Is one Betablocker better than the other ?

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2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

European Heart Journal (2015), 36, 2793

Risk stratification and management in Long QT Syndror

Recomn			
The follo recomme diagnosis (a) Avoi (http: (b) Corr abnor hypo that r diarr condi			
(c) Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).			
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B	435
ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B	436–438
Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	IIa	B	67

Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

Europace (2013) , 15, 1389 -1406

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Class IIa 6. Beta-blockers ***can be useful*** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.

Oral Beta -Blockers are still first-line therapy for the prevention of life- threatening arrhythmias in Long QT Syndrome

Which Betablockers are commonly used ?

Drug	Beta 1 selective	Liphophilicity	I- Na Block	Half-life (h)
Propranolol	No	High	Yes, late	5-7
Nadolol	No	Minimal	Yes, peak	14-24
Metoprolol	Yes	High	No	3-7 (sustained release -20 h)
Atenolol	Yes	Minimal	No	4-10
Bisoprolol	*Yes*	*Moderate*	*No*	*10-12*

Which Beta- Blocker is best in LQTS ?

- **There are no prospective studies comparing the efficacy of different Beta-blockers** (this is mainly due to low event rate)

- **Answers to the highly clinical question, "Is one b-blocker superior to another?" rely completely on retrospective analysis in available cohorts.**

Wilde A, Ackerman M, JACC 2014; 64; 1359

2 largest studies comparing Beta-Blockers in LQTS

382 genetically diagnosed LQTS 1 and LQTS 2 patients (index and familiy members)

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Heart Rhythm Disorders

Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

Priya Chockalingam, MBBS, PHD,*† Lia Crotti, MD, PHD,‡‖ Giulia Girardengo, MD,‡ Jonathan N. Johnson, MD,¶ Katy M. Harris, MS, RN,¶ Jeroen F. van der Heijden, MD, PHD,# Richard N. W. Hauer, MD, PHD,# Britt M. Beckmann, MD,** Carla Spazzolini, DVM, MS,‡ Roberto Rordorf, MD,§ Annika Rydberg, MD, PHD,†† Sally-Ann B. Clur, MBBCH, MSC (MED), PHD,† Markus Fischer, MD,‡‡ Freek van den Heuvel, MD, PHD,§§ Stefan Kääb MD, PHD,** Nico A. Blom, MD, PHD,†‖‖ Michael J. Ackerman, MD, PHD,¶ Peter J. Schwartz, MD,‡¶¶## Arthur A. M. Wilde, MD, PHD*

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Efficacy of Different Beta-Blockers in the Treatment of Long QT Syndrome

Abeer Abu-Zeitone, BS PHARM, MS, PHD,* Derick R. Peterson, PHD,† Bronislava Polonsky, MS,* Scott McNitt, MS,* Arthur J. Moss, MD*

1530 LQTS 1 /2 patients from the Rochester LQTS registry

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Amsterdam, Utrecht, and Groningen, the Netherlands; Pavia, Italy; Munich and Heidelberg, Germany; Rochester, Minnesota; Umeå, Sweden; Cape Town, South Africa; and Riyadh, Saudi Arabia

Multicenter study;
382 LQTS1/LQTS 2 patients

ECG and clinical parameters analysed; symptoms before first cardiac event documented

Symptomatic = symptoms before betablocker therapy

Table 1 Clinical Characteristics of Patients on Basis of Initial Beta-Blocker

Characteristics	Total (n = 382)	Propranolol (n = 134)	Metoprolol (n = 147)	Nadolol (n = 101)	p Value
Female	215 (56)	65 (49)	94 (64)	56 (55)	0.03
Symptoms before therapy					
Syncope	90 (24)	46 (34)	30 (20)	14 (14)	0.001
ACA	11 (3)	5 (4)	5 (3)	1 (1)	0.4
Genotype					<0.001
LQT1	207 (54)	79 (59)	59 (40)	69 (68)	
LQT2	175 (46)	55 (41)	88 (60)	32 (32)	
Baseline HR, beats/min	76 ± 16	78 ± 18	75 ± 15	74 ± 13	0.06
Baseline QTc, ms	472 ± 46	480 ± 47*	469 ± 49	465 ± 40	0.03
Median age at start of BB, yrs	14 (8–32)	10 (6–22)	21 (11–38)	14 (9–30)	<0.001
On-therapy HR, beats/min	64 ± 14	67 ± 16	64 ± 12	62 ± 13	0.05
On-therapy QTc, ms	454 ± 39	453 ± 37	456 ± 44	452 ± 34	0.8
Median TI, months	8 (4–13)	8 (3–13)	6 (3–13)	12 (8–14)	<0.001
ΔHR, beats/min	11 ± 12	12 ± 12	11 ± 12	11 ± 12	0.9
ΔQTc, ms	18 ± 34	27 ± 38†	14 ± 34	12 ± 28	0.001

