Pulmonary year in review

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Diplomate of the American Board of Internal Medicine In Internal Medicine

Pulmonary & Critical Care

UWI/ BAMP CME conference

November 14th 2015

NO RELEVANT FINANCIAL DISCLOSURES.

Objectives

- Review of clinically relevant studies (2013-2015) impacting pulmonary practice.
- Generate discussion with respect to the applicability of some of the study outcomes
- Highlight new developments

Methodology

- Pubmed
- Journal watch
- Journals: NEJM, Annals of internal medicine, Chest, The blue journal
- Society guidelines: ATS, BTS,ACCP,

Malignancy

- Low dose CT screening for lung cancer

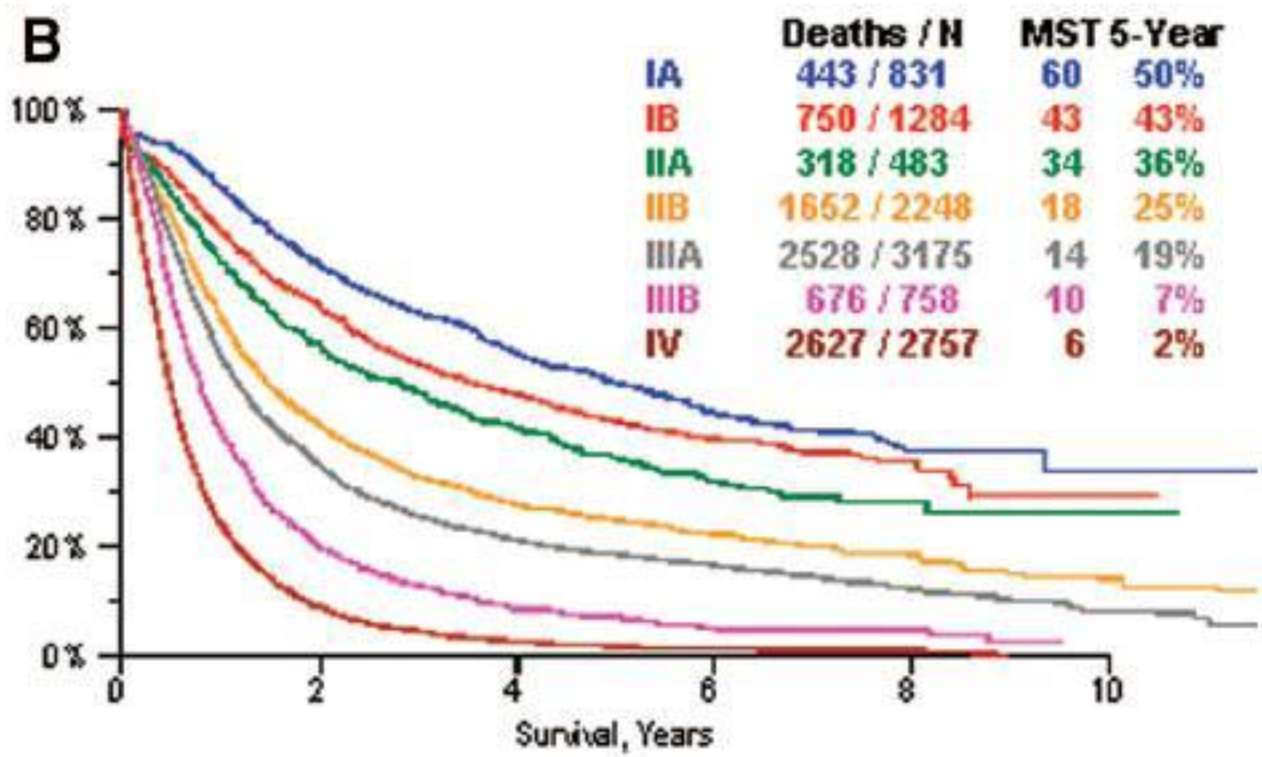
Here we go again….

- To screen or not to screen that is the question

Why screen for lung cancer?

- High prevalence (1 in 13 to 1 in 15 in US)
- High mortality
- –#1 cancer killer in US
- –#2 cause of death in US
- Risk factors to target screening
- –Tobacco exposure
- –Occupational history
- –Family history
- Outcomes related to stage at diagnosis

Overall survival for non-small cell lung cancer by clinical stage



NO Lung screening recommended until now

- Until the NLST, no screening modality had been identified to reduce lung cancer mortality
- Thus until 2012,no recommendations for a screening strategy for lung cancer.

Potential screening tests

- **CXR: (6+ Large RCTs)**
- Increased detection of early stage lung cancers
- But no reduction in mortality
- **Sputum (with CXR)**
- no reduction in mortality
- **Chest CT ➔ Low Dose Chest CT**

Humphrey LL et al. Lung cancer screening. USPSTF update 2004

Original Article

Results of Initial Low-Dose Computed Tomographic Screening for Lung Cancer

The National Lung Screening Trial Research Team

N Engl J Med
Volume 368(21):1980-1991
May 23, 2013

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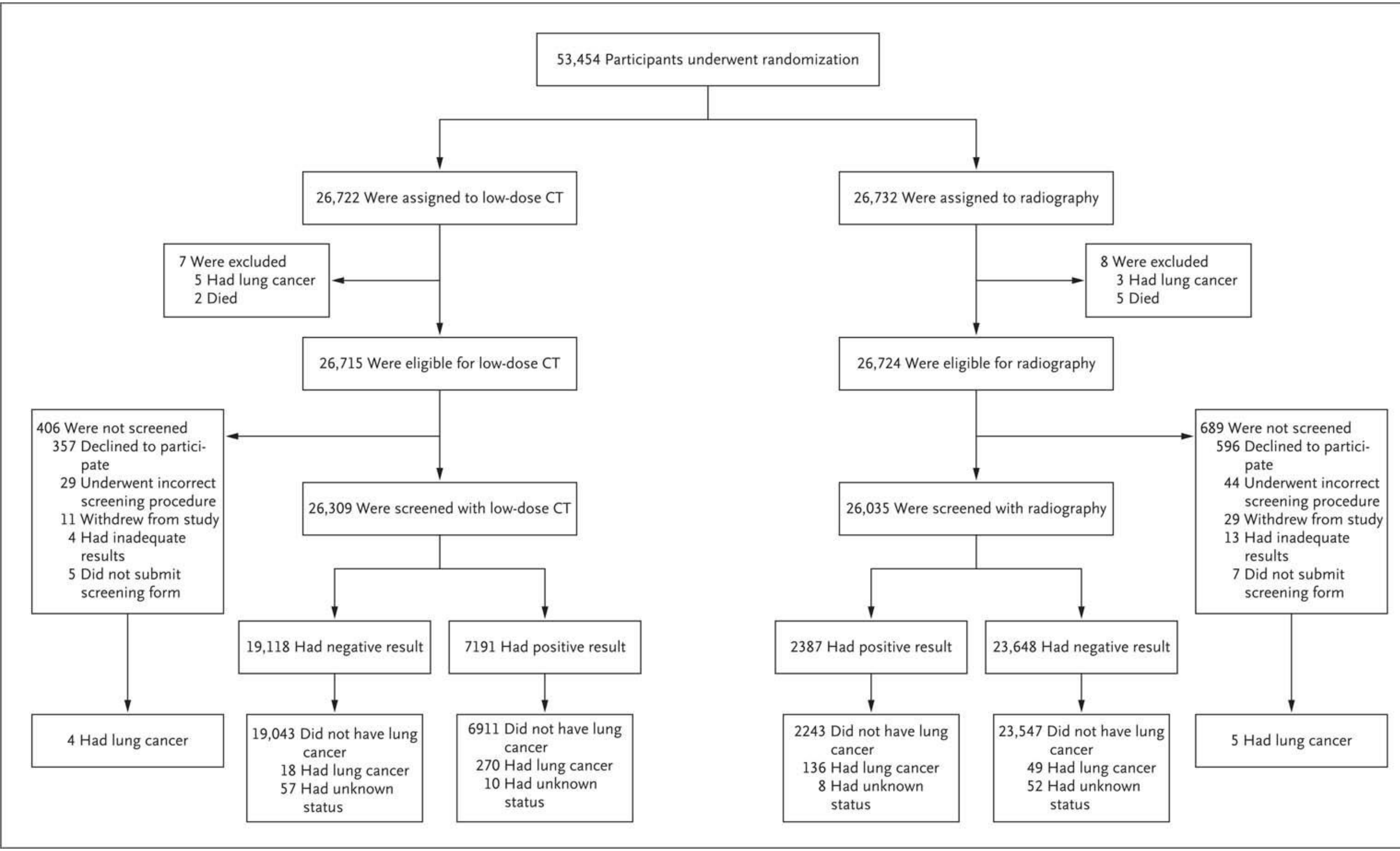
Enrollment and Follow-up of the Study Participants after the Initial Screening.



