Before you begin: This is a big topic, and big topics beget big slide-sets. There’s a natural break just past the halfway mark (slide 374ish); I placed a *break time!* slide at that point to mark it.
Age-related macular degeneration is the #1 cause of blindness in adults age # in resource-rich nations
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD?
What proportion of Americans 65+ have ARMD?
10%

Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD? 75+? 10%
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD? 75+?
10%. 25%!
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*

10%. 25%!

*Speaking of demographics: Is ARMD risk related to ethnicity?*

Yes, ______ have the highest risk and ______ the lowest.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*
10%. 25%!

*Speaking of demographics: Is ARMD risk related to ethnicity?*
Yes, whites have the highest risk and AAs the lowest.
Age-related macular degeneration is the #1 cause of blindness in **adults age 50+** in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*
10%. 25%!

*Speaking of demographics: Is ARMD risk related to ethnicity?*
Yes, whites have the highest risk and AAs the lowest; and Asians and Hispanics fall in-between.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD? 75+?
10%. 25%!

Speaking of demographics: Is ARMD risk related to ethnicity?
Yes, whites have the highest risk and AAs the lowest; Asians and Hispanics fall in-between.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

**Age** is the strongest risk factor for ARMD.

What are the other ARMD risk factors?

- Family history;
- Female;
- Light iris color;
- Age;
- Anglo (ie, white ethnicity);
- Smoking;
- Sun exposure;
- Hyperopia;
- Hypercholesterolemia;
- High CRP

The mnemonic is…
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

**Age** is the strongest risk factor for ARMD.

The mnemonic is... **FLASH**

- **F**amily history
- **F**emale
- **L**ight iris color
- **A**ge
- **A**nglo (i.e., white ethnicity)
- **S**moking
- **S**un exposure
- **H**yperopia
- **H**ypercholesterolemia
- **H**igh CRP
- Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations
- **Age** is the strongest risk factor for ARMD

What are the other ARMD risk factors?

- **F**amily history; **F**emale
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- **S**moking; **S**un exposure
- **H**yperopia; **H**ypercholesterolemia; **H**igh CRP

The mnemonic is…**FLASH**
What are the other ARMD risk factors?

- Family history; Female
- Light iris color
- Age; Anglo (ie, white ethnicity)
- Smoking; Sun exposure
- Hyperopia; Hypercholesterolemia; High CRP

Of the modifiable ones, which is most impactful?

Age is the strongest risk factor for ARMD
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

**Age** is the strongest risk factor for ARMD.

**What are the other ARMD risk factors?**

- Family history; Female
- Light iris color
- Age; Anglo (ie, white ethnicity)
- Smoking; Sun exposure
- Hyperopia; Hypercholesterolemia; High CRP

*Of the modifiable ones, which is most impactful?*

Smoking
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.
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- Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.
- Age is the strongest risk factor for ARMD.
- The clinical hallmark of ARMD is the presence of drusen in the macula.

**What are drusen?**

- Aggregates of material within the outer-retinal space.
- Constituted by proteins and lipids—detritus shed by photoreceptors, mainly.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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What are drusen?
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What are drusen?
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What sorts of substances constitute the material?
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How are drusen categorized?
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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**What are drusen?**
Aggregates of material within the outer-retinal space.

**What sorts of substances constitute the material?**
Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

- Drusen are categorized by their size.
- Drusen are categorized by their boundaries.
- Drusen are categorized by the retinal layer in which they're located.

Drusen are categorized by their **size**.

In which are described.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. Age is the strongest risk factor for ARMD. The clinical hallmark of ARMD is the presence of drusen in the macula.

What are drusen? Aggregates of material within the outer-retinal space. What sorts of substances constitute the material? Proteins and lipids—detritus shed by photoreceptors, mainly.

How are drusen categorized? There are several ways:
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--?
--?
--?

**Drusen are categorized by their boundaries**

**Drusen are categorized by the retinal layer in which they’re located**
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Aggregates of material within the outer-retinal space.

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**How are drusen categorized?**
There are several ways:

- Drusen are categorized by their **size**:
  - Small
  - Intermediate
  - Large
  - Drusenoid PED

- Drusen are categorized by the **retinal layer** in which they’re located.