Values are n (%), mean ± SD, or median (interquartile range). *$p < 0.05$ versus nadolol; †$p < 0.01$ versus metoprolol and versus nadolol.
ACA = aborted cardiac arrest; BB = beta-blocker; HR = heart rate; TI = time interval between baseline and on-therapy electrocardiograms; Δ = change in electrocardiography parameter with beta-blocker initiation.

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QTc shortening

QTc shortening most prominent with Propranolol
(probably due to late Na + current blocking activity ⇨ shortening of action potential ⇨QTc shortening)

Reports that QTc shortening might decrease the event rate

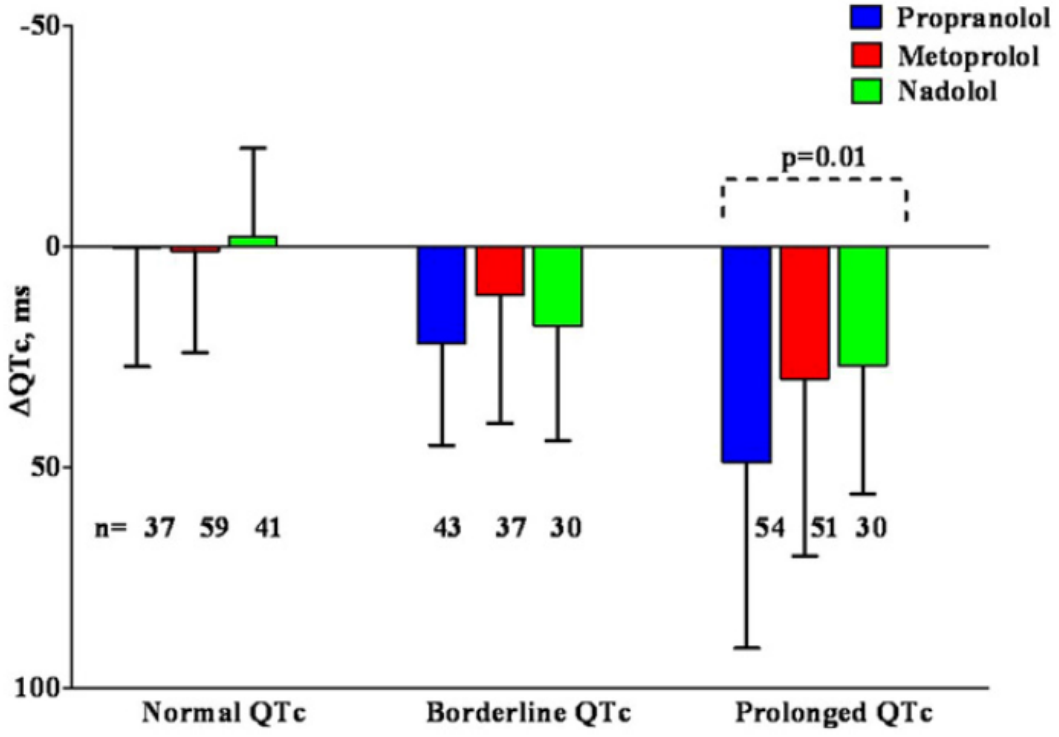

Figure 1 **Effect of Baseline QTc on QTc Shortening**

Baseline QTc was taken as normal if ≤450 ms, borderline if 451 ms to 480 ms, and prolonged if >480 ms. The Δ indicates change in electrocardiography parameter with beta-blocker initiation. **Blue bars** indicate propranolol; **red bars** indicate metoprolol; **green bars** indicate nadolol.

