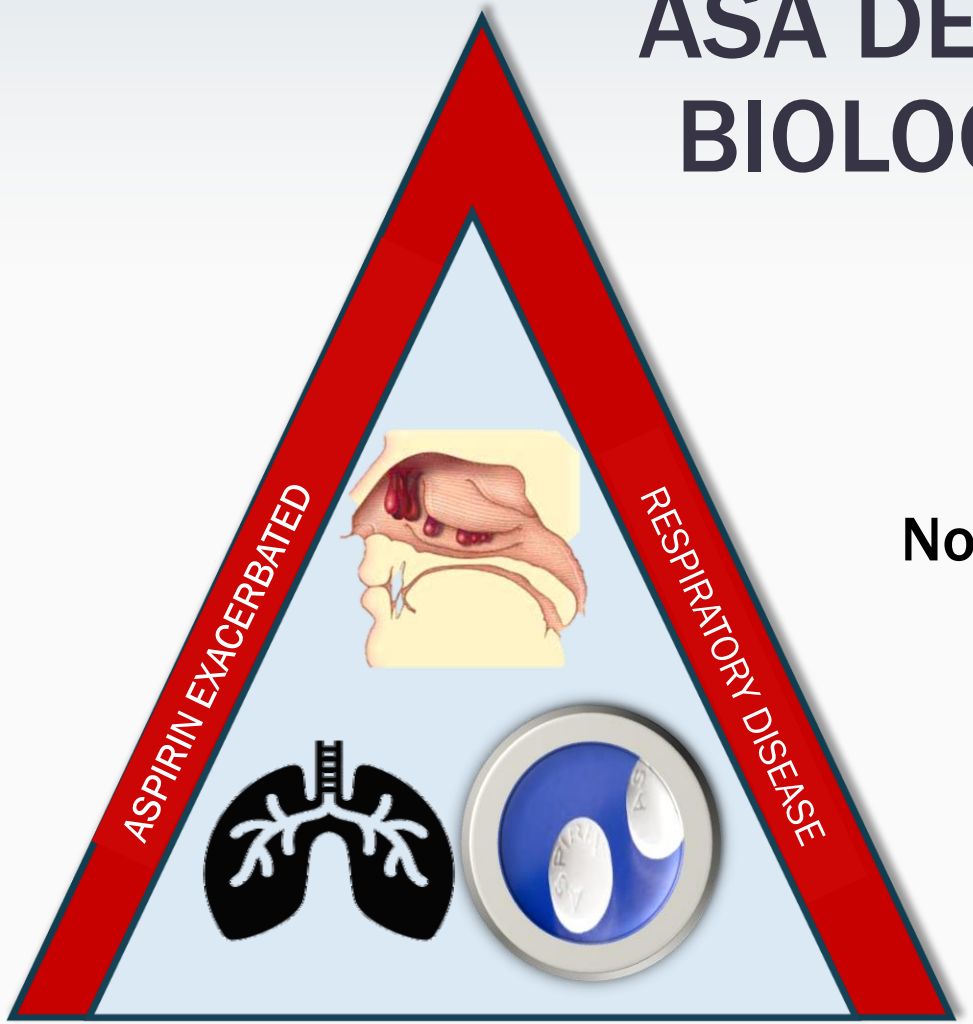
WEIGHING THE RISKS/BENEFITS OF: FESS ASA DESENSITIZATON &/or BIOLOGICS to treat Pam's CRSwNP

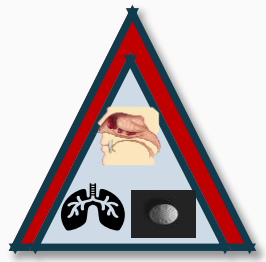


Dana V. Wallace, MD
Nova Southeastern University

Learning objectives

At the end of this educational activity, the participant should be able to:

1. List the advantages and disadvantages of ASA desensitization and therapy
2. Describe if and when is the best time for a patient with CRSwNP and asthma to have FESS
3. Discuss when to start, add, or switch biologics for asthma and CRSwP



PAM – Age 45
Current Diagnosis & Treatment choices

Diagnosis

- AERD
- Asthma, severe, controlled with mepolizumab
- CRSwNP- uncontrolled

Treatment options

- FESS
- ATAD (ASA treatment after ASA desensitization)
- Add new biologic
- Switch to new biologic

Pam's visit with with a prior allergist 10 years ago

- History of life-long asthma, getting progressively worse
- 2 ED visits/year for asthma exacerbation and acute sinusitis- Rx oral corticosteroids and antibiotics
- 1 PCP visit acute sinusitis—Rx antibiotics and oral corticosteroids
- On low-dose LABD/SABA + PRN SABA bid but frequently forgets
- ENT did CT 3 months ago- bilateral ethmoidal and maxillary polyps
- Recently developed wheeze with ingestion of ibuprofen ASA and naproxen
- Scheduled for labs and PFT
- Wants to avoid surgery
- Patient did not return– decided to just use urgent care when sick

PAM – Age 35
Diagnosis & Treatment choices

Diagnosis

- AERD
- Asthma, mild persistent with frequent exacerbations- uncontrolled
- CRSwNP
- Non-adherent patient

Treatment options

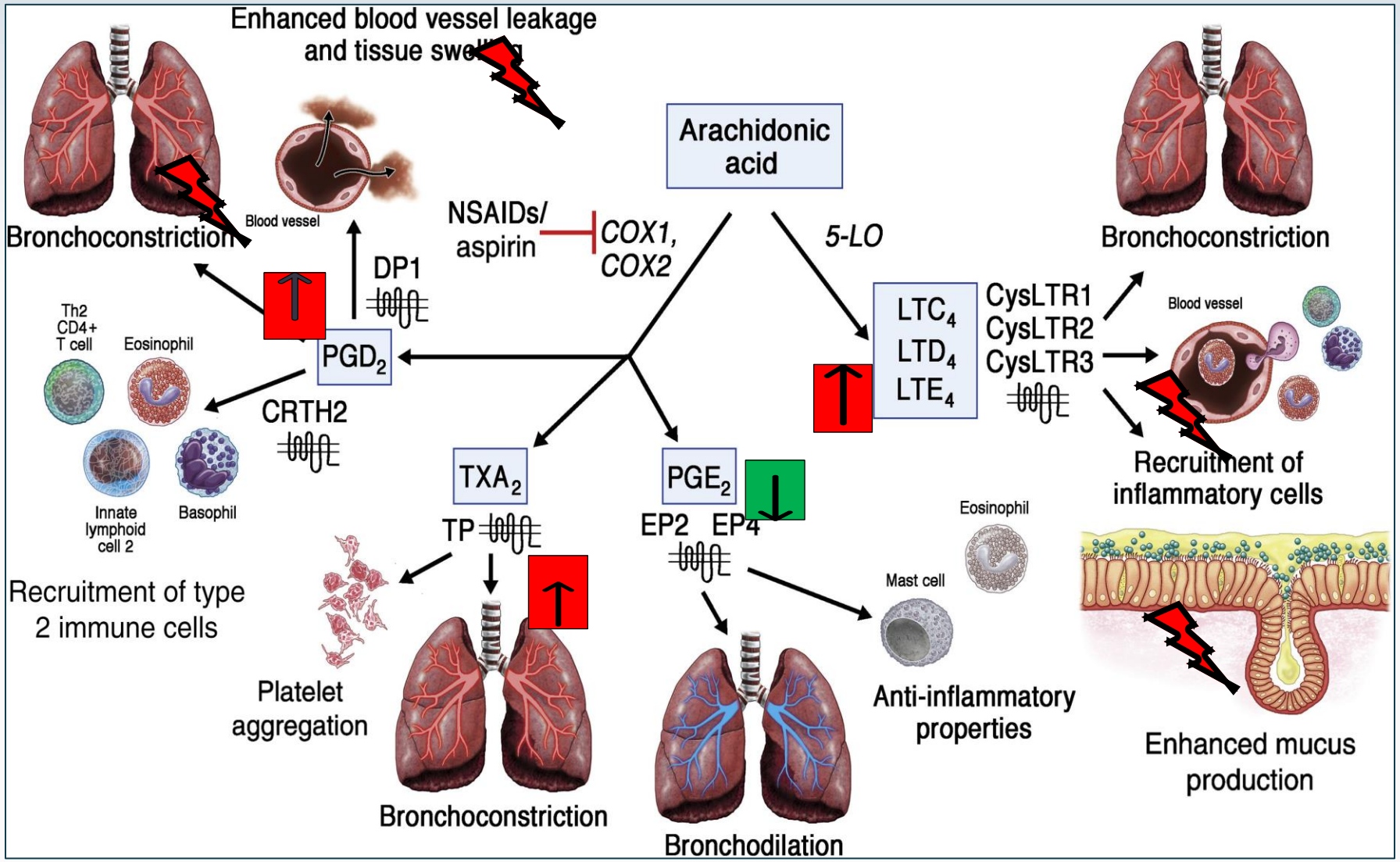
- FESS
- Nasal steroids in exhalation device
- Sinus irrigation with steroids
- ATAD (ASA treatment after ASA desensitization)
- Consider SMART therapy
- Enroll in biologic trial

Clinical Characteristics of AERD

- Chronic eosinophilic rhinosinusitis with polyposis
- Asthma (often severe)
- Respiratory (and extra-respiratory) reactions to ASA/NSAIDS
- Adult onset
- 50% following “URI”
- No prior sensitization, occurs on first exposure
- Alcohol reactivity
- Coronary vasospasm
- Esophageal eosinophilia
- Reactions to all COX1 inhibitors
- Highly selective COX-2 inhibitors typically tolerated
- Acetaminophen tolerated up to 1000 mg

Stevens, W. W.,et al. (2017). J Allergy Clin Immunol Pract **5**(4): 1061-1070 e1063.
Vanselow, N. A. et al. (1967). Ann Intern Med **66**(3): 568-572.
Samter, M. et al. (1968). Ann Intern Med **68**(5): 975-983.

Arachidonic acid metabolism dysfunction in AERD



Roca-Ferrer, J., et al.(2011). J Allergy Clin Immunol **128**(1): 66-72 e61.

Stevens, W. W., et al., (2021). " J Allergy Clin Immunol **147**(3): 827-844.

Provocative ASA challenge for dx of AERD

- 85% of patients can be diagnosed clinically without a challenge
- 15% of patients will require a challenge
  - Patients who have not used NSAIDS recently
  - Patients on a leukotriene-modifying drug (without a good history)
  - Patients who are less perceptive of symptoms
  - Patients already on low-dose ASA

Szczeklik, A., E. , et. al.(2000). Eur Respir J 16(3): 432-436.

AERD patients are unique

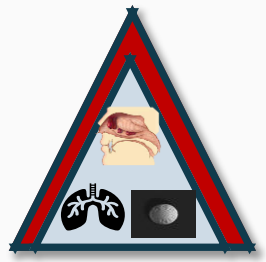
AERD affects:

7-15% of asthmatics

10-16% of CRSwNP

- High nasal polyp disease severity
- Rapid polyp recurrence after surgery
- Worse QOL
- Polyps rarely respond to conservative medical treatment
- The only patients that will benefit from ASA desensitization/high dose maintenance therapy
- There are new treatment options with approval of biologics

Laidlaw, T. M. et al. (2024). J Allergy Clin Immunol Pract 12(1): 79-84. Rajan, J. P., et al. (2015). " J Allergy Clin Immunol 135(3): 676-681 e671. Stevens, W. W.,et al. (2017). J Allergy Clin Immunol Pract 5(4): 1061-1070 e1063.

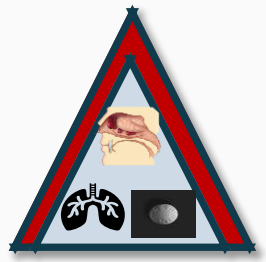


ENDOSCOPIC SINUS SURGERY

FESS : Should it be the Only or the 1st Treatment for CRSwNP & AERD?

Contraindications for ESS for CRSwNP

- Patient is a poor medical risk for general anesthesia and sinus surgery, e.g.,
  - Poorly controlled asthma
  - Severe COPD
  - Severe cardiac disease
  - Bleeding disorder/requires anticoagulants
- Unfavorable anatomy
- Patient inability/unwillingness to obtain appropriate postoperative follow-up care and treatment
- Patient refusal

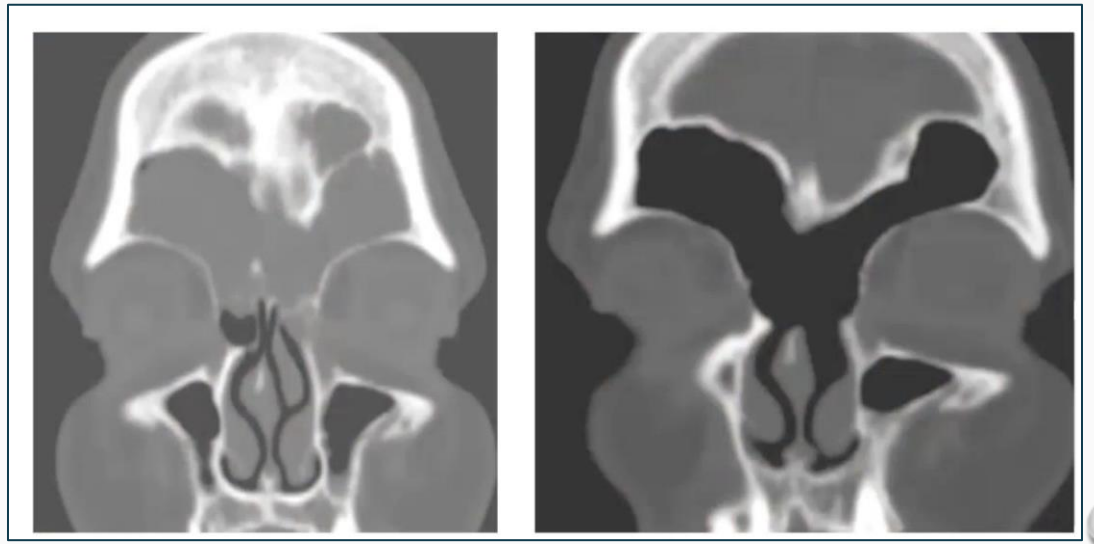


ESS Procedure, Goals, and Extent of Intervention

- Remove polys through the nostrils and suction out mucous/fungal elements while preserving mucosa
- Open drainage pathways, create large ostia, and connect small spaces to create a larger space
- Open all sinuses–"full house"– to allow for improved medication delivery and drainage & reduce need for repeated surgeries[1]
- When frontal sinuses openings are extremely narrow & there is widespread disease, remove bone to form one large cavity—"Large Hole"
- Extent of surgery does not significantly affect overall complication rate but can increase orbital injury

Preop Sinuses

"LARGE HOLE"



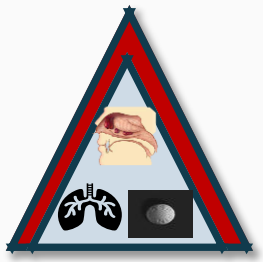
1. Ramkumar, S. P., et al (2023). Front Allergy **4**: 1137907. 2.Suzuki, S., H. et al. (2015). Laryngoscope 125(8): 1785-1791.

ESS complication rate based upon large studies

Source	CSF leak %	Orbital injury %	Hemorrhage %	# of patients	Setting
May et al[1] (1994)	0.47	0.05	0.19	2.108	Academic, multicenter
Keerl et al[2] (1999)	0.53%	0.45%	---	1,500	Academic, multicenter
Dalziel et al[3] (2006)	0.3%	2.6%	0.2%	12,239	Meta-analysis
Ramakrishnan et al[4] (2012)	0.17%	0.07%	0.76%	62823	Nationwide database
Suzuki et al[5] (2015)	0.10%	0.09%	0.10%	50,734	Japanese database

Note: Orbital injury and hemorrhage are variably defined within the studies

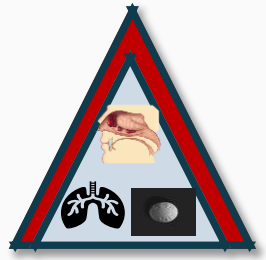
.
1. May, M., H. et al. (1994). Laryngoscope 104(9): 1080-1083. 2. Keerl, R., J. et al. (1999). Laryngoscope 109(4): 546-550.
3. Dalziel, K., K. (2006). Am J Rhinol 20(5): 506-519. 4. Ramakrishnan, V. R., et al. (2012). Int Forum Allergy 2(1):34-9. 5. Suzuki, S., H. et al. (2015). Laryngoscope 125(8): 1785-1791.



