Qantitative Sensory Testing (QST)

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Quantitative Sensory Testing (QST)

Definition (NeuPSIG)

QST is a psychophysical method used to quantify somato-sensory function in healthy subjects and in patients. It is based on measurements of responses to calibrated, graded innocuous or noxious stimuli (generally mechanical or thermal) and represents, in most respects, an extension of the routine bedside clinical examination of the sensory system.

Backonja et al.: Standards for conducting QST in neurological and pain disorders: NeuPSIG recommendations, Pain, in revision

Quantitative Sensory Testing (QST): Methods

Thermal thresholds

-

Tactile threshold

-

Vibration threshold

-
-

Pressure pain threshold

-

Pinprick threshold

-

Backonja et al.: Standards for conducting QST in neurological and pain disorders: NeuPSIG recommendations, Pain, in revision

QST Devices

Thermal thresholds

TSA II (Medoc)

CASE IV
(WR Medical Electronics)

Q-Sense
(Medoc)

MSA Thermotest
(Somedic)

Vibration thresholds

VSA 3000
(Medoc)

Vibrameter
(Somedic)

Vibratron II
(Physitemp)

Sensitometer

Biothesiometer

Neurothesiometer

Quantitative Sensory Testing (QST)

ADVANTAGES	LIMITATIONS
✓ Relatively simple, noninvasive	- Psychophysical (coop., attention)
✓ Small vs large fiber function	- Rel. high intra-/inter-rater variability
✓ Loss vs gain of function	- Lack of standardization
✓ Subclinical dysfunction detectable	- Few normative data
✓ Impact on morbidity/mortality	- Few validation studies
✓ Suitable for screening/epidemiol.	- Variable sensitivity (gold standard?)
	- Time consuming (forced choice)
	- Expensive (cost/benefit ratio?)

Quantitative Sensory Testing (QST)

Prerequisites for use in large clinical trials:

- **Major impact on morbidity/mortality**
- **Clinically meaningful study endpoint**
- **Progression with increasing diabetes duration**
- **Susceptible to long-term degree of glycemia**
- **Sufficient intra-/inter-observer repeatability**
- **Adequate training of investigator and patient**
- **Preferably non-invasive**

Clinical impact of QST in DSPN

- **VPT has been shown to predict mortality in people with diabetes (Coppini, 2000).**

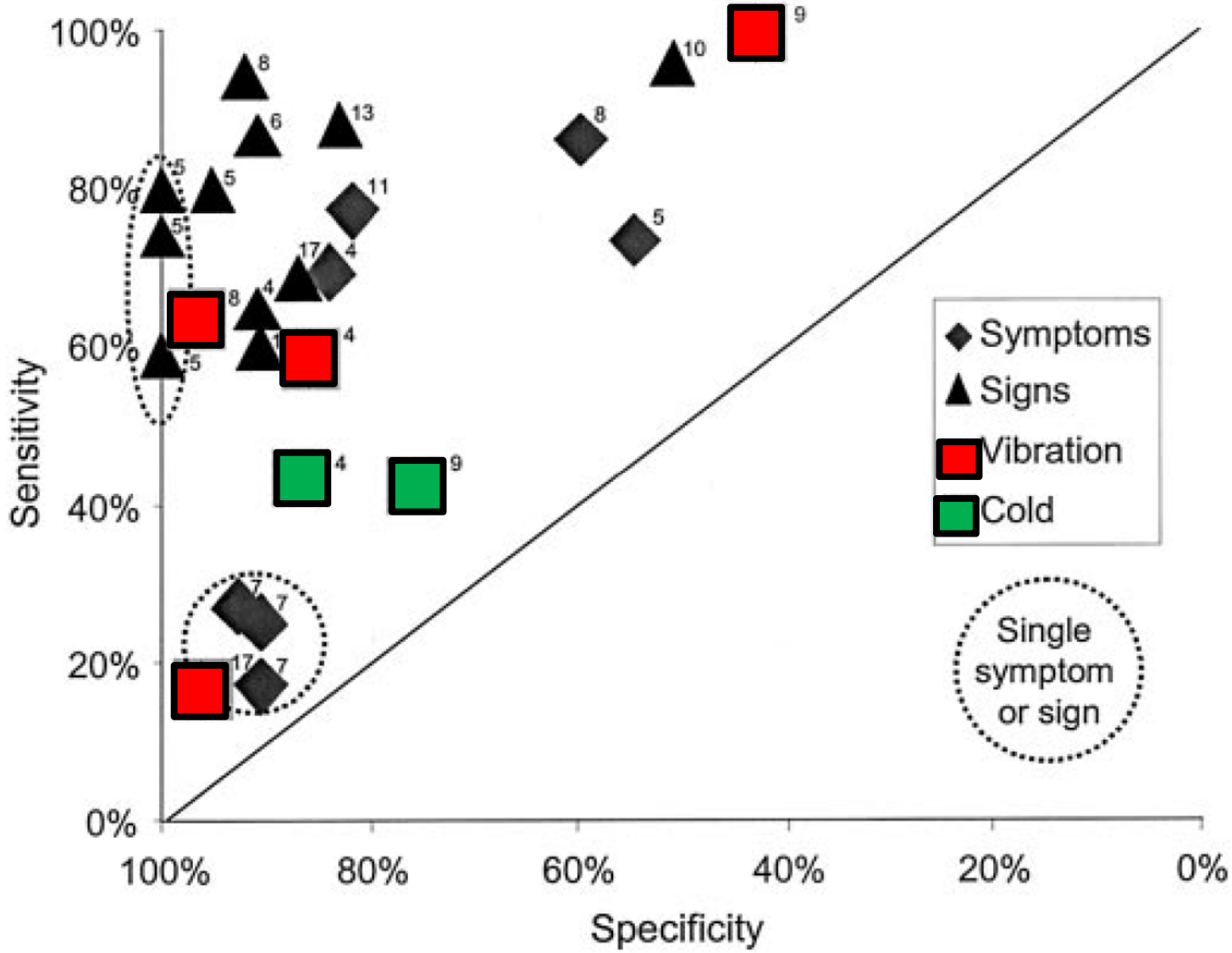
- **Elevated VPT and reduced temperature and pain sensation predict the development of neuropathic foot ulceration (Abbott, 1998; Abbott 2002).**