Events on Therapy

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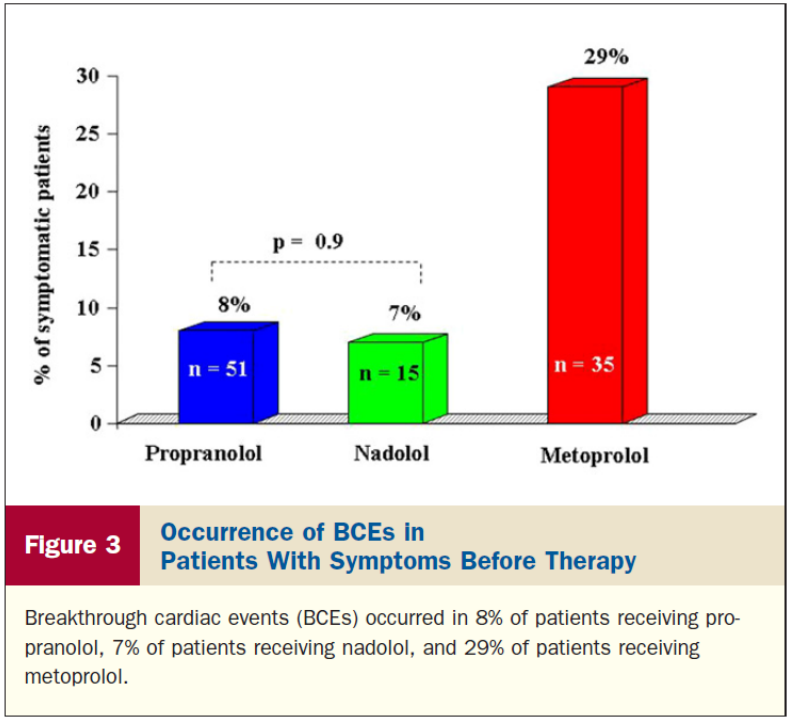


Figure 3 Occurrence of BCEs in Patients With Symptoms Before Therapy

Breakthrough cardiac events (BCEs) occurred in 8% of patients receiving propranolol, 7% of patients receiving nadolol, and 29% of patients receiving metoprolol.

Asymptomatic patients: **No events** during a median follow-up of 6 years with any betablocker

Among **symptomatic patients** (n= 101), 15 had events (syncope; no SCD)

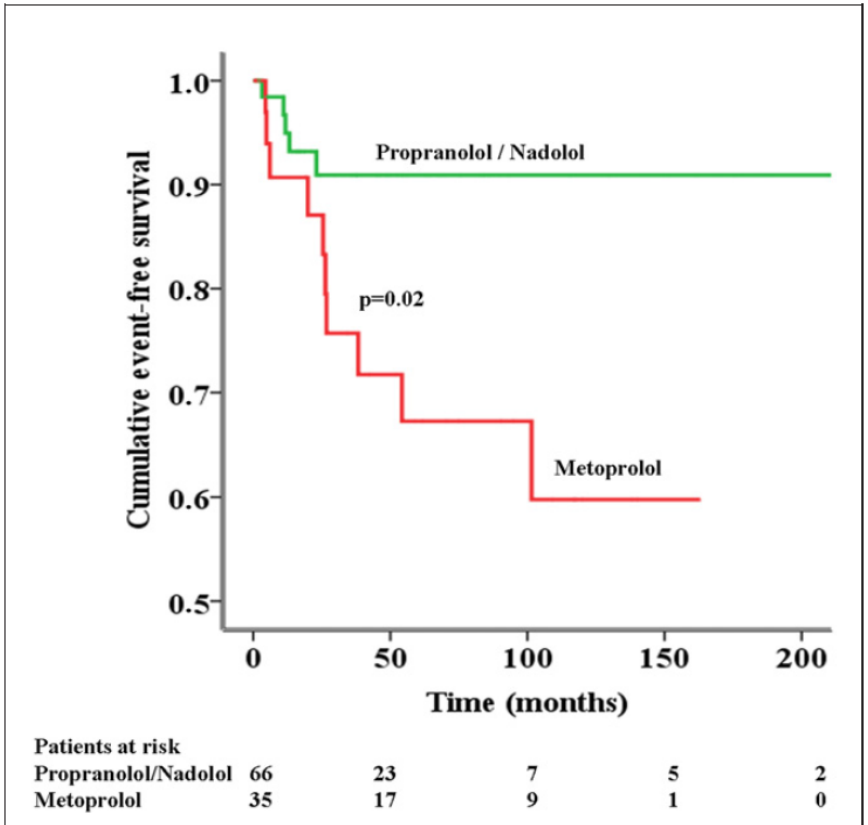
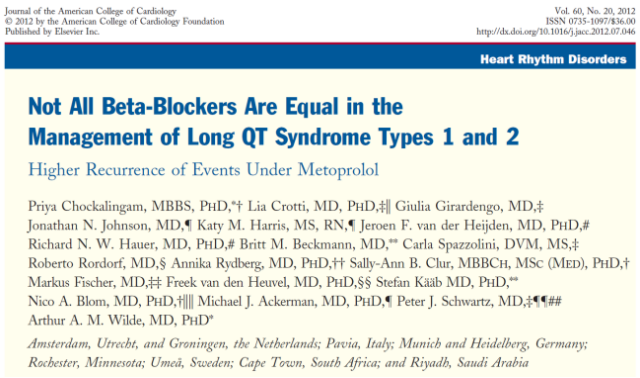


