Il Primo Cerchio

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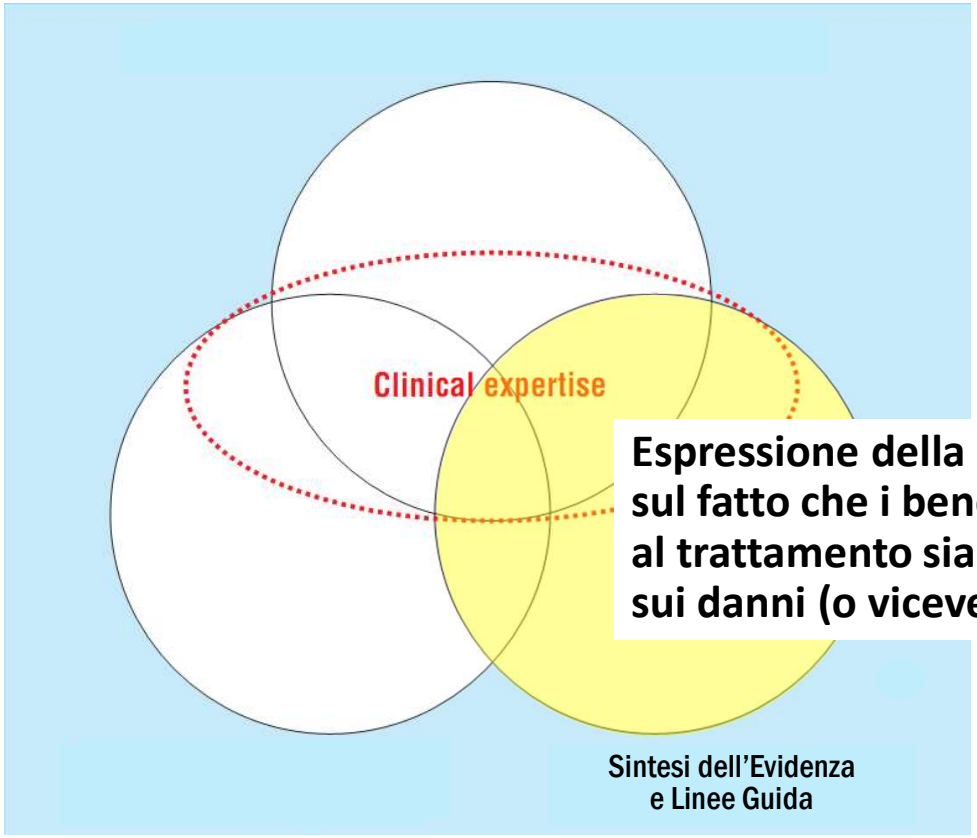
Physicians' and patients' choices in evidence based practice

Evidence does not make decisions, people do

R Brian Haynes P J Devereaux Gordon H Guyatt

BMJ 2002;324:1350



Espressione della "confidenza" sul fatto che i benefici ascrivibili al trattamento siano prevalenti sui danni (o viceversa)

The GRADE approach

- Considers
  - the evidence for each outcome in the review separately
  - magnitude of the effect
  - all factors to determine how confident we are in the results – quality of evidence
- Ensures
  - systematic process
  - transparency

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Strutturazione del Quesito Clinico sec. modello P.I.C.O.

P	Nei **P**azienti con…	(più o meno) specifiche caratteristiche di malattia	Pazienti con evidenza di mCSPC
I	l'**I**ntervento…	terapeutico oggetto del quesito clinico	"New ARTA" (Apalutamide, Darolutamide, Enzalutamide)
C	(è suscettibile di impiego) in **C**onfronto con…	il trattamento altrimenti considerabile in alternativa all'intervento in esame	SOC (LHRH-a ± NSAA ± docetaxel)
O	riguardo agli **O**utcome di beneficio/danno…	ritenuti essenziali per la proposta terapeutica	OS, TEAE G3-G4, SAE, TEAE → interruzione della terapia, TEAE → decesso del paziente