- **Reduced pressure sensation to a 10 g monofilament predict cardiac death or nonfatal MI in type 2 diabetic patients without symptomatic coronary artery disease (Young, 2009).**

Over 10 years the average patient with increased VPT≥25

→ **incurs 5-fold increased medical cost for foot ulcers/amputations**
→ **yields 0.18 fewer quality-adjusted life-years (QALYs)**
→ **lives for 2 months less than the average patient with VPT<25 (Gordois, 2003; Shearer, 2003)**

Diagnostic accuracy levels of symptoms, signs, or combinations of symptoms or signs (predictors) for the presence of DSPN



England et al., NEUROLOGY 2005;64:199–207

DCCT/EDIC

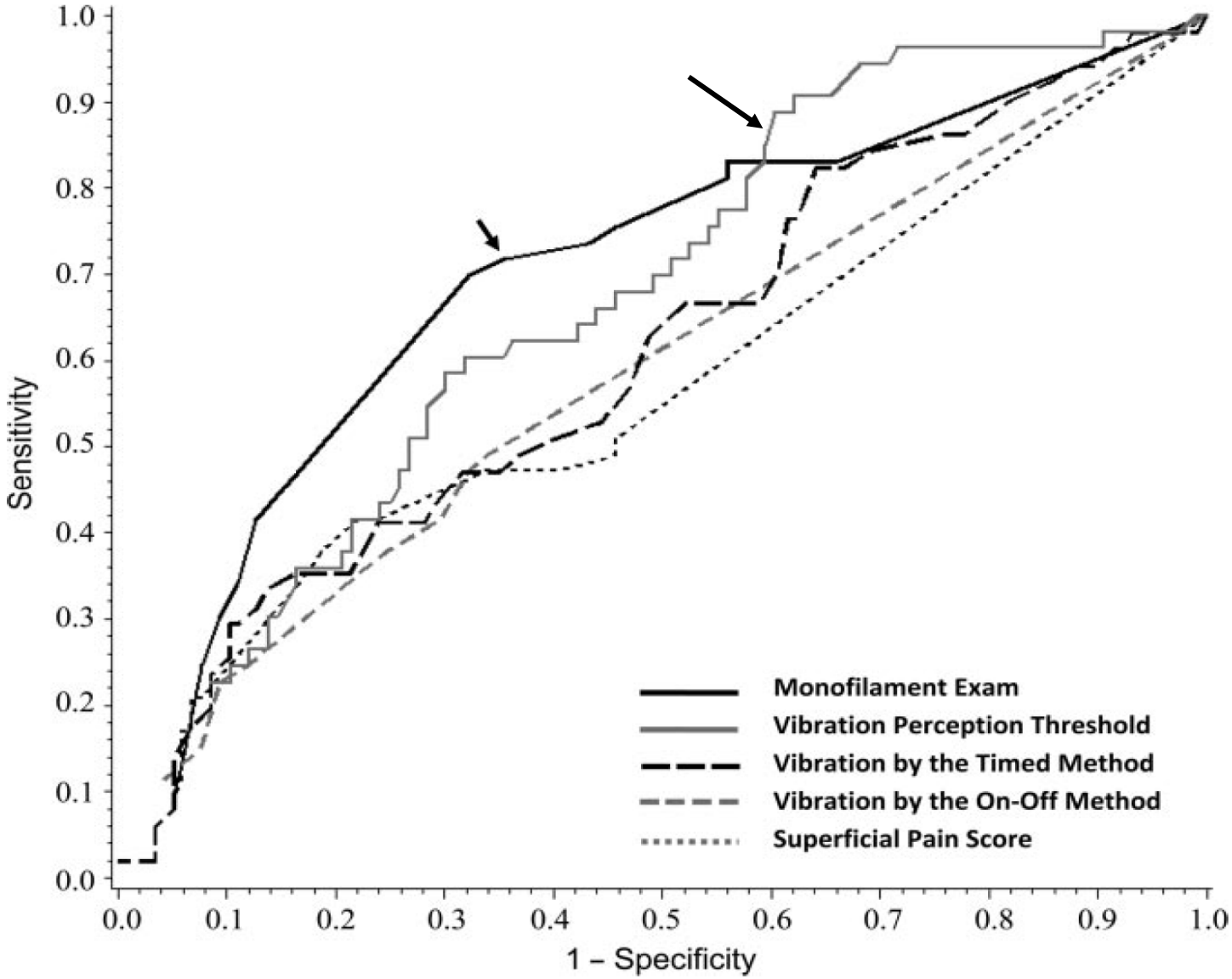
Vibration perception threshold (VPT)

