63° CONGRESSO NAZIONALE SIGG

GLI ANZIANI:
LE RADICI DA PRESERVARE
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# Meccanismi fisiopatologici dell'hypotensive susceptibility dell'anziano

**Martina Rafanelli, MD, PhD**

Syncope Unit , SOD di Geriatria e UTIG,
Università degli Studi di Firenze,
Azienda Ospedaliero-Universitaria Careggi, Firenze

# Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis

**Richard Sutton[1]* and Michele Brignole[2]**

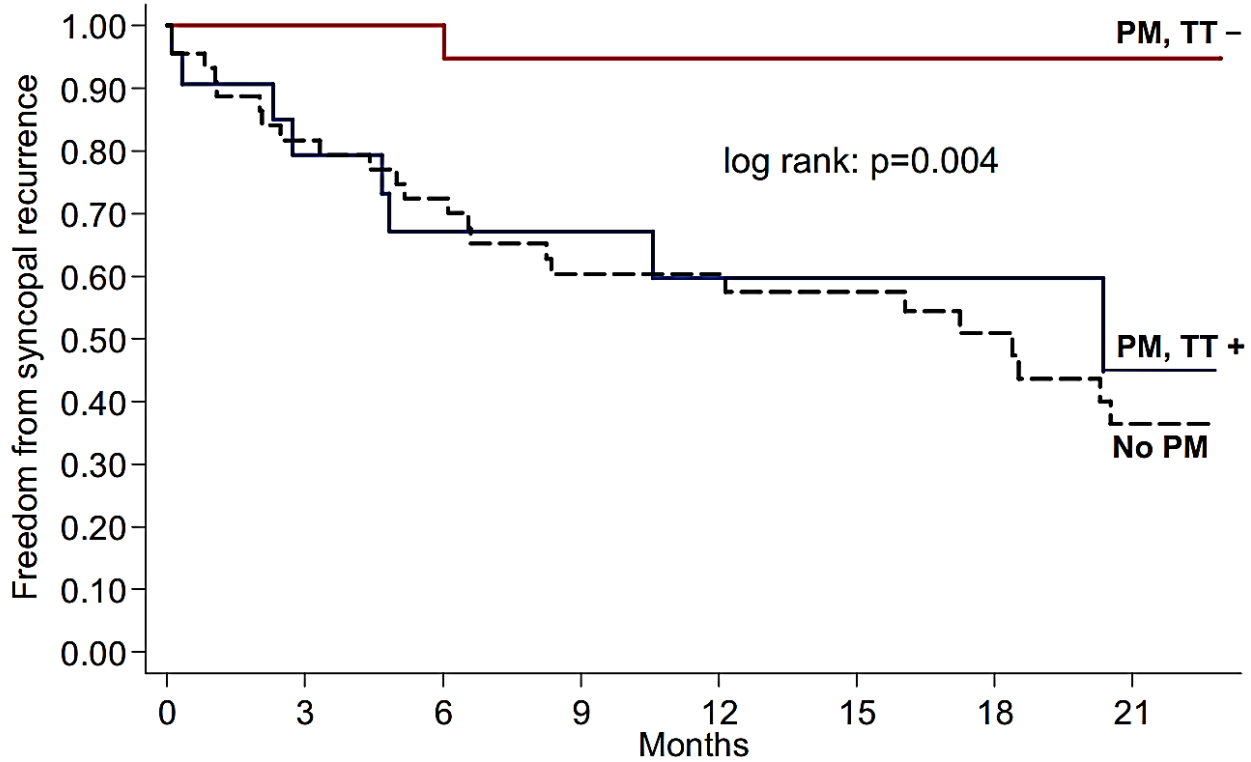
## Suscettibilità ipotensiva

Tendenza alla vasodepressione che può favorire la tpdc, indipendentemente dal meccanismo eziologico dominante la sincope.

European Heart Journal (2014) **35**, 2211–2212

# Benefit of Pacemaker Therapy in Patients With Presumed Neurally Mediated Syncope and Documented Asystole Is Greater When Tilt Test Is Negative

## An Analysis From the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)




Brignole M et al. Circ Arrhythm Electrophysiol 2014

# Benefit of Pacemaker Therapy in Patients With Presumed Neurally Mediated Syncope and Documented Asystole Is Greater When Tilt Test Is Negative

## An Analysis From the Third International Study on Syncope of Uncertain Etiology (ISSUE-3)

the benefit of pacemaker therapy in patients with presumed NMS and documented asystole was not substantial in those with a positive TT

…we speculate that pacing failure was because of hypotensive syncope…

hypotension plays a major role in all forms of TT-induced NMS and precedes/triggers bradycardia and syncope in the vast majority of patients even in those with cardioinhibitory syncope

Brignole M et al. Circ Arrhthm Electrophysiol 2014

# The pathophysiologic mechanisms associated with hypotensive susceptibility

**Ashish Chaddha[1] · Martina Rafanelli[2] · Michele Brignole[3] · Richard Sutton[4] · Kevin E. Wenzke[1] · Stephen L. Wasmund[1] · Richard L. Page[1] · Mohamed H. Hamdan[1]**

| | All VVS ($n = 366$) | Tilt positive ($n = 275$) | Tilt negative ($n = 91$) | (+) vs (−) $p$ value |
|---|---|---|---|---|
| Mean age (year) | 48 ± 20 | 50 ± 21 | 42 ± 18 | 0.002 |
| Gender (M/F) | 127/239 | 93/182 | 34/57 | 0.63 |
| Mean EF (%) | 64 ± 4 | 64 ± 5 | 65 ± 5 | 0.14 |
| Diabetes: *n* (%) | 21 (6) | 14 (5) | 7 (8) | 0.51 |
| Hypertension: *n* (%) | 86 (23) | 72 (26) | 14 (15) | 0.05 |
| Prodromes present: *n* (%) | 239 (65) | 173 (63) | 66 (73) | 0.12 |
| Multiple events: *n* (%) | 114 (31) | 90 (33) | 24 (26) | 0.32 |
| Autonomic symptoms: *n* (%) | 214 (58) | 120 (44) | 32 (35) | 0.19 |
| Medications | | | | |
| Beta-blockers: *n* (%) | 79 (22) | 56 (20) | 23 (25) | 0.40 |
| $Ca^{2+}$ channel blockers: *n* (%) | 8 (2) | 4 (1) | 4 (4) | 0.21 |
| Mean BRG (ms/mmHg) | 12.5 ± 6.3 | 12.5 ± 6.3 | 12.4 ± 6.3 | 0.72 |