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Author(s): glp (09-Mar-2022)
Question: New ARTA compared to SOC for mCSPC patients
Bibliography: Apalutamide: Chi KN, et al. N Engl J Med 2019;381:13-24. Chi KN, et al. J Clin Oncol 2021;39:2294-2303. Enzalutamide: Armstrong AJ, et al. J Clin Oncol 2019;37:2974-2986. Armstrong AJ, et al. Annals of Oncology (2021) 32 (suppl_5): S1283-S1346. J Clin Oncol 40, no. 6_suppl (February 20, 2022) 115-115. Davis ID, et al. N Engl J Med 2019;381:121-31. Sweeney CJ, et al Eur Urol 2021;80:275-279. Darolutamide: Smith MR, et al. published on February 17, 2022, at NEJM.org.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	new ARTA	SOC	Relative (95% CI)	Absolute (95% CI)		
Overall Survival, all-comers (assessed with: Kaplan-Meier product limit estimate)												
4	RCT	not serious [a,b]	not serious [c]	not serious [d]	not serious [e]	none	2313 -	2319 baseline risk 50.0%	**HR 0.67** (0.60 to 0.74)	risk difference **13 fewer per 100** (from 16 fewer to 10 fewer)	⨁⨁⨁⨁ High	CRITICAL
Overall Survival, de novo mCSPC (assessed with: Kaplan-Meier product limit estimate)												
4	RCT	not serious [a,b]	not serious [f]	not serious [d]	not serious [e]	none	1825 -	1854 baseline risk 45.0%	**HR 0.68** (0.61 to 0.76)	risk difference **12 fewer per 100** (from 14 fewer to 8 fewer)	⨁⨁⨁⨁ High	CRITICAL
Overall Survival, recurrent mCSPC (assessed with: Kaplan-Meier product limit estimate)												
4	RCT	not serious [a,b]	not serious [g]	not serious [d]	not serious [e]	none	443 -	427 baseline risk 51.0%	**HR 0.56** (0.42 to 0.75)	risk difference **18 fewer per 100** (from 25 fewer to 10 fewer)	⨁⨁⨁⨁ High	CRITICAL

a. Arasens, Arches and Titan studies double blinded. Enzamet open-label design.
b. low risk of detection bias related to the type of outcome
c. $Chi^2 = 0.22$, df = 3 (P = 0.97); $I^2 = 0\%$
d. SOC as adequate comparator
e. 95%CI of absolute effect consistent with a unique clinical interpretation
f. $Chi^2 = 0.65$, df = 3 (P = 0.88); $I^2 = 0\%$
g. $Chi^2 = 2.37$, df = 3 (P = 0.50); $I^2 = 0\%$

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	new ARTA	SOC	Relative (95% CI)	Absolute (95% CI)		
Overall Survival, high volume [e] disease (assessed with: Kaplan-Meier product limit estimate)												
3	RCT	not serious [a,b]	not serious [f]	not serious [c]	not serious [d]	none	934	956	**HR 0.66** (0.57 to 0.76)	risk difference **15 fewer per 100** (from 19 fewer to 10 fewer)	⊕⊕⊕⊕ High	CRITICAL
							-	baseline risk 60.0%				
Overall Survival, low volume [e] disease (assessed with: Kaplan-Meier product limit estimate)												
3	RCT	not serious [a,b]	not serious [g]	not serious [c]	not serious [d]	none	728	709	**HR 0.64** (0.51 to 0.82)	risk difference **12 fewer per 100** (from 17 fewer to 6 fewer)	⊕⊕⊕⊕ High	CRITICAL
							-	baseline risk 40.0%				

a. Arasens, Arches and Titan studies double-blinded. Enzamet open-label design.
b. low risk of detection bias related to the type of outcome
c. SOC as adequate comparator
d. 95%CI of absolute effect consistent with a unique clinical interpretation
e. CHAARTED criteria
f. $Chi^2 = 3.00$, df = 2 (P = 0.22); $I^2 = 33\%$
g. $Chi^2 = 3.33$, df = 2 (P = 0.19); $I^2 = 40\%$