Figure 4 Kaplan-Meier Estimates of Event-Free Survival of Symptomatic Patients Initiated on Different Beta-Blockers

The cumulative event-free survival of symptomatic patients initiated on metoprolol (n = 35) **(red line)** was significantly different (p = 0.02) from that of patients initiated on propranolol and nadolol combined (n = 66) **(green line)**.



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Conclusions

- Propranolol has a significantly better QTc shortening effect compared to Metoprolol or Nadolol, especially in patients with prolonged QTc

- None of the asymptomatic patients had events

- **Symptomatic** patients on Metoprolol significantly higher risk for events (OR 3.95) ⇨ **Metoprolol should not be used for symptomatic LQTS 1 and 2 patients**

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Efficacy of Different Beta-Blockers in the Treatment of Long QT Syndrome

Abeer Abu-Zeitone, BS Pharm, MS, PhD,* Derick R. Peterson, PhD,† Bronislava Polonsky, MS,* Scott McNitt, MS,* Arthur J. Moss, MD*

Study group: Pts <40 years who were prescribed Beta - blockers and were without ICD 1530 pts; also pts < 1 year included

Primary endpoint: Occurrence of first cardiac event (syncope, aborted cardiac arrest or SCD) **after** ß-Blocker initiation

TABLE 1 Clinical Characteristics of Patients With LQTS According to First β-Blocker Therapy*

	Atenolol (n = 441)	Metoprolol (n = 151)	Propranolol (n = 679)	Nadolol (n = 259)	p Value†
Demographics					
Age at first β-blocker, yrs	16 ± 10	24 ± 10	11 ± 11	18 ± 11	<0.001
Female sex: number, %	254 (58)	105 (70)	412 (61)	149 (58)	0.06
Calendar year of first β-blocker	1,998 ± 6	1,999 ± 6	1,993 ± 9	1,997 ± 8	<0.001
History					
Syncope or aborted cardiac arrest before first β-blocker	188 (43)	85 (56)	334 (49)	130 (50)	0.02
Family history of LQTS	76 (17)	20 (13)	148 (22)	52 (20)	0.06
ECG					
QTc-interval value, ms‡	492 ± 49	496 ± 52	500 ± 58	490 ± 51	0.13
RR interval value, ms‡	803 ± 218	842 ± 212	753 ± 247	863 ± 231	<0.001
Therapy before β-blocker					
Pacemaker before first β-blocker	15 (3)	5 (3)	31 (5)	8 (3)	0.64
Initial β-blocker doses					
Adults age 18 yrs old or older, mg/day	49 ± 29	70 ± 49	117 ± 105	54 ± 46	NA
Children younger than age 18 yrs, mg/day	40 ± 27	53 ± 47	52 ± 54	38 ± 30	NA
Adults age 18 yrs old or older, mg/kg/day§	0.7 ± 0.3	1.2 ± 0.9	2.1 ± 2.3	1 ± 0.8	NA
Children younger than age 18 years, mg/kg/day‖	1.0 ± 0.7	1.4 ± 1.0	2.3 ± 1.5	1.0 ± 0.8	NA

*Values are mean ± SD or n (%). †The p values are based on the Kruskal-Wallis test and refer to the significance of the difference across the 4 β-blocker groups. ‡First recorded QTc and RR values (baseline) in LQTS Registry. §Number of patients aged 18 years or older whose dose and weight at the initiation of β-blocker therapy were available (n = 157). ‖Number of patients younger than 18 years of age whose dose and weight at the initiation of β-blocker therapy were available (n = 379).