- Drusen are categorized by their **boundaries**.
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Age is the strongest risk factor for ARMD.

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Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

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  - Small: diameter < 63 μm
  - Intermediate
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**Drusen are categorized by their size:**
- **Small**: <63 μm diameter
- Intermediate
- Large
- Drusenoid PED

**Drusen are categorized by the retinal layer in which they're located**

**Drusen are categorized by their boundaries**
Small drusen
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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- **Small**: <63 μm diameter
- **Intermediate**
- **Large**
- **Drusenoid PED**

Drusen are categorized by the retinal layer in which they’re located.

Drusen are categorized by their boundaries.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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**What are drusen?**
Aggregates of material within the outer-retinal space.

**What sorts of substances constitute the material?**
Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

- **Drusen are categorized by their size:**
  - **Small:** <63 μm diameter
  - **Intermediate:** 63–124
  - **Large**
  - **Drusenoid PED**

- **Drusen are categorized by the retinal layer in which they’re located**

- **Drusen are categorized by their boundaries**
Intermediate drusen
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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What are drusen?
Aggregates of material within the outer-retinal space.

What sorts of substances constitute the material?
Proteins and lipids—detritus shed by photoreceptors, mainly.

How are drusen categorized?
There are several ways:

Drusen are categorized by their size:
- Small: <63 μm diameter
- Intermediate: 63–124
- Large: ≥125
- Drusenoid PED

Drusen are categorized by the retinal layer in which they’re located.

Drusen are categorized by their boundaries.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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**What are drusen?**
Aggregates of material within the outer-retinal space.

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Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

Drusen are categorized by their **size**:
- **Small**: <63 μm diameter
- **Intermediate**: 63–124
- **Large**: ≥125
- **Drusenoid PED**

Drusen are categorized by the **retinal layer** in which they’re located.

Drusen are categorized by their **boundaries**.
Large drusen
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. Age is the strongest risk factor for ARMD. The clinical hallmark of ARMD is the presence of drusen in the macula.

**What are drusen?**
Aggregates of material within the outer-retinal space.

**What sorts of substances constitute the material?**
Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

- Small: <63 µm diameter
- Intermediate: 63–124
- Large: ≥125

**Drusen are categorized by their size:**
- Small: <63 µm diameter
- Intermediate: 63–124
- Large: ≥125

**Drusen are categorized by the retinal layer in which they're located:**

**Drusen are categorized by their boundaries:**

**How the heck are you supposed to know the size of a druse in microns?**

*Drusen*
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

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**What are drusen?**
Aggregates of material within the outer-retinal space.

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Proteins and lipids—detritus shed by photoreceptors, mainly.

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There are several ways:

- Drusen are categorized by their **size**:
  - Small: <63 μm diameter
  - Intermediate: 63–124
  - Large: ≥125

- Drusen are categorized by the **retinal layer** in which they're located.

- Drusen are categorized by their **boundaries**.

**How the heck are you supposed to know the size of a druse in microns?**
By comparing it to the size of a retinal vein as it crosses the border of the ONH (their diameter is about 124 μm there, and thus make a convenient reference).

Lotsa words.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

What are drusen?

Drusen are aggregates of material within the outer-retinal space.

Aggregates of material—detritus shed by photoreceptors, mainly proteins and lipids.

How are drusen categorized?

There are several ways:

- By their size:
  - Small: <63 μm diameter
  - Intermediate: 63–124
  - Large: ≥125

- By their boundaries

- By the retinal layer in which they're located

How the heck are you supposed to know the size of a druse in microns?

By comparing it to the size of a retinal vein as it crosses the border of the ONH (their diameter is about 124 μm there, and thus make a convenient reference).
**Age-related macular degeneration (ARMD)**

- Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.
- Age is the strongest risk factor for ARMD.
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Proteins and lipids—detritus shed by photoreceptors, mainly.

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There are several ways:

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  - Small: < 63 μm diameter
  - Intermediate: 63–124
  - Large: ≥ 125

- **Drusen are categorized by the retinal layer in which they’re located.**
  - Drusenoid PED

**How the heck are you supposed to know the size of a druse in microns?**
By comparing it to the size of a retinal vein as it crosses the border of the ONH (their diameter is about 124 μm there, and thus make a convenient reference).
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How the heck are you supposed to know the size of a druse in microns? By comparing it to the size of a retinal vein as it crosses the border of the ONH (their diameter is about 124 µm there, and thus make a convenient reference).
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**What are drusen?**
Aggregates of material within the outer-retinal space.