*EF* ejection fraction; *BRG* baroreflex gain

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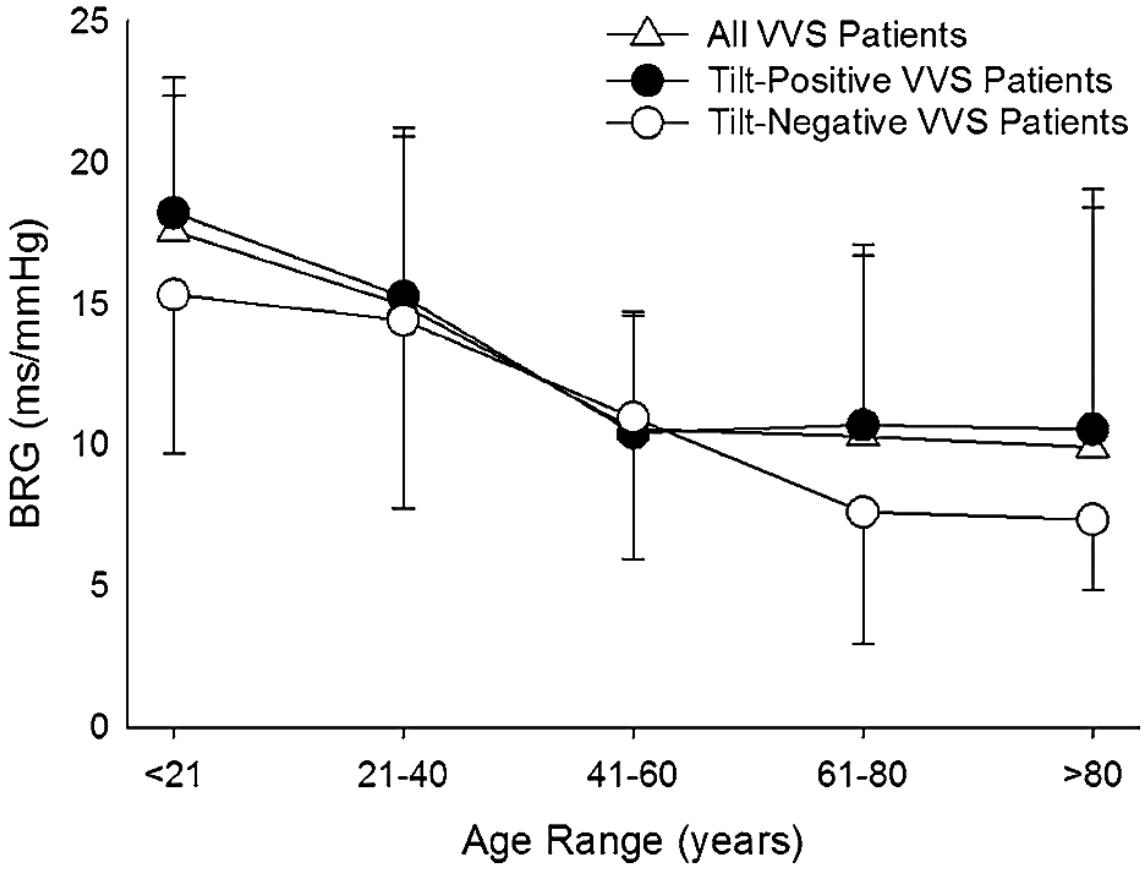


Mean BRG decreased with increasing age.

This relationship was seen in all patients, in tilt-positive and tilt-negative patients

Clin Auton Res (2016) 26:261–268

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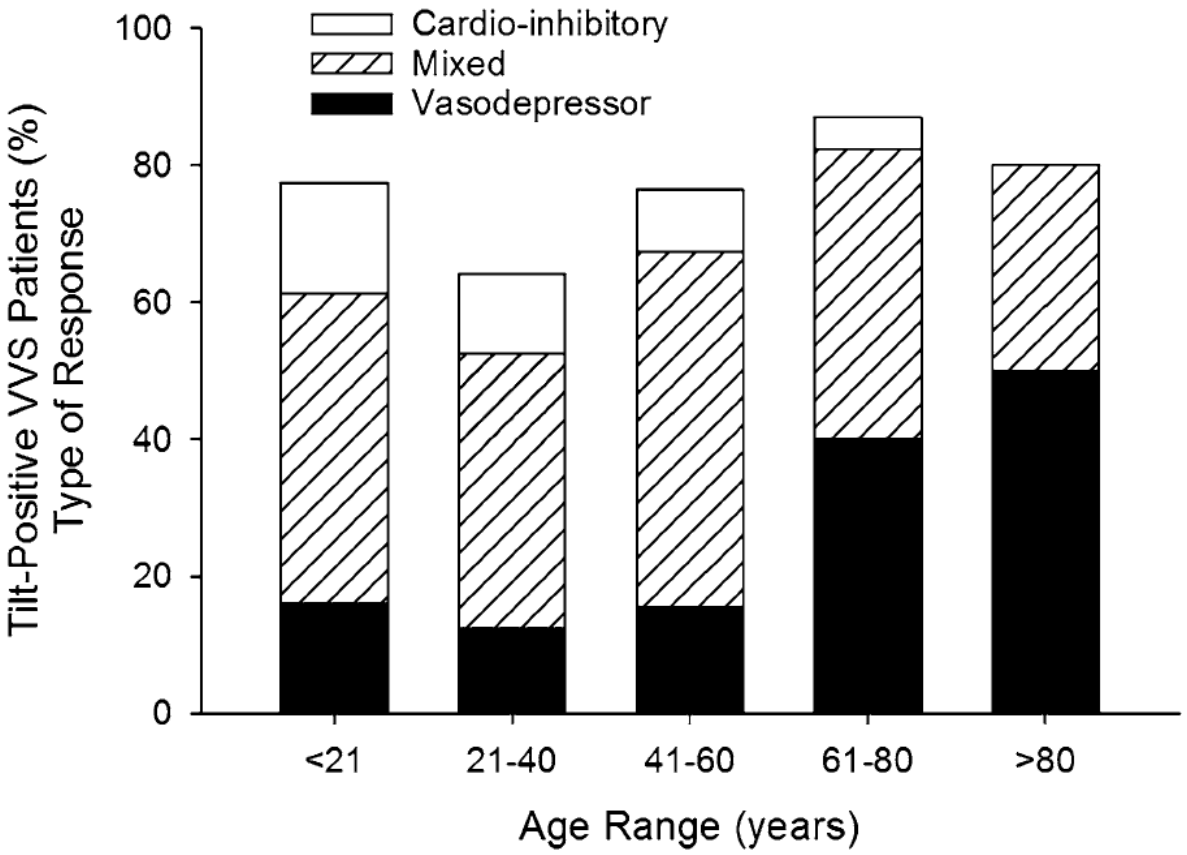


Concomitant with the decrease in BRG, the prevalence of a vasodepressor response increased in older subjects.

Clin Auton Res (2016) 26:261–268

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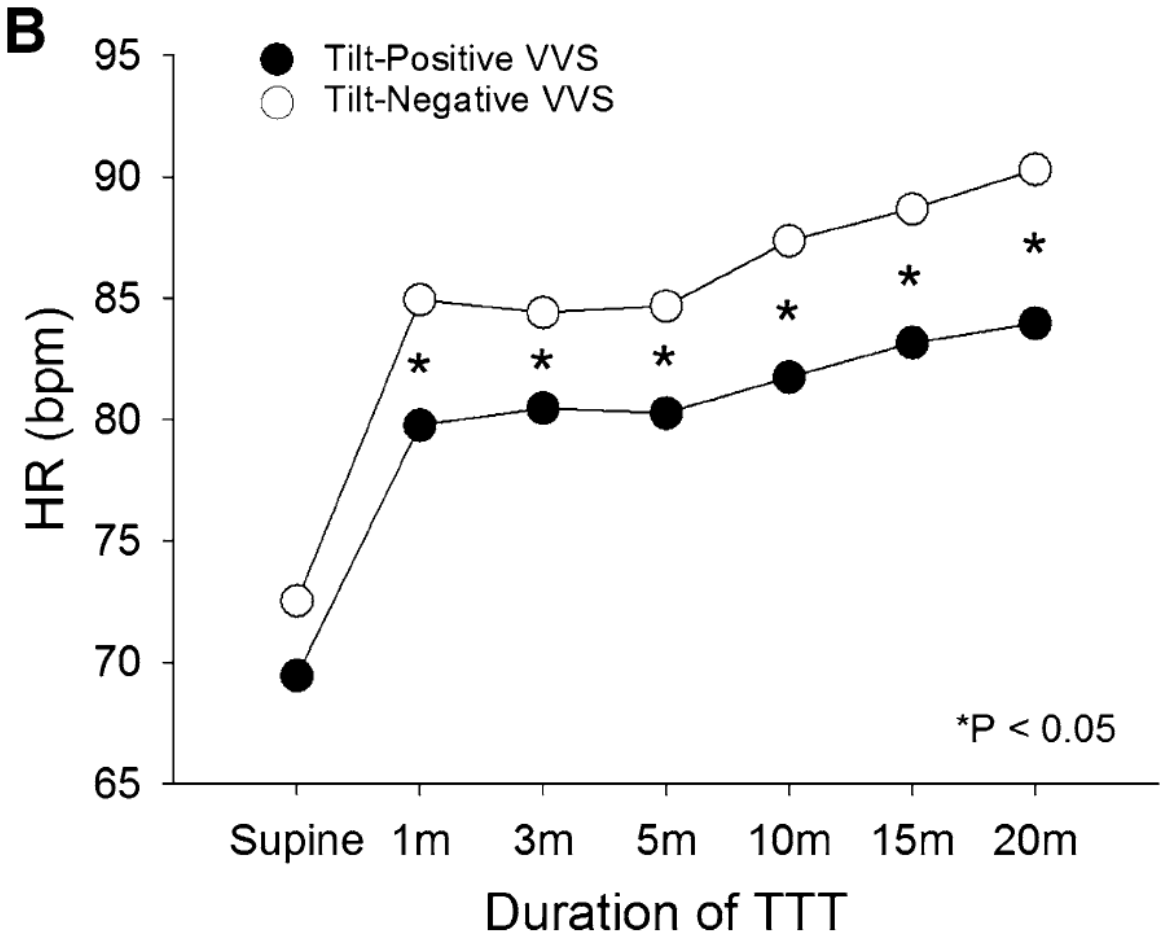



