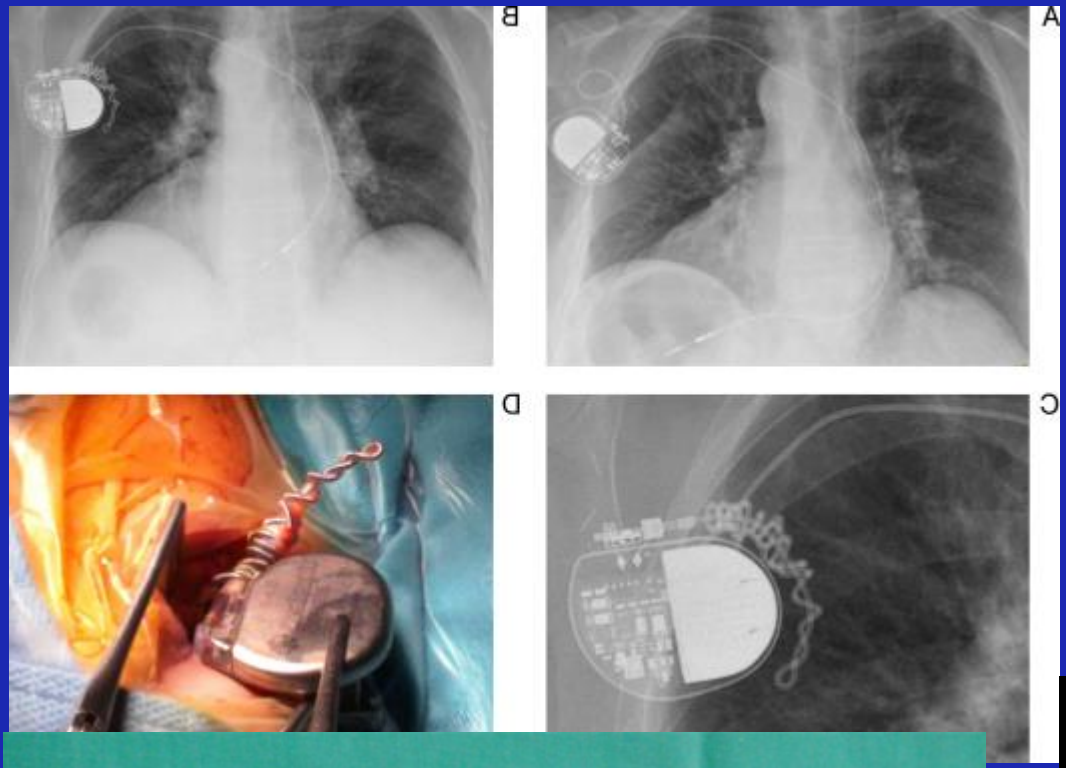


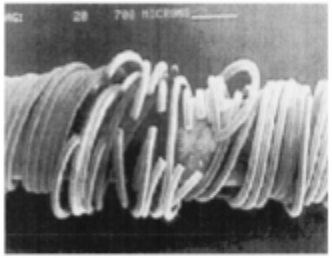
CPVT

Ryanodine receptor and CASQ2 mutations will cause spontaneous Calcium release which in turn causes DADs through stimulation of the NCX.

Annals of pharmacology 2010;59.1-30

This very young patient needs an ICD for secondary prevention..





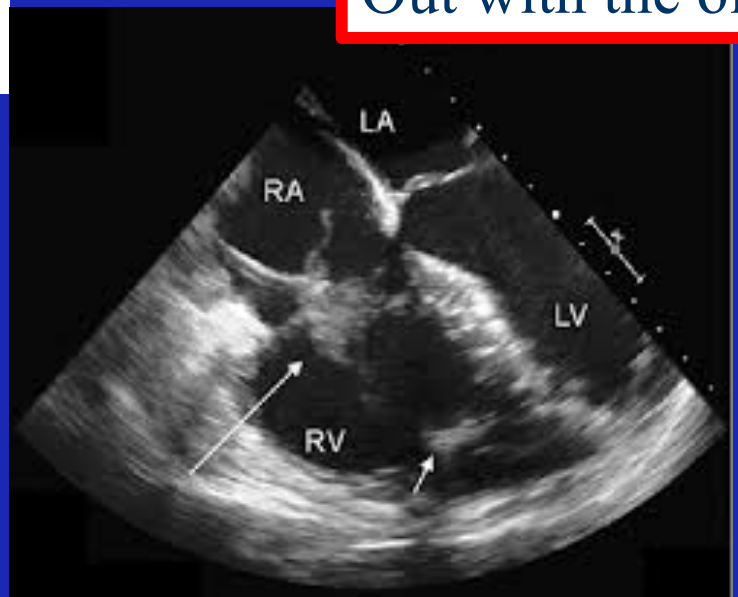
Conductor fracture secondary to compression