Vibratron II:
Diagnostic utility of VPT (great toe); n=1170

	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Definite clinical DPN (neurologist)	80	51	49	81
Reduced nerve conduction velocity (NCV)	75	62	76	61
Confirmed clinical DPN (neurologist + NCV)	87	51	43	90

Martin et al., Diabetes Care 2010; 33: 2635-2641

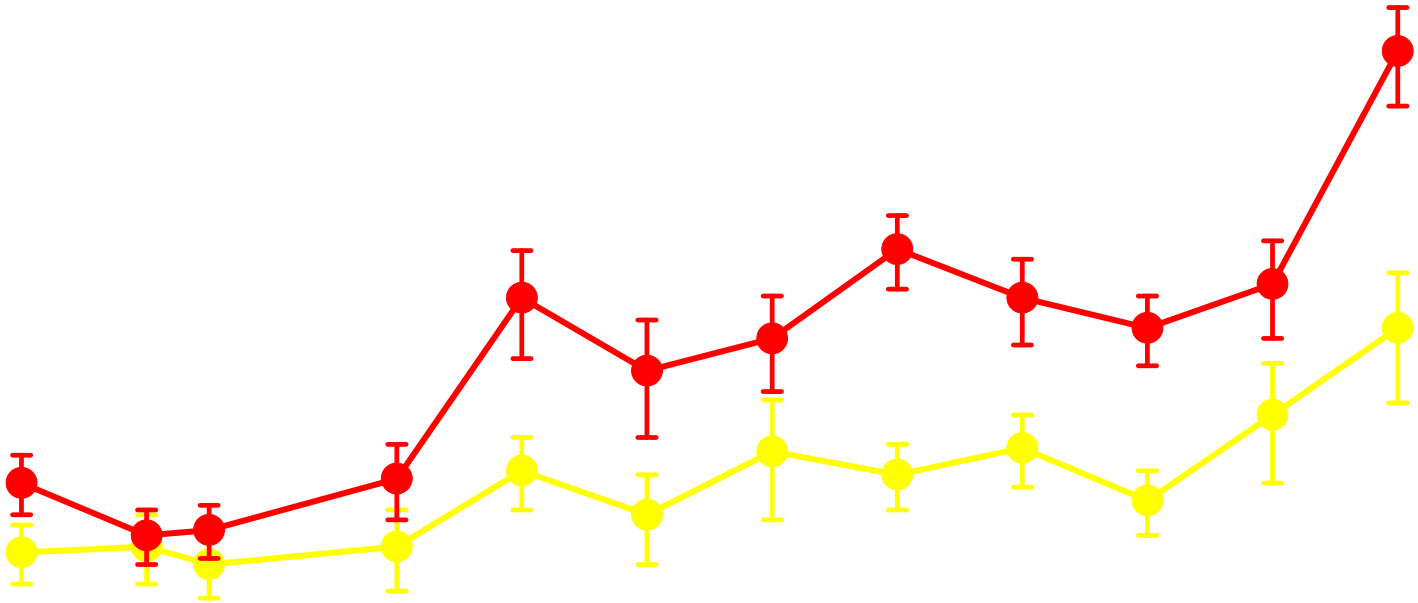
ROC curves for 4-year incident diabetic neuropathy (n=175)