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Baseline Characteristics of the Study Participants, According to Study Group.

Table 1. Baseline Characteristics of the Study Participants, According to Study Group.*

Characteristic	Low-Dose CT			Chest Radiography		
	Randomized	Screened	Positive Result	Randomized	Screened	Positive Result
	number (percent)					
All participants	26,715	26,309 (98.5)	7191 (27.3)	26,724	26,035 (97.4)	2387 (9.2)
Sex						
Male	15,765	15,539 (98.6)	4194 (27.0)	15,758	15,400 (97.7)	1504 (9.8)
Female	10,950	10,770 (98.4)	2997 (27.8)	10,966	10,635 (97.0)	883 (8.3)
Age						
≤54 yr	2	2 (100)	1 (50.0)	4	4 (100)	0
55–59 yr	11,436	11,245 (98.3)	2730 (24.3)	11,417	11,103 (97.2)	870 (7.8)
60–64 yr	8,168	8,059 (98.7)	2217 (27.5)	8,196	7,975 (97.3)	747 (9.4)
65–69 yr	4,755	4,689 (98.6)	1456 (31.1)	4,760	4,661 (97.9)	480 (10.3)
70–74 yr	2,353	2,313 (98.3)	787 (34.0)	2,344	2,289 (97.7)	289 (12.6)
≥75 yr	1	1 (100)	0	3	3 (100)	1 (33.3)
Smoking status†						
Former smoker						
0 to <30 pack-yr	4	4 (100)	0	11	11 (100)	0
30 to <35 pack-yr	1,824	1,798 (98.6)	433 (24.1)	1,905	1,859 (97.6)	140 (7.5)
35 to <40 pack-yr	2,043	2,010 (98.4)	518 (25.8)	1,966	1,926 (98.0)	172 (8.9)
40 to <45 pack-yr	1,813	1,802 (99.4)	491 (27.2)	1,761	1,728 (98.1)	162 (9.4)
45 to <50 pack-yr	1,423	1,407 (98.9)	394 (28.0)	1,354	1,325 (97.9)	122 (9.2)
≥50 pack-yr	6,749	6,645 (98.5)	1791 (27.0)	6,832	6,666 (97.6)	608 (9.1)
Total	13,856	13,666 (98.6)	3627 (26.5)	13,829	13,515 (97.7)	1204 (8.9)
Current smoker						
0 to <30 pack-yr	2	2 (100)	0	4	4 (100)	1 (25.0)
30 to <35 pack-yr	1,099	1,081 (98.4)	251 (23.2)	1,152	1,117 (97.0)	93 (8.3)
35 to <40 pack-yr	1,859	1,834 (98.7)	453 (24.7)	1,869	1,820 (97.4)	131 (7.2)
40 to <45 pack-yr	2,394	2,353 (98.3)	646 (27.5)	2,304	2,232 (96.9)	200 (9.0)
45 to <50 pack-yr	1,549	1,523 (98.3)	444 (29.2)	1,585	1,534 (96.8)	172 (11.2)
≥50 pack-yr	5,956	5,850 (98.2)	1770 (30.3)	5,981	5,813 (97.2)	586 (10.1)
Total	12,859	12,643 (98.3)	3564 (28.2)	12,895	12,520 (97.1)	1183 (9.4)

* Participants 54 years of age or younger and those 75 years of age or older at enrollment were ineligible for the study, as were those with less than 30 pack-years of smoking, but data for them were included in the intention-to-treat analysis.
† Former smokers were participants who reported having quit tobacco use; current smokers were participants who reported that they were currently using tobacco.

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Frequency and Positive Predictive Value of Positive Screening Results, According to Study Group.

Table 2. Frequency and Positive Predictive Value of Positive Screening Results, According to Study Group.*

Finding at Initial Screening	Low-Dose CT						Chest Radiography					
	Confirmed Lung Cancer			Total	PPV	PPV Range	Confirmed Lung Cancer			Total	PPV	PPV Range
	yes	no	unknown				yes	no	unknown			
					percent						*percent*	
Patients												
Positive screening	270	6911	10	7191	3.8	3.3–4.2	136	2243	8	2387	5.7	4.8–6.6
With subsequent biopsy	265 (98.1)	236 (3.4)	0	501 (7.0)	52.9	48.4–57.4	132 (97.1)	56 (2.5)	0	188 (7.9)	70.2	64.0–76.8
With noncalcified nodule or mass	267 (98.9)	6765 (97.9)	9 (90.0)	7041 (97.9)	3.8	3.3–4.2	123 (90.4)	1982 (88.4)	7 (87.5)	2112 (88.5)	5.8	4.9–6.9
Size of nodule or mass†												
<4 mm	0	1 (<1)	0	1 (<1)	0.0	0.0–0.0	1 (0.7)	40 (1.8)	1 (12.5)	42 (1.8)	2.4	0.0–7.9
≥4 mm	267 (98.9)	6743 (97.6)	9 (90.0)	7019 (97.6)	3.8	3.4–4.3	115 (84.6)	1807 (80.6)	6 (75.0)	1928 (80.8)	6.0	4.9–7.1
4–6 mm	18 (6.7)	3642 (52.7)	8 (80.0)	3668 (51.0)	0.5	0.3–0.7	5 (3.7)	491 (21.9)	2 (25.0)	498 (20.9)	1.0	0.2–2.0
7–10 mm	35 (13.0)	2079 (30.1)	1 (10.0)	2115 (29.4)	1.7	1.1–2.2	12 (8.8)	692 (30.9)	2 (25.0)	706 (29.6)	1.7	0.8–2.9
11–20 mm	111 (41.1)	821 (11.9)	0	932 (13.0)	11.9	9.8–13.9	38 (27.9)	481 (21.4)	2 (25.0)	521 (21.8)	7.3	5.1–9.7
21–30 mm	58 (21.5)	137 (2.0)	0	195 (2.7)	29.7	23.7–36.4	27 (19.9)	92 (4.1)	0	119 (5.0)	22.7	15.2–30.4
>30 mm	45 (16.7)	64 (0.9)	0	109 (1.5)	41.3	32.1–51.0	33 (24.3)	51 (2.3)	0	84 (3.5)	39.3	28.6–50.6
Unknown	0	21 (0.3)	0	21 (0.3)	0.0	0.0–0.0	7 (5.1)	135 (6.0)	0	142 (5.9)	4.9	1.8–8.7
Other findings												
Atelectasis, segmental or more extensive‡	3 (1.1)	69 (1.0)	0	72 (1.0)	4.2	0.0–9.0	4 (2.9)	24 (1.1)	0	28 (1.2)	14.3	3.4–29.5
Noncalcified hilar or mediastinal adenopathy or mass	51 (18.9)	225 (3.3)	1 (10.0)	277 (3.9)	18.5	14.1–23.4	8 (5.9)	78 (3.5)	0	86 (3.6)	9.3	3.8–15.8
Consolidation‡	7 (2.6)	80 (1.2)	0	87 (1.2)	8.0	2.6–14.4	3 (2.2)	41 (1.8)	1 (12.5)	45 (1.9)	6.8	0.0–14.4
Pleural thickening or effusion	16 (5.9)	439 (6.4)	1 (10.0)	456 (6.3)	3.5	1.9–5.3	10 (7.4)	161 (7.2)	1 (12.5)	172 (7.2)	5.8	2.5–9.4

* Data are number (percent) unless otherwise indicated. The patients with confirmed lung cancer do not include 76 participants in whom lung cancer was diagnosed during the initial-screening year: 9 who did not undergo the initial screening and 67 who had negative screening results. The positive predictive value (PPV) is defined as the proportion of patients with confirmed lung cancer among those with a positive result on screening whose lung-cancer status was known.