The HR was significantly lower in tilt-positive VVS patients when compared with tilt-negative VVS patients at all measured time points.

ept for SBP at 10 , there were no erences in BP ween the groups

Clin Auton Res (2016) 26:261–268

# The pathophysiologic mechanisms associated with hypotensive susceptibility

Ashish Chaddha[1] · Martina Rafanelli[2] · Michele Brignole[3] · Richard Sutton[4] · Kevin E. Wenzke[1] · Stephen L. Wasmund[1] · Richard L. Page[1] · Mohamed H. Hamdan[1]

Indeed, the presence of a blunted HR response in subjects with positive TTT supports the hypothesis that tilt-induced hypotension is primarily due to a drop in cardiac output with the HR playing a role. It is important to note that a

Clin Auton Res (2016) 26:261–268

# The pathophysiologic mechanisms associated with hypotensive susceptibility

Ashish Chaddha[1] · Martina Rafanelli[2] · Michele Brignole[3] · Richard Sutton[4] · Kevin E. Wenzke[1] · Stephen L. Wasmund[1] · Richard L. Page[1] · Mohamed H. Hamdan[1]

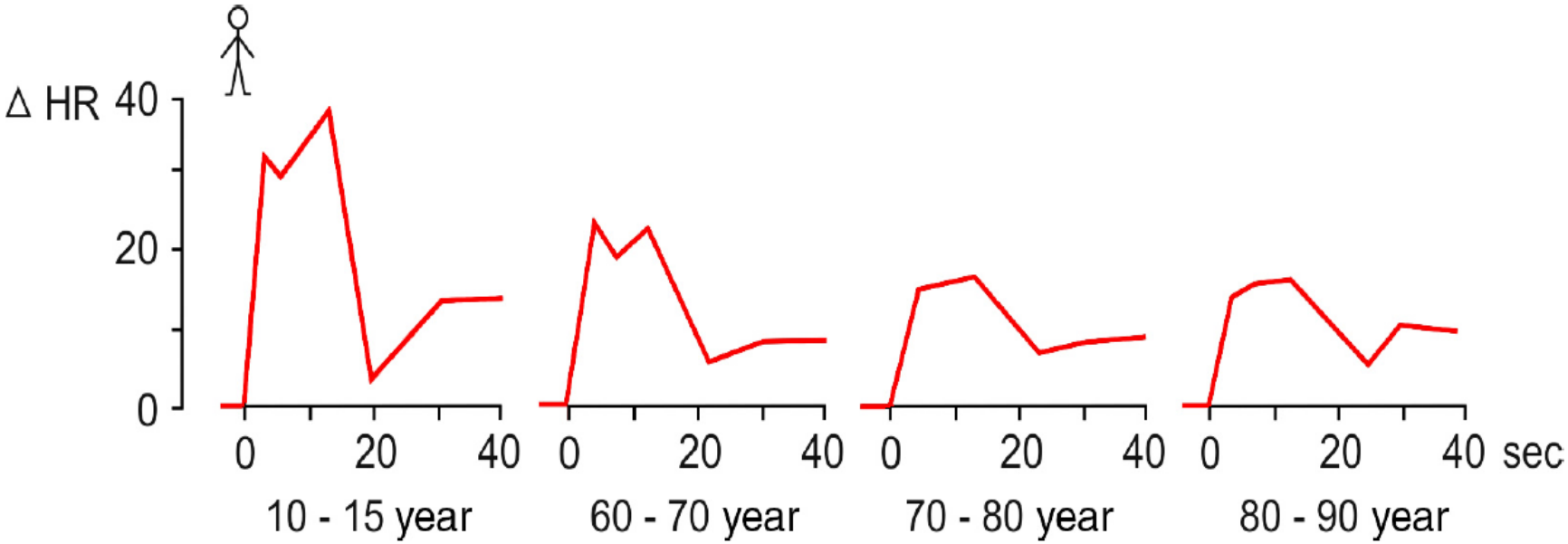
There are possible explanations for the blunted HR response:

greater HR variability during TTT in patients with tilt-positive VVS when compared to patients with tilt-negative VVS;

Age-related sinus node dysfunction

Clin Auton Res (2016) 26:261–268

# Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages




the initial biphasic HR response on active standing decreases with age; the primary peak at 3 s is no longer present in old age