Perkins et al., Diabetes Care 2010; 33:1549–1554

Malleolar Vibration Perception Threshold (VPT)

Group 1: Mean HbA1c <7.0% (6.5±0.1%)
Group 2: Mean HbA1c ≥7.0% (8.3±0.2%)



Ziegler et al., Diabetologia 2010; 53, Suppl 1: S16 (abstract)

Intensive insulin therapy reduces the progression of increased vibration threshold in type 1 diabetes

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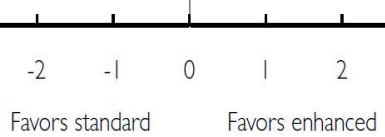
Study or subgroup	Enhanced N	Enhanced Mean(SD)	Standard N	Standard Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Holman 1983	33	0.45 (2.25)	31	-1 (2.85)		35.8 %	0.56 [0.06, 1.06]
Jakobsen 1988	12	0.5 (1.54)	12	-0.8 (1.125)		12.4 %	0.93 [0.08, 1.78]
Reichard 1993	42	-0.32 (1.02)	47	-0.33 (1.02)		51.8 %	0.01 [-0.41, 0.43]
Total (95% CI)	**87**		**90**			**100.0 %**	**0.32 [0.02, 0.62]**

Heterogeneity: $Chi^2 = 5.00$, df = 2 (P = 0.08); $I^2 = 60\%$

Test for overall effect: Z = 2.10 (P = 0.036)

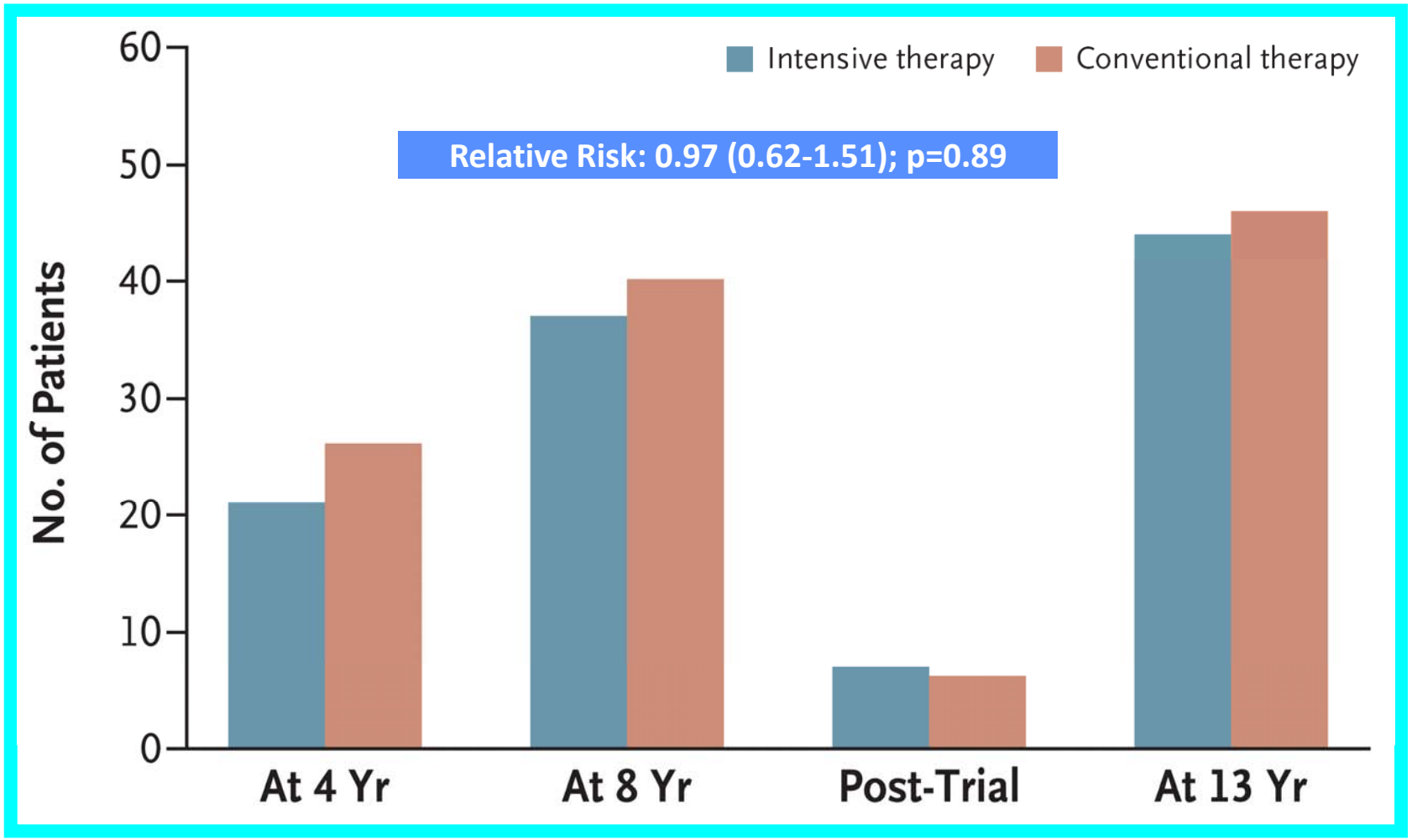
Test for subgroup differences: Not applicable