ESS Complication rate based upon type of surgery and/or Image guided surgery (IGS)

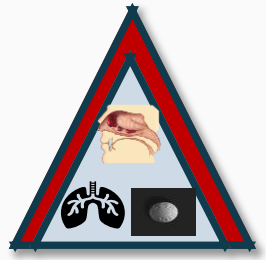
- 2005-2008 payor data base[1]:
  - Primary ESS 78,944 patients- major complications 0.36%
  - Revision ESS 4151 patients- major complications 0.46% (p=.34)
  - Complication rates higher in sphenoid (0.45%) and frontal (0.53%) sinus surgery
  - IGS, used in 7% of patients, had a higher complication rate (0.65%)
    - Likely more complex cases using IGS
    - Possibly overconfidence and false sense of security with IGS
- Prospective non-R case-control study (222 pts) trend to less major complications with IGS[2]
- Ramakirishnan 2012 study compared with (5568-8639 pts)/without (35,070-50,113) IGS[3]
  - IGS: CSF leak (0.14%); orbital injury (0.14%); hemorrhage (0.61%)
  - No IGS: CSF leak (0.17%); orbital injury (0.06%); hemorrhage (0.76%)
  - Orbital injury p=0.0043 favoring “No IGS”

1. Krings, J. G., et al. (2014). Laryngoscope 124(4): 838-845.2. Tschopp, K. P. et al. (2008). Rhinology 46(2): 116-120.
3. Ramakrishnan, V. R., et al. (2012). Int Forum Allergy 2(1):34-9.



Balloon vs. Conventional FESS

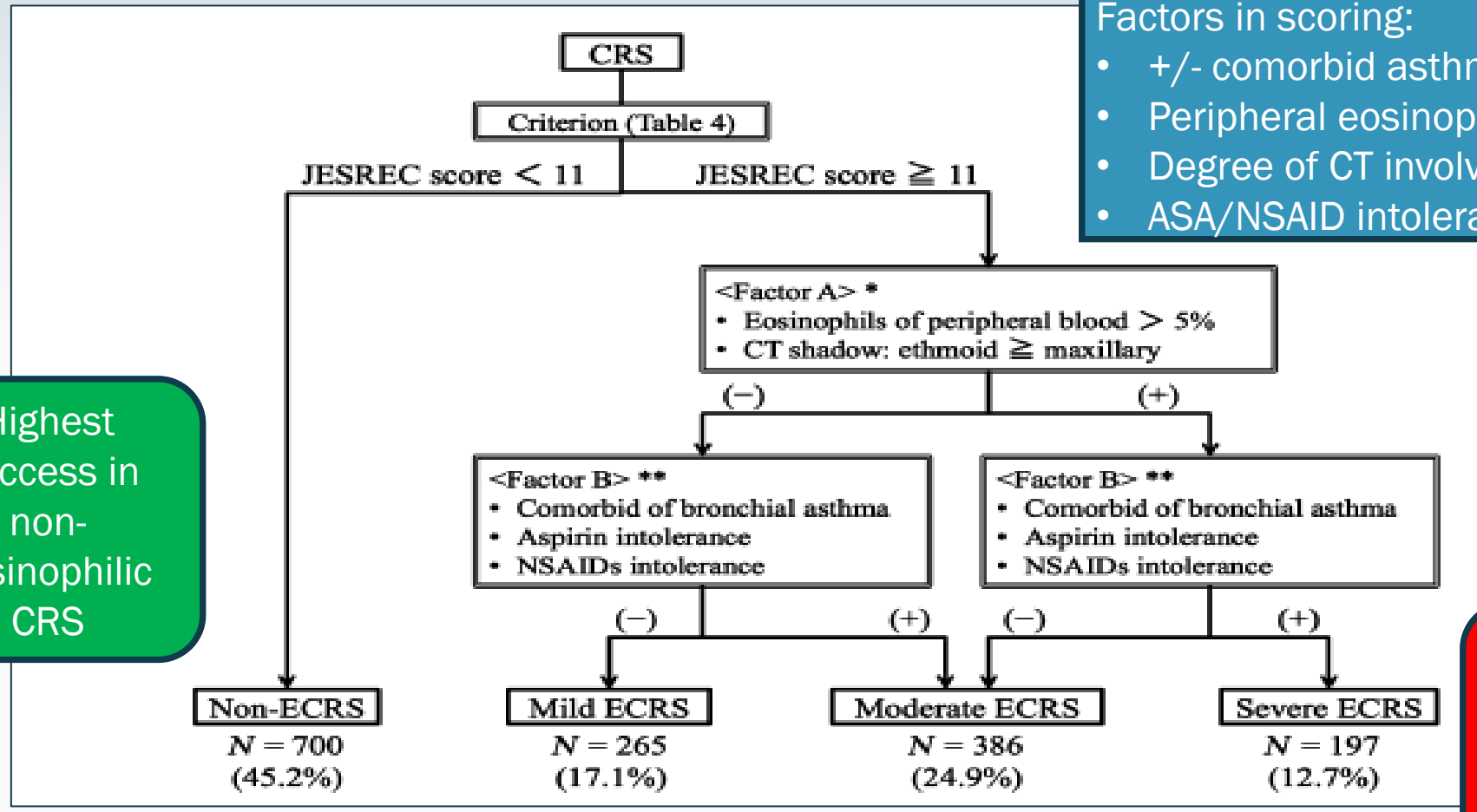
- Chaaban 2011-2014 administrative commercial database 16,400 patients[1]
  - Conventional ESS: 11,955 pts.
    - Complication rate 7.35% (orbital 3.4%, bleeding 3.26%, skull base/CNS 0.39%)
    - Revision 16.85%
  - Balloon surgery: 2851 pts.
    - Complication rate 5.26% (Orbital 2.95%, bleeding 2.03%, Skull base/CNS 0.35%)
    - Revision: 7.89%
    - Likely less complex disease
  - Hybrid (balloon + conventional) 1234 patients
    - Revision 15.5%



1. Chaaban, M. R., et al. (2018). Am J Rhinol Allergy 32(5): 388-396.

Surgical success using JESREC scoring system

Factors in scoring:
- +/- comorbid asthma
- Peripheral eosinophil level
- Degree of CT involvement
- ASA/NSAID intolerance



Highest success in non-eosinophilic CRS

Lowest success in severe eosinophilic CRS

* Factor A (+): all of 2 factors are applied; (-): at lease one factor is applied

** Factor B (+): at least 1 factor is applied; (-) all 3 factors are not applied

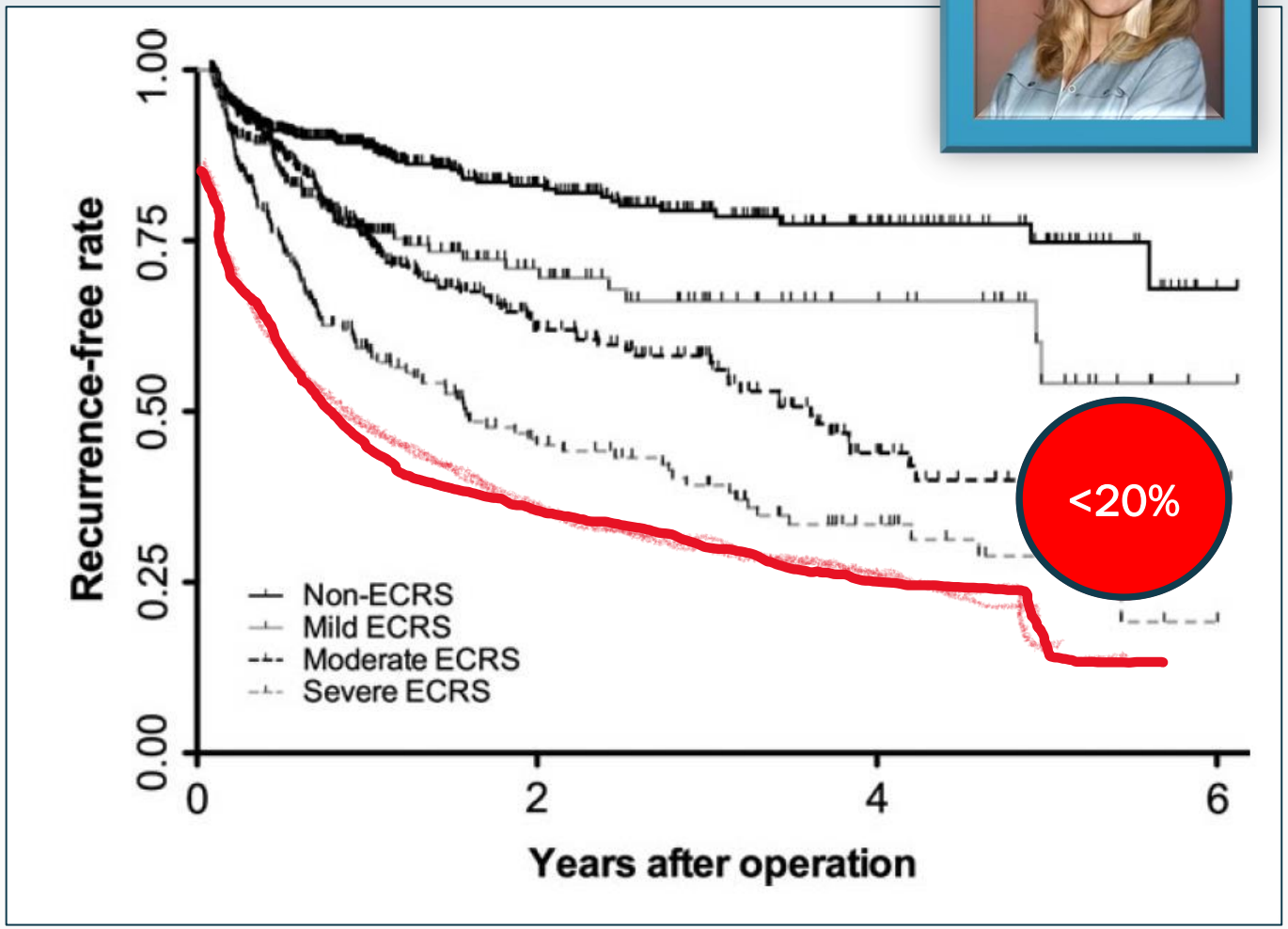
JESREC: Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis

Tokunaga, T., M. et al. (2015). Allergy 70(8): 995-1003.

Surgical success using JESREC scoring system

Severe category or ECRS

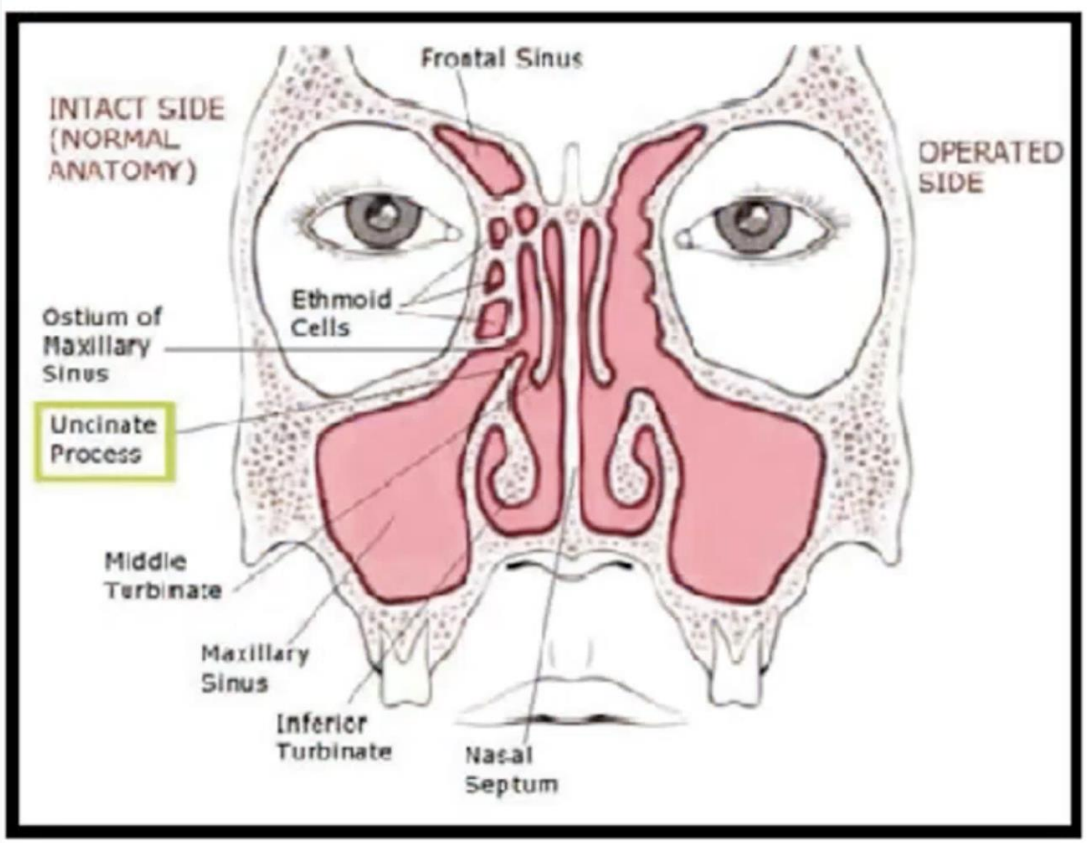
- Eosinophils >5%
- CT shadow ethmoid>maxillary
- Asthma
- ASA/NSAID intolerance



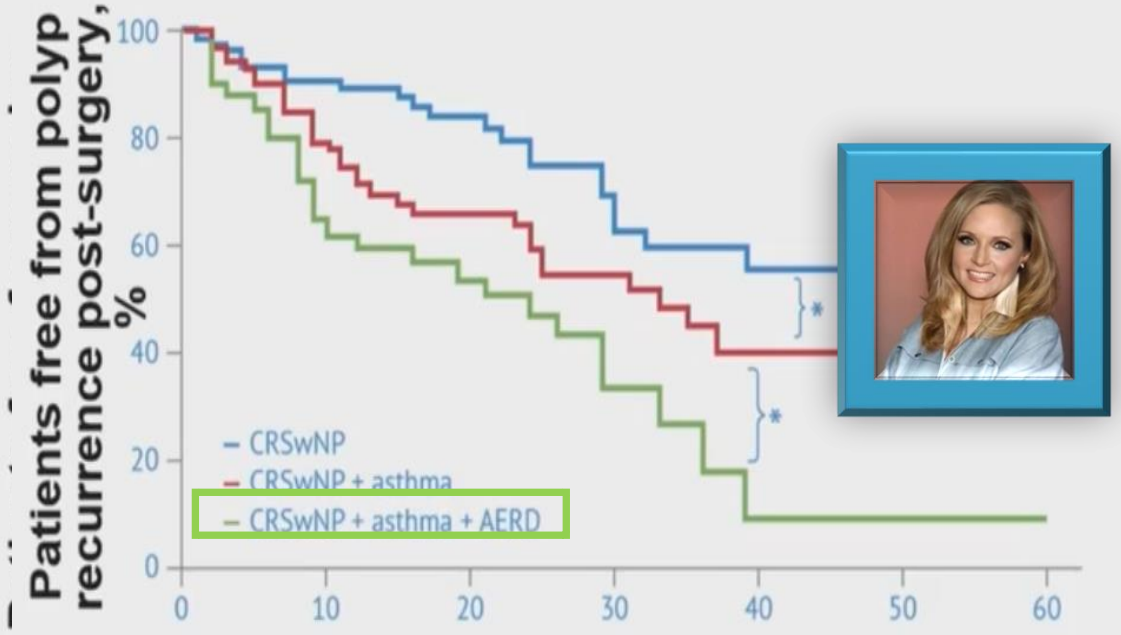
Tokunaga, T., M. et al. (2015). Allergy 70(8): 995-1003.

Ethmoid and Sphenoid disease is worse prognosis

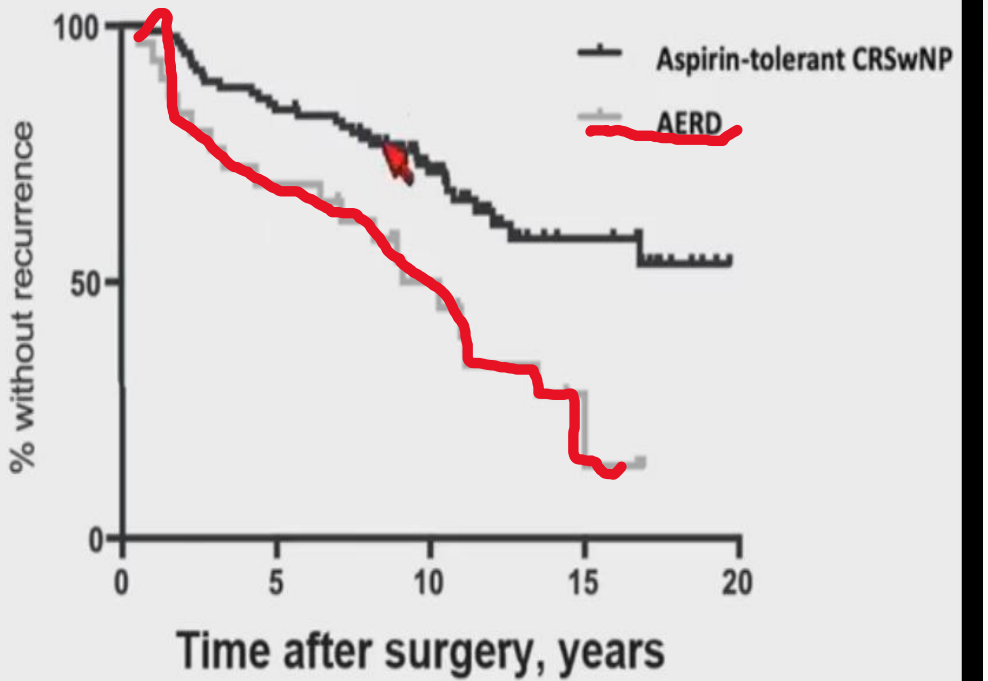
- Increased ratio urokinase plasminogen activator (u-PA)/tissue plasminogen activator (t-PA) in nasal polyps=inflammation.
- Reduced t-PA means reduced fibrinolysis
- Both u-PA and t-PA lower in unincate compared to inferior turbinate



NP recurrence after ESS in CRSwNP and AERD patients



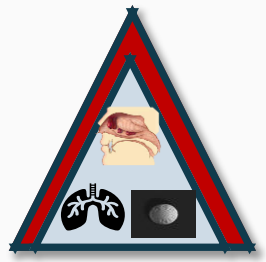
*P < .05.
***P < 0.001
Bassiouni et al. Laryngoscope. 2013 Jan; 123(1):36-41.