V. K. van Wijnen et al. J Intern Med 2017

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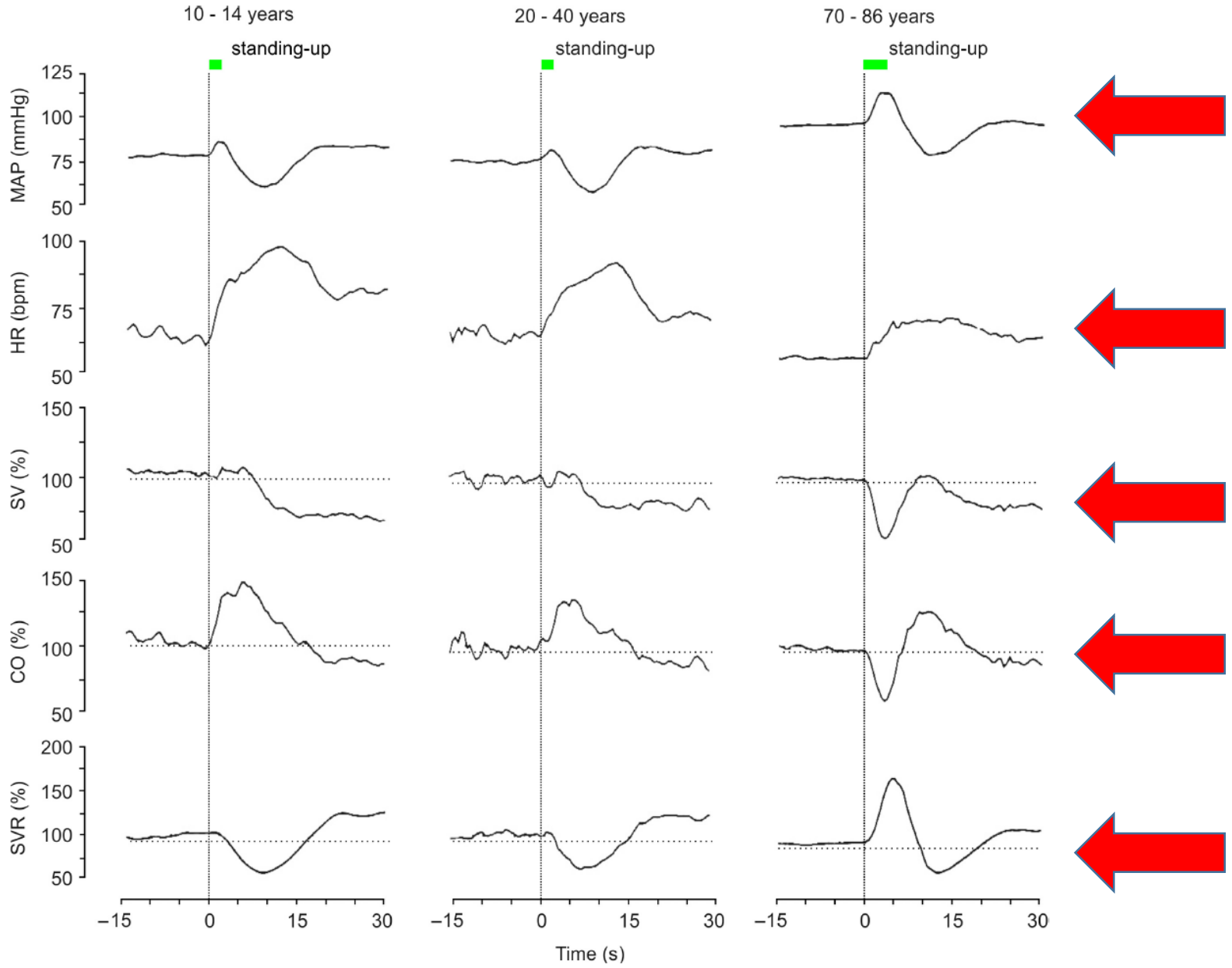
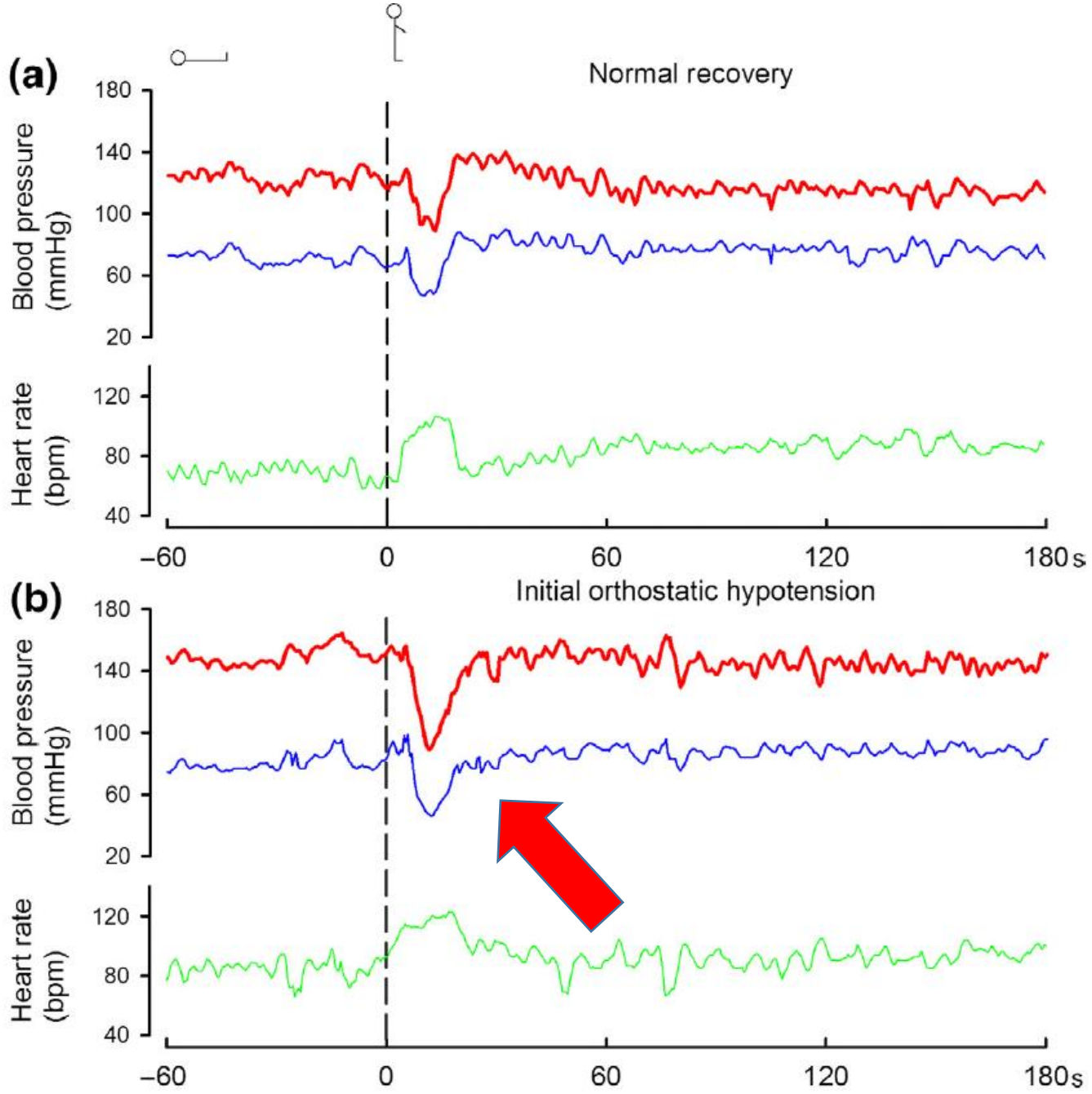
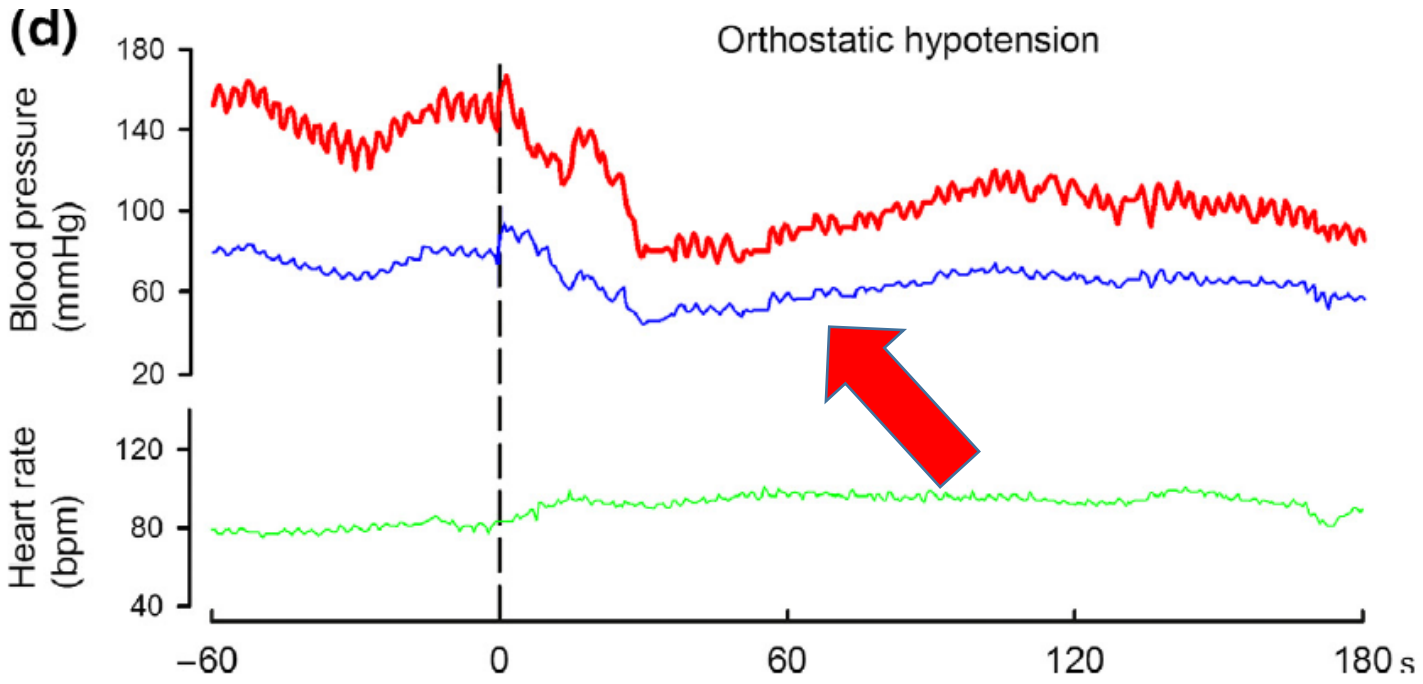
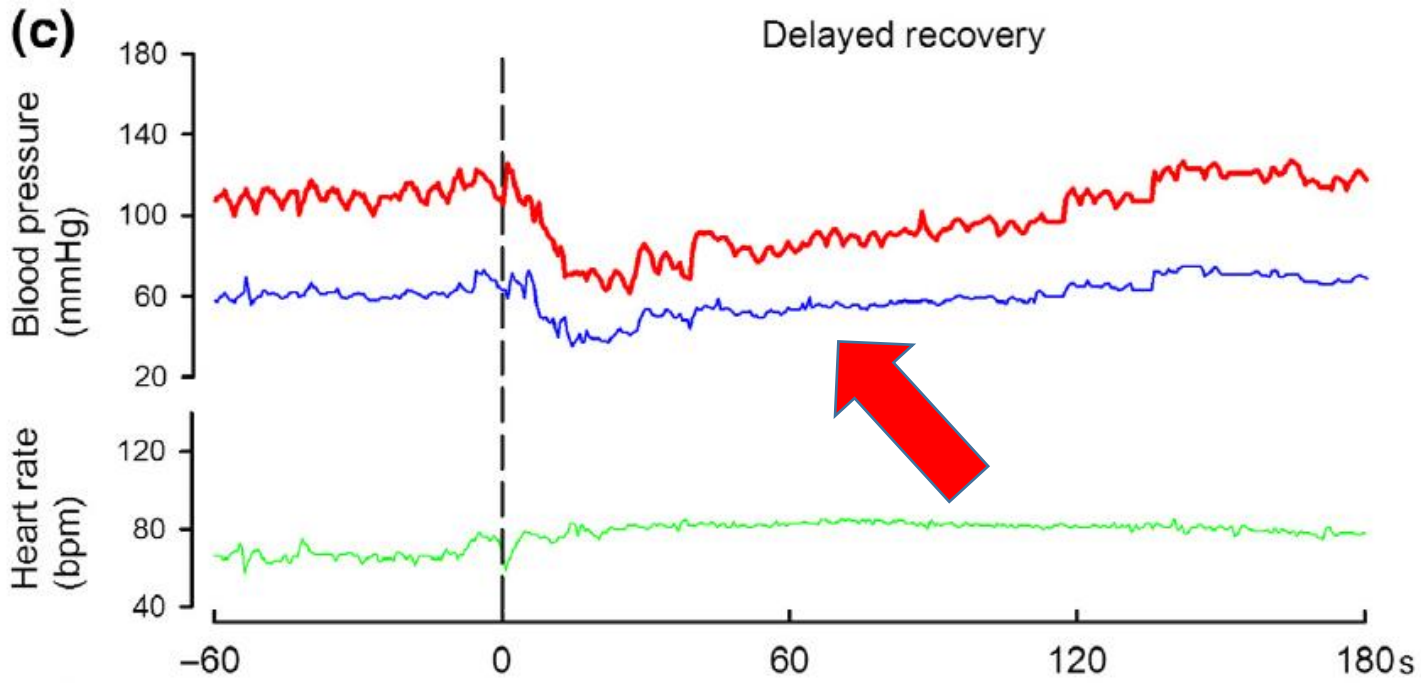