Callaghan BC et al., Cochrane Database Syst Rev. 2012 Jun 13;6:CD007543.

Steno Type 2 Study: Follow-Up after 13 Years

No effect of multifactorial intervention on the progression of increased VPT in type 2 diabetes

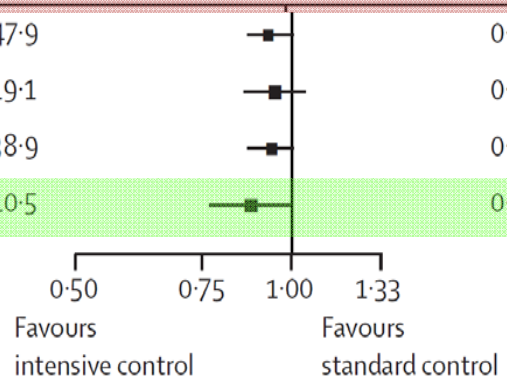


Gæde et al., *N Engl J Med* 2008; 358: 580-591

ACCORD Study: Neurological impairment

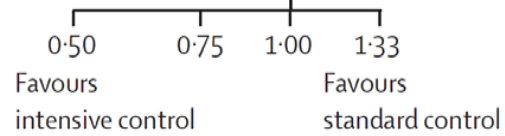
At transition to standard therapy (3.7 years): standard vs intensive

	Glycaemia control				Hazard ratio (95% CI)	p value	NNT
	Intensive		Standard				
	Events/n	%	Events/n	%			
Neuro-1: neuropathy (MNSI score >2·0)	1277/2815	45·4	1338/2791	47·9	0·93 (0·87–1·01)	0·0819	
Neuro-2: loss of vibratory sensation	766/4209	18·2	805/4209	19·1	0·95 (0·86–1·05)	0·2926	
Neuro-3: loss of ankle jerk	1225/3298	37·1	1270/3265	38·9	0·94 (0·87–1·01)	0·0997	
Neuro-4: loss of sensation to light touch	424/4577	9·3	481/4564	10·5	0·88 (0·77–1·00)	0·0451	78