Insulation defect and conductor fracture secondary to pinching

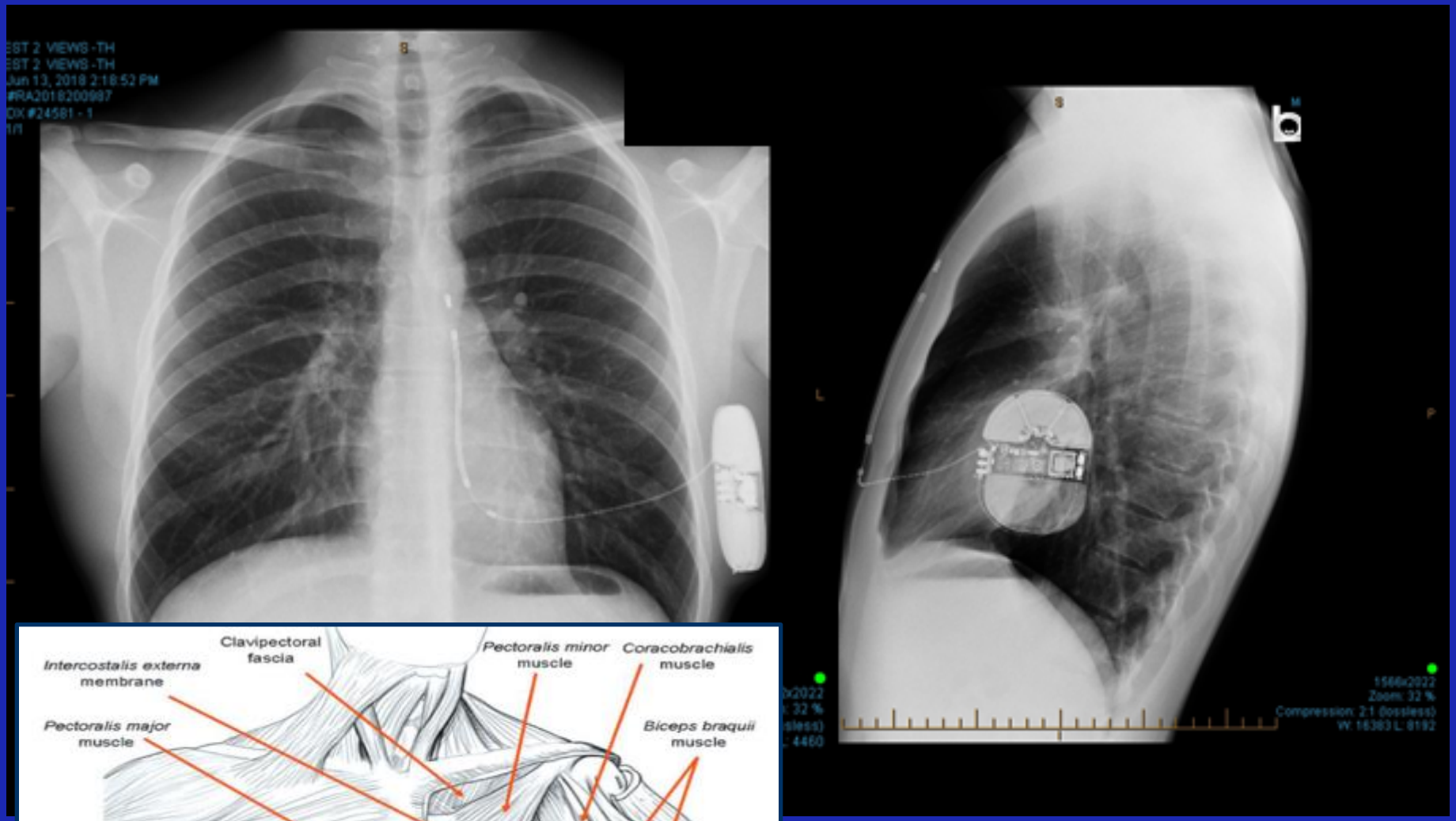
Gnadu et al. PACE 2003;26:649