(a)
Normal recovery
Blood pressure (mmHg)
180
140
100
60
20
Heart rate (bpm)
120
80
40
–60
0
60
120
180 s
(b)
Initial orthostatic hypotension
Blood pressure (mmHg)
180
140
100
60
20
Heart rate (bpm)
120
80
40
–60
0
60
120
180 s



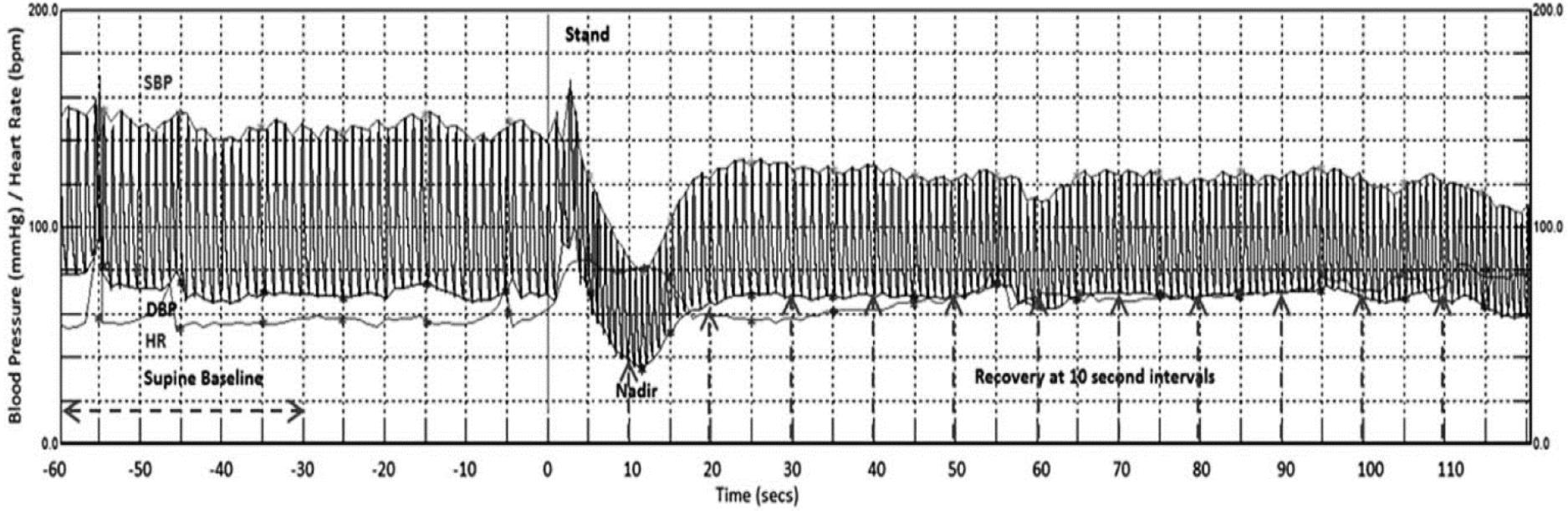

**Diagnostic criteria:** Abnormal BP fall is defined as a progressive and sustained fall in systolic BP from baseline value ≥20 mmHg or diastolic BP ≥10 mmHg, or a decrease in systolic BP to <90 mmHg.




A delayed BP recovery is the inability of systolic BP to recover to >20 mmHg below baseline value at 30 s of standing

# Age-Related Normative Changes in Phasic Orthostatic Blood Pressure in a Large Population Study

## Findings From The Irish Longitudinal Study on Ageing (TILDA)




The active stand response in a selected TILDA (The Irish Longitudinal Study on Ageing) participant. Beat-to-beat systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) waveforms are shown.

