Semplificare la burocrazia per migliorare l’accesso alle cure da parte del paziente: la titolazione dei farmaci per lo scompenso

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While HF is associated with substantial morbidity and mortality, a number of treatments have been shown to improve outcomes in large-scale randomised controlled trials (RCT), including pharmacological inhibition of the renin–angiotensin system (with or without neprilysin inhibition), beta-blockers, mineralocorticoid receptor antagonists, sinus node inhibition, cardiac resynchronisation therapy with biventricular pacing

At first glance, it would appear that the administration of pharmacological therapies for HF should be relatively straightforward, but such therapies are also ***highly dependent on the individual prescribers, rely on substantial infrastructure and staffing support, and involve real complexities around medication persistence and patient adherence***

Clinical Trial Evidence for Target Doses

The majority of studies or analyses that have been undertaken to address the question of whether lower doses of ACEIs and beta-blockers achieve similar benefits were either underpowered for major clinical outcomes or based on post-hoc, non-randomised comparisons

Nonetheless, the major efficacy studies were all based upon forced up-titration aiming for specified target doses. For this reason, **clinical guidelines recommend up titrating to maximal tolerated doses**

Am Heart J 1988;116:480–8.
Eur Heart J 1996;17:1223–3.
Eur Heart J 1998;19:481–9.
Circulation 1999;100:2312–8.

Target Dose Achievement in Clinical Practice

HF prescription rates for both ACEIs/ARBs and beta-blockers have increased substantially over the past two decades, such that 92 % of patients were on ACEI or ARB therapy and 93 % were on beta-blockers in the recent European Society of Cardiology Heart Failure Long-term Registry, with most of those patients not on treatment having a documented contraindication or previous medication intolerance

[Eur J Heart Fail 2013;15:1173–84]

Despite this, only 29 % of patients were on target doses of ACEIs and 18 % were on target doses of beta-blockers, with approximately one third having no reason documented for the failure to up-titrate

[Eur J Heart Fail 2013;15:1173–84]

This contrasts with the RCTs, where at least 50–60 % of patients achieved target doses

[SOLVD Investigators. N Engl J Med 1991;325:293–302.
Carvediol Prospective Randomized Cumulative Survival Study Group.
N Engl J Med 2001;344:1651–8.
CHARM Investigators and Committees. Lancet 2003;362:772–6.]

Clinicians have generally paid greater attention to the up-titration of beta-blockers, given the impressive benefits achieved in clinical trials that involved the forced up-titration of these drugs to target doses on top of background therapy (which included an ACEI or ARB in >90 % of patients)

[CIBIS-II Investigators and Committees. Lancet 1999;353:9–13.
MERIT-HF Study Group. Lancet 1999;353: 2001–7.]

Furthermore, while ACEIs can be safely up-titrated in a relatively short time period, a ‘start low and go slow’ approach is generally taken with beta-blockers, given their short-term, negative inotropic effects

[Eur J Cardiovasc Nurs 2003;2:183–8.]