ECG = electrocardiogram; LQTS = long QT syndrome; NA = p values not applicable.

First cardiac event

TABLE 2 Drug-Specific Cardiac Event Rates on β-Blocker Therapy and Covariate-Adjusted Hazard Ratios Relative to Discontinuing β-Blockers*

Time-Dependent Variable	First Cardiac Events†	Hazard Ratio‡ (95% CI)	p Value	Aborted Cardiac Arrest/Sudden Cardiac Death†	Hazard Ratio‡ (95% CI)	p Value
Atenolol	100/414 (24.2)	0.71 (0.50–1.01)	0.06	18/418 (4.3)	0.38 (0.20–0.74)	0.004
Metoprolol	25/147 (17.0)	0.70 (0.43–1.15)	0.16	1/147 (0.7)	0.08 (0.01–0.62)	0.02
Propranolol	160/395 (40.5)	0.65 (0.46–0.90)	0.01	42/352 (11.9)	0.42 (0.24–0.74)	0.002
Nadolol	61/363 (16.8)	0.51 (0.35–0.74)	<0.001	12/386 (3.1)	0.29 (0.14–0.61)	<0.001
Any β-blocker (pool of all 4 groups)	346/1,319 (26.2)	0.63 (0.47–0.86)	0.004	73/1,303 (5.6)	0.37 (0.22–0.61)	<0.001
Test of equality of 4 drug-specific hazard ratios§			0.19			0.16

Values are n/N (%), unless otherwise noted. *Numbers of patients who discontinued β-blocker therapy at the end of follow-up were 211 for first cardiac events analysis (total events = 49, 23.2%) and 227 for aborted cardiac arrest/sudden death (total events = 20, 8.8%). Total first cardiac events = 395, of which aborted cardiac arrest = 25 and death = 31. †Number of patients in each group at the end of follow-up (n). These are different from baseline counts because the analyses were time dependent, allowing patients to switch and go on and off drugs during follow-up. ‡Adjusted hazard ratios: see the methods section for covariates included in the Cox models when computing hazard ratios. §There was insufficient evidence of differential effects by type of β-blocker for first cardiac event or aborted cardiac arrest/sudden cardiac death (3-df likelihood ratio test p = 0.19 and p = 0.16, respectively).

CI = confidence interval

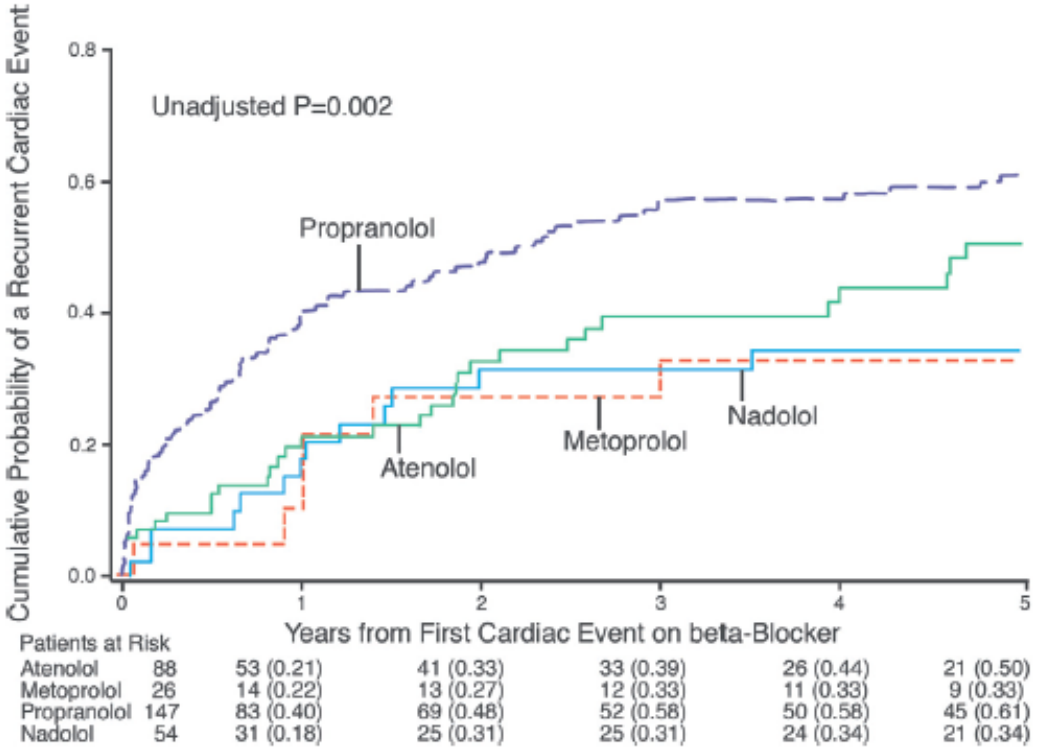
- No significant difference between the 4 betablockers in preventing a primary cardiac event
- Nadolol more effective in LQTS 2 in subgroup analysis