Sella et al. JACI IP. 2020 Jan;8(1):302-309.

Defining Surgical Success

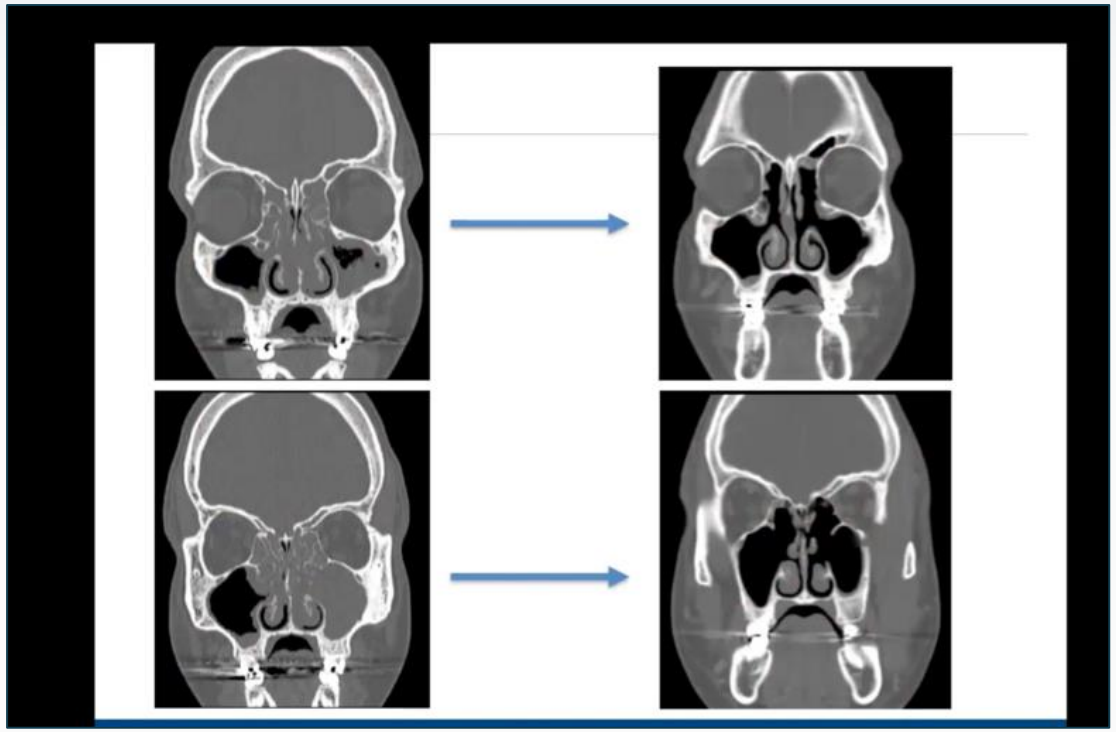
- Patient's subjective feeling on a daily basis
- Fewer number of oral steroids courses
- Isolated polyp return without significant symptoms does not mean surgical failure or need for repeat surgery or more aggressive treatment
- Following appropriate, "good" surgery, with return of nasal polyp disease, biologics may be the treatment of choice.



Indications for Endoscopic Sinus Surgery [EES] in CRSwNP

- Need for improvement in symptoms
  - Congestion
  - Anosmia, hyposmia
- For improved topical medication delivery
- Pt has failed conservative medical treatment topical/oral steroids and has extensive disease
- Patient who is sinus surgery naïve
- Pt has no contraindications for surgery
- Patient agrees following a shared-decision making discussion
- When above criteria are fulfilled, efficacy and cost-analysis support EES

Pre and Post ESS



Ramkumar, S. P., et al. (2023). Front Allergy 4: 1137907.

ATAD

ASA Treatment after ASA desensitization

ASA Desensitization and Maintenance for AERD

Candidate

- Reoccurrence of nasal polyps shortly after sinus surgery
- Uncontrolled CRSwNP
- Frequent bursts of oral corticosteroids
- Need for ASA for cardiovascular prevention/treatment
- Need for NSAIDS for other medical issues
- Patient agrees with daily ASA administration ??

Not a candidate

- Poorly controlled asthma
- Significant polyp burden at time of desensitization
- Pregnancy (?? In near future)
- History of EoE
- History of gastric and/or peptic ulcer
- History of bleed disorder or coagulopathy
- Renal impairment
- History of medication nonadherence
- Caution with history of NSAID anaphylaxis
- Caution with patients >70 years & <13 yrs.—limited studies

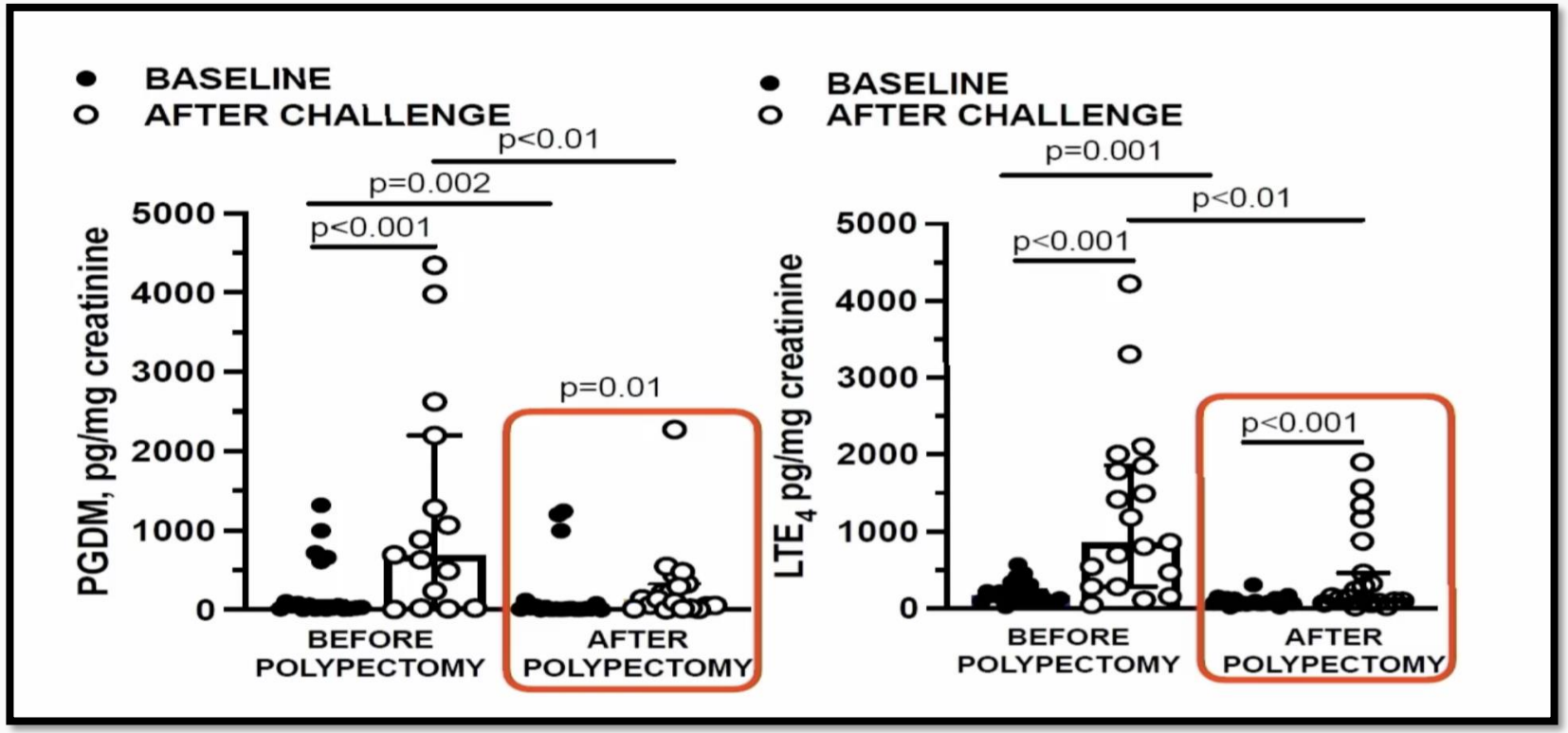
2021 INTERNATIONAL CONSENSUS STATEMENT ON ALLERGY AND RHINOLOGY: RHINOSINUSITIS 2021.

- Grade of Evidence: A for ATAD
- Benefit: Reduced polyp formation, increased QoL, reduced systemic corticosteroids and surgery
- Harm: Gastrointestinal bleeding, renal and coagulation issues
- Cost: Initial cost of desensitization, minimal direct costs of ASA, decreased cost from reduced surgery
- Benefits-Harm assessment: Clear benefit over harm
- Value Judgements: ASA desensitization followed by daily ASA therapy is 1 of the very few disease-modifying medical treatment options available for patients with AERD
- Policy Level: Recommendation
- Intervention: ASA desensitization should be considered in AERD patients after surgical removal of NPs to prevent recurrence

Orlandi, R. R., et al. (2021). "International consensus statement on allergy and rhinology: rhinosinusitis 2021." Int Forum Allergy Rhinol 11(3): 213-739.

When to conduct ASA Desensitization

- Levels of PGD2 and LTE4 depend upon level of nasal polyp presence[1]
- 3-4 wks. after NP surgery, ideal time for safety & tolerability[2]
- ASA desensitization/therapy does cause regression of NPs



1. Jerschow, E., et al. (2019). J Allergy Clin Immunol Pract 7(5): 1580-1588. 2. Han, J. K., et al.(2021). Int Forum Allergy Rhinol.

Effectiveness of ATAD

- Quality of evidence[1,2]
  - 1 meta-analysis
  - 5 RDBPC trials
  - 14 case series (918 pts)

	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	209.21 (8.30,901.87) RR 3.84 (1.11,12.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

1. Oykhman, P., et al. (2022). J Allergy Clin Immunol. 149 (4):1286-1295. 2. Stevens, W. W., (2021). J Allergy Clin Immunol 147(3): 827-844. 3. Jerschow, E.,et al. (2019). J Allergy Clin Immunol Pract 7(5): 1580-1588.

Effectiveness of ATAD

- Quality of evidence[1,2]
  - 1 meta-analysis
  - 5 RDBPC trials
  - 14 case series (918 pts)
- Onset of improvement within 4 wks.[3]
- Improvement in TNSS, reduced systemic steroids & revision surgery and improved QoL[4]
- Asthma symptoms reduced and improved FEV1, but to limited degree[5]
- Dose dependent effect up to 650 mg bid
- Inflammatory markers vary
  - Reduced PGE-M, PGD-M, & PGD2
  - LTE4 remains elevated or increases
  - Increase in blood eosinophils

1. Oykhman, P., et al. (2021). J Allergy Clin Immunol. 149 (4):1286-1295. 2. Stevens, W. W., (2021). J Allergy Clin Immunol 147(3): 827-844. 3. Jerschow, E.,et al. (2019). J Allergy Clin Immunol Pract 7(5): 1580-1588. 4. Orlandi, R. R., et al. (2021). Int Forum Allergy Rhinol 11(3): 213-739. 5. Mortazavi, N., H. Esmaeilzadeh, M. Abbasinazari, D. Babaie, S. Alyasin, H. Nabavizadeh and

ATAD Patient-reported benefits

- 10-year survey 62% remained on ATAD with benefit[1]
  - 38% discontinued ATAD
    - Lack of clinical benefit (26%)
    - Adverse reactions (26%)
    - Need for repeat surgery (23%)
  - Of those remaining on ATD, 85% report good control upper/lower airway symptoms, however:
    - No reduction in # of additional surgeries
    - No delay in first surgery after starting ATAD
- Tertiary care center 67% reported subjective improvement at 5 years[2]
- Some studies have shown reduced poly growth and reduced # of surgeries [3,4,5]
- BDPC trial (20 pts) on 6 months ATAD[6]
  - Symptom improvement asthma, upper airway, smell
  - Reduced inhaled corticosteroids

1. Berges-Gimeno, M. P., et al.(2003). Ann Allergy Asthma Immunol 90(3): 338-341. 2. Walters, K. M., et al. (2018). Am J Rhinol Allergy 32(4): 280-286. 3. McMains, K. C. et al. (2006). Am J Rhinol 20(6): 573-576. 4. Rozsasi, A., D. et al. (2008). Allergy 63(9): 1228-1234. 5. Levy, J. M., et al. (2016). Int Forum Allergy Rhinol 6(12): 1273-1283. 6.Swierczynska-Krepa, M., M. et al.(2014). J Allergy Clin Immunol 134(4): 883-890.

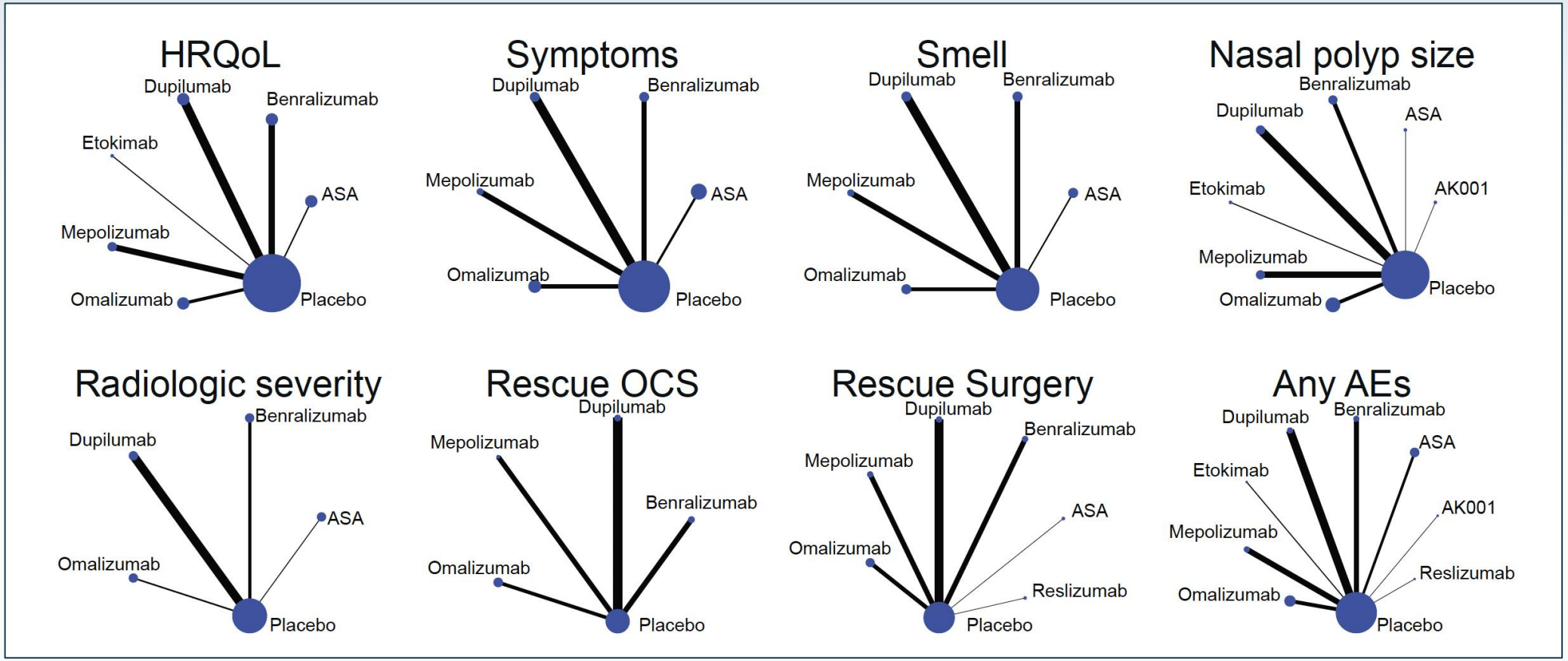
ATAD in the biologic era

- 103 AERD patients had surgery followed by ATAD
  - 6-month follow-up: 2/103 on biologics[1]
- Real-world cross-sectional study (98 pts)[2]
  - 76% (n=59)of ATAD treated patients (n=78) reported effectiveness and continued use for a mean of 46 ± 40.5 months (range 1-240 months)
  - 24.4% used ATAD + biologic (older, more severe group)
  - Dupilumab most successful biologic agent
  - SNOT-22, ACT, # of lifetime sinus surgeries— no sign. difference in
    - ATAD
    - Biologic
    - ATAD + biologic
    - No ATAD or biologic

1. Sweis, A. M., et al. (2021). Allergy Asthma Proc 42(2): 136-141. 2.Mullur, J., et al. (2022). Ann Allergy Asthma Immunol 128(5): 575-582.