† Nodule size refers to the diameter of the largest nodule recorded on the screening examination.

‡ Because these conditions were not always considered positive, the PPV could not be reliably estimated.

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Table 3. Diagnostic Follow-up of Positive Screening Results among the 9397 Patients with Data, According to Study Group and Lung-Cancer Status.*

Follow-up	Low-Dose CT			Chest Radiography		
	Confirmed Lung Cancer†		Total (N=7049)	Confirmed Lung Cancer†		Total (N=2348)
	yes (N=270)	no (N=6779)		yes (N=136)	no (N=2212)	
	number (percent)					
Any diagnostic follow-up	270 (100)	6099 (90.0)	6369 (90.4)	136 (100)	2040 (92.2)	2176 (92.7)
Clinical evaluation	248 (91.9)	4841 (71.4)	5089 (72.2)	117 (86.0)	1297 (58.6)	1414 (60.2)
Imaging studies	258 (95.6)	5459 (80.5)	5717 (81.1)	136 (100)	1874 (84.7)	2010 (85.6)
Chest radiography	112 (41.5)	1172 (17.3)	1284 (18.2)	63 (46.3)	804 (36.3)	867 (36.9)
Chest CT	181 (67.0)	4972 (73.3)	5153 (73.1)	131 (96.3)	1415 (64.0)	1546 (65.8)
FDG-PET or FDG-PET and CT	171 (63.3)	557 (8.2)	728 (10.3)	90 (66.2)	89 (4.0)	179 (7.6)
Percutaneous cytologic analysis or biopsy	98 (36.3)	57 (0.8)	155 (2.2)	66 (48.5)	17 (0.8)	83 (3.5)
Transthoracic	77 (28.5)	43 (0.6)	120 (1.7)	54 (39.7)	13 (0.6)	67 (2.9)
Extrathoracic	23 (8.5)	16 (0.2)	39 (0.6)	16 (11.8)	4 (0.2)	20 (0.9)
Bronchoscopy	158 (58.5)	148 (2.2)	306 (4.3)	76 (55.9)	31 (1.4)	107 (4.6)
With neither biopsy nor cytologic analysis	84 (31.1)	42 (0.6)	126 (1.8)	34 (25.0)	11 (0.5)	45 (1.9)
With biopsy or cytologic analysis	86 (31.9)	108 (1.6)	194 (2.8)	51 (37.5)	23 (1.0)	74 (3.2)
Surgical procedure	207 (76.7)	90 (1.3)	297 (4.2)	96 (70.6)	25 (1.1)	121 (5.2)
Mediastinoscopy or mediastinotomy	48 (17.8)	12 (0.2)	60 (0.9)	22 (16.2)	0	22 (0.9)
Thoracoscopy	44 (16.3)	38 (0.6)	82 (1.2)	14 (10.3)	8 (0.4)	22 (0.9)
Thoracotomy	156 (57.8)	41 (0.6)	197 (2.8)	78 (57.4)	18 (0.8)	96 (4.1)
Other procedure	46 (17.0)	122 (1.8)	168 (2.4)	17 (12.5)	38 (1.7)	55 (2.3)

* Numbers refer to the number of participants with a positive screening result who underwent any diagnostic procedure at least once. Not included are participants with a positive screening result for whom information on diagnostic procedures was incomplete (142 in the low-dose CT group and 39 in the radiography group). Diagnostic procedures were defined as follows: clinical evaluation (evaluation during an outpatient visit — physical examination, pulmonary-function testing, sputum cytologic assessment, or comparison of screening results with historical images), chest CT (diagnostic, low-dose, or limited-anatomy chest CT, with or without concurrent CT examination of the abdomen, pelvis, head and neck, or brain), fluorodeoxyglucose–positron-emission tomography (FDG-PET) CT (F-18 or fusion), extrathoracic percutaneous cytology or biopsy (extrathoracic lymph-node biopsy or percutaneous biopsy of liver, adrenal, or other extrathoracic tissue), thoracoscopy (with or without biopsy), or other procedures (other cytologic or biopsy procedures, procedures coded as "unknown," and procedures other than those listed by name on data-collection forms).

† The participants with confirmed lung cancer do not include the 8 participants who were ineligible for the initial screening because of a prior lung-cancer diagnosis and 76 participants who received a diagnosis of lung cancer during the initial-screening year (9 who did not undergo screening and 67 with a negative screening result). "No" denotes lung cancer that was not confirmed because of a negative diagnostic result or an unknown reference standard.

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Stage and Histologic Features of Lung Cancers, According to Study Group and Screening Result.

Table 4. Stage and Histologic Features of Lung Cancers, According to Study Group and Screening Result.*

Stage or Finding	Low-Dose CT				Chest Radiography			
	Positive (N=270)	Negative (N=18)	None (N=4)	Total (N=292)	Positive (N=136)	Negative (N=49)	None (N=5)	Total (N=190)
	number/total number (percent)							
Stage								
IA	130/266 (48.9)	2/18 (11.1)	0	132/288 (45.8)	40/133 (30.1)	6/48 (12.5)	0	46/185 (24.9)
IB	25/266 (9.4)	1/18 (5.6)	0	26/288 (9.0)	22/133 (16.5)	2/48 (4.2)	0	24/185 (13.0)
IIA	7/266 (2.6)	2/18 (11.1)	1/4 (25.0)	10/288 (3.5)	3/133 (2.3)	0	0	3/185 (1.6)
IIB	11/266 (4.1)	1/18 (5.6)	0	12/288 (4.2)	8/133 (6.0)	2/48 (4.2)	0	10/185 (5.4)
IIIA	31/266 (11.7)	2/18 (11.1)	1/4 (25.0)	34/288 (11.8)	19/133 (14.3)	8/48 (16.7)	2/4 (50.0)	29/185 (15.7)
IIIB	21/266 (7.9)	7/18 (38.9)	2/4 (50.0)	30/288 (10.4)	15/133 (11.3)	12/48 (25.0)	0	27/185 (14.6)
IV	41/266 (15.4)	3/18 (16.7)	0	44/288 (15.3)	26/133 (19.5)	18/48 (37.5)	2/4 (50.0)	46/185 (24.9)
Unknown†	4/270 (1.5)	0	0	4/292 (1.4)	3/136 (2.2)	1/49 (2.0)	1/5 (20.0)	5/190 (2.6)
Histologic features								
Bronchioloalveolar carcinoma	38/268 (14.2)	0	0	38/290 (13.1)	8/136 (5.9)	0	0	8/189 (4.2)
Adenocarcinoma	118/268 (44.0)	4/18 (22.2)	1/4 (25.0)	123/290 (42.4)	53/136 (39.0)	15/48 (31.2)	3/5 (60.0)	71/189 (37.6)
Squamous-cell carcinoma	47/268 (17.5)	6/18 (33.3)	1/4 (25.0)	54/290 (18.6)	32/136 (23.5)	7/48 (14.6)	0	39/189 (20.6)
Large-cell carcinoma	14/268 (5.2)	3/18 (16.7)	0	17/290 (5.9)	8/136 (5.9)	5/48 (10.4)	0	13/189 (6.9)
Non–small-cell carcinoma, other classification‡	34/268 (12.7)	1/18 (5.6)	1/4 (25.0)	36/290 (12.4)	20/136 (14.7)	9/48 (18.8)	1/5 (20.0)	30/189 (15.9)
Small-cell carcinoma	15/268 (5.6)	4/18 (22.2)	1/4 (25.0)	20/290 (6.9)	15/136 (11.0)	11/48 (22.9)	1/5 (20.0)	27/189 (14.3)
Carcinoid	2/268 (0.7)	0	0	2/290 (0.7)	0	1/48 (2.1)	0	1/189 (0.5)
Unknown	2/270 (0.7)	0	0	2/292 (0.7)	0	1/49 (2.0)	0	1/190 (0.5)

* Cancer-stage classification is based on the sixth edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer.[21] The denominators for cancer stage and histologic features were the total number of cancers with a known stage and the total number of cancers with known histologic features, respectively. Negative screening results include findings that were classified as either minor or clinically significant abnormalities that were not suggestive of lung cancer.