Second cardiac event

Patients experiencing a second event on treatment commonly clinically considered as „high-risk“ group

Propranolol worse in preventing a second event

? due to propranolol´s undesirable hERG potassium channel - blocking actions ?



CENTRAL ILLUSTRATION Cumulative Probability of a Subsequent Cardiac Event Among Patients With 1 Cardiac Event While Taking β-Blocker Therapy

Kaplan-Meier estimates of the cumulative probability of a subsequent cardiac event following 1 cardiac event while taking β-blocker therapy, stratified by type of β-blocker: atenolol, metoprolol, nadolol, or propranolol. The p value was based on the 4-group log-rank test, unadjusted for covariates or time-dependent changes to β-blocker status. The numbers of subjects at risk are given yearly, up to 5 years, for a first recurrent cardiac event while taking β-blockers.

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Abeer Abu-Zeitone, BS PHARM, MS, PHD,* Derick R. Peterson, PHD,† Bronislava Polonsky, MS,* Scott McNitt, MS,* Arthur J. Moss, MD*

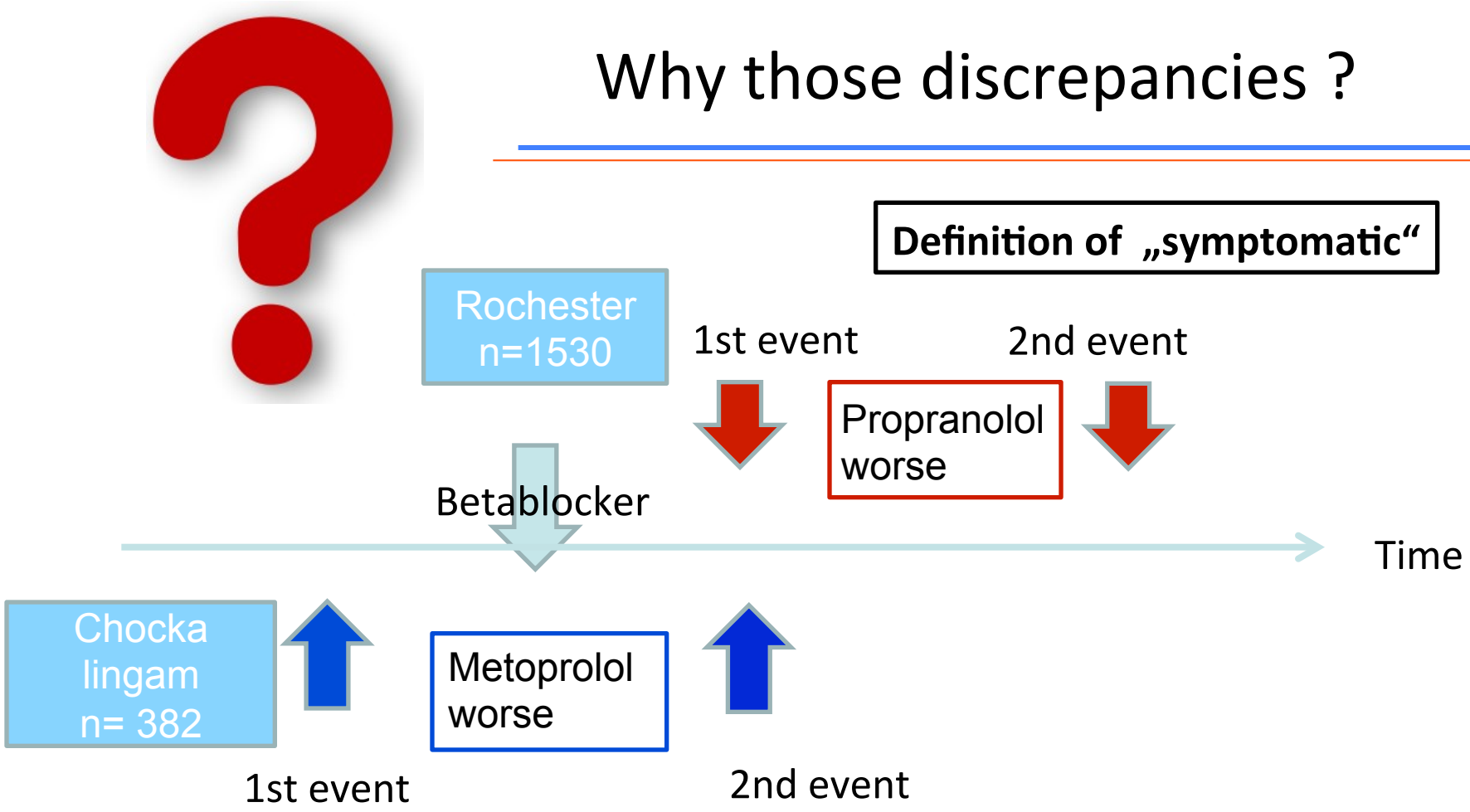
Conclusions

- All **4 Beta-blockers were equally effective** in reducing the risk of **a first cardiac event** in LQTS

- In subgroup analysis, **Nadolol** was associated with a significant risk reduction in patients with **LQT2** (longest half-life, most stable lasting degree of betablockade ?).

- **Propranolol was the least effective drug in** patients experiencing recurrent cardiac events during Beta-blocker therapy

Why those discrepancies ?



Rochester: Patients included with diagnosis < 1 year mostly treated with propranolol; significantly higher risk profile; results seem driven by the < 1 year group; after 12 months event curves no longer deviate.

Wilde A, Ackerman M, JACC 2014; 64; 1359

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MULTIMEDIA REPORT

Experience with bisoprolol in long-QT1 and long-QT2 syndrome