Table 1: Beta-blocker Titration Achievement in Clinical Practice

Study	Design	Description	Target Dose Achievement
Tandon et al., 2004[53]	Prospective observational	• n=479 • Median age 69 years • 75 % with systolic dysfunction • Contraindications excluded • On beta-blockers • Multidisciplinary heart function clinic	• 1989–2001: 18 % on beta-blockers • 1998–2001: 24 % on beta-blockers
Franciosa et al., 2004[54]	Prospective observational	• n=4,280 • Mean age 67 years • Mean LVEF 31 % (including normal EF) • Contraindications excluded • Community-based registry • Patients initiated on carvedilol	• Primary care physicians: 27 % • Cardiologists: 49 %
Mehta et al., 2004[55]	Prospective audit	• n=62 • Mean age 67 years • Eligible patients • Contraindications excluded • District hospital • Patients initiated on carvedilol	6.6 %
Moyer-Knox et al., 2004[42]	Prospective observational	• n=70	71 %
Jain et al., 2005[34]	Prospective audit		
Lenzen et al., 2005[29]	Retrospective au		
Gustafsson et al., 2007[30]	Prospective audit		
Lainscak et al., 2007[56]	Prospective observational	• n=3,721 • Median age 65 years • Eligible patients • Contraindications excluded • Physician managed outpatients	26 %
de Groote et al., 2007[57]	Prospective survey	• n=1,100 • Mean age 70 years (whole group) • Eligible patients • Contraindications excluded • On beta-blockers • Cardiologist-managed outpatients	18 % on ESC-recommended beta-blockers
Fonarow et al., 2008[33]	Prospective observational	• n=1,863 • Mean age 70 years (whole group) • Eligible patients • Contraindications excluded • On beta-blockers • Post-HF hospitalisation	• 8 % on carvedilol • 18 % on metoprolol succinate

Table 1: Cont.

Study	Design	Description	Target Dose Achievement
Rector et al., 2008[58]	Retrospective cohort	• n=26,112 • Median age 74/75 years • On beta-blockers (>1 script) • Veteran Health Administrative nationwide dataset	• 22 % on carvedilol • 4 % on metoprolol succinate
Calvert et al., 2009[59]	Retrospective cohort	• n=2,315 • Mean age 78 years (whole group) • Contraindications excluded • On beta-blockers • General practice dataset	17 % on ESC-recommended beta-blockers
Maggioni et al., 2010[35]	Prospective, observational	• n=2,774 • Mean age 68 years (whole group) • Contraindications excluded • On beta-blockers • Hospital cardiology departments	• 37 % on carvedilol • 21 % on bisoprolol • 21 % on metoprolol succinate
			n beta-blockers
			l care: 36 % on beta-blockers e-led: 48 % on beta-blockers
			on beta-blockers
		• Median age 68 years (whole group) • Contraindications excluded • On beta-blockers • Hospital cardiology departments	
Martinez et al., 2013[37]	Retrospective chart review	• n=144 • Mean age 69 years • Eligible patients (HFrEF) • HF clinic with telemonitoring for weight, HR and BP	• Baseline: 25 % • Pharmacist-managed with telephone support: 49 %
Hickey et al., 2016[48]	Retrospective and prospective audits	• n=280 • Mean age 69 years • Eligible patients (HFrEF) • Contraindications excluded • Hospital-based HF services	Baseline cohort A: 38 % Intervention cohort B: 33 % Intervention cohort C: 51 %

BP = blood pressure; EF = ejection fraction; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure associated with a reduced left ventricular ejection fraction; HR = heart rate; LEVF = left ventricular ejection fraction.

Despite the benefits, however, only 10–30% of patients achieve target doses of beta-blockers in most real-world studies

Cardiac Failure Review 2017;3(1):25–32.

Medication Titration Intervention Studies

Barriers to medication titration include health-provider knowledge, self-efficacy and attitudes; patient-related factors, including age, body mass index, comorbidities and polypharmacy; and limited time and support structures to facilitate regular monitoring

Patients also frequently transition between the acute and community healthcare sectors, which further complicates care coordination, as there is unclear role delineation for healthcare providers

Eur J Heart Fail 2007;9:910–6.
JAMA 1999;282:1458–65.
Int J Cardiol 2016;216:121–7.

A number of strategies have been evaluated to improve medication prescribing in HF, including *case management*, *educational initiatives*, *decision support*, *telephone-based monitoring*, *clinical audit and feedback*, *strategies to improve communication between healthcare providers and extended scope of clinical practice*

While education, decision support and clinical audit and feedback have been successfully applied to improve prescribing behaviour, these approaches alone appear to be insufficient to improve medication titration. **Successful strategies have generally involved multifaceted interventions and are likely to be context-specific**

- Care coordination with timely, written communication between healthcare providers in the acute and primary care sectors.
- Data collection built into the clinical workflow with regular audit and timely feedba
- Clear rc le for medica
- 'Forced onitoring of symptoms, signs and biochemistry.
- Point-of-care decision support.
- Extended scope of clinical practice for nurses and pharmacists to prescribe/up-titrate medical therapy.