† The 9 lung cancers of unknown stage included 2 carcinoids, 1 occult carcinoma, 2 with stage information that could not be classified, and 4 for which medical records were missing.

‡ The 66 lung cancers in this category included 8 adenosquamous carcinomas, 2 sarcomatoid carcinomas, 5 unclassified carcinomas, and 51 carcinomas coded only as "non–small-cell carcinoma."

- The NLST initial screening results are consistent with the existing literature on screening by means of low-dose CT and chest radiography, suggesting that a reduction in mortality from lung cancer is achievable at U.S. screening centers that have staff experienced in chest CT.

- In participants who underwent initial screening in the National Lung Cancer Screening Trial, low-dose CT scanning showed positive results three times as frequently as did chest radiography (27% vs. 9%) and detected more than twice as many stage I cancers (158 vs. 70).

Lung screening today

- Screening with LDCTs
- LDCT can detect early stage lung cancers
- Has high "false positive" rate leading to additional testing (serial imaging ➔invasive procedures)
- Decreases lung cancer mortality by 20% and all cause mortality by 6.7% in 1 large RCT

Prevention

- “Single best way to prevent lung cancer deaths is to
- never start smoking, and
- if already smoking, to quit permanently.”

- NLST 2011

Original Article

Screening for Occult Cancer in Unprovoked Venous Thromboembolism

Marc Carrier, M.D., Alejandro Lazo-Langner, M.D., Sudeep Shivakumar, M.D., Vicky Tagalakis, M.D., Ryan Zarychanski, M.D., Susan Solymoss, M.D., Nathalie Routhier, M.D., James Douketis, M.D., Kim Danovitch, C.C.R.P., Agnes Y. Lee, M.D., Gregoire Le Gal, M.D., Philip S. Wells, M.D., Daniel J. Corsi, Ph.D., Timothy Ramsay, Ph.D., Doug Coyle, Ph.D., Isabelle Chagnon, M.D., Zahra Kassam, M.D., Hardy Tao, M.D., Marc A. Rodger, M.D., for the SOME Investigators

N Engl J Med
Volume 373(8):697-704

The NEW ENGLAND JOURNAL of MEDICINE

Screening, Randomization, Follow-up, and Analysis of the Study Patients.

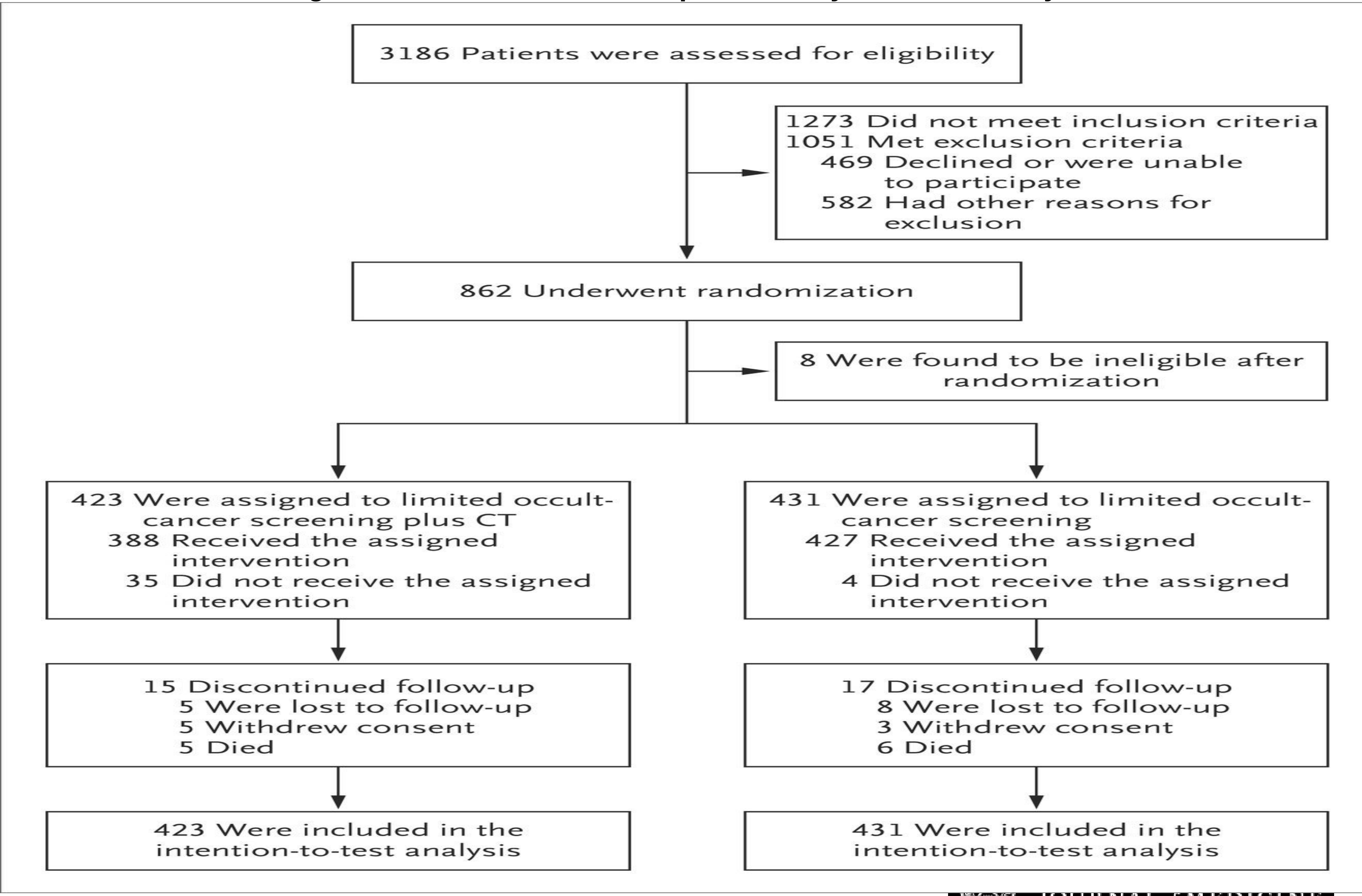

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Table 1. Baseline Characteristics of the Intention-to-Test Population.*

Characteristic	Limited Occult-Cancer Screening (N=431)	Limited Occult-Cancer Screening plus CT (N=423)
Age — yr	53.7±13.8	53.4±14.2
Male sex — no. (%)	277 (64.3)	299 (70.7)
White race — no. (%)†	395 (91.6)	397 (93.9)
Weight — kg	89.8±18.3	90.4±17.7
Medical history — no. (%)		
Hypertension	86 (20.0)	101 (23.9)
Myocardial infarction	13 (3.0)	9 (2.1)
Stroke	5 (1.2)	6 (1.4)
Congestive heart failure	2 (0.5)	0
Diabetes	17 (3.9)	22 (5.2)
Previous cancer	20 (4.6)	30 (7.1)
Prior provoked venous thromboembolism	29 (6.7)	18 (4.3)
Current smoker	69 (16.0)	63 (14.9)
Past smoker	140 (32.5)	144 (34.0)
Venous thromboembolism — no. (%)		
Deep-vein thrombosis	289 (67.1)	287 (67.8)
Pulmonary embolism	142 (32.9)	136 (32.2)
Deep-vein thrombosis and pulmonary embolism	52 (12.1)	53 (12.5)
Medications — no. (%)		
Oral contraceptive	29 (6.7)	19 (4.5)
Exogenous estrogen	8 (1.9)	11 (2.6)
Antiplatelet agent	21 (4.9)	19 (4.5)

* Plus–minus values are means ±SD. There were no significant between-group differences, except for the difference in sex (P=0.045). Patients who were assigned to the strategy of limited occult-cancer screening plus computed tomography (CT) underwent comprehensive CT of the abdomen and pelvis.