Christian Steinberg[1] · Gareth J. Padfield[1] · Basil Al-Sabeq[2] · Arnon Adler[3] · John A. Yeung-Lai-Wah[1] · Charles R. Kerr[1] · Marc W. Deyell[1] · Jason G. Andrade[1] · Matthew T. Bennett[1] · Raymond Yee[2] · George J. Klein[2] · Martin Green[3] · Zachary W. M. Laksman[1] · Andrew D. Krahn[1] · Santabhanu Chakrabarti[1,4]

Any other betablocker in sight ?

Table 1 Clinical characteristics at initiation of beta-blocker

Total $N=114$	Bisoprolol $N=59$	Atenolol $N=39$	Nadolol $N=16$	
Mean age at start of beta-blocker (years)	35 ± 17	37 ± 19	27 ± 13	
Female, *n* (%)	33 (56)	23 (59)	11 (69)	
Genotype, *n* (%)				
LQT-1	42 (71.2)	19 (49)	10 (63)	
LQ				
Schw				
Type				
Pro				
Far				
Famil				
Famil				
Symptoms before therapy, *n* (%)	14 (23.7)	13 (33)	6 (38)	
Syncope	13 (22)	10 (26)	8 (50)	
Sudden cardiac arrest	2 (3.4)	0	2 (13)	
Documented polymorphic VT	2 (3.4)	1 (3)	2 (13)	
ICD implantation, (%)	4 (6.8)	1 (3)	3 (19)	
Patients with QTc >500 ms pre BB, *n* (%)	14 (24)	4 (10)	2 (13)	0.19
Patients with QTc >500 ms on BB, *n* (%)	7 (12)	3 (8)	0	0.32

- **Bisoprolol**: might be an option for “low-risk” patients;
- long half-life, beta 1 selective, well tolerated during long-term administration; Further large-scale studies required

Table 3 Clinical outcomes based on beta-blocker therapy

Total $N=114$	Bisoprolol $N=59$
Follow-up[a], years	3 (1–6)
Documented polymorphic VT	0
Syncope	0
Appropriate ICD shocks, *n* (%)	0
Inappropriate ICD shocks, *n* (%)	1 (1.7)

Summary

- Event rate in asymptomatic LQTS 1 and 2 patients very low; all 4 Beta Blockers (Nadolol, Propranolol, Metoprolol, Atenolol) might be equal in this group
- **Nadolol** seems superior in LQTS 2 patients; Main disadvantage: not available in some European countries
- Conflicting data in **symptomatic** patients concerning **Metoprolol** and **Propranolol**
- **Propranolol-** main disadvantage: multiple daily dosing ⇨ Compliance ? No data on sustained-release propranolol in children
- **Bisoprolol** in „low-risk“ adolescents/adults ?
- In symptomatic/high risk patients, think about alternative treatment (sympathectomy, ICD)

Thank you for your attention !