BIOLOGICS

Meta-analysis of Current Therapies for CRSwNP



Nodes are weighted proportional to the number of studies evaluating each treatment
Spokes are weighted proportional to degree of improvement or adverse effect (AE)
** Only 1/3 of total patients had AERD

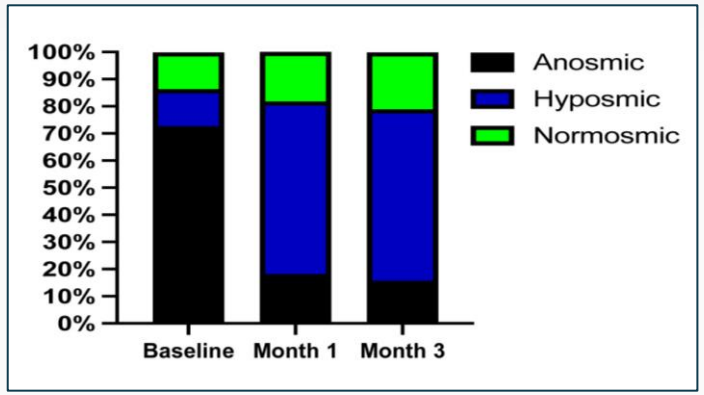
Oykhman, P., et al. (2022). J Allergy Clin Immunol. 149 (4):1286-1295.

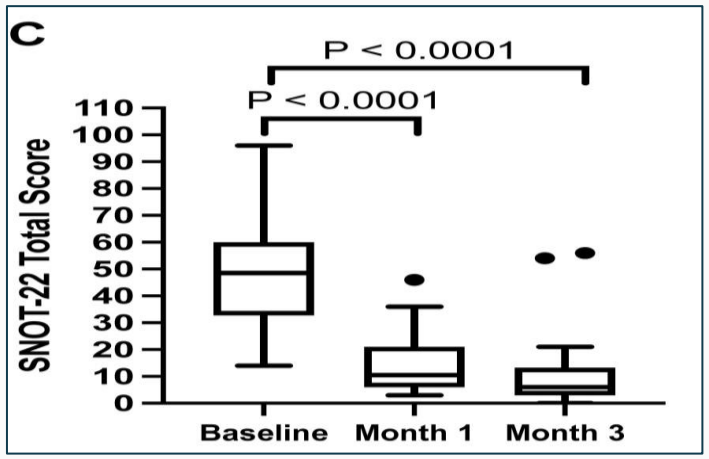
Dupilumab for AERD improves Upper & Lower airway symptoms

Buchheit, K. M., et al. (2022). J Allergy Clin Immunol 150(2): 415-424.

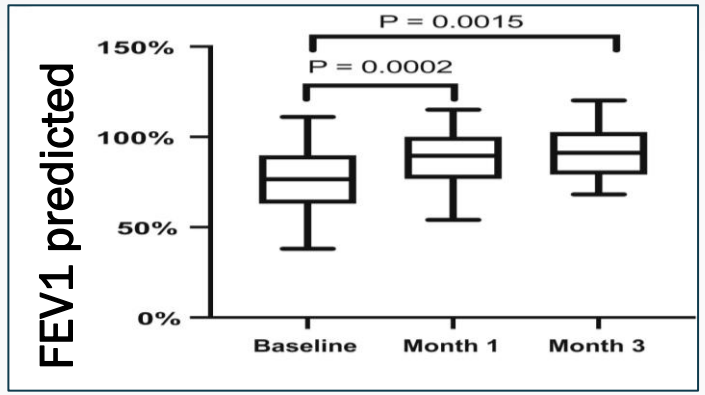
22 patients

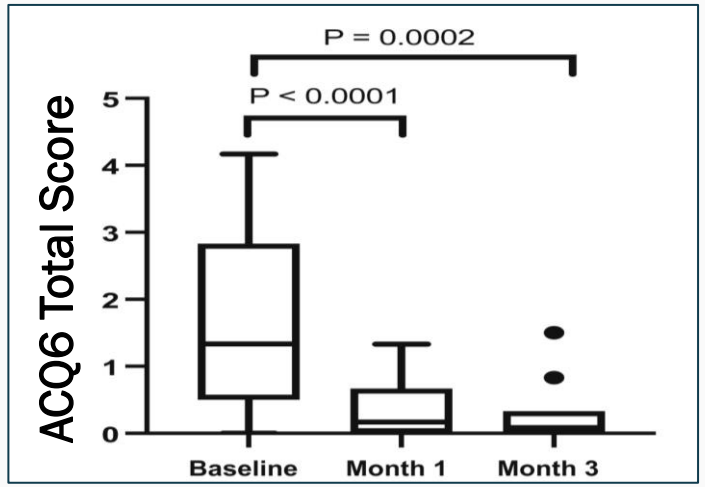
Upper airway





Lower airway

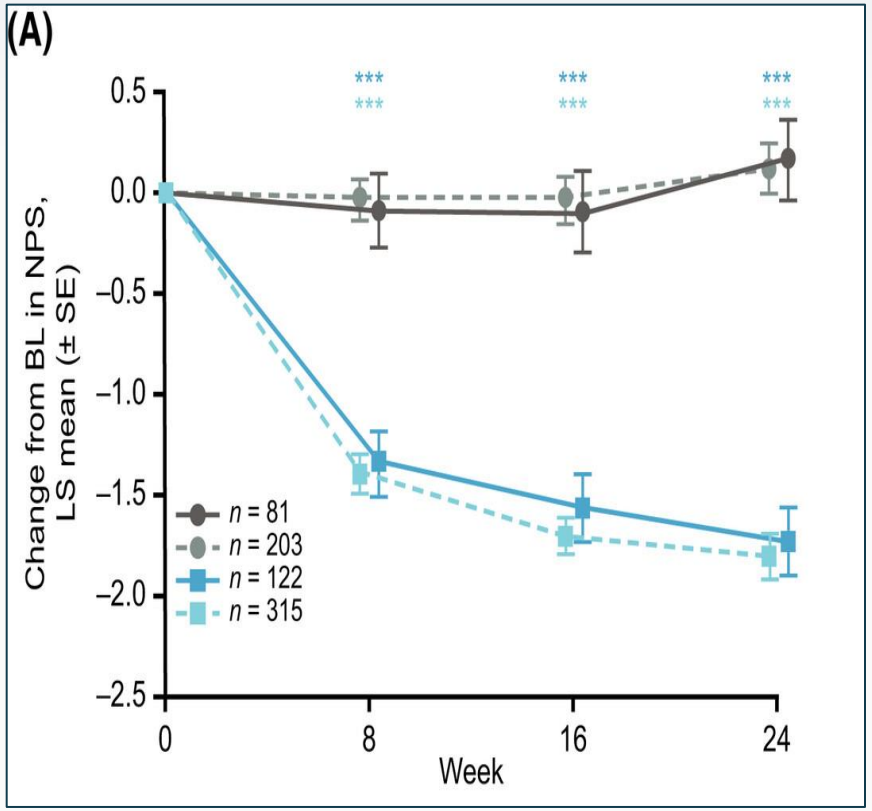




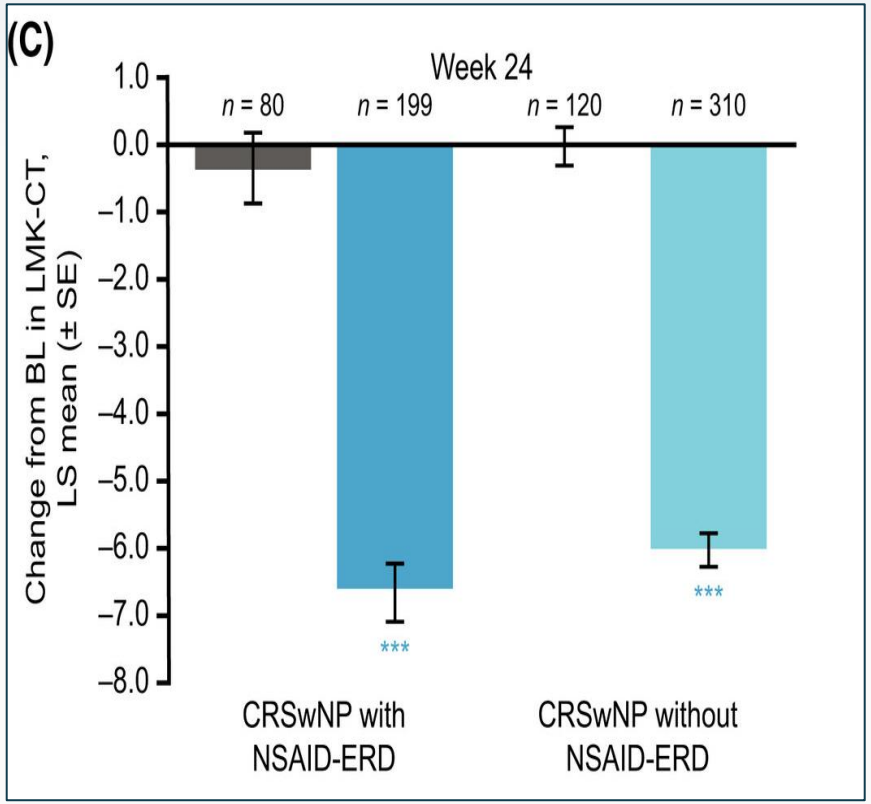
Dupilumab in CRSwNP in AERD

204 patients from 2 phase 3 trials at 24 wks

Reduction in Nasal polyp Score



Reduction in Lund-Mackay CT Score



Placebo AERD

Placebo No AERD

Dupi AERD

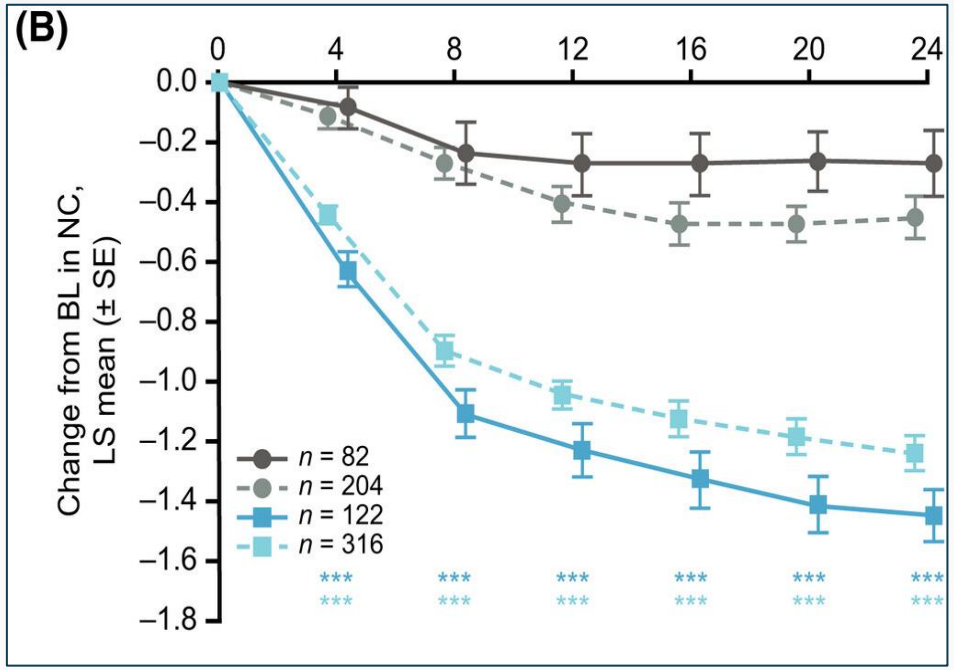
Dupi No AERD

Allergy, Volume: 77, Issue: 4, Pages: 1231-1244, First published: 30 August 2021, DOI: (10.1111/all.15067)

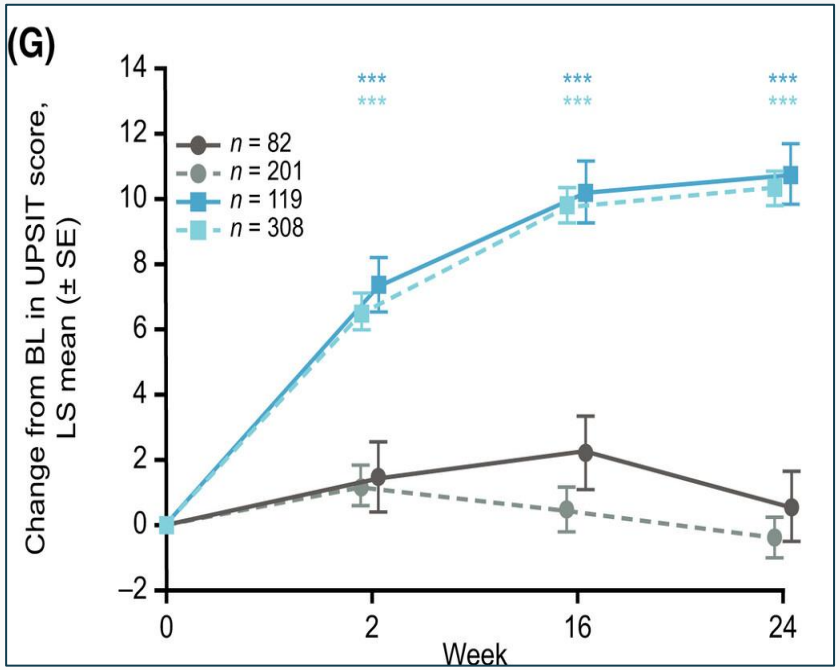
Dupilumab in CRSwNP in AERD

204 patients from 2 phase 3 trials at 24 wks

Reduction in Nasal congestion Score



Increase in UPSIT Score



Placebo AERD

Placebo No AERD

Dupi AERD

Dupi No AERD

Allergy, Volume: 77, Issue: 4, Pages: 1231-1244, First published: 30 August 2021, DOI: (10.1111/all.15067)

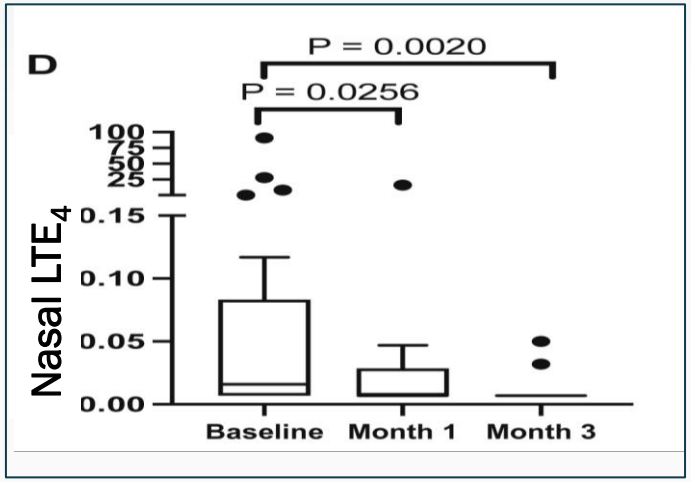
Dupilumab improves Nasal & Urinary eicosanoids

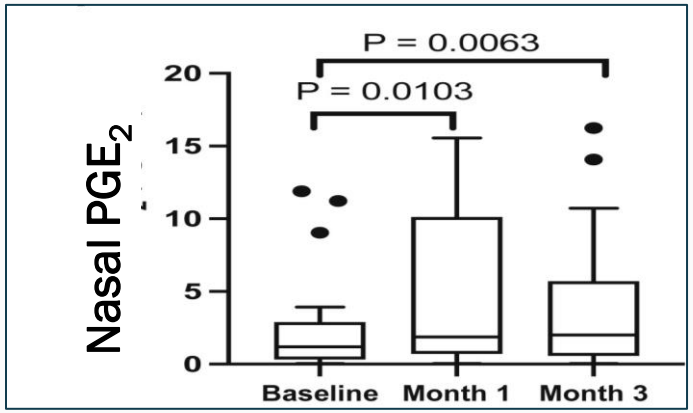
Buchheit, K. M., et al. (2022). J Allergy Clin Immunol 150(2): 415-424.