† Race was self-reported.

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Table 2. Occult Cancer Tumor Types.

Tumor Type	Limited Occult-Cancer Screening (N=14)	Limited Occult-Cancer Screening plus CT (N=19)
	no. of tumors/total no. (%)	
During screening period		
Acute leukemia	0/10	0/14
Gynecologic	3/10 (30)	0/14
Skin: melanoma	1/10 (10)	0/14
Colorectal	0/10	3/14 (21)
Prostate	2/10 (20)	0/14
Pancreatic	2/10 (20)	0/14
Cholangiocarcinoma	1/10 (10)	2/14 (14)
Lymphoma	1/10 (10)	3/14 (21)
Breast	0/10	2/14 (14)
Urologic	0/10	3/14 (21)
Unknown primary	0/10	1/14 (7)
During follow-up period		
Acute leukemia	1/4 (25)	1/5 (20)
Gynecologic	1/4 (25)	1/5 (20)
Skin: melanoma	0/4	1/5 (20)
Colorectal	1/4 (25)	1/5 (20)
Prostate	0/4	1/5 (20)
Pancreatic	1/4 (25)	0/5

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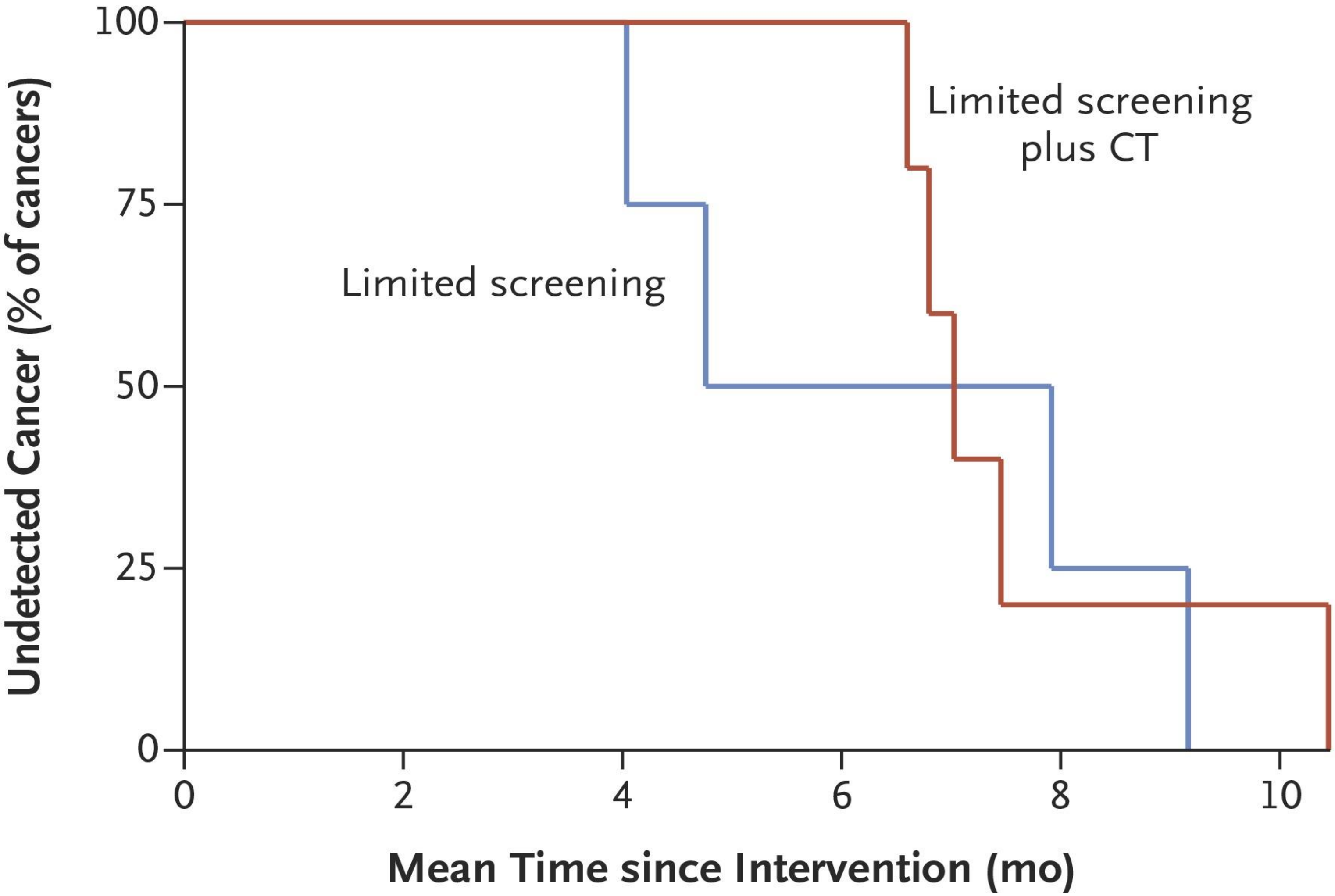

No. at Risk

Limited screening	4	4	4	2	1	0
Limited screening plus CT	5	5	5	5	1	1

- The prevalence of occult cancer was low among patients with a first unprovoked venous thromboembolism.
- Routine screening with CT of the abdomen and pelvis did not provide a clinically significant benefit.

Coming soon to a hospital/ clinic near you…

Original Article

Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma

Hector G. Ortega, M.D., Sc.D., Mark C. Liu, M.D., Ian D. Pavord, D.M., Guy G. Brusselle, M.D., J. Mark FitzGerald, M.D., Alfredo Chetta, M.D., Marc Humbert, M.D., Ph.D., Lynn E. Katz, Pharm.D., Oliver N. Keene, M.Sc., Steven W. Yancey, M.Sc., Pascal Chanez, M.D., Ph.D., for the MENSA Investigators