PRESCRIBING BUROCRACY TO BE ELIMINATED!!!

Cardiac Failure Review 2017;3(1):25–32.

Guide for initiation and up-titration of ACE inhibitors for patients with heart failure

Start with a low dose
Start only if:

- Blood pressure at least 100mmHg systolic
- Potassium no higher than 5.5mmol/L
- Creatinine less than 250micromol/L or eGFR at least 50
- Arrange to check potassium and creatinine **one week** after first dose
- Ask them to arrange another GP appointment at least two weeks after first dose
- Provide a Heart Failure Action Plan

When up-titrating dose...

- Double dose at not less than two weekly intervals
- Aim for target dose or highest tolerated dose
- Make sure they have a biochemistry form to check electrolytes before next dose titration

Ask about:

- Cough – if troubling consider angiotensin receptor blocker (ARB)
- Hypotensive symptoms – consider reducing other blood pressure lowering medicines (eg. diuretics), or dosing at night
- Angioedema – STOP the ACE inhibitor (consider ARB)
- Symptoms that may be exacerbated by a drug interaction eg. NSAID

Up-titrate ONLY if:

Blood pressure at least 95mmHg mmHg (systolic)
Potassium is no higher than 5.5mmol/L
 If potassium is between 5-5.9mmol/L – consider adjustments of potassium sparing
medications or high potassium food and repeat electrolytes
 If potassium is above 5.9mmol/L - **STOP** ACE inhibitor and seek specialist advice

Creatinine is no more than 25% above baseline (or seek specialist opinion)

Note: During **initiation** of treatment an increase in creatinine up to 30% above baseline is acceptable (provided creatinine is no greater than 250micromol/L) and should stabilise within the first two months. Consider other medications that may affect renal function

Increase dose:

	Cilazapril	Lisinopril	Enalapril	Quinapril
Start dose	0.5mg daily	2.5mg daily	2.5mg BD	2.5mg BD
1st titration	1mg daily	5mg daily	5mg BD	5mg BD
2nd titration	2.5mg daily	10mg daily	10mg BD	7.5mg BD
3rd titration	**5mg daily**	**20mg daily**	**20mg BD**	**10mg BD**

Higher doses may be indicated for some patients (e.g. those with coexisting hypertension)

Explain:

- The benefits of ACE inhibitors – improving symptoms and mortality related to heart failure
- Symptoms should improve within a few weeks to a few months after starting treatment
- Adverse effects such as dizziness, cough should be reported
- Self-medicating with NSAIDs and salt substitutes should be avoided

Arrange:

- Potassium and creatinine to be checked one week after changed dose
- Another GP appointment at least two weeks after any dose increase

Guide for initiation and up-titration of beta blockers for patients with heart failure

If initiating beta blocker...

Start only if:

- Heart failure has stabilised and there are no symptoms of worsening heart failure such as
- paroxysmal nocturnal dyspnoea
- No symptomatic bradycardia, hypotension or heart block

Start with low dose

metoprolol 23.75mg daily or **carvedilol 3.125mg twice daily** or **bisoprolol 1.25mg daily**

When up-titrating dose...