Finucane C et al. Circulation 2014

# Age-Related Normative Changes in Phasic Orthostatic Blood Pressure in a Large Population Study

## Findings From The Irish Longitudinal Study on Ageing (TILDA)

**Table 3. Prevalence of IOH, Impaired Blood Pressure Stabilization, and OH Stratified by Age, Sex, and Time Since Stand (n=4475)**

| | IOH | OH Nadir | OH(10) | OH(20) | OH(30) | OH(40) |
|---|---|---|---|---|---|---|
| Men | 35.6 (33.3–38.0) | 96.7 (95.8–97.5) | 85.1 (83.3–86.8) | 28.1 (25.7–30.6) | 16.4 (14.4–18.3) | 14.3 (12.4–16.1) |
| Women | 30.4 (28.0–32.8) | 96.1 (95.1–97.1) | 81.1 79.0–83.3) | 35.9 (33.3–38.4) | 21.2 (18.9–23.5) | 16.9 (14.7–19.2) |
| Age, y | | | | | | |
| 50–59 | 35.0 (32.8–37.2) | 96.7 (95.9–97.5) | 82.6 (80.8–84.4) | 21.2 (19.1–23.3) | 11.3 (9.8–12.9) | 9.1 (7.7–10.5) |
| 60–69 | 31.1 (28.6–33.6) | 96.2 (95.1–97.2) | 83.5 (81.4–85.5) | 33.2 (30.6–35.8) | 17.9 (15.9–20.0) | 14.3 (12.4–16.3) |
| 70–79 | 32.4 (27.7–37.1) | 95.6 (93.5–97.8) | 83.0 (78.8–87.2) | 48.0 (42.9–53.1) | 31.0 (26.2–35.8) | 25.7 (21.1–30.4) |
| ≥80 | 29.8 (19.6–40.1) | 98.1 (95.7–100.4) | 84.7 (75.8–93.6) | 57.9 (46.7–69.1) | 43.1 (32.0–54.1) | 41.2 (30.0–52.4) |

In the full TILDA cohort, there was a marked age gradient in the proportion with BP that failed to stabilize within 40 s of standing, from 9.1% of the 50- to 59-year-old subjects to 41.2% of those ≥80 years

Finucane C et al. Circulation 2014

# Association between orthostatic hypotension and cardiovascular risk, cerebrovascular risk, cognitive decline and falls as well as overall mortality: a systematic review and meta-analysis

Anna Angelousi[a], Nicolas Girerd[b], Athanase Benetos[c], Luc Frimat[d], Sylvie Gautier[c], Georges Weryha[a], and Jean-Marc Boivin[b]

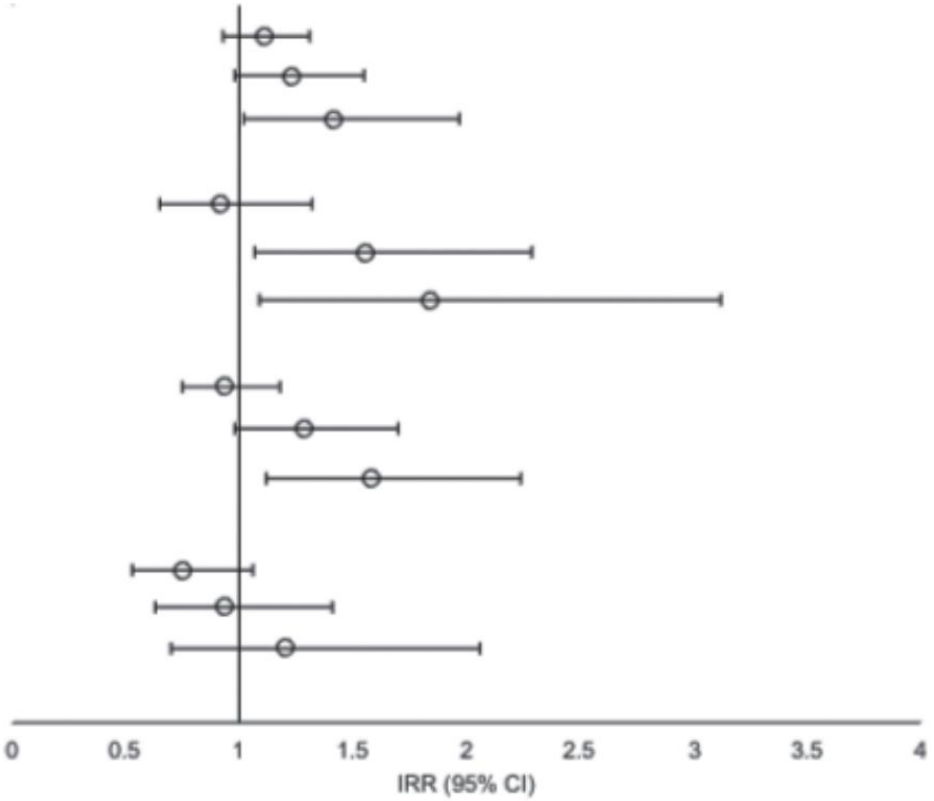
The main finding of our study is that, in the meta-regression of the available evidence, orthostatic hypotension is associated with an increase in ACM greater than 30%.

orthostatic hypotension is strongly and independently associated with an increased risk of cardiovascular and ischemic cardiac events.

Journal of Hypertension 2014, 32:1562–1571

# Impaired Orthostatic Blood Pressure Recovery Is Associated with Unexplained and Injurious Falls

| | IRR/RR *(95% CI)* | P |
|---|---|---|
| **All-Cause Falls** | | |
| **IOH** | 1.10 (0.93-1.31) | 0.250 |
| **OH(40)** | 1.23 (0.98-1.55) | 0.074 |
| **OH** | **1.40 (1.01-1.96)** | **0.044*** |
| **Unexplained Falls** | | |
| **IOH** | 0.92 (0.65-1.32) | 0.657 |
| **OH(40)** | **1.52 (1.03-2.26)** | **0.039*** |
| **OH** | **1.81 (1.06-3.09)** | **0.029*** |
| **Injurious Falls** | | |
| **IOH** | 0.94 (0.75-1.18) | 0.582 |
| **OH(40)** | 1.29 (0.98-1.7) | 0.068 |
| **OH** | **1.58 (1.12-2.24)** | **0.010†** |
| **Syncope** | | |
| **IOH** | 0.75 (0.53-1.06) | 0.101 |
| **OH(40)** | 0.94 (0.63-1.41) | 0.774 |
| **OH** | 1.20 (0.70-2.06) | 0.505 |




Failure of systolic BP to stabilize by 40 s was significantly associated with increased relative risk of unexplained falls 2 years later with trends towards an increased relative risk of all-cause and injurious falls

Finucane C et al. JAGS 2017

# Low blood pressure levels for fall injuries in older adults: the Health, Aging and Body Composition Study

(*N* = 1819; age 76.6 ± 2.9 years)

| | Total sample *N* = 1819 | With fall injury *N* = 570 | Without fall injury *N* = 1249 |
|---|---|---|---|
| Systolic blood pressure (SBP), mmHg | 134.7 ± 19.7 | 135.1 ± 20.6 | 134.5 ± 19.2 |
| SBP ≤ 120 mmHg, *n* (%)[a] | 457 (25.1) | 140 (24.6) | 317 (25.4) |
| SBP ≤ 130 mmHg, *n* (%)[a] | 849 (46.7) | 261 (45.8) | 588 (47.1) |
| SBP ≤ 140 mmHg, *n* (%)[a] | 1221 (67.1) | 376 (66.0) | 845 (67.7) |
| SBP > 150 mmHg, *n* (%) | 314 (17.3) | 102 (17.9) | 212 (17.0) |
| Diastolic blood pressure (DBP), mmHg | 71.4 ± 10.9 | 70.5 ± 11.2[b] | 71.8 ± 10.7 |
| DBP ≤ 60 mmHg, *n* (%)[a] | 329 (18.1) | 125 (21.9)[c] | 204 (16.3) |
| DBP ≤ 70 mmHg, *n* (%)[a] | 957 (52.6) | 325 (57.0)[b] | 632 (50.6) |
| DBP ≤ 80 mmHg, *n* (%)[a] | 1522 (83.7) | 479 (84.0) | 1043 (83.5) |
| DBP > 90 mmHg, *n* (%) | 60 (3.3) | 18 (3.2) | 42 (3.4) |

[a]Blood pressure levels are not mutually exclusive

$P <$ [b]0.01, $P <$ [c]0.001 (with vs. without fall injury)