Conflicts of interest

Lecture fees and travel support

St. Jude Medical
Biosense Webster
Boston Scientific

2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death

European Heart Journal (2015), 36, 2793

Risk stratification and management in Long QT Syndrome

Recommendations	Class[a]	Level[b]	Ref.[c]
The following lifestyle changes are recommended in all patients with a diagnosis of LQTS: (a) Avoidance of QT-prolonging drugs (http://www.crediblemeds.org). (b) Correction of electrolyte abnormalities (hypokalaemia, hypomagnesaemia, hypocalcaemia) that may occur during diarrhoea, vomiting or metabolic conditions. (c) Avoidance of genotype-specific triggers for arrhythmias (strenuous swimming, especially in LQTS1, and exposure to loud noises in LQTS2 patients).	I	B	434
Beta-blockers are recommended in patients with a clinical diagnosis of LQTS.	I	B	435
ICD implantation with the use of beta-blockers is recommended in LQTS patients with previous cardiac arrest.	I	B	436–438
Beta-blockers should be considered in carriers of a causative LQTS mutation and normal QT interval.	IIa	B	67

Executive summary: HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes

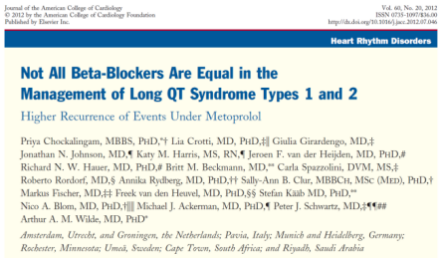
Europace (2013) , 15, 1389 -1406

Class I

2. Beta-blockers ***are recommended*** in patients with a diagnosis of LQTS who are:
   a. Asymptomatic with QTc ≥470 ms *and/or*
   b. Symptomatic for syncope or documented ventricular tachycardia/ventricular fibrillation (VT/VF).

Class IIa

6. Beta-blockers ***can be useful*** in patients with a diagnosis of LQTS who are asymptomatic with QTc ≤470 ms.



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Heart Rhythm Disorders

Not All Beta-Blockers Are Equal in the Management of Long QT Syndrome Types 1 and 2

Higher Recurrence of Events Under Metoprolol

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Symptomatic patients

Table 3 Clinical Characteristics of Symptomatic Patients on the Basis of Initial Beta-Blocker

Characteristics	Total (n = 101)	Propranolol (n = 51)	Metoprolol (n = 35)	Nadolol (n = 15)	p Value
Female	73 (72)	36 (71)	26 (74)	11 (73)	0.9
LQT1	56 (55)	32 (62)	14 (41)	10 (67)	0.07
Baseline HR, beats/min	74 ± 14	74 ± 14	75 ± 14	69 ± 11	0.3
Baseline QTc, ms	499 ± 51	502 ± 52	497 ± 48	493 ± 54	0.8
Median age at start of BB, yrs	22 (10–34)	18 (8–34)	25 (17–38)	22 (9–32)	0.2
On-therapy HR, beats/min	62 ± 12	63 ± 14	61 ± 9	60 ± 13	0.7
On-therapy QTc, ms	474 ± 41	469 ± 40	478 ± 44	478 ± 35	0.5
Median TI, months	6 (3–17)	8 (3–16)	5 (2–17)	8 (3–20)	0.7
ΔHR, beats/min	12 ± 12	11 ± 12	14 ± 12	9 ± 9	0.3
ΔQTc, ms	26 ± 37	33 ± 39	19 ± 37	15 ± 28	0.1
BCE	15 (15)	4 (8)	10 (29)	1 (7)	0.02

Values are n (%), mean ± SD, or median (interquartile range).
BCE = breakthrough cardiac event; other abbreviations as in Table 1.