 The dose may be doubled every two weeks (some people may require a slower titration)

 Aim for target dose **metoprolol 190mg daily** or **carvedilol 25mg twice daily** or **bisoprolol 10mg daily** (or the maximum tolerated dose)

Ask about:

 Any problems they have been experiencing (If symptomatic bradycardia, hypotension or heart block has occurred **do not increase** the beta blocker)

 Any symptoms of worsening heart failure (occasionally the furosemide dose may have to be increased)

 Dizziness - this is common with carvedilol, but often decreases as treatment continues

Up-titrate only if:

- No symptomatic bradycardia
- No signs of overt congestion
- No symptomatic hypotension

Note: They may have systolic blood pressure below 100mmHg and be asymptomatic

- Euvolaemic ie no recent severe diuresis
- Repeat ECG every visit if they have first degree heart block at the initiation of a beta blocker

Increase dose:

	Metoprolol	Carvedilol	Bisoprolol**
Start dose	23.75mg daily	3.125mg twice daily	1.25mg daily
1st titration	47.5mg daily	6.25mg twice daily	2.5mg daily
2nd titration	95mg daily	12.5mg twice daily	5mg daily
Target dose	**190mg daily**	**25mg twice daily***	**10mg daily**

*May increase up to 50mg twice daily for those over 85kg

**Some people may require a more gradual titration (eg 1.25mg, 2.5mg, 3.75mg, 5mg, 7.5mg then 10mg daily)

Explain:

- The benefits of beta blockers – mortality (30-35% reduction), admissions (28% reduction), promotes wellness
- The beta blocker must not be stopped suddenly
- Some side effects are common (tiredness, shortness of breath) but improve with time; it may take a while to feel better
- If they are worried about symptoms from increasing doses, advise them to start the new dose on a Monday, rather than just before or during the weekend when you may not be available
- How to respond to any symptoms experienced with the new dose (eg tiredness, shortness of breath)

Arrange:

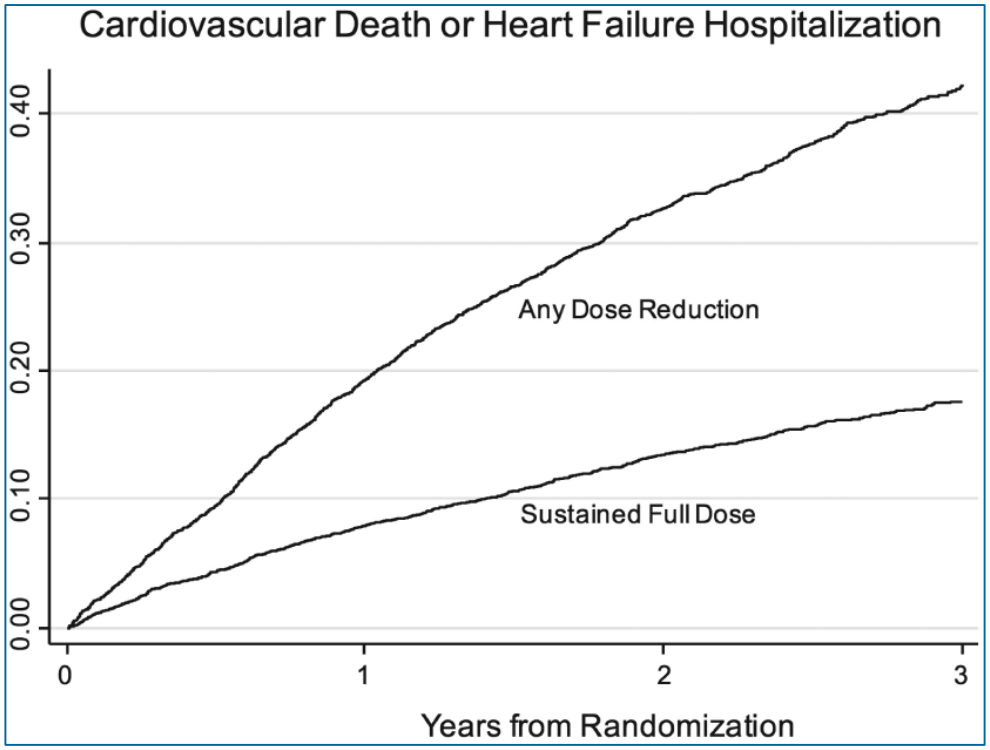
- Another GP appointment at least 2 weeks after a dose increase