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Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

**Drusen are categorized by their size:**
- **Small:** <63 μm diameter
- **Intermediate:** 63–124
- **Large:** ≥125
- **Drusenoid PED:** >350

**Drusen are categorized by the retinal layer in which they’re located**

**Drusen are categorized by their boundaries**
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. Age is the strongest risk factor for ARMD. The clinical hallmark of ARMD is the presence of drusen in the macula.

What are drusen?
Aggregates of material within the outer-retinal space.

What sorts of substances constitute the material?
Proteins and lipids—detritus shed by photoreceptors, mainly.

In this context, what does PED stand for?
Pigment epithelium detachment.

Drusen are categorized by:
- Size:
  - Small: <63 μm diameter
  - Intermediate: 63–124 μm
  - Large: ≥125 μm
  - Drusenoid PED: >350 μm
- Boundaries
- Retinal layer in which they’re located.

In this context, PED stands for pigment epithelium detachment. The RPE is no longer in direct contact with its basement membrane, or the RPE/basement membrane complex is separated from the underlying structure. This separation leads to RPE dysfunction, death, and atrophy. This in turn can lead to photoreceptor dysfunction, death, and atrophy, which results in vision loss.

There are three basic forms of PED:
- Drusenoid: Uniformly hyperreflective
- Serous/hemorrhagic: Solid with 'clefts'
- Fibrovascular: Sub-RPE space 'empty'
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Drusen are categorized by their boundaries.

Drusen are categorized by the retinal layer in which they’re located.

In this context, what does PED stand for?
Pigment epithelium detachment.

Drusen are categorized by their appearance on OCT:
- Uniformly hyperreflective
- Solid with ‘clefts’
- Empty

Recall that the RPE plays an indispensable role in the health of the photoreceptors. Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris. Thus, a PED can lead to RPE dysfunction, death, and atrophy. This in turn can lead to photoreceptor dysfunction, death, and atrophy, which results in vision loss.

There are three basic forms of PED:
- Drusenoid: Uniformly hyperreflective
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What are drusen? Aggregates of material within the outer-retinal space.

What sorts of substances constitute the material? Proteins and lipids—detritus shed by photoreceptors, mainly.

In this context, what does PED stand for? Pigment epithelium detachment.

What does it mean to say the RPE is ‘detached’? Recall that the RPE plays an indispensable role in the health of the photoreceptors. Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris. Thus, a PED can lead to RPE dysfunction, death and atrophy. This in turn can lead to photoreceptor dysfunction, death and atrophy, which results in vision loss.

There are three basic forms of PED—drusenoid, serous/hemorrhagic, and fibrovascular. Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?

--Drusenoid: Uniformly hyperreflective
--Serous/hemorrhagic: Solid with ‘clefts’
--Fibrovascular: Sub-RPE space ‘empty’
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Drusen are categorized by their boundaries:

Drusen are categorized by the retinal layer in which they’re located.

In this context, what does PED stand for?
Pigment epithelium detachment.

What does it mean to say the RPE is ‘detached’?
It means the RPE is no longer in direct contact with its basement membrane, or that the RPE/basement membrane complex is separated from the underlying structure.

Recall that the RPE plays an indispensable role in the health of the photoreceptors. Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris. Thus, a PED can lead to RPE dysfunction, death and atrophy. This in turn can lead to photoreceptor dysfunction, death and atrophy, which results in vision loss.

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OCT: Drusenoid PED

Coalescence of large soft drusen over time to form a drusenoid PED with increasing accumulation of vitelliform material (red arrow) and overlying pigmentary changes, as seen on color fundus photograph (CFP) and OCT.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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- Drusen are categorized by their boundaries.

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In this context, what does PED stand for?
Pigment epithelium detachment.

What does it mean to say the RPE is ‘detached’?
It means the RPE is no longer in direct contact with its basement membrane, or that the RPE/basement membrane complex is separated from the underlying structure.