Sagawa N et al. European Journal of Aging 2018

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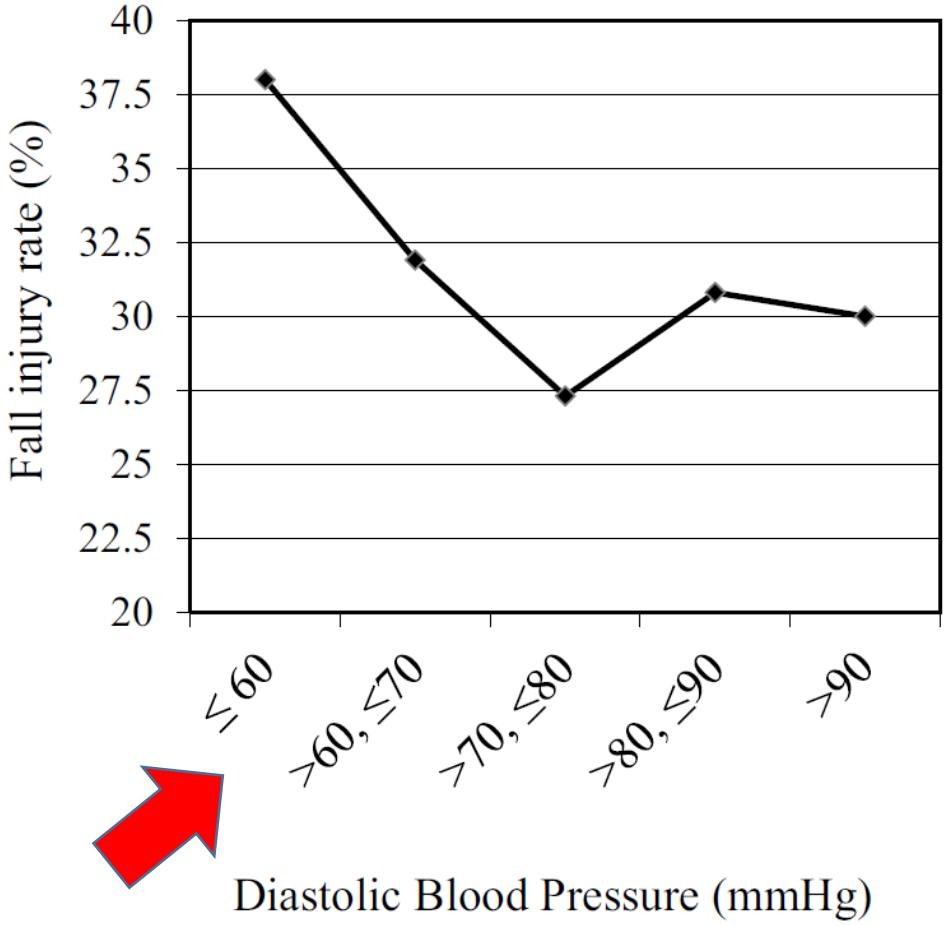


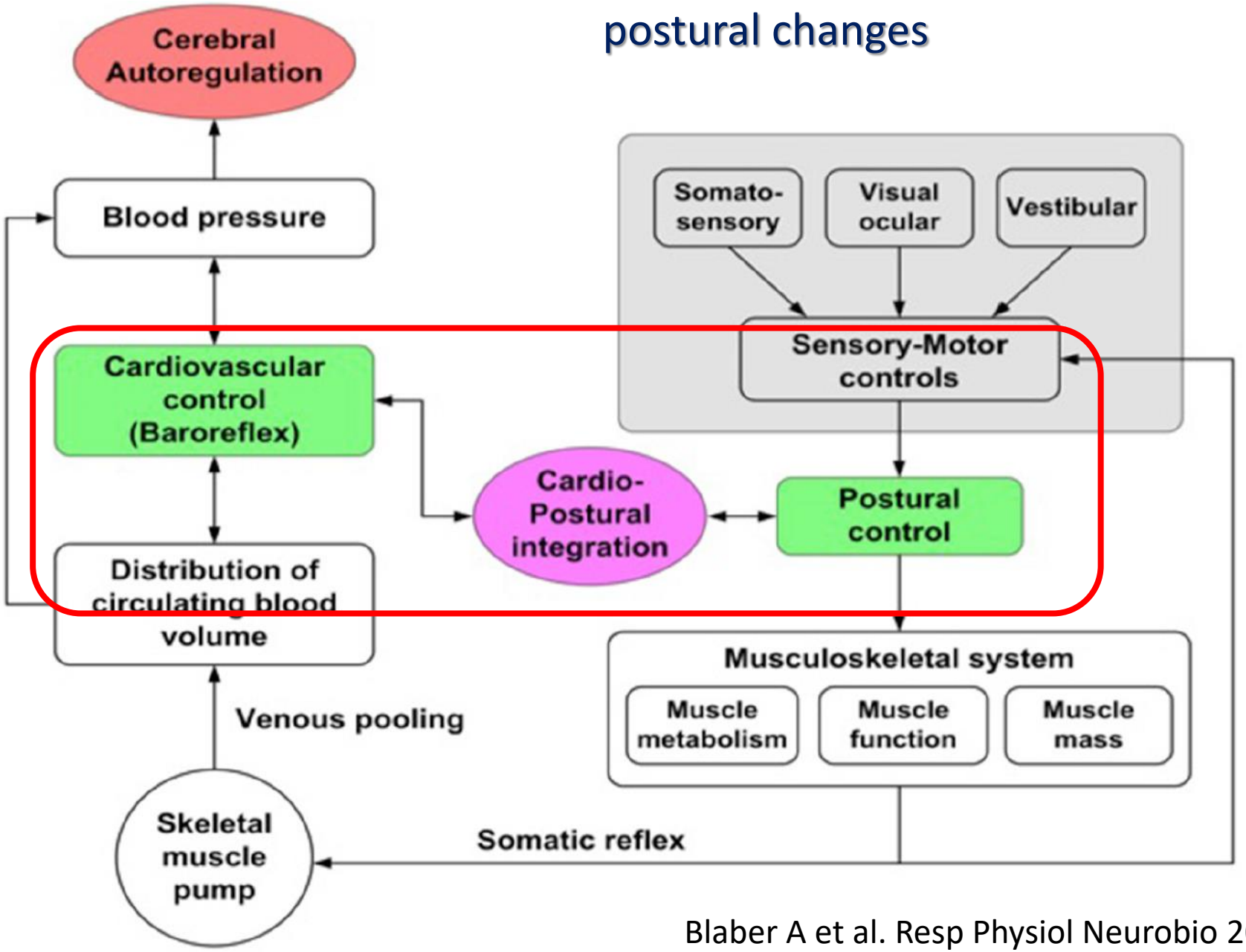

DBP subgroups with ≤ 70 mmHg had the highest proportion of incident fall injury:
38% of participants with DBP ≤ 60 mmHg and 32% of those with 60 < DBP ≤ 70 mmHg

Sagawa N et al. European Journal of Aging 2018

# Meccanismi fisiopatologici dell'hypotensive susceptibility dell'anziano

## Quale intervento?

# interactions between cardiovascular control and postural changes




Blaber A et al. Resp Physiol Neurobio 2009

# Orthostatic Intolerance in Older Persons: Etiology and Countermeasures

frontiers in Physiology

## Intolleranza Ortostatica…che fare?

intolerance. It is important, for example, when intervening in the process in which bedrest confinement leads to orthostatic intolerance and falls, that a holistic multifactorial approach which takes into account key factors such as nutrition, (de)conditioning, muscle loss, cardiovascular and vestibular effects, is followed.