..the case of sacubitril/valsartan

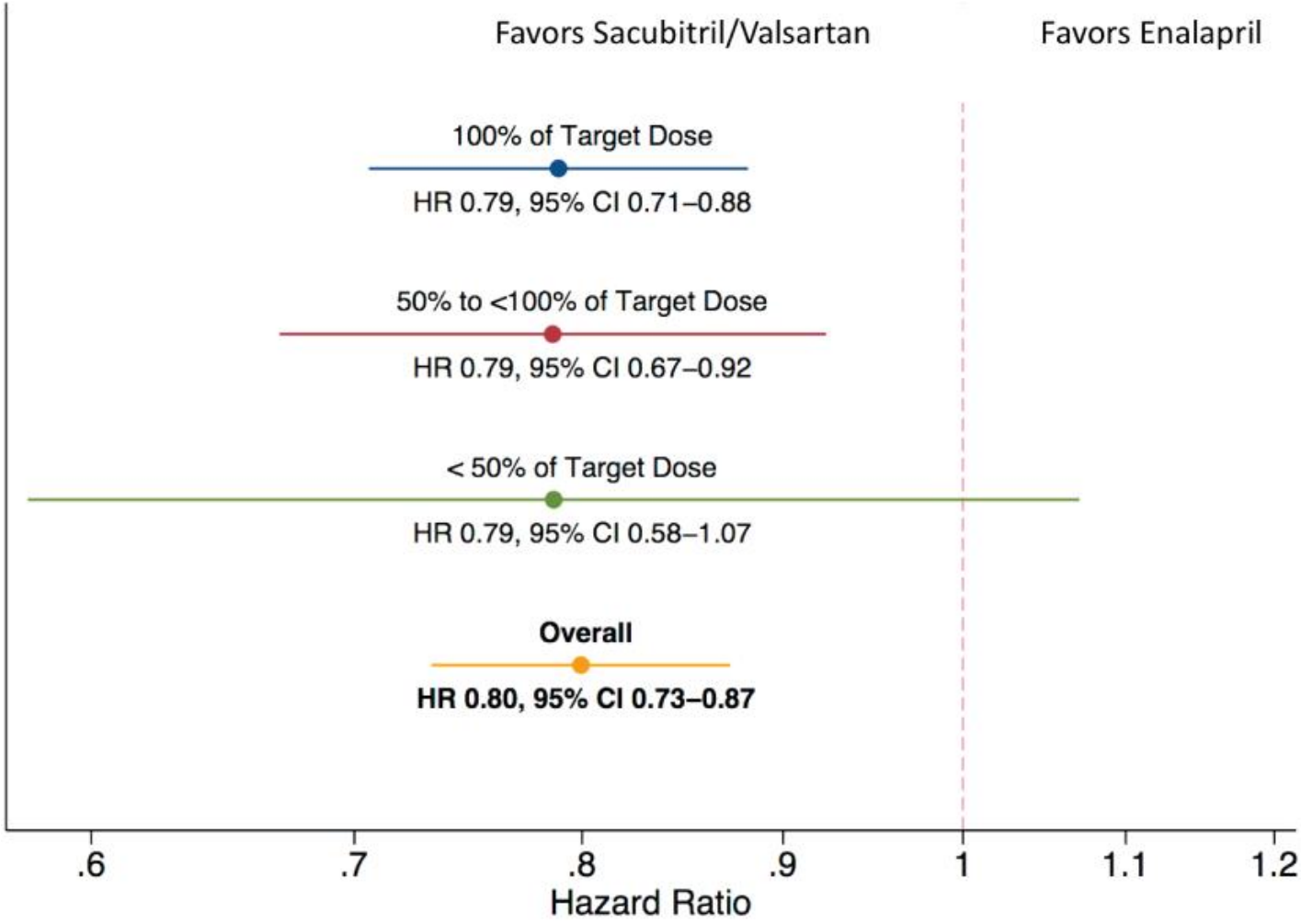
European Journal of Heart Failure (2016)
doi:10.1002/ejhf.580

Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

Orly Vardeny[1], Brian Claggett[2], Milton Packer[3], Michael R. Zile[4], Jean Rouleau[5], Karl Swedberg[6], John R. Teerlink[7], Akshay S. Desai[2], Martin Lefkowitz[8], Victor Shi[8], John J.V. McMurray[9], Scott D. Solomon[2]*, for the Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) Investigators



Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial



Vardeny et al. European Journal of Heart Failure 10 JUN 2016 DOI: 10.1002/ejhf.580

T .O.S.CA. REGISTRY STUDY

Trattamento Ormonale nello Scompenso CArdiaco

AIM: EVALUATE THE PREVALENCE OF HORMONE -METABOLIC DEFICITS IN CHRONIC HEART FAILURE AND ITS PREDICTIVE VALUE ON DISEASE PROGRESSION

n=15 cardiovascular centers in Italy

PRIMARY END-POINT: All-cause mortality

SECONDARY END-POINTS: Cardiac mortality, hospitalization, VO_2max, Cardiac Volumes

Centro 01
(n=110)

- 7 deaths (6 cardiac)
- 18 hospitalization

Why is TOSCA Registry a great scientific opportunity for investigating polypharmacy-related issues?

a) ↑ sample size (n=≈500)

b) Multiple assays

c) Comprehensive longitudinal evaluation of functional capacity and cardiovascular performance

TOSCA serum bank

Serum extraction every year

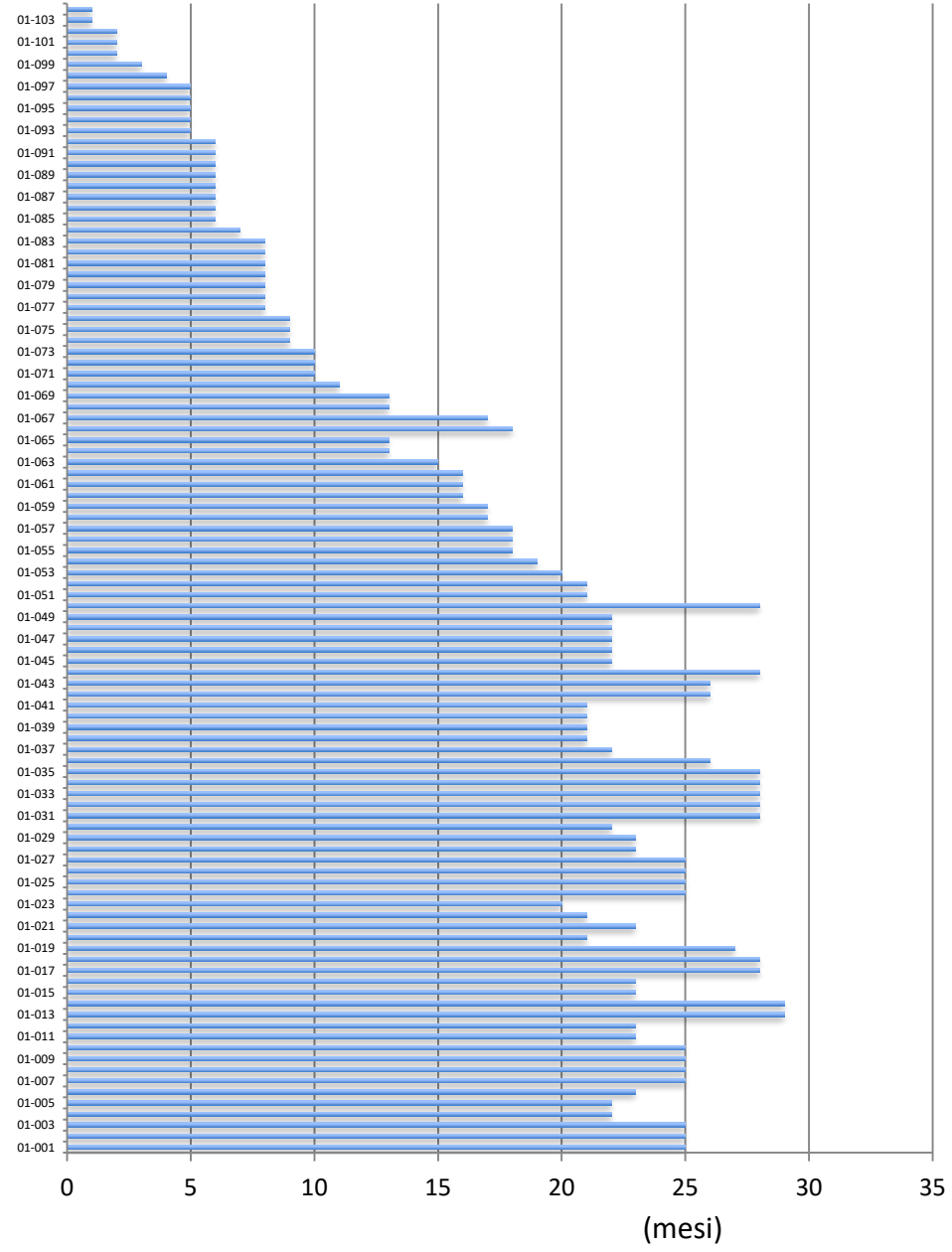
Hormones assay:
- IGF-1
- Total Testosterone
- DHEA-S
- Insuline