Why is it a big deal if the RPE is separated from its BM, or deeper structures?
Recall that the RPE plays an indispensable role in the health of the photoreceptors. Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris. Thus, a PED can lead to RPE dysfunction, death and atrophy. This in turn can lead to photoreceptor dysfunction, death and atrophy, which results in vision loss.

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What do drusen look like?

- Small: <63 μm diameter
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--Large: ≥125
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Drusen are categorized by their boundaries:

Drusen are categorized by the retinal layer in which they’re located.

In this context, what does PED stand for?
Pigment epithelium detachment

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What does it mean to say the RPE is ‘detached’?
It means the RPE is no longer in direct contact with its basement membrane, or that the RPE/basement membrane complex is separated from the underlying structure.

Why is it a big deal if the RPE is separated from its BM, or deeper structures?
Recall that the RPE plays an indispensable role in the health of the photoreceptors. Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

What are drusen?
Aggregates of material within the outer-retinal space

What sorts of substances constitute the material?
Proteins and lipids—detritus shed by photoreceptors, mainly

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There are three basic forms of PED—what are the other two?
- Drusenoid
- ?
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**There are three basic forms of PED—what are the other two?**
--Drusenoid
--Serous
--Fibrovascular
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**There are three basic forms of PED—what are the other two?**
Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?

--Drusenoid: ?
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There are three basic forms of PED—what are the other two? Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?
- Drusenoid: Uniformly hyperreflective
- Serous
- Fibrovascular
Drusenoid PEDs have a uniform (aka ‘homogenous’), mildly hyper-reflective interior.
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---

**There are three basic forms of PED—what are the other two?** Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?

--Drusenoid: Uniformly hyperreflective

--Serous: Sub-RPE space ‘empty’

--Fibrovascular
Serous PEDs are seen on OCT as areas of smooth, sharply demarcated, dome-shaped RPE elevation, typically overlying a homogenously hyporeflective space.

Serous PED
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**There are three basic forms of PED—what are the other two?** Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?
--Drusenoid: Uniformly hyperreflective
--Serous: Sub-RPE space ‘empty’
--Fibrovascular: Solid with ‘clefts’
Fibrovascular PEDs appear to be filled with solid layers of material of medium reflectivity *separated by hyporeflective clefts*

Fibrovascular PED
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**How are drusen categorized?**
There are several ways:

**Drusen are categorized by their size:**
- Small: <63 μm diameter
- Intermediate: 63–124
- Large: ≥125
- Drusenoid PED: >350

**Drusen are categorized by the retinal layer in which they’re located**

**Drusen are categorized by their boundaries:**
- ?
- ?
- ?
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  - Hard
  - Soft
  - Confluent
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Which are described as being...
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  - **Soft
  - **Confluent**

Which are described as being...
Hard drusen
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**Drusen are categorized by the retinal layer in which they’re located**

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---

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**Drusen are categorized by the retinal layer in which they're located**

**Drusen are categorized by their boundaries:**
- Hard: Discrete, well demarcated
- Soft: Amorphous, poorly demarcated
- Confluent

Which are described as being…
Soft drusen
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*Drusen are categorized by their boundaries:*
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*Which are described as being...*
A, Color fundus photograph shows soft, *confluent*, large drusen in a patient with ARMD. 
B, Corresponding SD-OCT of the soft drusen. C, Autofluorescence image of an eye with areas of confluent drusen.
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**Drusen are categorized by the retinal layer in which they’re located:**
- Which type(s) carry a greater risk of dz progression?
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Which type(s) carry a greater risk of disease progression?
Soft for sure, and probably confluent as well.

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- **Drusen are categorized by the retinal layer in which they’re located:**
  - Basal
  - Reticular

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Drusen are categorized by the retinal layer in which they're located:
- **Basal laminar**
- **Basal linear**
- **Reticular pseudodrusen**

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  - Basal linear: ?
  - Reticular pseudodrusen: ?

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- By their boundaries:
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Before identifying the location for each drusen, let’s review the anatomy of the outer retina.
**But first:**

What are the five layers of Bruch’s membrane?

1) (Start here)
2)
3)
4)
5)

**Innermost**

**Outermost**
**But first:**

What are the five layers of Bruch’s membrane?