Out with the old…

Staph and strep bacteria species create biofilms in contact with lead



In with the new…? Subcutaneous ICD



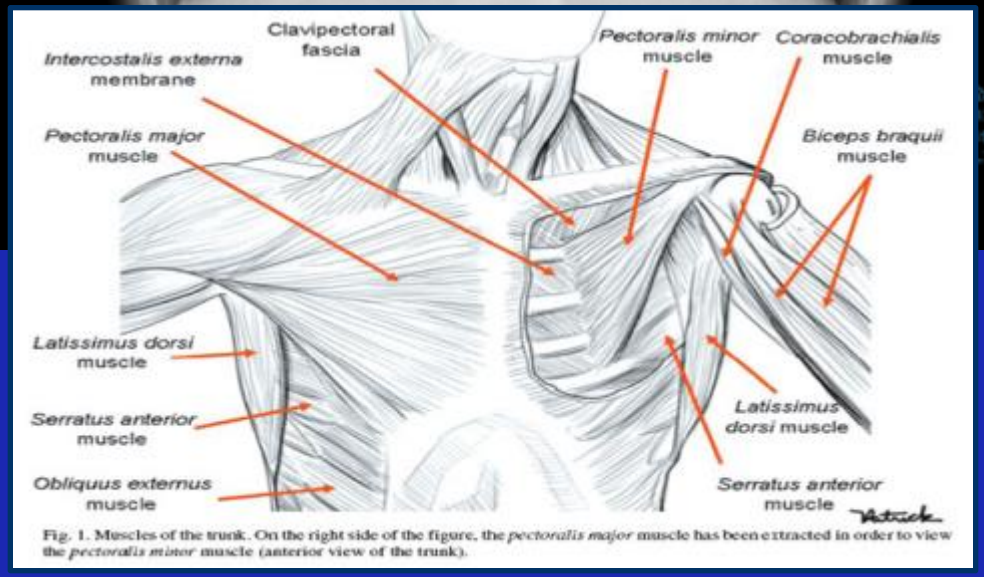