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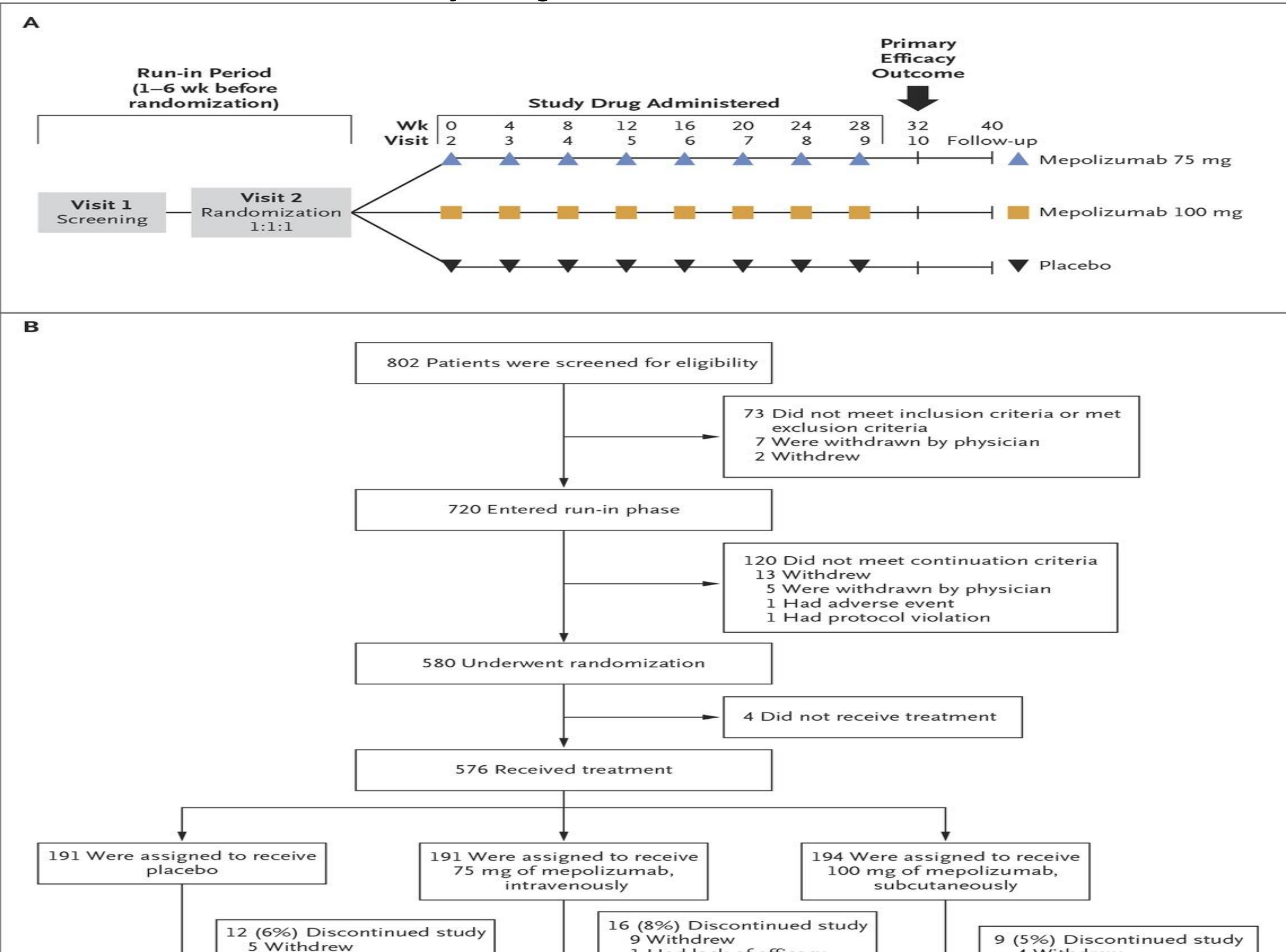
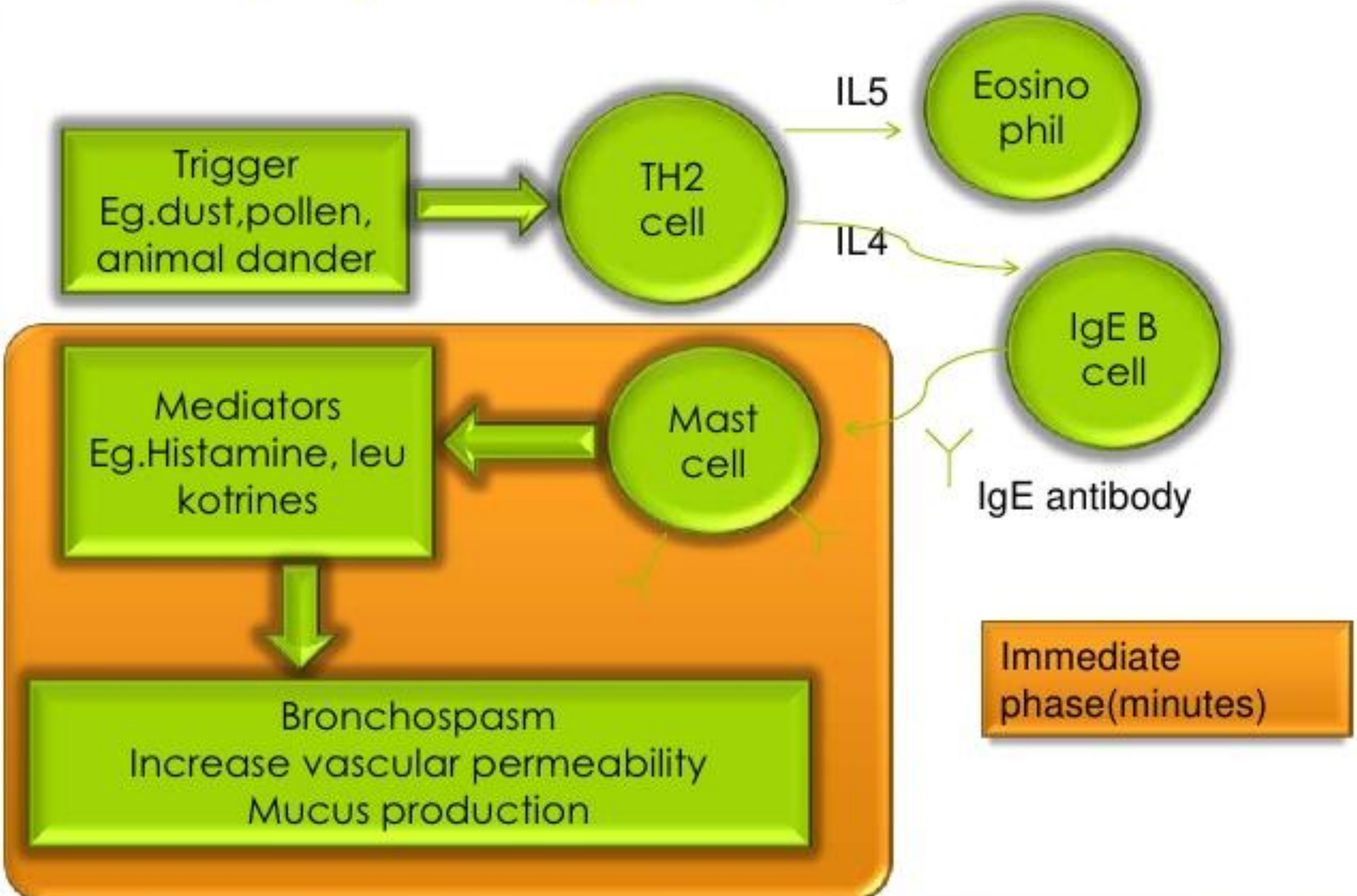
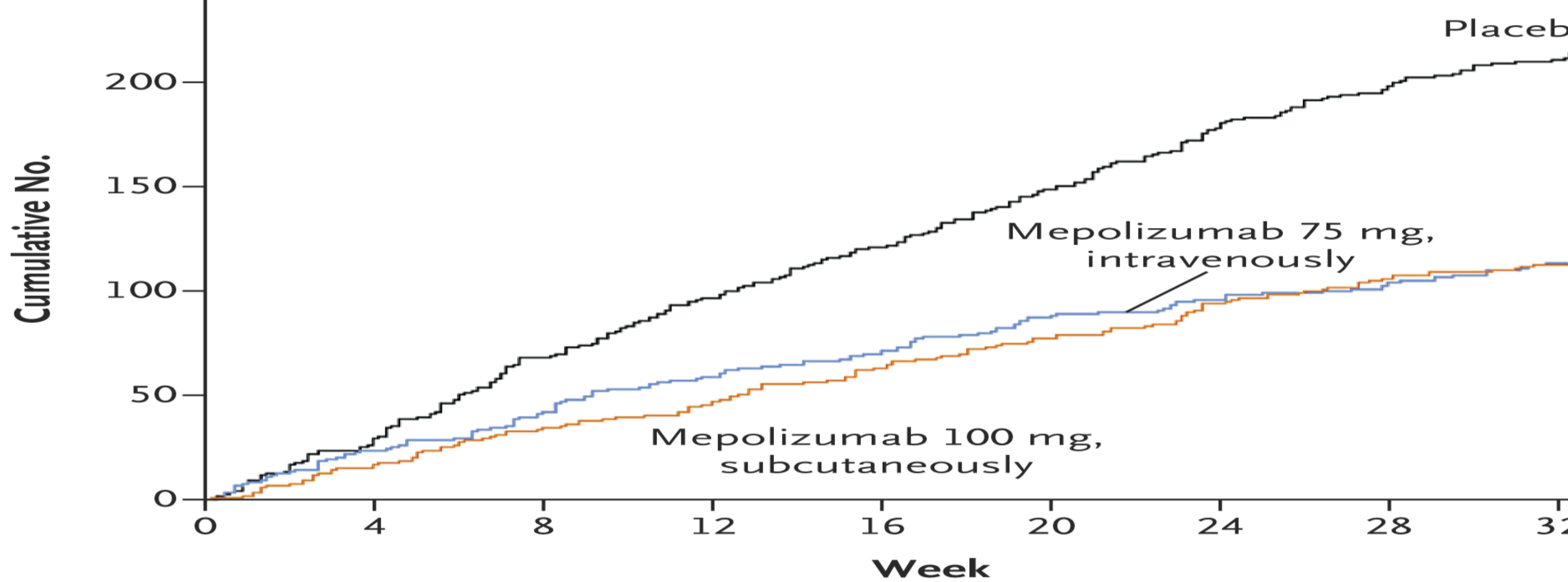
Study Design and Enrollment and Outcomes.