1) 2) 3) 4) 5) of RPE

1) Innermost

2) Outermost
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE

(Note: This line represents the RPE basement membrane)
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) *(next)*
3)
4)
5)
But first:

What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner layer
3) One word
4) 
5) 

Innermost

Outermost
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) **Inner collagenous** layer
3) (etc)
4)
5)
But first:

What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Innermost layer
4) 
5) Outermost
But first:

What are the five layers of Bruch’s membrane?

- 1) Basement membrane of RPE
- 2) Inner collagenous layer
- 3) Elastic layer
- 4) 
- 5)
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) **Inner collagenous** layer
3) **Elastic** layer
4) **Outer** layer (one familiar word)
5)
**But first:**

What are the five layers of Bruch’s membrane?

- 1) **Basement membrane** of RPE
- 2) **Inner collagenous** layer
- 3) **Elastic** layer
- 4) **Outer collagenous** layer
- 5)
But first:

What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) two familiar words of choriocapillaris
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) Inner **collagenous** layer
3) **Elastic** layer
4) Outer **collagenous** layer
5) **Basement membrane** of choriocapillaris

(Note: This line represents the c’capillaris basement membrane)
What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

But first:

What (non-Bruch’s) structure goes here?

0) ?
What are the five layers of Bruch’s membrane?

0) **RPE cells**

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

*What (non-Bruch’s) structure goes here? The RPE cells themselves*
What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

But first:

So, the basal plasma membranes of the RPE cells…
What are the five layers of Bruch’s membrane?

0) RPE cells

1) Basement membrane of RPE

2) Inner collagenous layer

3) Elastic layer

4) Outer collagenous layer

5) Basement membrane of choriocapillaris

But first:

So, the basal plasma membranes of the RPE cells... sit directly on their BM (as you would expect)
What are the five layers of Bruch’s membrane?

0) RPE cells

1) Basement membrane of RPE

2) Inner collagenous layer

3) Elastic layer

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5) Basement membrane of choriocapillaris

Foreshadowing alert: Another name for the basal plasma membrane of a cell is ‘basal lamina’

But first:
What are the five layers of Bruch's membrane?

1. Basement membrane of RPE
2. Inner collagenous layer
3. Elastic layer
4. Outer collagenous layer
5. Basement membrane of choriocapillaris

But first:

The photoreceptor outer segments

What (non-RPE) structures go here?

0) RPE cells RPE cells

-1) ?

ARMD
What are the five layers of Bruch’s membrane?

1. Basement membrane of RPE
2. Inner collagenous layer
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What (non-RPE) structures go here? The photoreceptor outer segments
What are the five layers of Bruch's membrane?

1. Basement membrane of RPE
2. Inner collagenous layer
3. Elastic layer
4. Outer collagenous layer
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But first:

- PR outer segs
- RPE cells RPE cells

0) RPE cells RPE cells

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

What cell type is this?

Bipolar cells

ARMD
What are the five layers of Bruch’s membrane?

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What cell type is this?

-1) PR outer segs
0) RPE cells
-2) Bipolar cells

ARMD

But first:

But first:

What cell type is this?
Bipolar cells

PR outer segs
RPE cells
RPE cells
Bipolar cells

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Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

**What are drusen?**
Aggregates of material within the outer-retinal space.

**What sorts of substances constitute the material?**
Proteins and lipids—detritus shed by photoreceptors, mainly.

**How are drusen categorized?**
There are several ways:

- **Drusen are categorized by their size:**
  - Small: <63 μm diameter
  - Intermediate: 63–124
  - Large: ≥125
  - Drusenoid PED: >350

- **Drusen are categorized by the retinal layer in which they’re located:**
  - Basal laminar?
  - Basal linear
  - Reticular pseudodrusen

- **Drusen are categorized by their boundaries:**
  - Hard: Discrete, well demarcated
  - Soft: Amorphous, poorly demarcated
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What are the five layers of Bruch’s membrane?

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2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

But first:

0) RPE cells

-1) PR outer segs

-2) Bipolar cells
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- **Basal laminar**: Between RPE cells and their BM
- **Basal linear**: Within inner aspect of Bruchs membrane
- **Reticular pseudodrusen**: Between the apical surface of the RPE cells and the overlying photoreceptors

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- **Confluent**: Contiguous drusen without clear boundaries
What are the five layers of Bruch’s membrane?