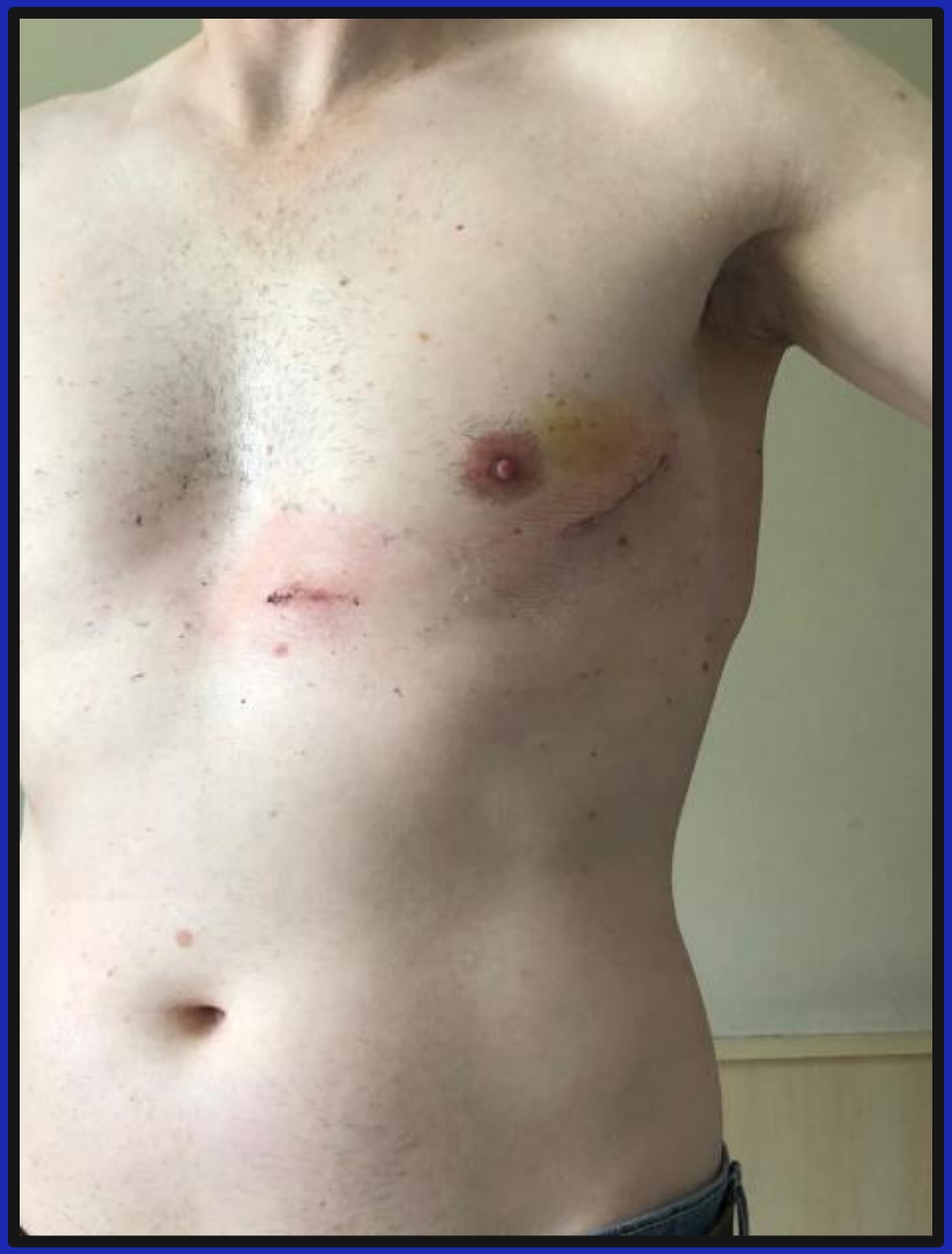
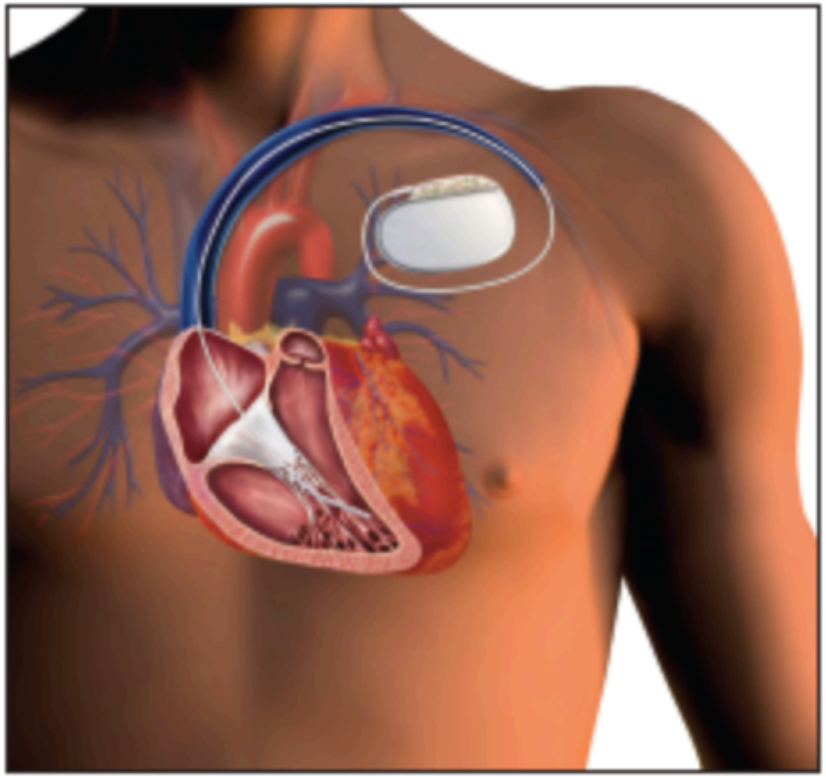
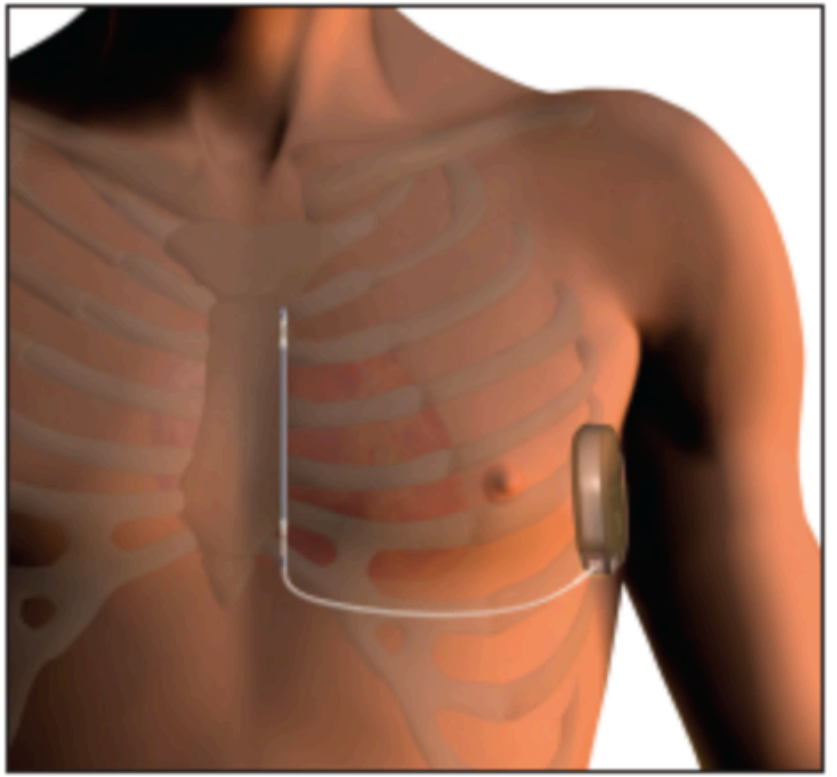