At study end (5 years): standard vs intensive/standard

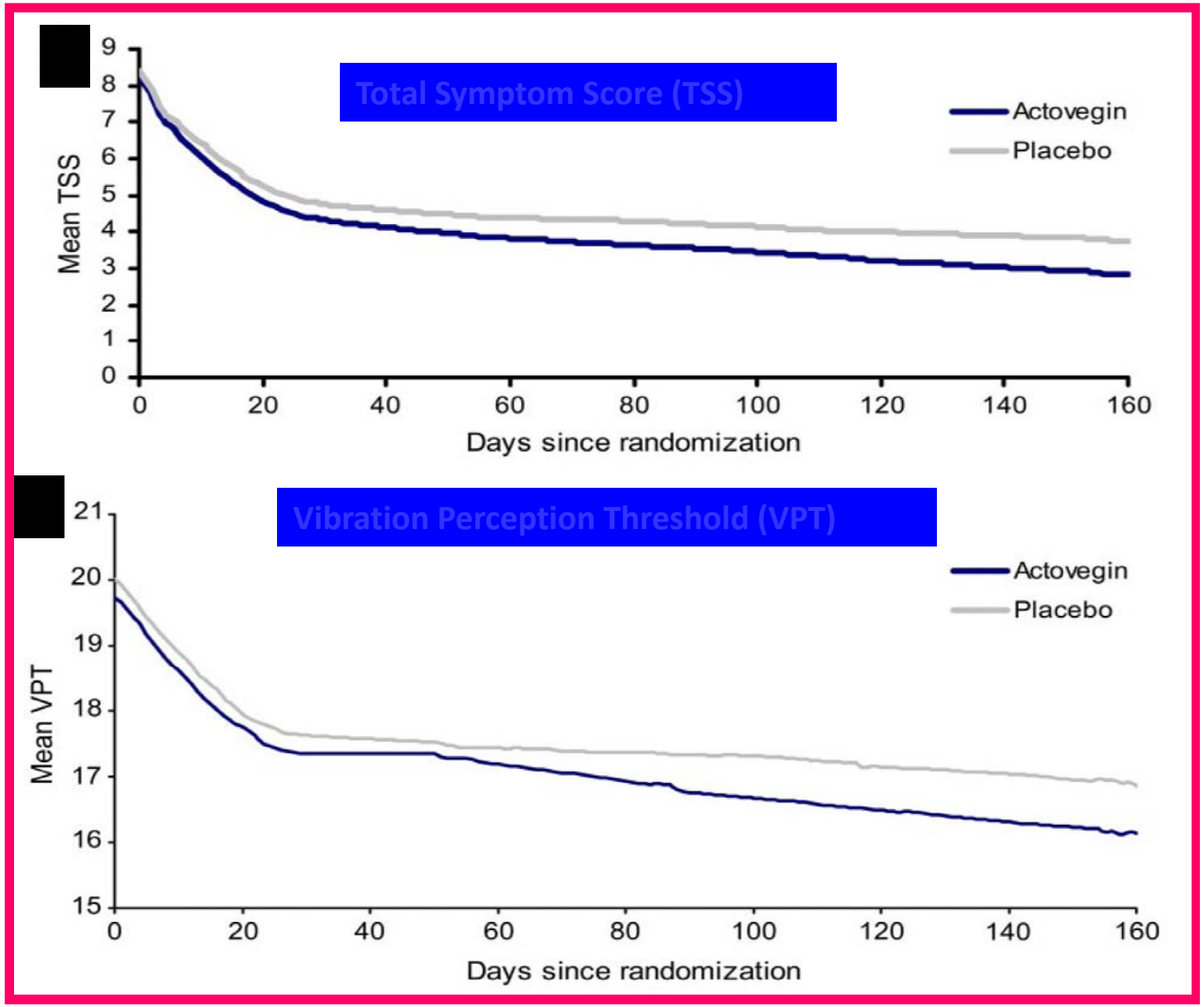
Neuro-1: neuropathy (MNSI score >2·0)	1573/2829	55·6	1640/2797	58·6	0·92 (0·86–0·99)	0·0265	33
Neuro-2: loss of vibratory sensation	981/4227	23·2	1050/4217	24·9	0·93 (0·85–1·01)	0·0808	
Neuro-3: loss of ankle jerk	1514/3312	45·7	1612/3271	49·3	0·90 (0·84–0·97)	0·0050	28
Neuro-4: loss of sensation to light touch	554/4596	12·1	645/4573	14·1	0·85 (0·76–0·95)	0·0043	49



Ismail-Beigi et al., Lancet 2010; 376 (9739): 419-30

Actovegin in symptomatic DPN

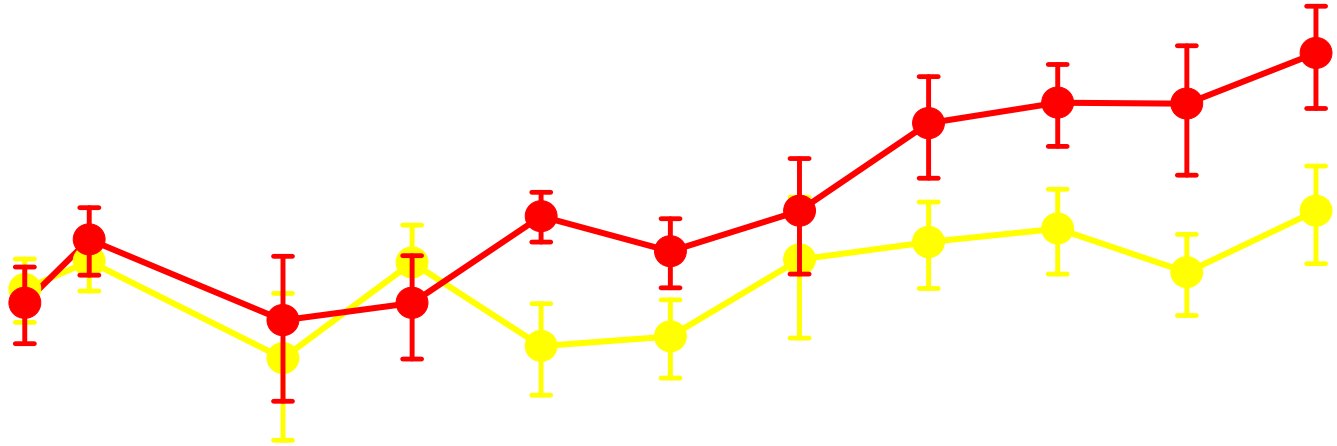
20 infusions: 250 ml i.v. qd (20-36 days) → 600 mg tid orally (20 wk)