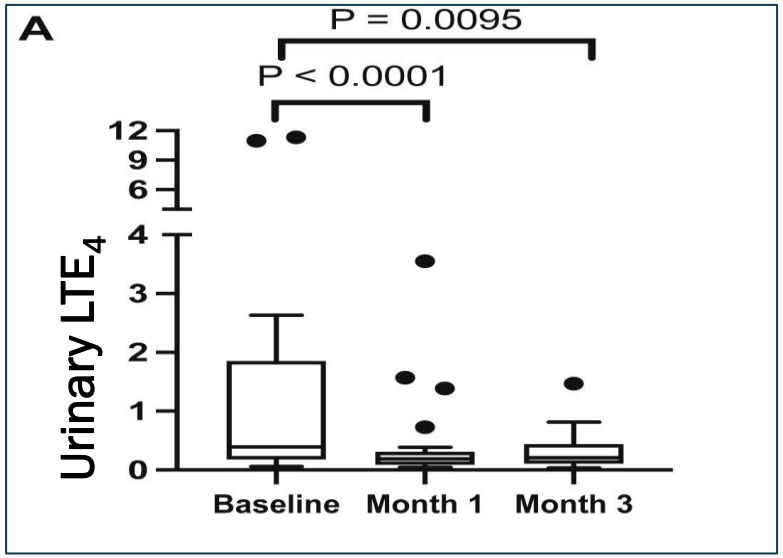
Nasal eicosanoids

22 patients

Urinary eicosanoids

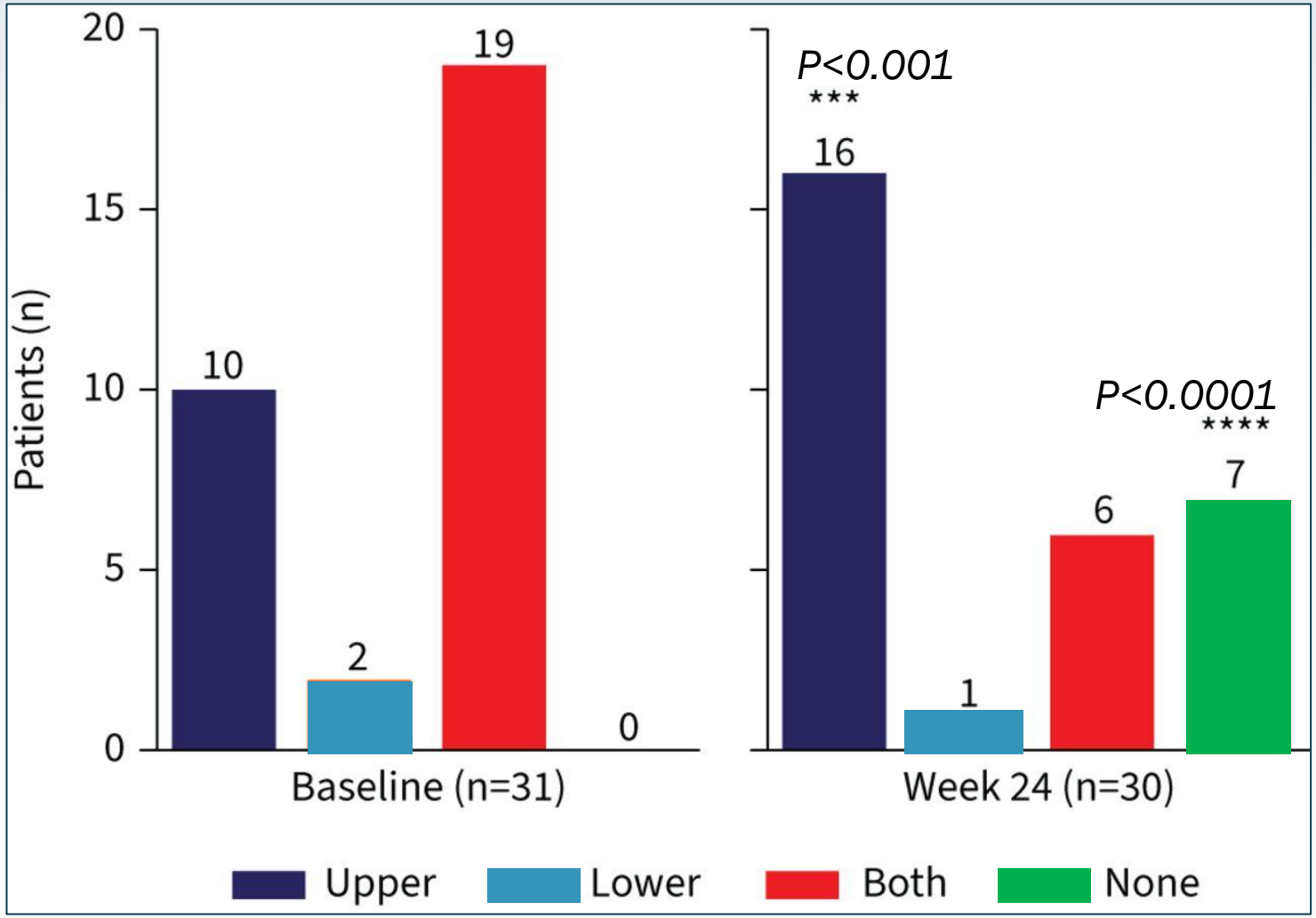






- No reduction in IL4, IL13, IL33, TSLP
- The decrease in nasal IgE Is less for dupilumab than for omalizumab

ASA provocation following Dupilumab Tx
Respiratory symptoms shift to upper airway



Schneider, S., et al. (2023). Eur Respir J 61(3).

Omalizumab for AERD improves Upper & Lower airway symptoms

Placebo
Omalizumab

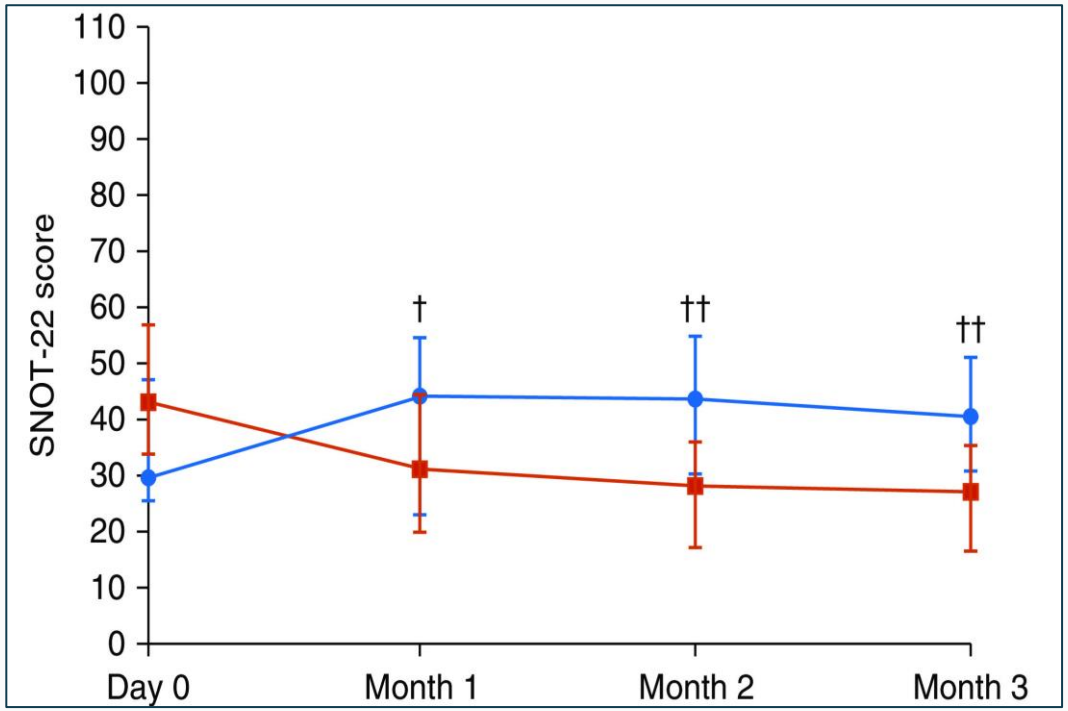
Upper airway

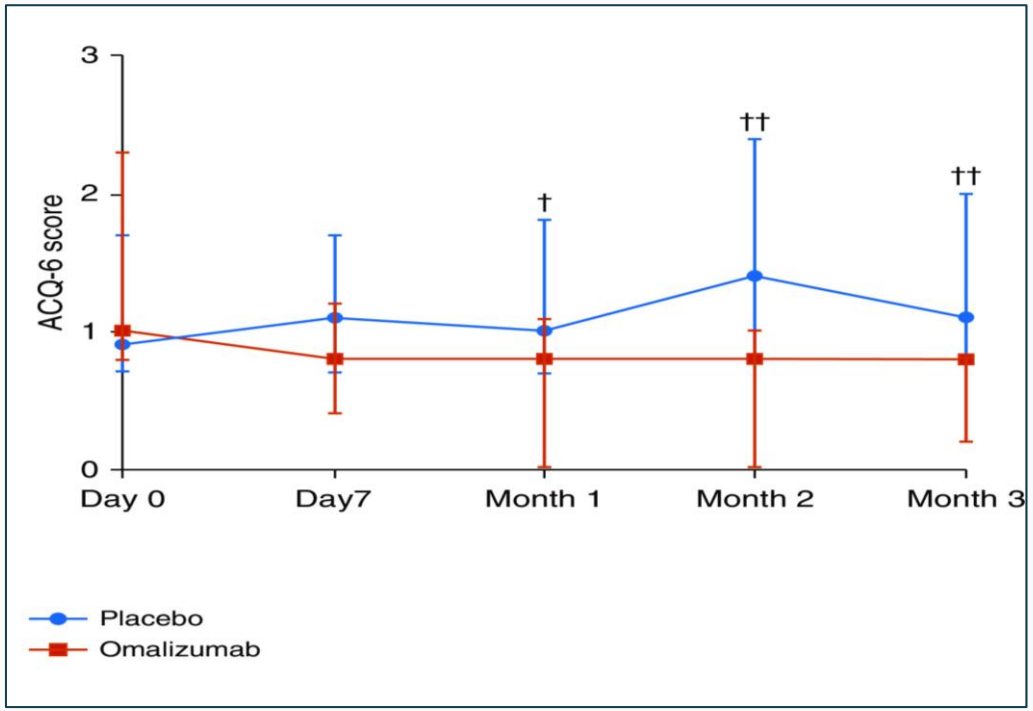
SNOT-22

16 patients

Lower airway

ACQ6 Total Score



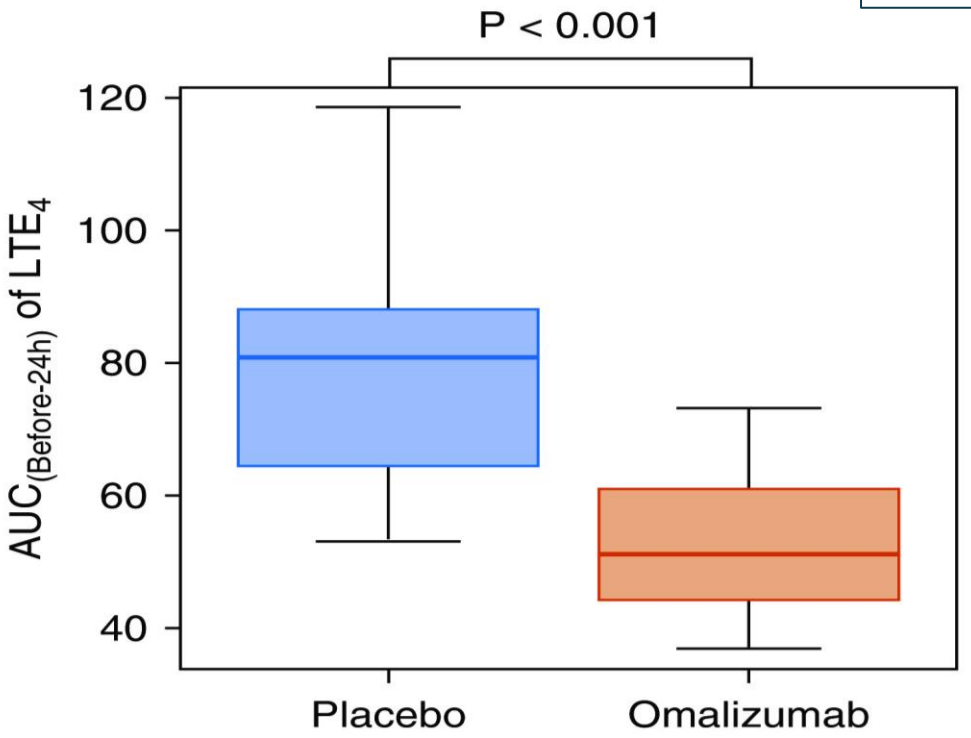


Hayashi, H., Y. et al. (2020). Am J Respir Crit Care Med 201(12): 1488-1498.

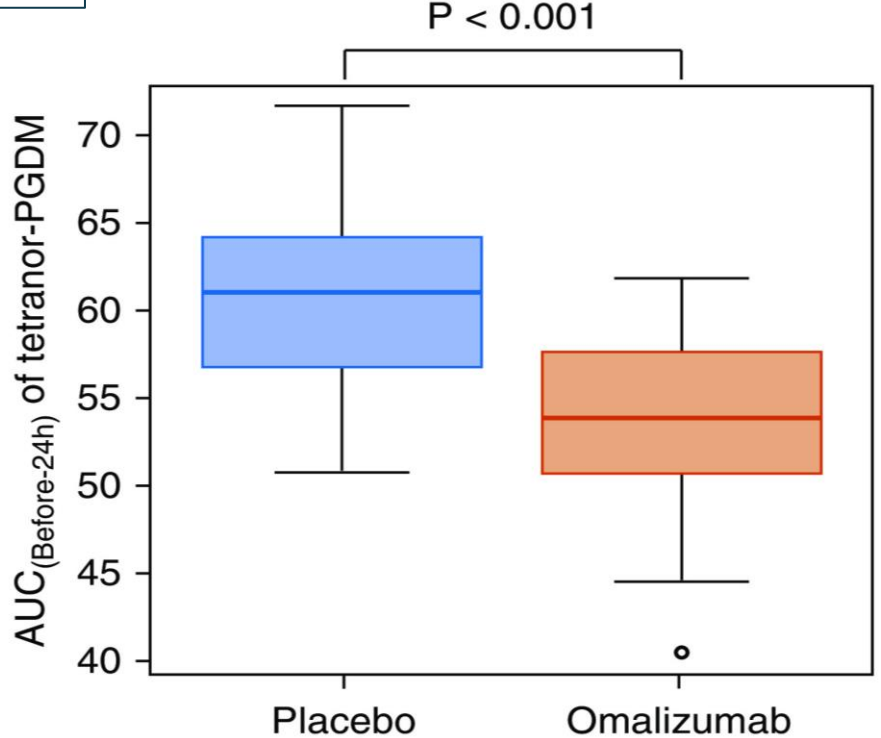
ASA challenge after Omalizumab Tx

Urinary LTE_4 Before-24 hours

16 patients

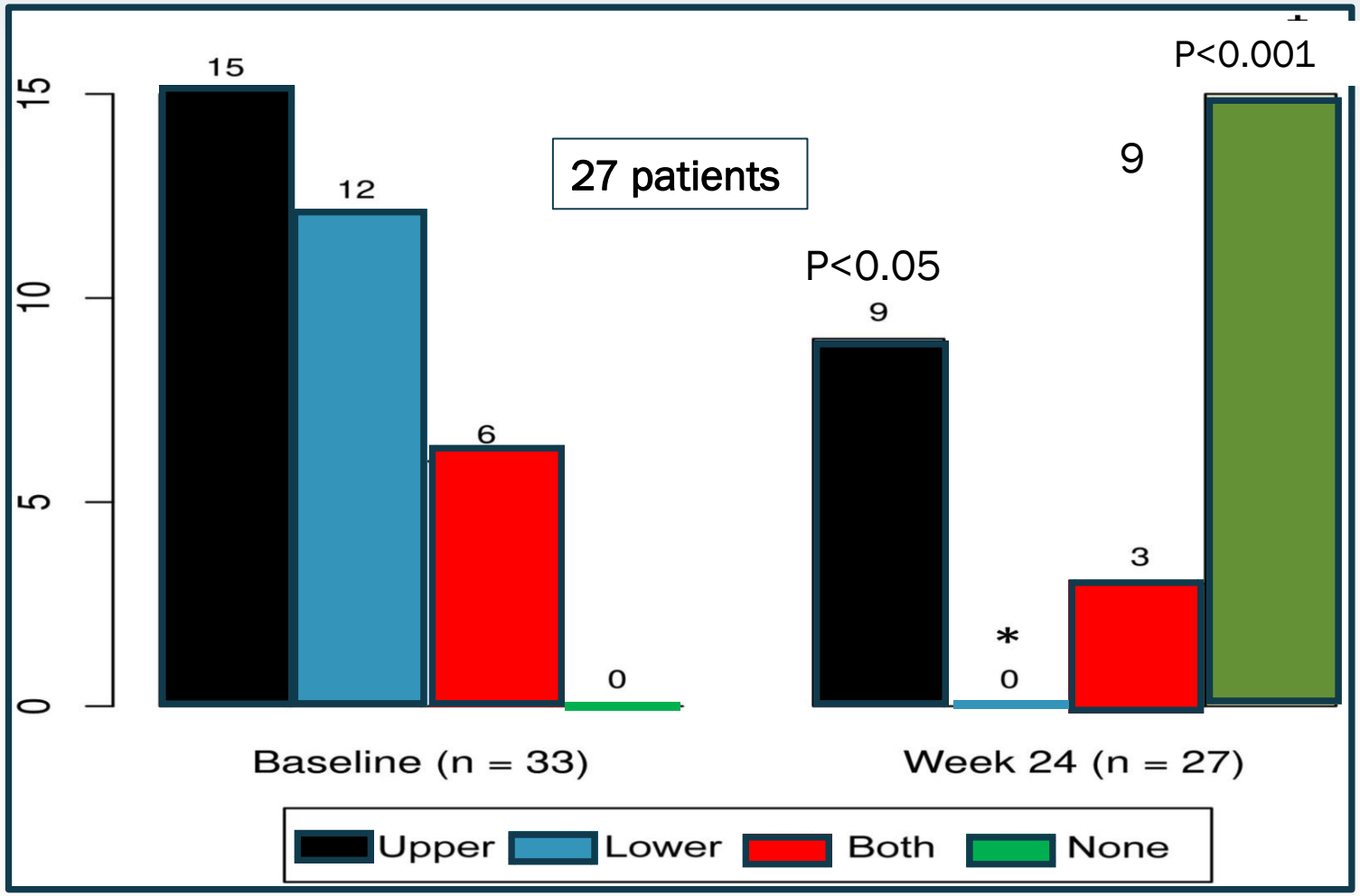


Urinary PGD-M Before-24 hours



Hayashi, H., Y. et al. (2020). Am J Respir Crit Care Med 201(12): 1488-1498.