Fig. 1. Muscles of the trunk. On the right side of the figure, the *pectoralis major* muscle has been extracted in order to view the *pectoralis minor* muscle (anterior view of the trunk).



Subcutaneous vs Transvenous ICD?

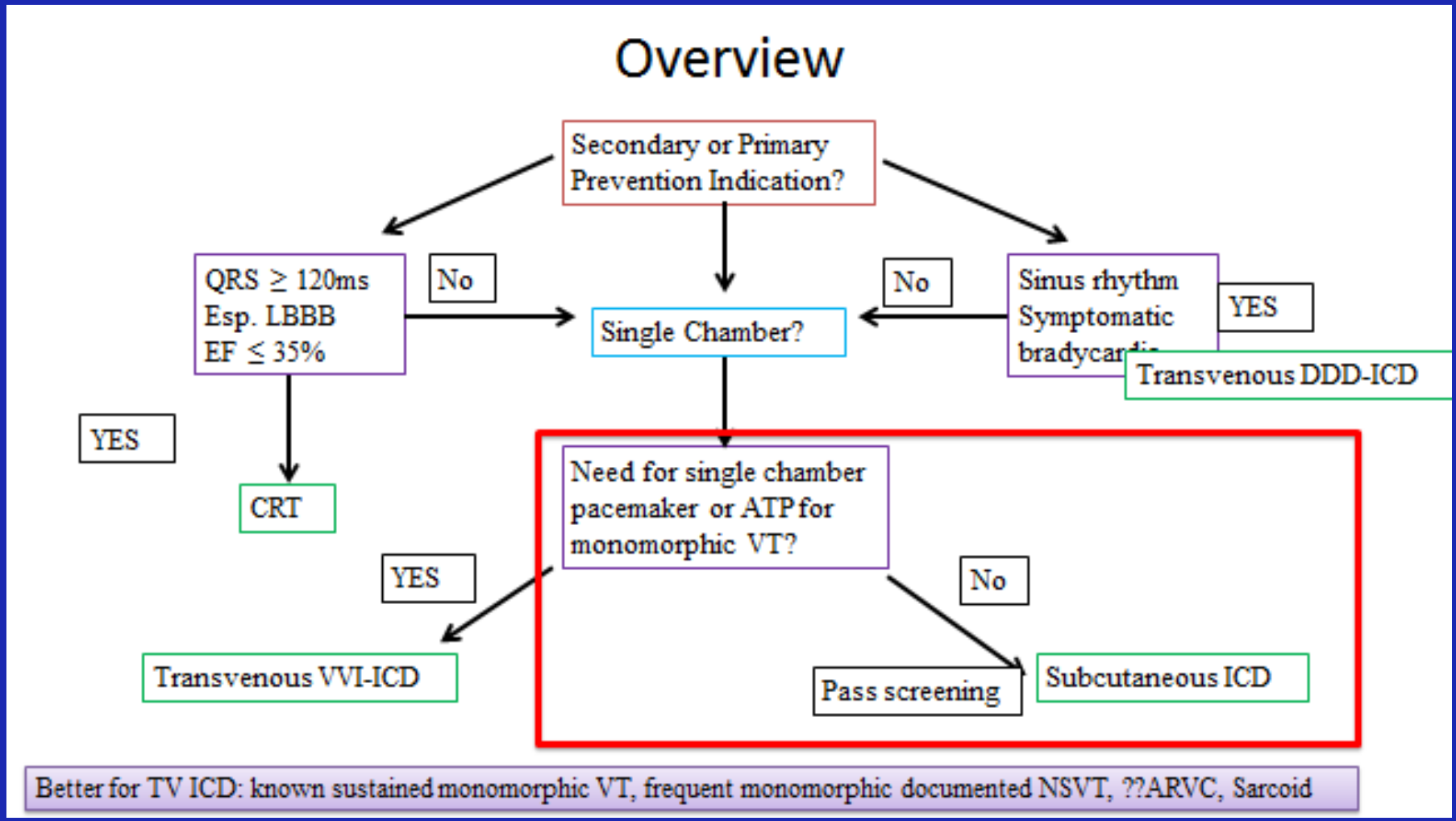




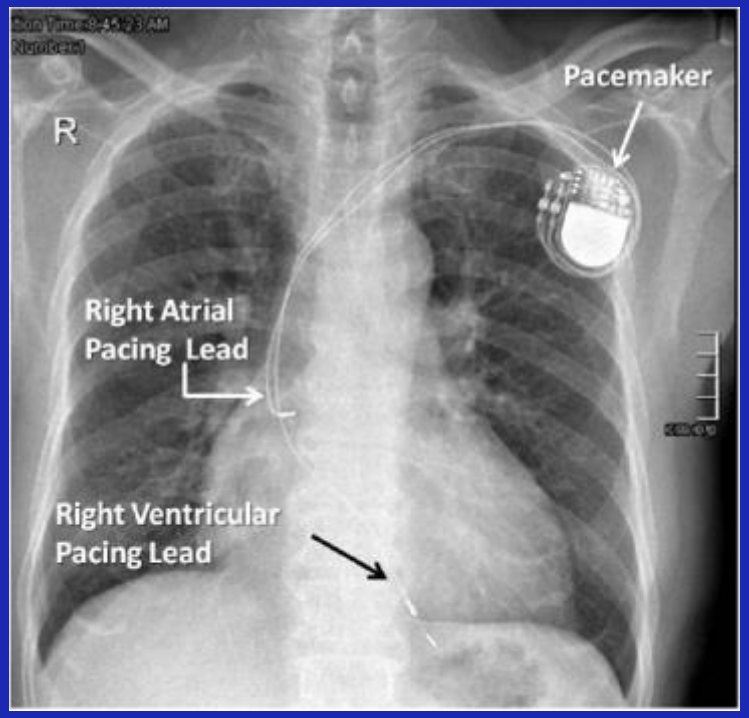
- able to pace
- greater battery longevity
- less expensive
-standard of care

- avoids lead fracture/lead complications
- can be more easily removed
- More aesthetically appealing