1) PR outer segs
2) Bipolar cells
3) Basement membrane of RPE
4) Inner collagenous layer
5) Elastic layer
6) Outer collagenous layer
7) Basement membrane of choriocapillaris
8) Basement membrane of RPE
9) RPE cells
10) RPE cells
11) RPE cells
12) PR outer segs

But first:

-0) RPE cells
-1) PR outer segs
-2) Bipolar cells

Reticular pseudodrusen

ARMD
Reticular pseudodrusen: Classic distribution in the superior macula
Reticular pseudodrusen can be seen as multiple areas of granular hyperreflectivity between the RPE and photoreceptors.
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  - Reticular pseudodrusen: Between the apical surface of the RPE cells and the overlying photoreceptors

- **Circling back to drusenoid PEDs for a moment...**

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But first:

What are the five layers of Bruch's membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

So now we can see how basal laminar drusen, if extensive enough, can cause a drusenoid PED.

-2) Bipolar cells

-1) PR outer segs

0) RPE cells RPE cells

-1) PR outer segs

0) RPE cells RPE cells

1) Basement membrane

2) Inner collagenous layer

3) Elastic layer

4) Outer collagenous layer

5) Basement membrane of choriocapillaris
-2) Bipolar cells

But first:

-1) PR outer segs

0) RPE cells RPE cells

Likewise, we can see that extensive basal linear drusen can also producing a drusenoid PED

Basement membrane of RPE

1) Inner collagenous layer

2) Inner collagenous layer

3) Elastic layer

4) Outer collagenous layer

5) Basement membrane of choriocapillaris

Outermost
-2) **Bipolar cells**

**But first:**

-1) **PR outer segs**

0) **RPE cells**

1) **Basement membrane** of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) **Basement membrane** of choriocapillaris

However, *reticular pseudodrusen* do **not** separate the RPE from Bruch’s, so they **cannot** cause a PED.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

There are two types: nonexudative and exudative.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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By what two other names are each condition commonly known? Nonexudative: ? Exudative
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What are the three hallmark findings in nonexudative ARMD?

--?

--?

--?
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--Drusen
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--Geographic atrophy
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--RPE changes
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*We have already discussed drusen, and will look at RPE change in detail a little later in the set.*
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What are the three hallmark findings in nonexudative ARMD?
- Drusen
- RPE changes
- Geographic atrophy

What is geographic atrophy (GA)?

**Geographic atrophy** is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris. It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
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--RPE changes

--**Geographic atrophy**

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What are the three hallmark findings in nonexudative ARMD?

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--**Geographic atrophy**

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What is geographic atrophy (GA)?

It is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris.

How large must the area of atrophy be to qualify as GA?

By definition, it must have a diameter of at least 175 µm.
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What is its typical pattern of progression?
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It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
Progression of GA over a 2.5 year period. Note the characteristic perifoveal→foveal center pattern.
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What does GA look like on...

**FA**?

A well-circumscribed area of hyperfluorescence

**Autofluorescence**?

Dense hypofluorescence with a ring of hypofluorescence

**OCT**?

RPE loss; thinning/loss of the outer retinal layers
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations

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**OCT?** RPE loss; thinning/loss of the outer retinal layers
Geographic atrophy in ARMD: FA
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Speaking generally: What are the four causes of hyperfluorescence on FA?

- Drusen
- RPE changes
- Geographic atrophy

What does GA look like on FA? A well-circumscribed area of hyperfluorescence.

Geographic atrophy (GA) is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior retina manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris. It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
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What are the four causes of hyperfluorescence on FA?

- Pooling
- Leaking
- Staining
- Window defect

What does GA look like on FA?

A well-circumscribed area of hyperfluorescence.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. Age is the strongest risk factor for ARMD. The clinical hallmark of ARMD is the presence of drusen in the macula.

- **Nonexudative ARMD:**
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  - Geographic atrophy

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  - Neovascular ARMD; 'wet' ARMD

Speaking generally: What are the four causes of hyperfluorescence on FA?
- Pooling?
- Leaking?
- Staining?
- Window defect?