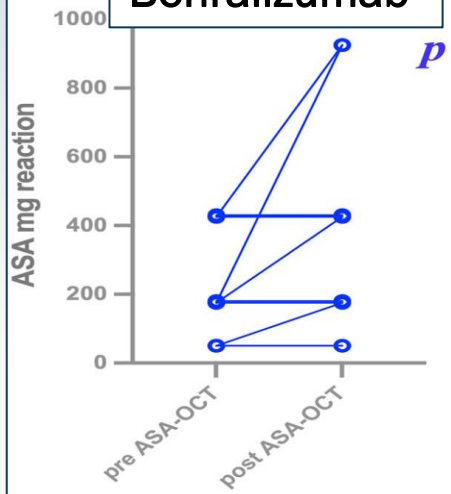
ASA provocation following Omalizumab Tx upper and lower respiratory symptoms reduced



Quint, T., V. et al. (2022). J Allergy Clin Immunol Pract 10(2): 506-516 e506.

ASA tolerance after 6 mo. of biological Tx

Benralizumab

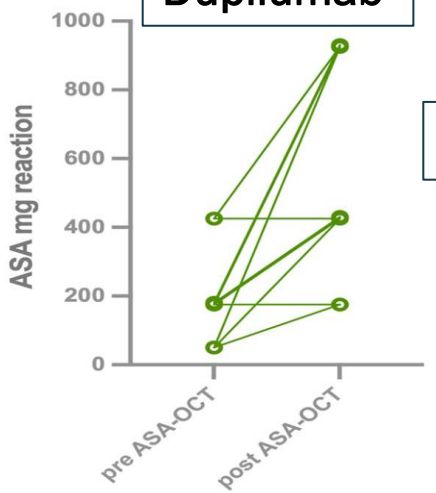


$p = 0.24$

22% complete tolerance

22% (2/9) Complete tolerance
22% (2/9) Higher tolerance
55% (5/9) Equal tolerance

Dupilumab

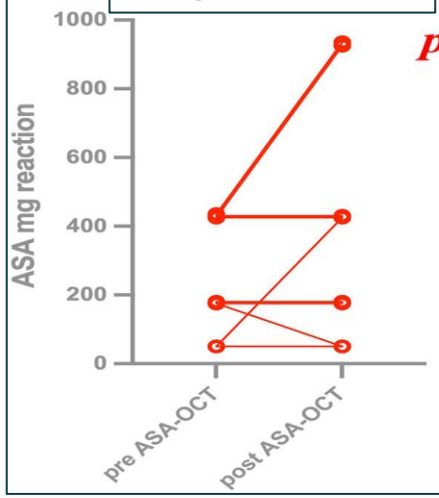


$p = 0.004$

40% complete tolerance

40% (4/ 10) Complete tolerance
40% (4/10) Higher tolerance
20% (2/10) equal tolerance

Mepolizumab

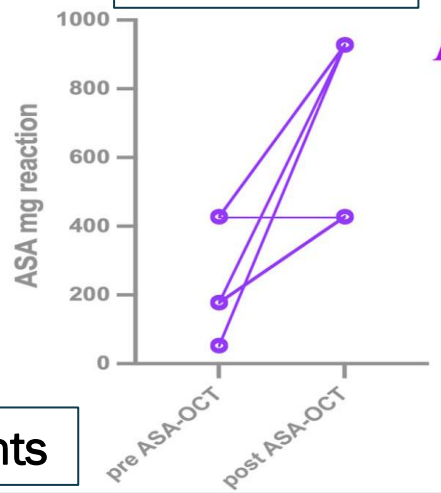


$p = 0.58$

22% complete tolerance

22% (2/9) Complete tolerance
11% (1/9) Higher tolerance
55% (5/9) Equal tolerance
11% (1/9) Lower tolerance

Omalizumab



$p < 0.001$

60% complete tolerance

60% (6/10) Complete tolerance
30% (3/10) Higher tolerance
10% (1/10) equal tolerance

38 patients

Sanchez, J., E. et al. (2023). J Allergy Clin Immunol Pract 11(7): 2172-2179.

Meta-analysis 29 RCTs: comparing biologics in CRSwNP

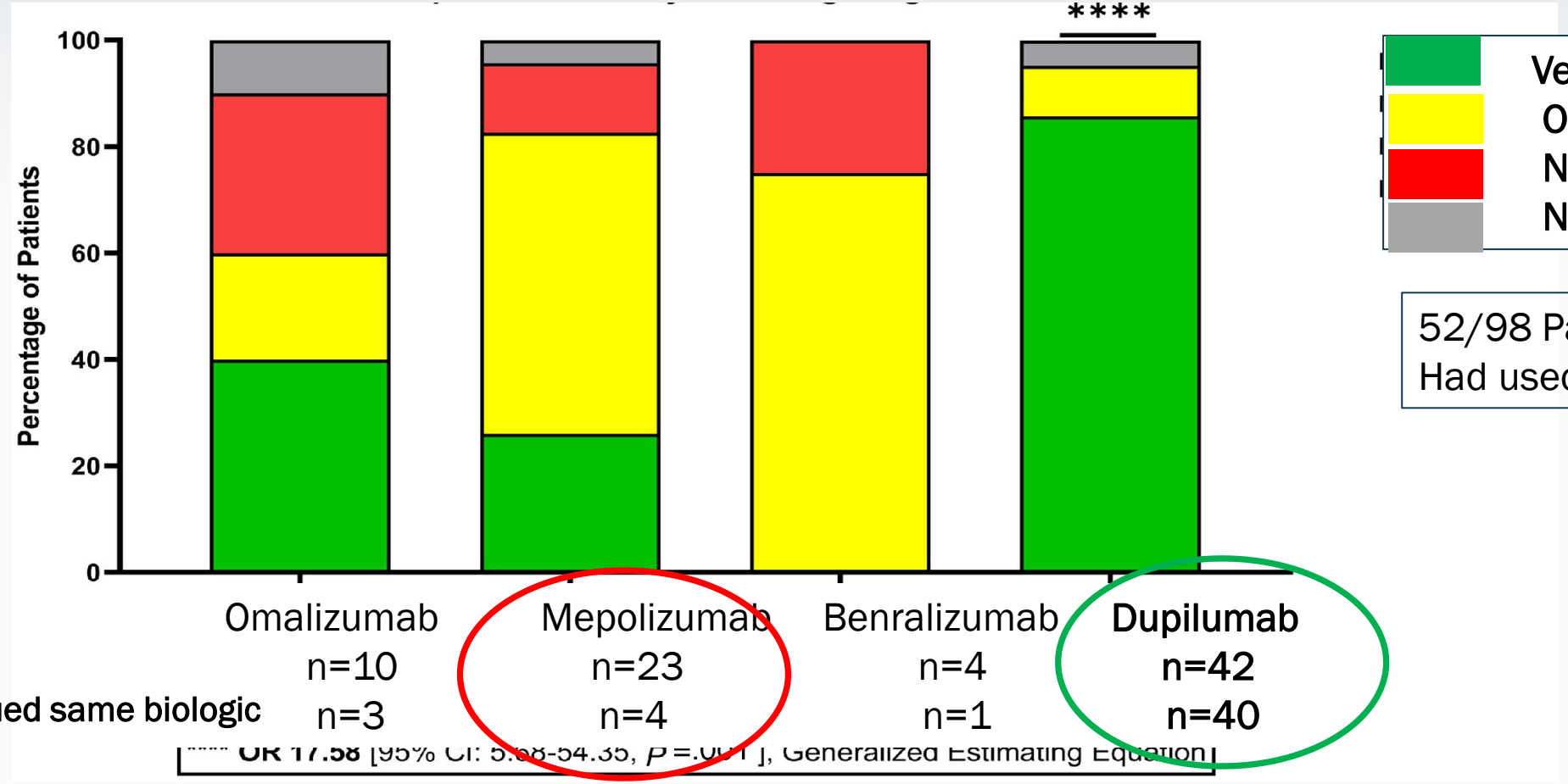
	Patient-important outcomes						Surrogate outcomes	
	HRQoL SNOT-22 (0-110)‡	Symptoms VAS (0-10 cm)	Smell UPSIT (0-40)†	Rescue OCS	Rescue polyp surgery	Adverse events	Nasal polyp size (0-8)	CT score LMK (0-24)
Standard care*	50.11	6.84	14.04	31.96%	21.05%	73.78%	5.94	18.35
Dupilumab	**-19.91** (-22.50, -17.32)	**-3.25** (-4.31, -2.18)	**10.96** (9.75, 12.17)	**-21.73** (-24.61, -18.22) RR 0.32 (0.23, 0.43)	**-16.35** (-18.13, -13.48) RR 0.22 (0.14, 0.36)	**0.13** (-8.12, 9.88) RR 1.00 (0.88, 1.13)	**-2.04** (-2.73, -1.35)	**-7.51** (-10.13, -4.89)
Omalizumab	**-16.09** (-19.88, -12.30)	**-2.09** (-3.15, -1.03)	**3.75** (2.14, 5.35)	**-12.46** (-23.65, 12.78) RR 0.61 (0.26, 1.40)	**-7.40** (-11.04, -2.43) RR 0.65 (0.48, 0.88)	**-2.60** (-15.58, 13.28) RR 0.96 (0.79, 1.18)	**-1.09** (-1.70, -0.49)	**-2.66** (-5.70, 0.37)
Mepolizumab	**-12.89** (-16.58, -9.19)	**-1.82** (-3.13, -0.50)	**6.13** (4.07, 8.19)	**-10.23** (-15.98, -2.88) RR 0.68 (0.50, 0.91)	**-12.33** (-15.56, -7.22) RR 0.41 (0.26, 0.66)	**-3.07** (-13.44, 9.07) RR 0.96 (0.82, 1.12)	**-1.06** (-1.79, -0.34)	
Benralizumab	**-7.68** (-12.09, -3.27)	**-1.15** (-2.47, 0.17)	**2.95** (1.02, 4.88)	**-9.91** (-16.30, -0.96) RR 0.69 (0.49, 0.97)	**-2.53** (-9.05, 7.16) RR 0.88 (0.57, 1.34)	**-1.48** (-13.28, 12.54) RR 0.98 (0.82, 1.17)	**-0.64** (-1.39, 0.12)	**-1.00** (-3.83, 1.83)
Reslizumab					**-18.82** (-20.93, 20.56) RR 0.11 (0.01, 1.98)	**-2.55** (-19.49, 19.18) RR 0.97 (0.74, 1.26)		
AK001						**2.54** (-27.11, 51.03) RR 1.03 (0.63, 1.69)	**-0.20** (-1.61, 1.21)	
Etokimab	**-1.30** (-8.99 to 6.40)					**188.14** (-59.76, 4879.1) RR 3.55 (0.19, 67.13)	**-0.33** (-1.58, 0.92)	
ASA Desensitization	**-10.61** (-14.51, -6.71)	**-2.74** (-3.92, -1.57)	**2.72** (-1.17, 6.61)		**-16.00** (-19.79, 0.21) RR 0.24 (0.06, 1.01)	**209.21** (8.30, 901.87) RR 3.84 (1.11, 13.22)	**-0.95** (-2.44, 0.55)	**-0.31** (-3.50, 2.88)

Classification of intervention (colour)[24]				Certainty (shading)[24, 29]
Among most beneficial	Among intermediate beneficial	Among least beneficial/not clearly different from placebo	No data (blank)	High/moderate (solid)
Among most harmful	Among intermediate harmful			Low/very low (shaded)

1/3 of patients had been diagnosed to have AERD

Oykhman, P., et al. (2022). J Allergy Clin Immunol. 149 (4):1286-1295.

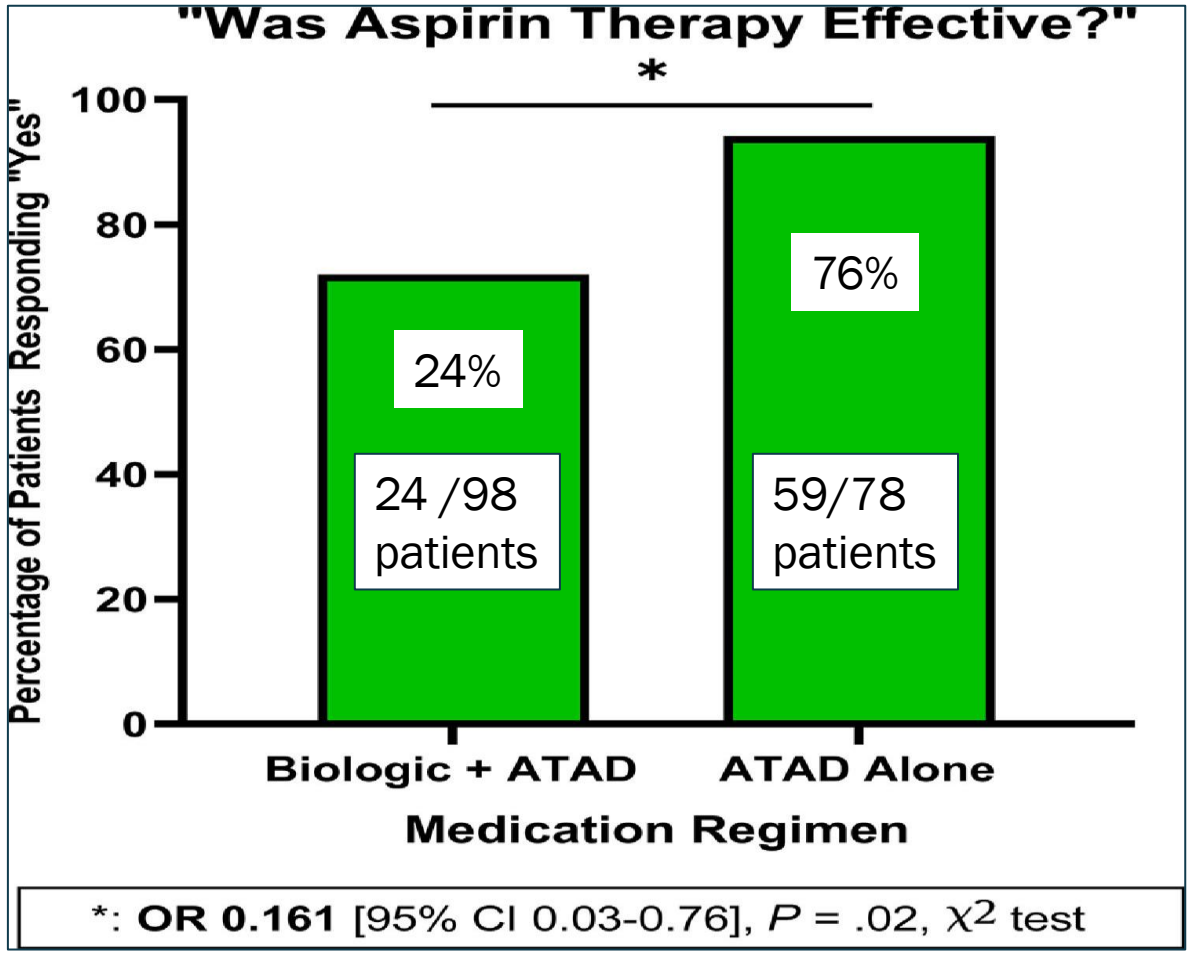
Patient Reported Efficacy of Biologic Agents in AERD: Registry survey



52/98 Patients
Had used a biologic

Mullur, J., et al. (2022). Ann Allergy Asthma Immunol 128(5): 575-582.