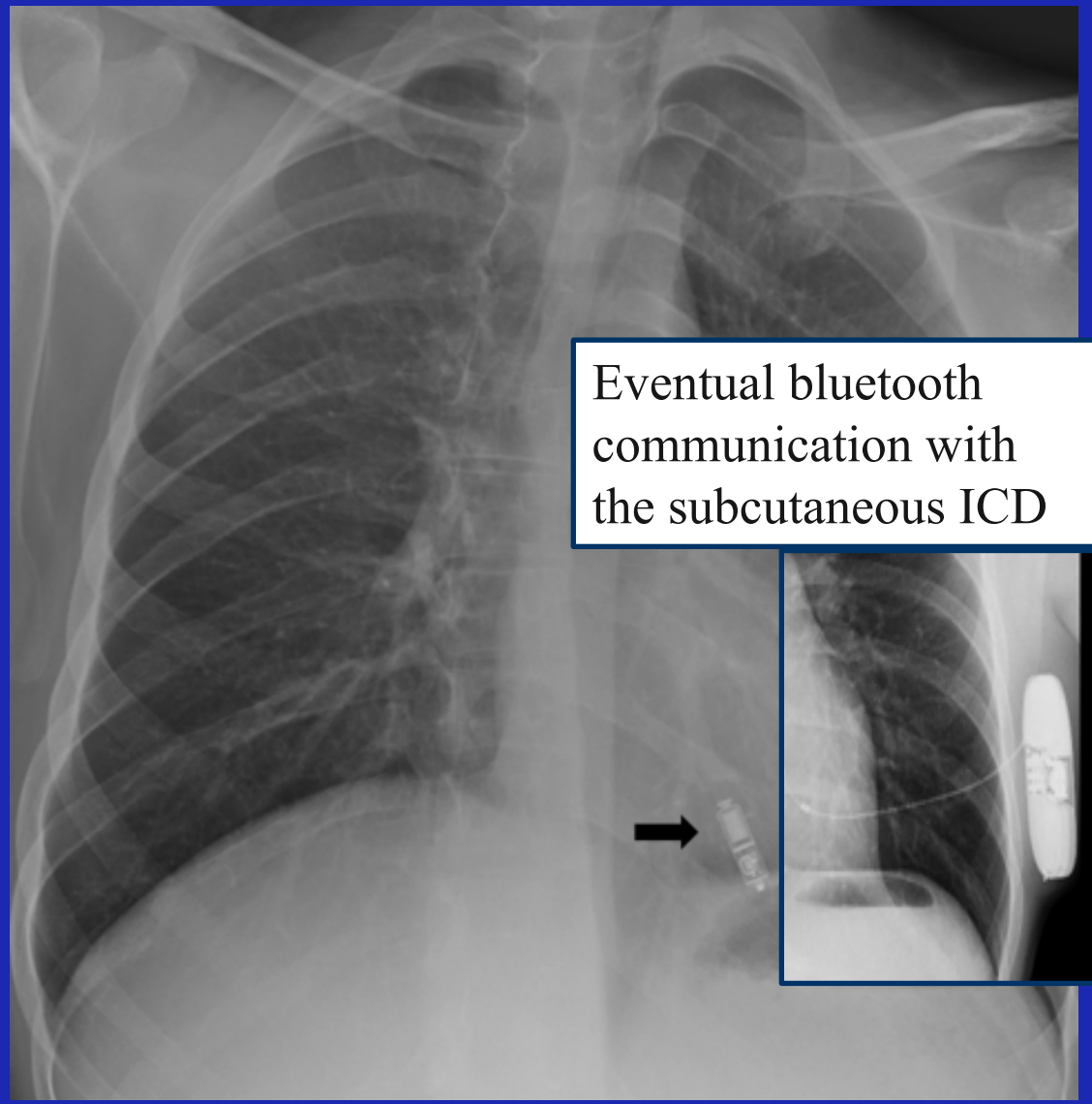
My algorithm for deciding which ICD best for which patient



Leadless Pacemakers: what's new?



MICRA leadless pacemaker:
Will have atrial sensing capacity in 2020!



Conclusions

1. Apple Watch: the future of monitoring? Yes – let's embrace it
2. Colchicine, an old friend returns but does not quite meet expectations for myocardial infarction
3. SGLT2 blockers for nondiabetics with heart failure? YES. Stay tuned for the guidelines
4. Patients with HF with preserved EF: anything new? Not yet
5. How low can you get your LDL? PCSK9 inhibition post Mi
6. Not too much, not too little, just enough sleep will prevent an Mi: now get to bed on time tonight
7. Subcutaneous ICDs: let's spare the vein! The future is here

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