Goswami N et al. 2017

ESC
European Society of Cardiology

# 2018 ESC Guidelines for the diagnosis and management of syncope

ESC GUIDELINES

**The Task Force for the diagnosis and management of syncope of the European Society of Cardiology (ESC)**

| **Syncope due to OH** |
|---|
| *Note that hypotension may be exacerbated by venous pooling during exercise (exercise-induced), after meals (postprandial hypotension), and after prolonged bed rest (deconditioning).* |
| Drug-induced OH (most common cause of OH): |
| - e.g. vasodilators, diuretics, phenothiazine, antidepressants |
| Volume depletion: |
| - haemorrhage, diarrhoea, vomiting, etc. |
| Primary autonomic failure (neurogenic OH): |
| - pure autonomic failure, multiple system atrophy, Parkinson's disease, dementia with Lewy bodies |
| Secondary autonomic failure (neurogenic OH): |
| - diabetes, amyloidosis, spinal cord injuries, auto-immune autonomic neuropathy, paraneoplastic autonomic neuropathy, kidney failure |

Compromissione Irreversibile del SNA
IO Neurogena

ESC European Society of Cardiology

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Compromissione Reversibile del SNA

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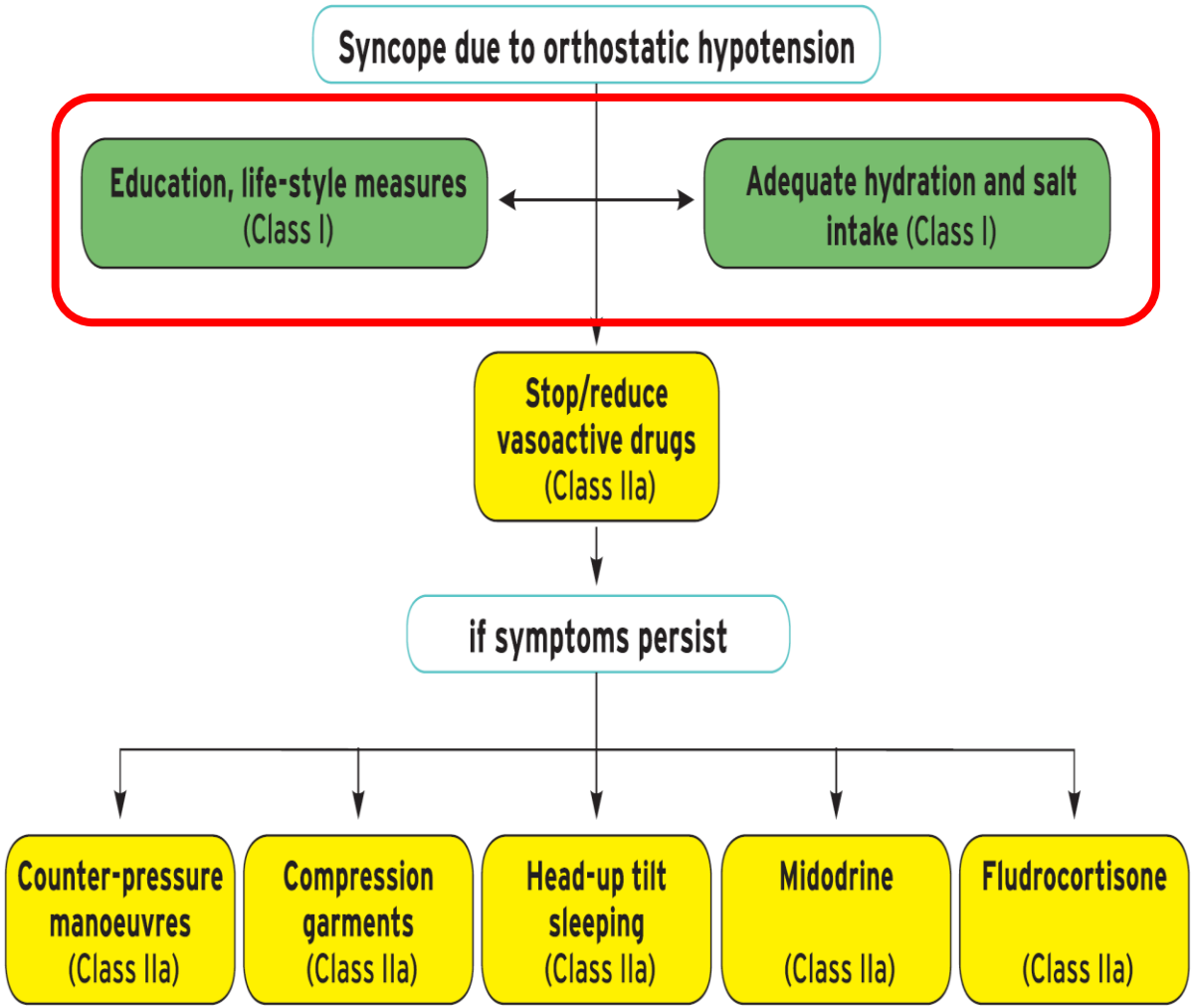


In assenza di ipertensione, I pz. devono essere istruiti ad assumere 2-3 lt di acqua/die e 10 g di NaCl.

Nell'ipotensione post-prandiale, ingestione rapida di boli di acqua 500 cc.

European Heart Journal (2018) **00**, 1–69

# Trattamento: **sincope riflessa**

Sincope Riflessa

**Educazione, misure comportamentali**
(Classe I)

Forme severe/ricorrenti

***There is moderate evidence that discontinuation/reduction of hypotensive therapy targeting a systolic BP of 140 mmHg should be effective in reducing syncopal recurrences in patients with hypotensive susceptibility. Further research is likely to***

**- Fludrocortisone**
**- Midodrina**
(Classe IIb)

**Manovre di contropressione**
(Classe IIa)

**Tilt training**
(Classe IIb)

**Gestione LRI-guidata**
in casi selezionati
(Classe I);

**Stop/riduzione terapia ipotensivante**
(Classe IIa)

**Pacemaker**
(Classe IIa/Iib)

**Giovani**

**Anziani**

European Heart Journal (2018) **00**, 1–69

# The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension

| Class of medications | Common examples |
|---|---|
| Dopaminergic agents | Levodopa, dopamine agonists |
| Antidepressants (particularly tricyclic agents)[a] | Amitriptyline, nortriptyline, imipramine, desipramine |
| Anticholinergics | Atropine, glycopyrrolate, hyoscyamine |
| Anti-hypertensive agents | |
| *Preload reducers* | |
| Diuretics[a] | Furosemide, torsemide, acetazolamide, hydrochlorothiazide, spironolactone |
| Nitrates[a] | Nitroprusside, isosorbide dinitrate, nitroglycerin |
| Phosphodiesterase E5 inhibitors | Sildenafil, vardenafil, tadalafil |
| *Vasodilators* | |
| Alpha-1 adrenergic antagonists[a] | Alfuzosin, doxazosin, prazosin, terazosin, tamsulosin (used primarily for benign prostatic hyperplasia) |
| Dihydropyridine calcium channel blockers | Amlodipine, nifedipine, nicardipine |
| Other direct vasodilators | Hydralazine, minoxidil |
| *Negative inotropic/chronotropic agents* | |
| Beta-adrenergic blockers | Propranolol, metoprolol, atenolol, bisoprolol, nebivolol (also vasodilator), carvedilol (also alpha-1 antagonist), labetalol (also alpha-1 antagonist) |
| Non-dihydropyridine calcium channel blockers | Verapamil, diltiazem |
| *Central sympatholytic agents* | |
| Centrally acting alpha-2 agonists | Clonidine |
| False neurotransmitters | Alpha-methyldopa |
| *Renin–angiotensin system (RAS) antagonists* | |
| Angiotensin converting enzyme (ACE) inhibitors | Captopril, enalapril, perindopril, |
| Angiotensin receptor type II blockers (ARB) | Losartan, telmisartan, candesartan |

Gibbons C.H et al. J Neurol 2017

# Grazie per l'attenzione

**Martina Rafanelli, MD, PhD**

Syncope Unit , SOD di Geriatria e UTIG,
Università degli Studi di Firenze,
Azienda Ospedaliero-Universitaria
Careggi, Firenze