Registry patients with history of ATAD use
Patient response as to ATAD effectiveness



84/98 patients had undergone ASA desensitization

78/98 had continued with ATAD
Mean use ATAD: 46.2 mo. +/- 40.5 mo.

24/98 added a biologiv

Biologic + ATAD patients may be have been mo severe subset

Mullur, J., et al. (2022). Ann Allergy Asthma Immunol 128(5): 575-582.

Mepolizumab ⟹ Dupilumab

- 20 patients with severe asthma and CRSwNP, all with prior ESS (average of 2)
- 1 year or more of mepolizumab
  - Asthma controlled
  - CRSwNP not controlled
- Switch to dupilumab and followed for 18 months
  - All patients had improvement in IgE, SNOT22, NPS, ACT, Olfactory function; Eos increased at 6 months but decreased by 18 months
  - 1 patient had uncontrolled asthma and returned to mepolizumab
  - 2 other patients dropped out due to other reasons
- Dupilumab will mean dosing every other week

.

Rosso, C., E. (2024). Eur Arch Otorhinolaryngol. DOI: 10.1007/s00405-024-08461-y

Switching biologics

- Patients failing to respond to omalizumab or mepolizumab/benralizumab often respond to dupilumab[1]
- When switching to 2nd biologic, when dupilumab is 2nd biologic, it seems to be associated with more adverse events than when used as 1st biologic or another biologic, esp. hypereosinophilia[1]
  - Consider making 2nd switch or
  - Combine with anti-IL-5 agent
- Omalizumab switch to dupilumab associated with keratoconjunctivitis sicca in 4.3%[1]
- Look for unexplored cross-reactions when adding 2nd biologic or switching biologics[3]
  - What will be the incidence of duplimab associated joint pain, eosinophilic granulomatosis with pol7angitis?
- SUCRA (FDA) values reported slightly higher frequencies of cough, bronchitis, arthralgia for dupilumab (all dx) compared to other biologics

1. Otten, J., R. (2023). Expert Rev Clin Immunol 19(8): 1041-1049. 2. Brkic, F. F (2023). Rhinology 61(4): 320-327.
3 Nitro, L., A. (2022). Acta Otorhinolaryngol Ital 42(3): 199-204.

Real-world biologic effectiveness in AERD

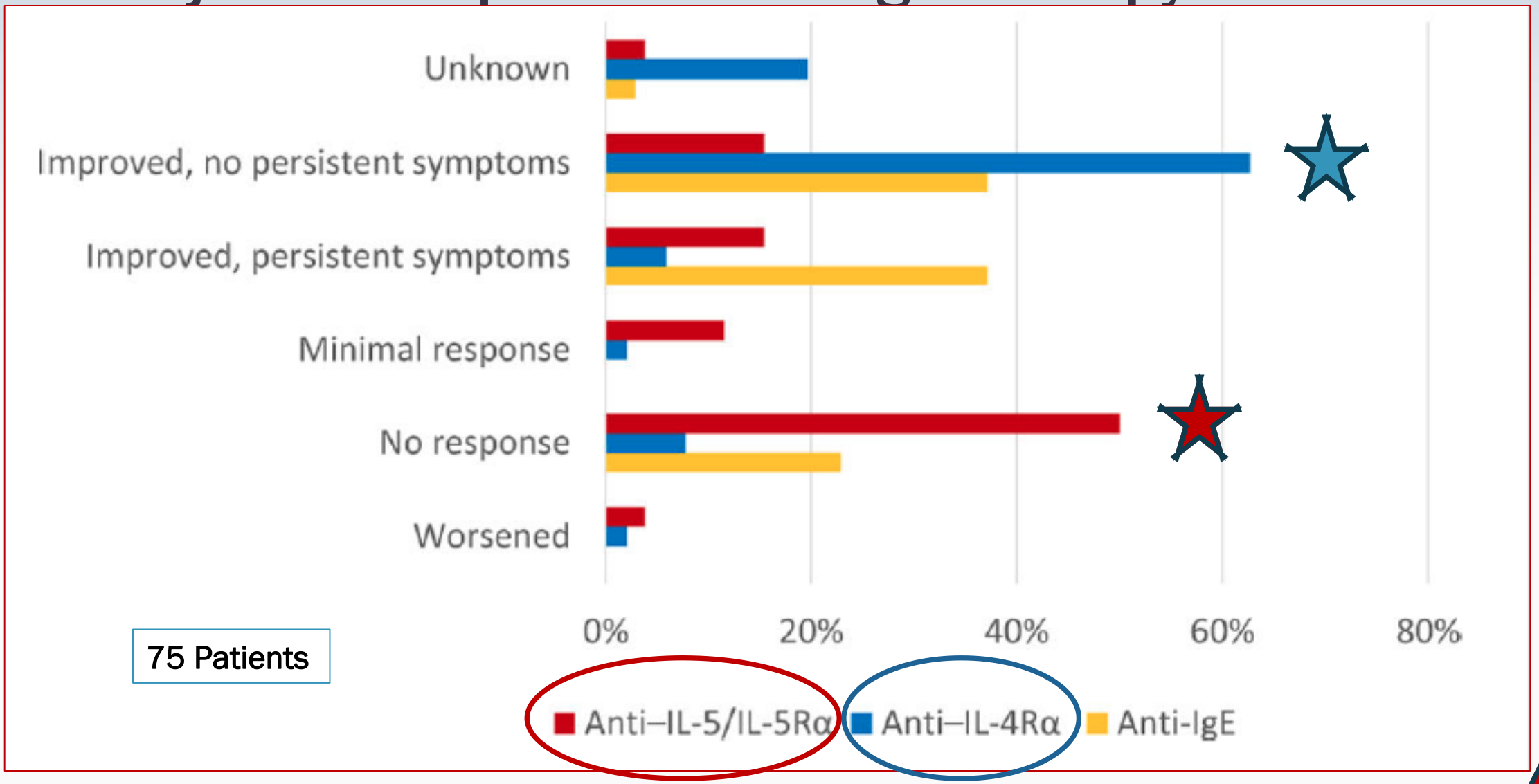
75 Patients

Historical Use of Biologic* $N = 111$	Last Prescribed Biologic** $N = 75^{+}$				
	Omalizumab $n = 17^{+}$	Benralizumab $n = 3$	Mepolizumab $n = 2^{+}$	Reslizumab $n = 2$	Dupilumab $n = 51$
Omalizumab $n = 35^{+}$	$17^{+}/35$ 49%	2/35 6%	$1^{+}/35$ 3%	1/35 3%	15/35 43%
Benralizumab $n = 13$	1/13 8%	3/13 23%	0/13 0%	0/13 0%	9/22 69%
Mepolizumab $n = 10^{+}$	$1^{+}/10$ 10%	0/10 0%	$2^{+}/10$ 20%	0/10 0%	8/10 80%
Reslizumab $n = 3$	0/3 0%	1/3 33%	0/3 0%	2/3 67%	0/3 0%
Dupilumab $n = 50$	0/50 0%	1/50 2%	0/50 0%	0/50 0%	49/50 98%

0-20%
21-40%
41-60%
61-80%
>-80%

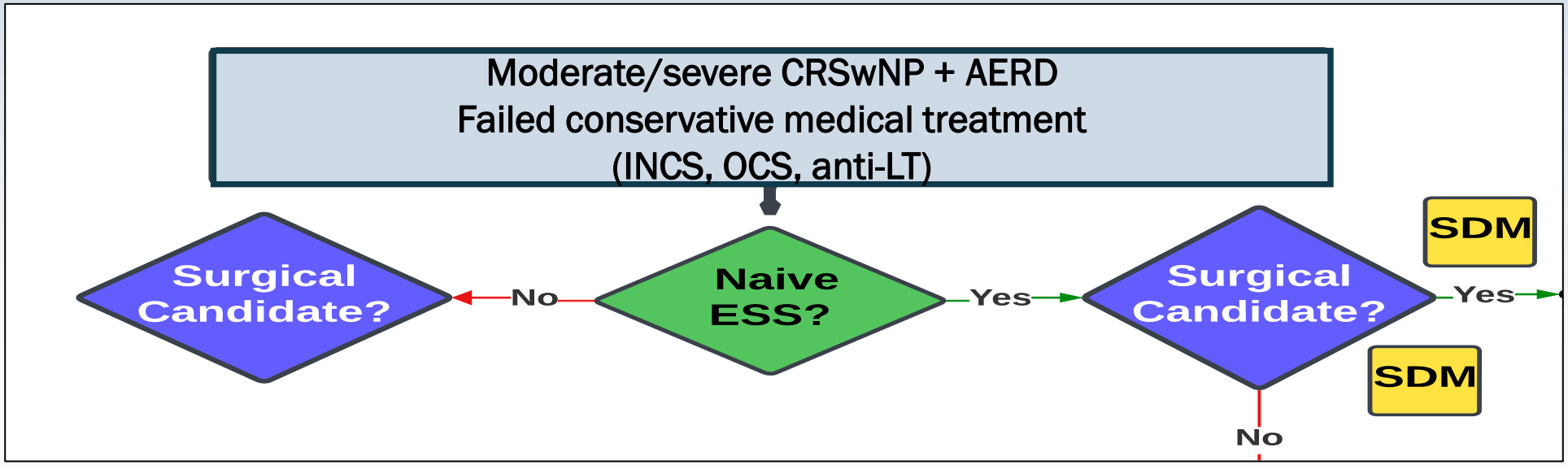
~~Wangberg~~, H., et al. (2022). J Allergy Clin Immunol Pract 10(2): 478-484 e473.

Subjective response to biologic therapy in AERD

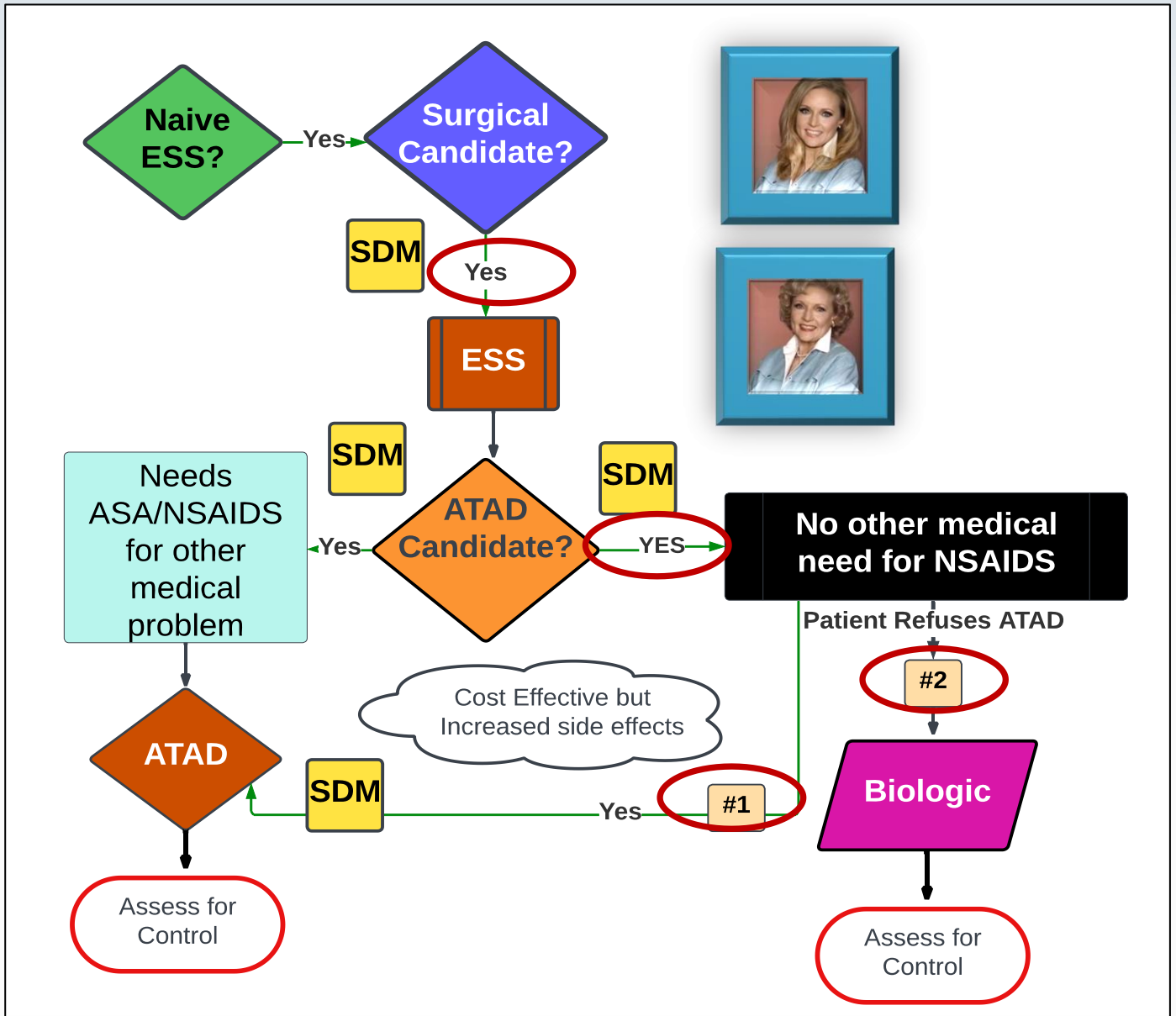


Wangberg, H., et al. (2022). J Allergy Clin Immunol Pract 10(2): 478-484 e473.