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№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	new ARTA	SOC	Relative (95% CI)	Absolute (95% CI)		
Overall Survival, no previous/early docetaxel (assessed with: Kaplan-Meier product limit estimate)												
3	RCT	not serious [a,b]	not serious [e]	not serious [c]	not serious [d]	none	1247 -	1259 baseline risk 44.0%	**HR 0.61** (0.53 to 0.70)	risk difference **14 fewer per 100** (from 18 fewer to 11 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Overall Survival, early docetaxel (assessed with: Kaplan-Meier product limit estimate)												
2	RCT	not serious [a,b]	not serious[f]	not serious[c]	not serious[d]	none	754 -	756 baseline risk 59.0%	**HR 0.70** (0.59 to 0.82)	risk difference **13 fewer per 100** (from 18 fewer to 7 fewer)	⊕⊕⊕⊕ High	IMPORTANT
Overall Survival, previous docetaxel (assessed with: Kaplan-Meier product limit estimate)												
2	RCT	not serious [a,b]	not serious[g]	not serious[c]	serious[h]	none	312 -	304 baseline risk 57.0%	**HR 0.95** (0.69 to 1.31)	risk difference **2 fewer per 100** (from 13 fewer to 10 more)	⊕⊕⊕◯ Moderate	IMPORTANT

a. Arasens, Arches and Titan studies double blinded. Enzamet open-label design.
b. low risk of detection bias related to the type of outcome
c. SOC as adequate comparator
d. 95%CI of absolute effect consistent with a unique clinical interpretation
e. $Chi^2 = 0.77$, df = 2 (P = 0.68); $I^2 = 0\%$
f. $Chi^2 = 0.07$, df = 1 (P = 0.79); $I^2 = 0\%$
g. $Chi^2 = 0.33$, df = 1 (P = 0.56); $I^2 = 0\%$
h. 95%CLs of absolute effect consistent with opposite clinical interpretations