Ziegler et al., Diabetes Care 2009; 32: 1479-84

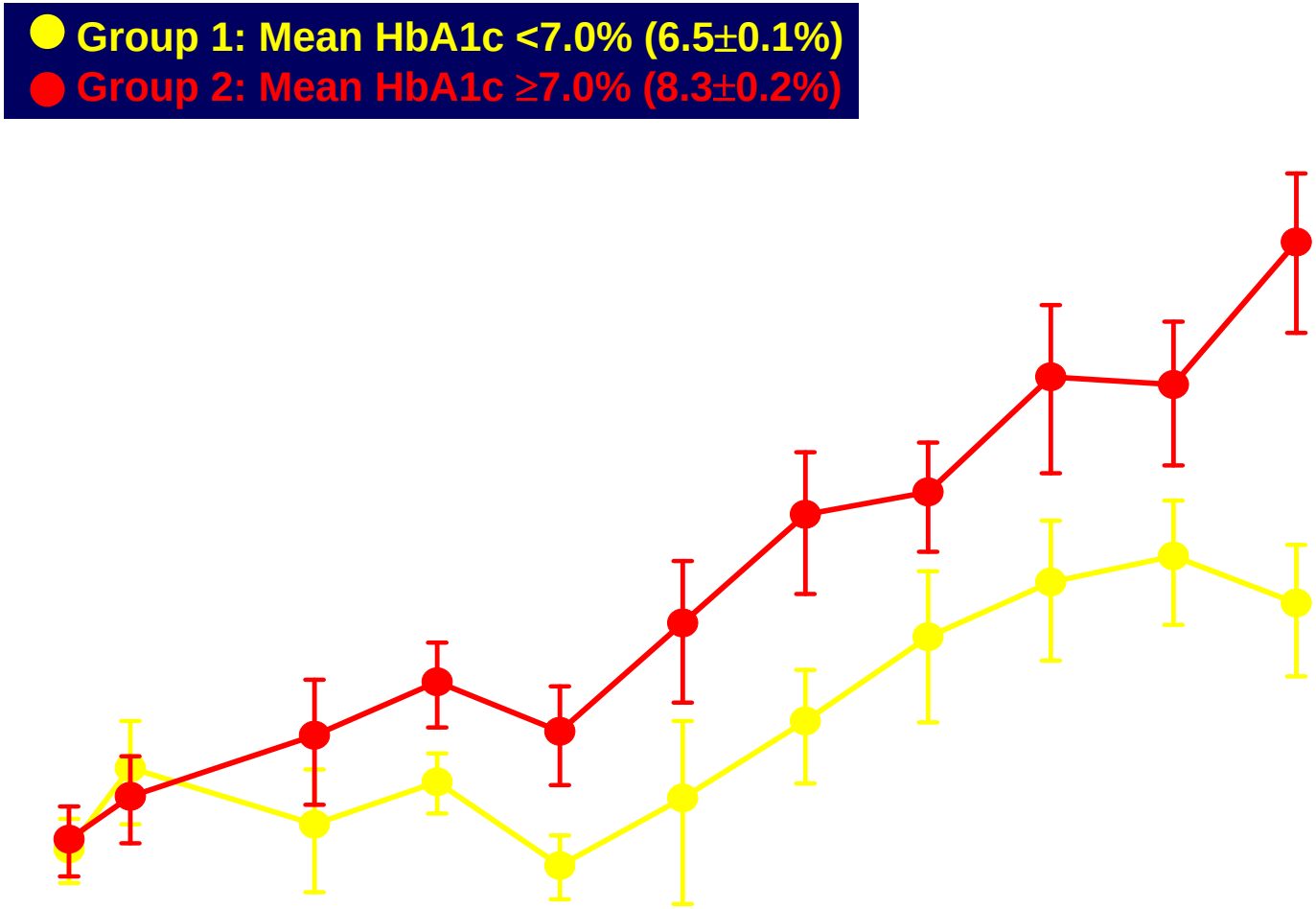
Warm Thermal Perception Threshold (TPT) Foot