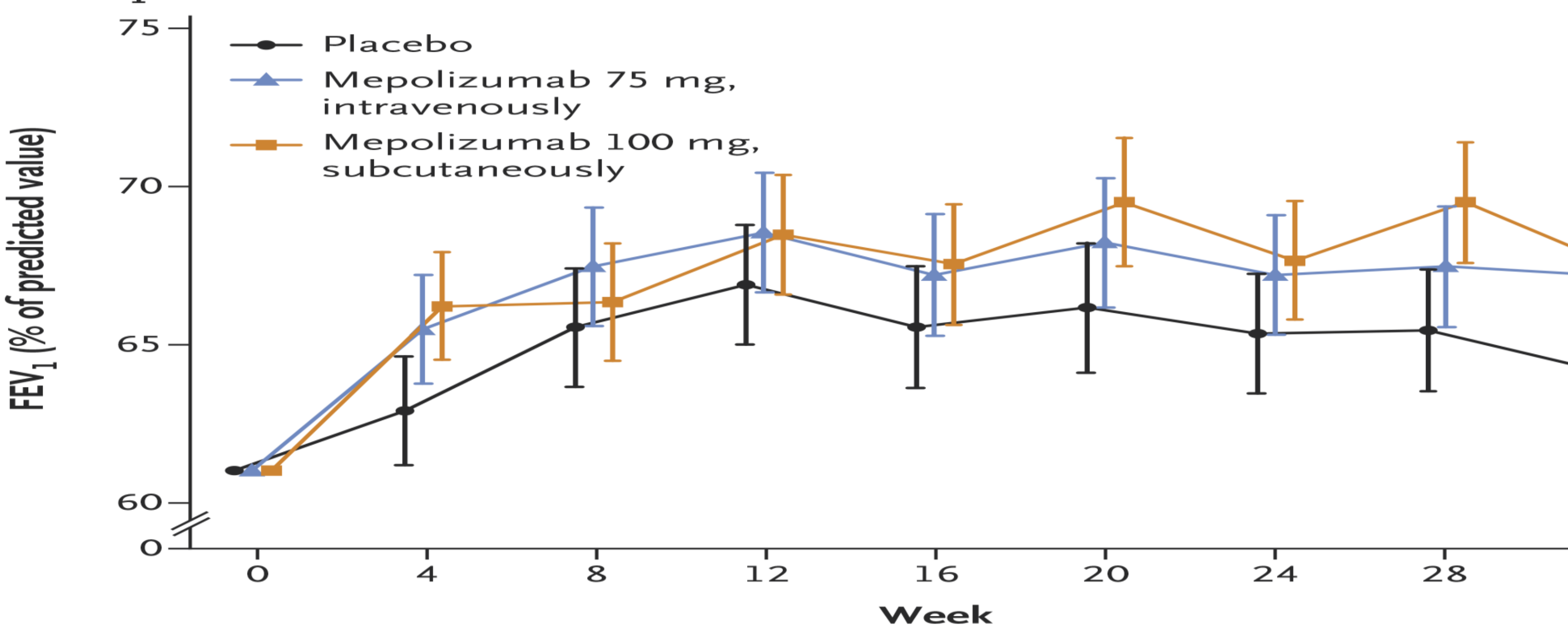
Pathophysiology

- Atopic Asthma




Placebo
Mepolizumab 75 mg, intravenously
Mepolizumab 100 mg, subcutaneously
Cumulative No.
0
50
100
150
200
0
4
8
12
16
20
24
28
32
Week

B FEV$_1$


Placebo
Mepolizumab 75 mg, intravenously
Mepolizumab 100 mg, subcutaneously
FEV$_1$ (% of predicted value)
0
60
65
70
75
0
4
8
12
16
20
24
28
Week

Characteristics of the Patients at Baseline in the Intention-to-Treat Population.

Table 1. Characteristics of the Patients at Baseline in the Intention-to-Treat Population.*

Characteristic	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
Mean age (range) — yr	49 (12–76)	50 (13–82)	51 (12–81)
Female sex — no. (%)	107 (56)	106 (55)	116 (60)
Body-mass index†	28.0±5.6	27.7±5.7	27.6±6.2
Former smoker — no. (%)	57 (30)	52 (27)	50 (26)
Duration of asthma — yr	19.5±14.6	19.8±14.0	20.5±12.9
Use of oral glucocorticoids			
Maintenance use — no. (%)	44 (23)	48 (25)	52 (27)
Mean daily dose (range) — mg‡	15.1 (5–80)	12.0 (1–40)	12.6 (2–50)
Allergic rhinitis — no. (%)	95 (50)	91 (48)	95 (49)
FEV_1			
Before bronchodilation — liters§	1.86±0.63	1.86±0.70	1.73±0.66
Percent of predicted value before bronchodilation¶	62.4±18.1	61.4±18.3	59.3±17.5
Reversibility — %	27.4±20.8	25.4±19.6	27.9±24.0
FEV_1:FVC ratio — %‖	64±13	64±13	63±13
Morning peak expiratory flow — liters/min	277±106	269±112	255±108
Score on Asthma Control Questionnaire**	2.28±1.19	2.12±1.13	2.26±1.27
Score on St. George's Respiratory Questionnaire††	46.9±19.8	44.4±19.4	47.9±19.4
Geometric mean IgE on $\log_e$ scale — U/ml	150±1.5	180±1.5	150±1.5
Geometric mean blood eosinophil count on $\log_e$ scale — cells/μl‡‡	320±938	280±987	290±1050
Asthma exacerbations			
Severe episodes in previous year — no./patient	3.6±2.8	3.5±2.2	3.8±2.7
Necessitating hospitalization in previous year — no. (%)	35 (18)	41 (21)	33 (17)
History of asthma-related intubation — no. (%)	3 (2)	10 (5)	8 (4)

* Plus–minus values are means (or geometric means) ±SD. There were no significant between-group differences at baseline. More detailed data are provided in Table S3 in the Supplementary Appendix. FEV_1 denotes forced expiratory volume in 1 second, and FVC forced vital capacity.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The listed value is the prednisone equivalent.
§ Reversibility was measured at baseline.
¶ The percent of the predicted value before bronchodilation was assessed at the screening visit.
‖ The FEV_1:FVC ratio was calculated by dividing the FEV_1 by the FVC and then multiplying by 100 to express the value as a percentage.
** Scores on the Asthma Control Questionnaire range from 0 to 6, with higher scores indicating worse control; a change of 0.5 points is the minimal clinically important difference.
†† Scores on St. George's Respiratory Questionnaire range from 0 to 100, with higher scores indicating worse function; a change of 4 points is considered to be clinically relevant.
‡‡ Values below the lower limit of quantification (LLQ) were replaced by a value that was 50% of the LLQ.

Summary of Efficacy Outcomes.

Table 2. Summary of Efficacy Outcomes.*

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.74	0.93	47 (28 to 60)†	<0.001	0.83	53 (36 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (−41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (−66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV_1 — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33	138 (43 to 232)	0.004
Change from baseline in score on Asthma Control Questionnaire	−0.50±0.07	−0.92±0.07	−0.42 (−0.61 to −0.23)	<0.001	−0.94±0.07	−0.44 (−0.63 to −0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	−9.0±1.2	−15.4±1.2	−6.4 (−9.7 to −3.2)	<0.001	−16.0±1.1	−7.0 (−10.2 to −3.8)	<0.001

* Plus–minus values are means ±SE.

† The between-group difference in this category is the percent reduction as compared with the placebo group.

Summary of Adverse Events.