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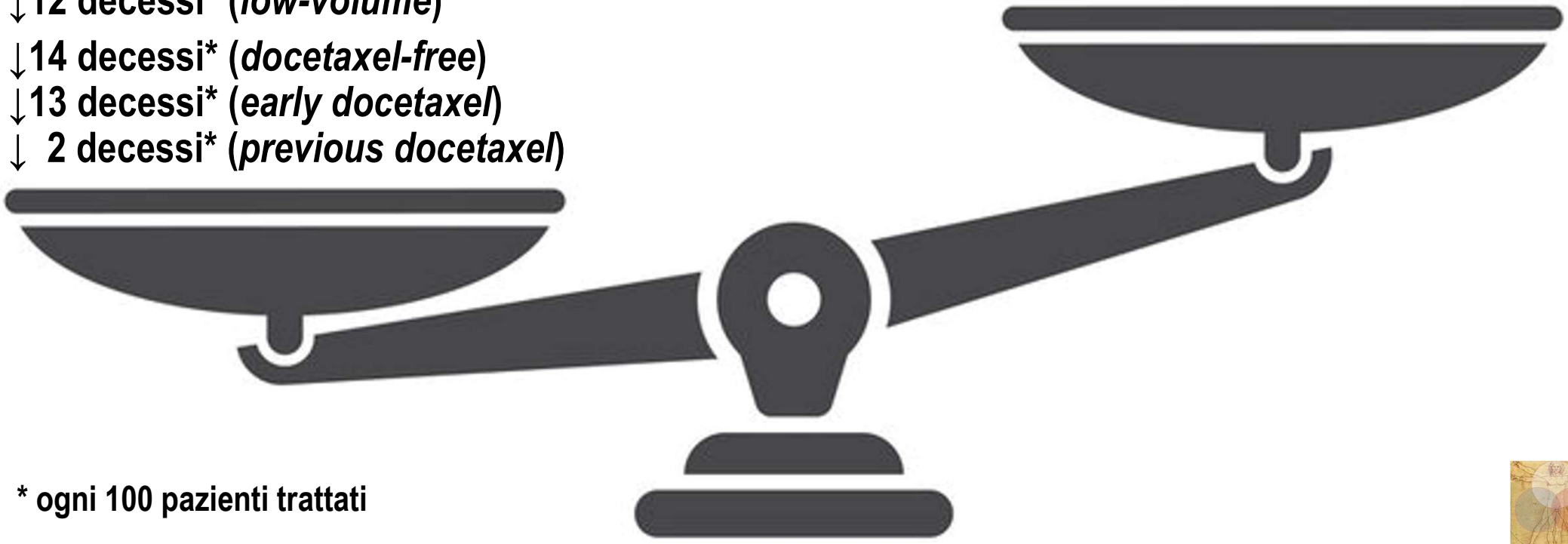
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	new ARTA	SOC	Relative (95% CI)	Absolute (95% CI)		
TEAE G3-G4 (assessed with: cumulative incidence)												
4	RCT	not serious [a,d]	serious [e]	not serious [b]	serious [f]	none	1106/2311 (47.9%)	1009/2309 (43.7%)	**RR 1.09** (0.95 to 1.25)	**4 more per 100** (from 2 fewer to 11 more)	⊕⊕◯◯ Low	CRITICAL
SAE (assessed with: cumulative incidence)												
4	RCT	not serious [a,d]	not serious [g]	not serious [b]	not serious [h]	none	735/2311 (31.8%)	683/2309 (29.6%)	**RR 1.07** (0.99 to 1.17)	**2 more per 100** (from 0 fewer to 5 more)	⊕⊕⊕⊕ High	IMPORTANT
TEAE causing permanent discontinuation of ARTA/SOC (assessed with: cumulative incidence)												
4	RCT	not serious [a,d]	not serious [i]	not serious [b]	not serious [h]	none	204/2311 (8.8%)	141/2309 (6.1%)	**RR 1.45** (1.18 to 1.78)	**3 more per 100** (from 1 more to 5 more)	⊕⊕⊕⊕ High	CRITICAL
TEAE causing death (assessed with: cumulative incidence)												
4	RCT	not serious [a,d]	not serious [j]	not serious [b]	not serious [c]	none	57/2311 (2.5%)	59/2309 (2.6%)	**RR 0.97** (0.67 to 1.38)	**0 fewer per 100** (from 1 fewer to 1 more)	⊕⊕⊕⊕ High	IMPORTANT

a. Arasens, Arches and Titan studies double blinded. Enzamet open-label design.
b. SOC as adequate comparator
c. 95%CI of absolute effect consistent with a unique clinical interpretation
d. high risk of performance bias for Enzamet study
e. $Tau^2 = 0.02$; $Chi^2 = 14.19$, df = 3 (P = 0.003); $I^2 = 79\%$
f. 95%CLs of absolute effect consistent with both greater and comparable toxicity
g. $Chi^2 = 5.14$, df = 3 (P = 0.16); $I^2 = 42\%$
h. wide 95%CI of absolute effect, but consistent with a unique clinical interpretation; may not be downgraded
i. $Chi^2 = 3.15$, df = 3 (P = 0.37); $I^2 = 5\%$
j. $Chi^2 = 2.12$, df = 3 (P = 0.55); $I^2 = 0\%$

Riepilogando…

↓13 decessi* (*all-comers*)
↓12 decessi* (*de novo*)
↓18 decessi* (*recurrent*)
↓15 decessi* (*high-volume*)
↓12 decessi* (*low-volume*)
↓14 decessi* (*docetaxel-free*)
↓13 decessi* (*early docetaxel*)
↓ 2 decessi* (*previous docetaxel*)

↑ 4 TEAE G3-G4*
↑ 3 TEAE → interruzione*
↑ 2 SAE*
↑ 0 TEAE causa di decesso*



* ogni 100 pazienti trattati

Isn't Androgen Deprivation Enough? Optimal Treatment for Newly Diagnosed Metastatic Prostate Cancer

Alicia K. Morgans, MD, MPH[1]; and Himisha Beltran, MD[1]

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