Group 1: Mean HbA1c <7.0% (6.5±0.1%)
Group 2: Mean HbA1c ≥7.0% (8.3±0.2%)



Ziegler et al., Diabetologia 2010; 53, Suppl 1: S16 (abstract)

Cold Thermal Perception Threshold (TPT) Foot



Ziegler et al., Diabetologia 2010; 53, Suppl 1: S16 (abstract)

Thermal detection thresholds in recent trials

Trial	Duration (years)	*n*	Effect
NATHAN 1*	4	460	None
Ranirestat+	1	549	None
C-peptide#	0,5	139	None

*Ziegler et al., Diabetes Care 2011; 34: 2054–2060
+Bril et al., Diabetes Care 2009; 32: 1256–1260
#Eckberg et al., Diabetes Care 2007; 30: 71–76

DSPN: End points assessed longitudinally for change and monotonicity in 3 studies

Median regression slopes of various neuropathic end points over time

	Placebo arms					
	Rochester Cohort		NATHAN 1 Trial		Ruboxistaurin Trial	
Cohort	$\bar{b}$ per 4 years	P*	$\bar{b}$ per 4 years	P	$\bar{b}$ per year	P
Entry criteria	NIS(LL) ≥2 points					
Number of patients (mode)	83		191		234	
Ankle reflexes† (0–4 pts)	−0.35	0.02	−0.27	<0.01	0.24	0.73
Great toe vibration† (0–4 pts)	0.40	<0.01	0.12	0.30	−0.25	<0.01
NIS(LL)† (pts)	0.82	0.99	0.16	0.81	0.35	0.02
NSC(LL) severity† (pts)	−0.13	0.29	−0.52	0.23	−3.27	<0.01
Σ DCCT criteria† (0–12 pts)	−0.21	0.21	−0.27	0.10	−0.38	<0.01
Peroneal motor CV nd	0.08	0.33	−0.00	0.54	0.05	0.05
Tibial motor DL nd	−0.11	0.27	−0.10	0.09	−0.04	0.10
Sural SNAP nd	0.23	<0.01	+0.00	0.05	0.14	<0.01
Σ 5 NC tests nd	−0.20	0.44	−0.21	0.05	0.29	0.05
VDT (CASE IV) nd	0.53	0.02	+0.00	0.34	−0.40	<0.01
Σ 3 QST nd	2.48	<0.01	−0.28	0.02		
HRDB nd	+0.00	0.67	0.05	0.55	0.10	0.13

Σ 3 QST = CASE IV: summated normal deviates of VDT, cooling detection threshold and heat-pain 5 threshold

Dyck et al., Diabetes Care 2007; 30: 2619–2625

Ruboxistaurin trial: no DSPN progression in placebo group (n=348) after 3 years

	Baseline	Endpoint	Change at study end
NIS-LL+4+VDT (pts, nd)	10.12	9.5	-0.73* improved
VPT (JND)	19.39	19.17	-0.26* improved
NIS-LL (pts)	4.73	4.46	-0.39* improved
Peroneal MNCV (m/s)	43.11	42.78	-0.31* worsened
Peroneal MNA (mV)	4.61	4.39	-0.18* worsened
Peroneal F wave lat. (ms)	51.59	51.73	0.13

Bastyr et al., Diabetologia 2007; 50, suppl 1: S 62

QST: Test-retest reliability and inter-observer reliability

NeuPSIG Recommendations

- **The test-retest reliability of mechanical, vibration or thermal testing is good, particularly for short intervals, such as days.**
- **The inter-observer reliability within days seems adequate, provided that investigators have undergone the same set of training and use the same set of written instructions to their patients.**
- **To limit the possible examiner bias, we recommend that the same QST examiner performs repeated measurements over time in individual patients.**

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Summary: Quantitative Sensory Testing

Measure	Predictor of ulcers/ mortality	Progressed in RCTs	Validated	Used in RCTs	Improved in RCTs
QST	*	+	+	++	-
Thermal thresholds	+	-	+	+	-
Vibration threshold	++	+	+	++	- / (+)
Mono-filament	++	? individual components	+	(+)	(+)

++ strong, + moderate, (+) weak, - no

Suggestions for the future

- Standardization (see nerve conduction)!
- Adequate normative database (anthropometrics!)
- Validation against appropriate gold standard
- Natural history in relation to signs/symptoms
- Strategies to limit intra-/inter-rater variability
- Predictors of progression/improvement
- Better definition of overall clinical impact

Thank you