Table 3. Summary of Adverse Events.*

Variable	Placebo (N=191)	Mepolizumab	
		Intravenous (N=191)	Subcutaneous (N=194)
	number of patients (percent)		
All adverse events	158 (83)	161 (84)	152 (78)
Nonasthma event	157 (82)	161 (84)	152 (78)
Worsening of asthma	29 (15)	18 (9)	13 (7)
Drug-related event, per investigator assessment†	30 (16)	33 (17)	39 (20)
Leading to study withdrawal	4 (2)	0	1 (1)
Serious adverse events			
During treatment	27 (14)	14 (7)	16 (8)
Drug-related event, per investigator assessment†	1 (1)	0	1 (1)
Fatal	1 (1)	0	0
Most common adverse events‡			
Nasopharyngitis	46 (24)	45 (24)	33 (17)
Headache	33 (17)	46 (24)	39 (20)
Upper respiratory tract infection	27 (14)	22 (12)	24 (12)
Sinusitis	18 (9)	11 (6)	18 (9)

- Mepolizumab administered either intravenously or subcutaneously significantly reduced asthma exacerbations and was associated with improvements in markers of asthma control.

Original Article
Idarucizumab for Dabigatran Reversal

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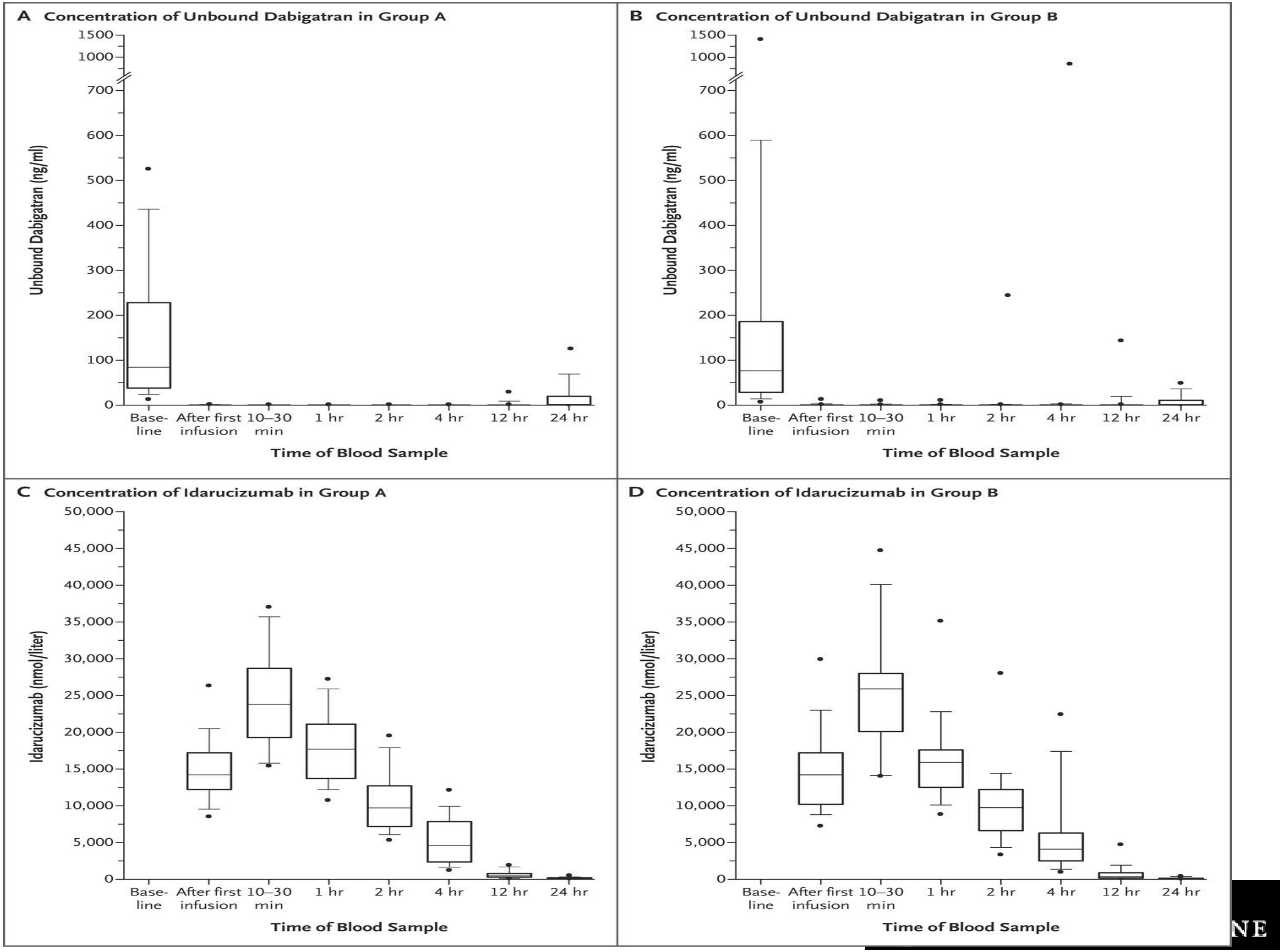
Clinical Characteristics of the Patients.

Table 1. Clinical Characteristics of the Patients.*

Characteristic	Group A (N=51)	Group B (N=39)	Total (N=90)
Age — yr			
Median	77.0	76.0	76.5
Range	48–93	56–93	48–93
Male sex — no. (%)	32 (63)	18 (46)	50 (56)
Race or ethnic group — no. (%)†			
Asian	5 (10)	1 (3)	6 (7)
Hawaiian or Pacific Islander	3 (6)	3 (8)	6 (7)
White	43 (84)	35 (90)	78 (87)
Weight — kg			
Median	70.5	73.0	71.9
Range	42.4–127.5	49.5–116.0	42.4–127.5
Creatinine clearance‡			
Value — ml/min			
Mean	59±33	65±36	62±35
Median	54	60	58
Range	16–187	11–171	11–187
Distribution — no. (%)			
<30 ml/min	5 (10)	7 (18)	12 (13)
30 to <50 ml/min	14 (27)	6 (15)	20 (22)
50 to <80 ml/min	16 (31)	11 (28)	27 (30)
≥80 ml/min	6 (12)	9 (23)	15 (17)
Missing data	10 (20)	6 (15)	16 (18)

Time Courses of Plasma Concentrations of Unbound Dabigatran and Idarucizumab before and after the Administration of Idarucizumab.



Serious Adverse Events Leading to Death.

Table 2. Serious Adverse Events Leading to Death.

Event	Characteristics of the Patients		Study Group*	Time from Treatment to Death
	Age	Sex		
	yr			*days*
Cardiac arrest	82	Female	B	<1
Circulatory collapse	93	Male	B	<1
Hemodynamic collapse	88	Female	B	<1
Septic shock	87	Female	B	1
Sepsis, shock, and gastrointestinal bleeding	60	Male	B	1
Progression of respiratory failure	60	Male	A	1
New intracranial hemorrhage	77	Male	A	1
Progression of intracranial hemorrhage	69	Male	A	2
Multiorgan failure	87	Male	B	2
Progression of intracranial hemorrhage	69	Male	A	4
Pulmonary edema	83	Female	A	11
Cardiac arrest	78	Female	B	21
Ischemic stroke	72	Female	B	26
Congestive heart failure	73	Male	A	30
Parkinson's disease	80	Male	A	43
General health deterioration	83	Male	A	42
Pneumonia	86	Female	A	94
Progression of cancer	80	Male	B	101

* Group A included patients who had serious bleeding. Group B included patients who required urgent surgery or intervention.

- Intravenous idarucizumab, an antibody fragment of a human antibody specific for dabigatran, produced rapid reversal of the anticoagulant effect in patients with bleeding or an urgent surgical indication with no apparent toxic effects or rebound hypercoagulable state.
- Idarucizumab completely reversed the anticoagulant effect of dabigatran within minutes.

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Take home points

- Consider screening of persistent smokers with low dose chest CT
- No benefit to performing testing other than that which is age appropriate for patients with unprovoked VTE
- Idarucizumab for urgent reversal of dabigatran.
- Anti IL5 therapy with mepolizumab for patients with uncontrolled asthma & eosinophilia, despite maximal therapy

QUESTIONS?