Follow-up assay

Centralized samples for **480** patients

200 assays processed

170 processing



FOLLOW-UP DURATION

N= 110 (Center 01)

MEAN DURATION (SD):
16,9 (8,5) months

MEDIAN OF DURATION
(intQ range): **20 (8 - 24.5) months**

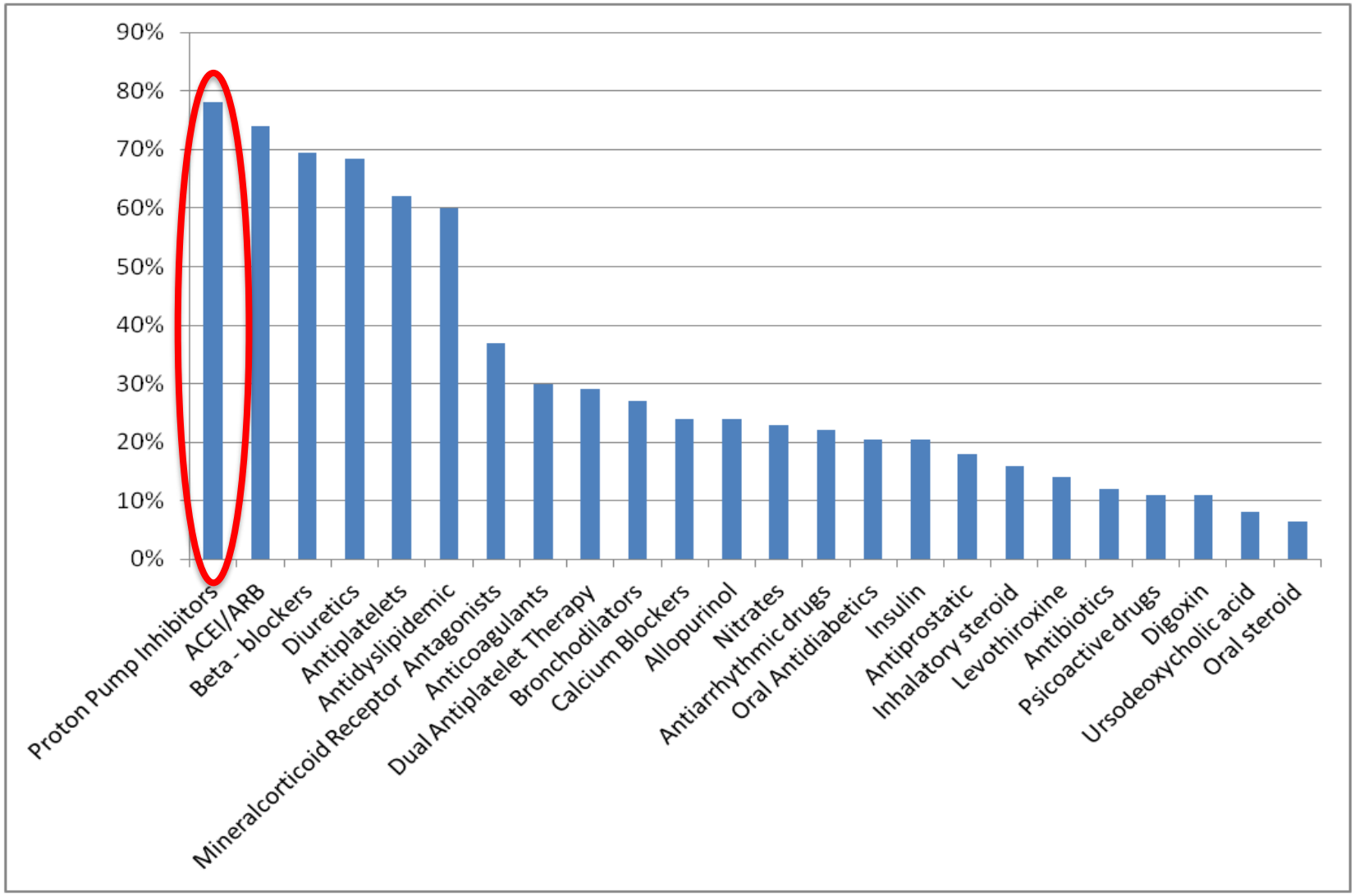
TARGET

MEAN DURATION: **42 months**

Polypharmacotherapy: our experience

	INPATIENTS	OUTPATIENTS	TOSCA REGISTRY
Mean Age (Yrs)	73,4 ± 5,7	70,7 ± 2,8	74,4 ± 6,9
Pts ≥65 Yrs (%)	49,5	39	40
Daily drugs assumed (nr)	9,1 ± 2,2	8,0 ± 1,9	10,5 ± 2,4
Polypharmacy (% of Pts ≥65 Yrs)	82	60	90
Excessive Polypharmacy (% of Pts in polipharmacy)	36	44	55,5

Polypharmacotherapy: our TOSCA experience



An example of a POLYPHARMACY-related issue:

The PPI paradox

- 78% of patients are treated with PPI, but only 13% had an appropriate indication (previous or active peptic ulcer, chronic gastritis, GERD);

- 88% of patients on excessive Polypharmacy take a PPI;

- 77% of patients receiving Clopidogrel take a PPI; and only 20% of them choose Pantoprazole

[i.e. Clopidogrel does not exert antiplatelet activity since it is not activated by CYP2C19 enzymatic activity; however, Omeprazole interferes with this enzymatic system reducing the efficacy of Clopidogrel]

Federico II University Hospital Involvement

•-WP2, Dissemination of the project, aims to ensure that the results and deliverables of the project will be made available to the target groups and secure the commitment of policymakers and interdisciplinary healthcare professional associations to a task force for the development of polypharmacy and adherence policies – in collaboration with CIRFF (Centro Interdipartimentale di Ricerca in Farmacoeconomia e Farmacoutilizzazione)

•-WP 4, Case studies, aims to conduct in-depth case studies to understand current practices in the management of polypharmacy and adherence in the elderly in a variety of sites that showcase different approaches in the EU

•- WP 7, EU knowledge sharing on polypharmacy and adherence, aims to share the outputs of the SIMPATHY project best practice models and process with a wide network of relevant EU stakeholders