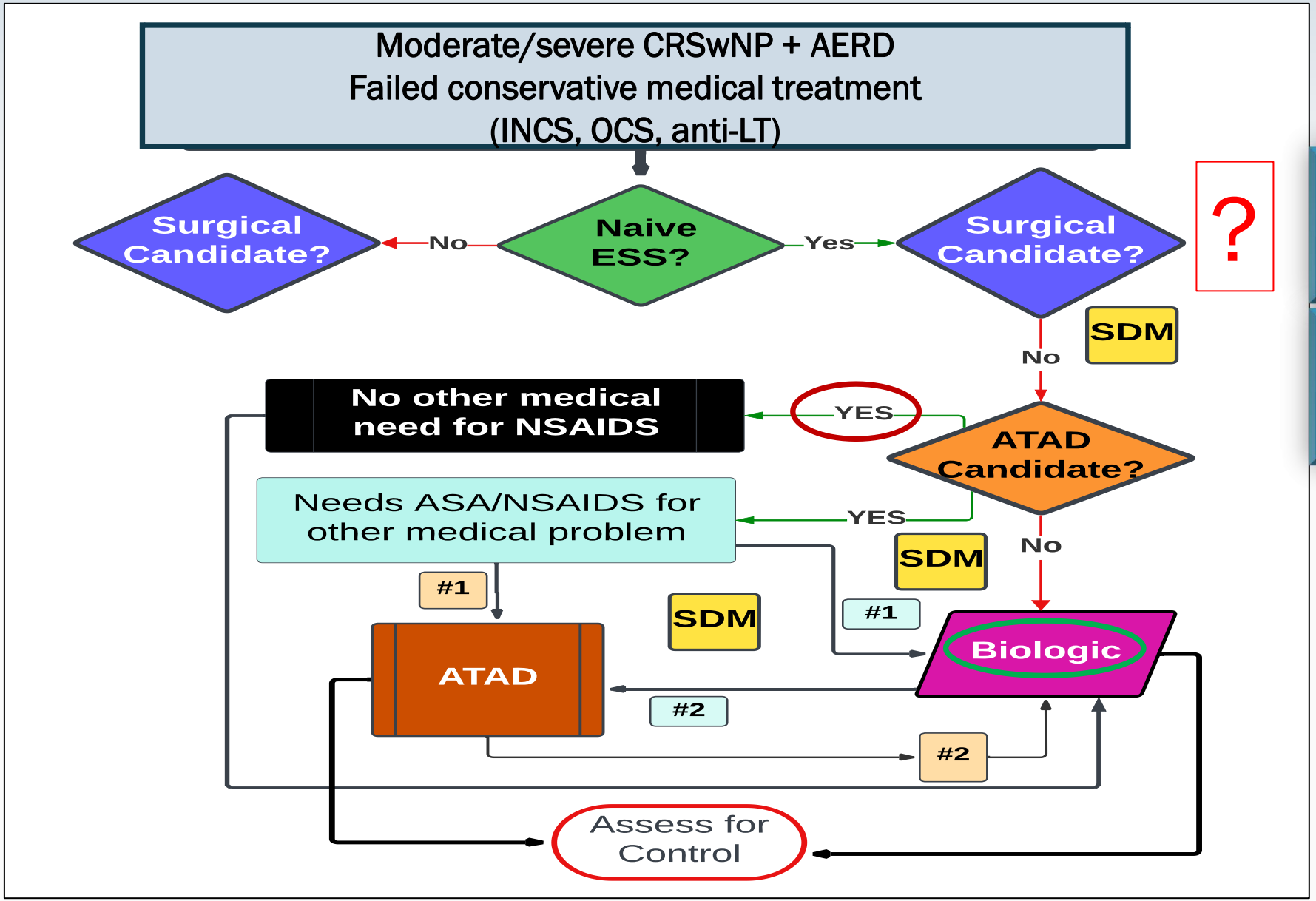
Decision point # 1a



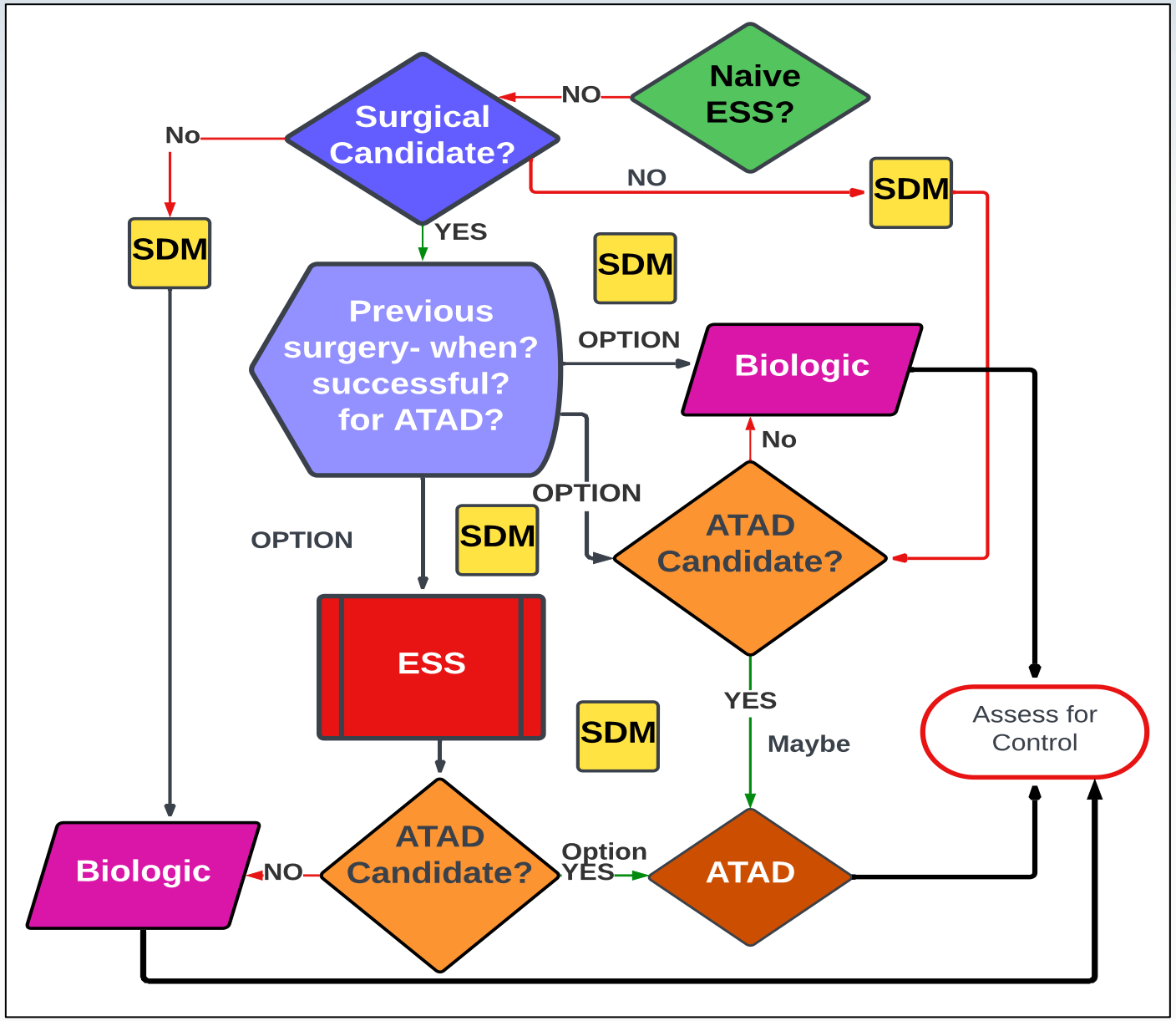
Decision point # 1b



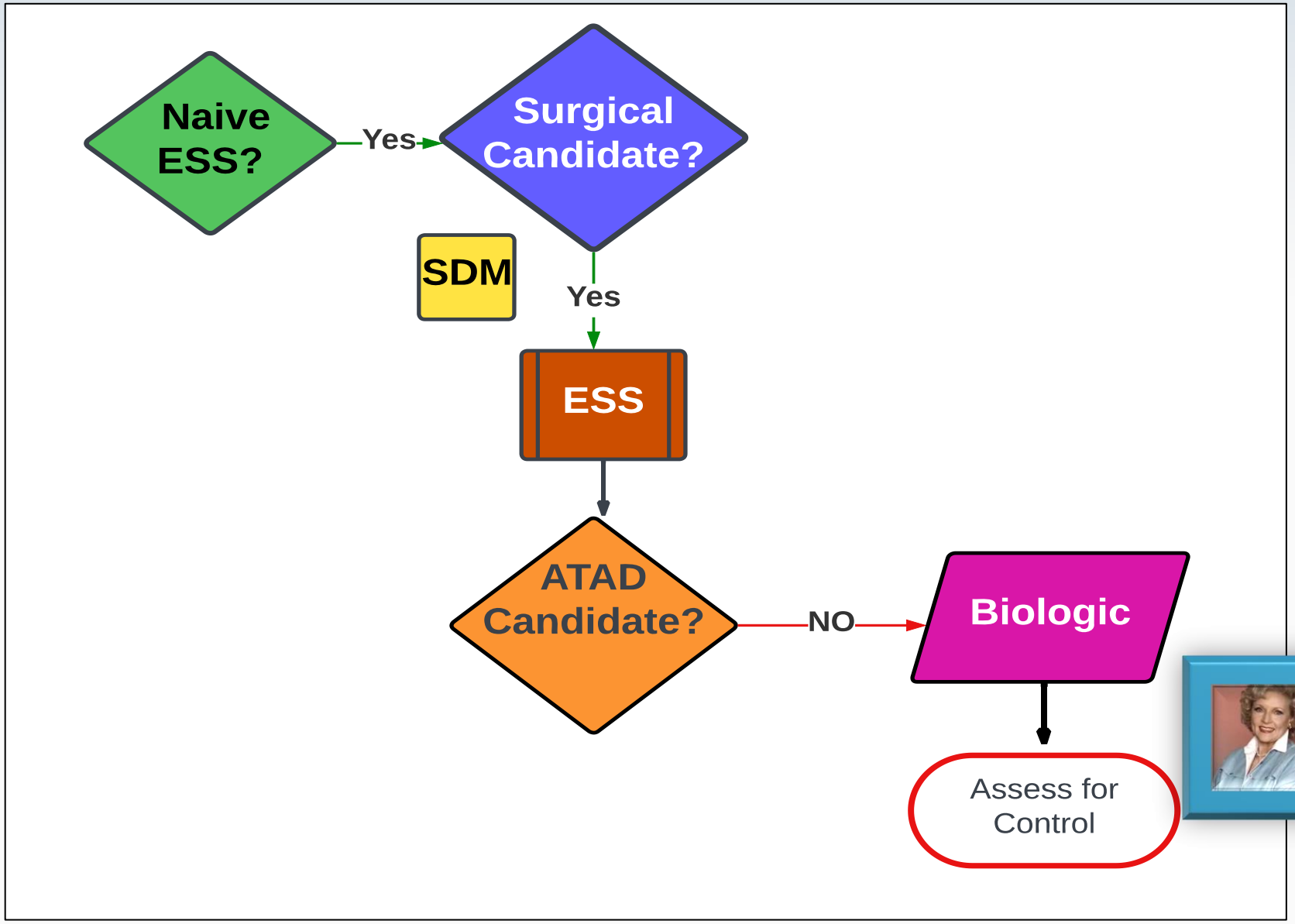
Decision point # 2a



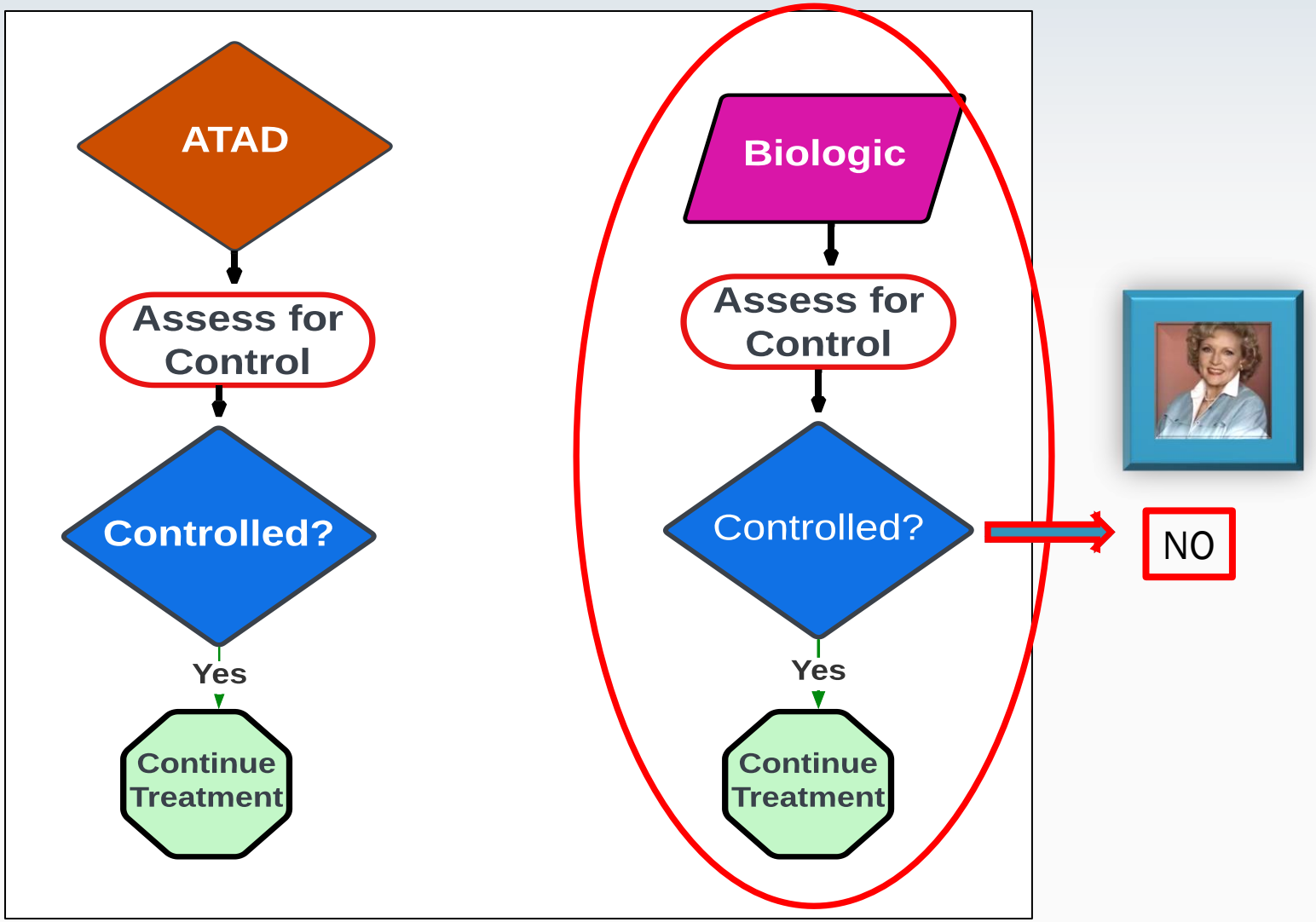
Decision point # 2c (Not for our patient)



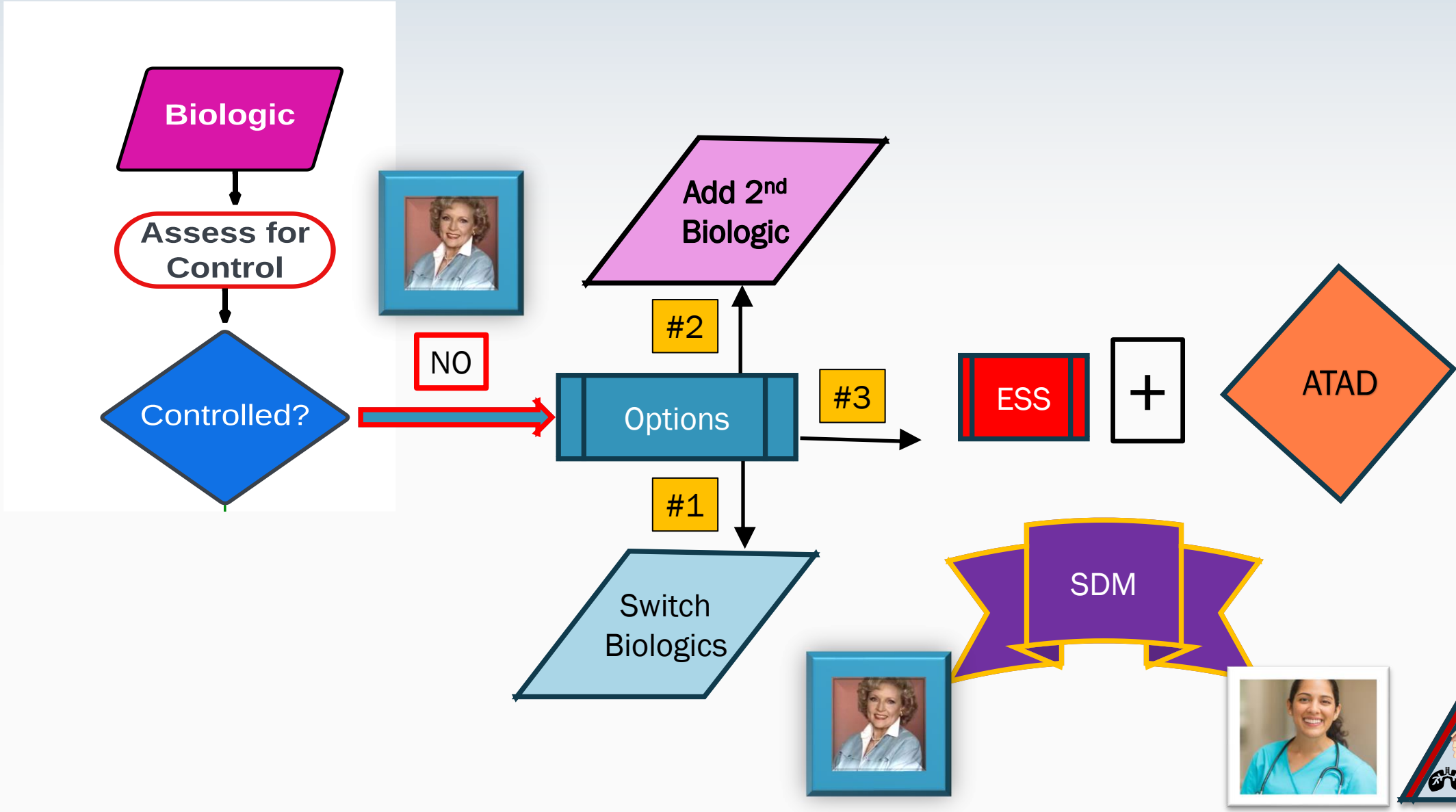
Decision point # 3



Decision point # 4



Decision point # 5



Cost effectiveness studies

- ATAD (prior to biologics) cost effective at <$50,000 per QALY
- ATAD more cost effective than clopidogrel for cardiovascular prophylaxis
- Dupilumab vs ESS for CRSwNP
  - ESS: $50,436 with 9.8 QALYs
  - Dupilumab: $537,420 for 8.94 QALYs
  - Dupilumab would need to be $855/year to be more cost effective than ESS
- For AERD, surgery + ATAD more cost effective than dupilumab first
- Surgery + ATAD with salvage dupilumab was cost effective with ICER of $135, 517
  - Upfront dupilumab was not cost effective with ICER of $273,181
- Surgery + ATAD= QALY of 4.96 vs. upfront Dupilumab=QALY of 5.8

QALY= Quality adjusted life year; ICER= incremental cost effectiveness ratio

Laidlaw, T. M. et al. (2024).J Allergy Clin Immunol Pract **12**(1): 79-84.

Unanswered questions

- What is the most cost-effective long-term treatment for AERD patients?
- Should any AERD patients be started on ATAD prior to a first ESS?
- What is the role of biologics before or paired with ESS?
  - Some or all AERD patients?
  - Presence of moderate/severe asthma?
  - Patient preference?
- Can biologics replace both ESS and ATAD?
- When biologics are ineffective, will adding ATAD be helpful?