*Which one of these accounts for the hyperfluorescence of GA?*

**Geographic atrophy**

*What does GA look like on…*

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- Neovascular ARMD; 'wet' ARMD
- Pooling
- Leaking
- Staining

Geographic atrophy (GA) is one of the two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris.

Window defect accounts for the hyperfluorescence of GA.

What does GA look like on FA?
- A well-circumscribed area of hyperfluorescence
Geographic atrophy. **A**, Fundus photo. **B**, On fluorescein angiography, there is a “window defect” during the early frames with transmission of choroidal fluorescence. **C**, Note the absence of leakage in later frames.
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What are the three hallmark findings in nonexudative ARMD?
--Drusen
--RPE changes
---Geographic atrophy

What is geographic atrophy (GA)?
It is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris.

What does GA look like on…
**FA?** A well-circumscribed area of hyperfluorescence
**Autofluorescence?** Dense hypoautofluorescence with a ring of hypofluorescence
**OCT?** RPE loss; thinning/loss of the outer retinal layers

Eventually involves the foveal center.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

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It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
ARMD

FAF: Normal retina for comparison

FAF: GA
Geographic atrophy (GA). *Top*, Color fundus photographs of right (*left panel*) and left (*right panel*) eyes, demonstrating advanced GA. *Bottom*, Corresponding autofluorescent images of GA in the same patient with atrophic AMD. The areas of RPE atrophy are hypoautofluorescent (*dark gray or black*), the areas of “sick” RPE are hyperautofluorescent (*brighter than background*), and the areas of healthy RPE are *gray*. 
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OCT over the fovea in a patient with non-exudative AMD and geographic atrophy. There is loss of outer retinal layers and RPE.
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It starts in the perifoveal region, expanding over time to eventually involve the foveal center.

What is the other form that defines advanced ARMD?

It is neovascularization.
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**What about early and intermediate ARMD—how are they defined?**

- **Early ARMD:** drusen +/- a few intermediate drusen
- **Intermediate ARMD:** extensive intermediate drusen, or presence of large drusen

**Advanced ARMD:** Defined by the presence of either geographic atrophy or a neovascular membrane.

**Exudative:** Neovascular ARMD; ‘wet’ ARMD

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**What about early and intermediate ARMD—how are they defined?**

**Early ARMD**: Defined by the presence of small drusen +/- a “few” intermediate drusen.

**Intermediate ARMD**: Defined by the presence of large drusen or drusen with RPE changes.

**What are the three hallmark findings in nonexudative ARMD?**

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Time to tackle exudative ARMD. But before doing so, we need to review the vascular supply of the retina.
What are the five layers of Bruch's membrane?

- **Basement membrane of RPE**
- **Inner collagenous layer**
- **Elastic layer**
- **Outer collagenous layer**
- **Basement membrane of choriocapillaris**

What structure is this?
What are the five layers of Bruch’s membrane?

- 1) Basement membrane of RPE
- 2) Inner collagenous layer
- 3) Elastic layer
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What structure is this?

- RPE cells
- Bipolar cells
- PR outer segs
- Choriocapillaris
What are the five layers of Bruch's membrane?

- **Basement membrane of RPE**
- Inner collagenous layer
- Elastic layer
- Outer collagenous layer
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But first:

- **RPE cells**
- **PR outer segs**

1. **Basement membrane of RPE**
2. Inner collagenous layer
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5. Basement membrane of choriocapillaris
6. Choriocapillaris
7. ?

What structure is this?
What are the five layers of Bruch’s membrane?

- 1) PR outer segs
- 2) Bipolar cells
- 0) RPE cells RPE cells
- 1) Basement membrane of RPE
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- 5) Basement membrane of choriocapillaris
- 6) Choriocapillaris
- 7) Choroid

What structure is this? The choroid
What are the five layers of Bruch’s membrane?

- 0) RPE cells
- 1) Basement membrane of RPE
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What is the deepest retinal layer in which branches of the retinal vasculature can be found?

Retinal vessels

-3) Retinal vessels

-2) Bipolar cells

-1) PR outer segs
What are the five layers of Bruch's membrane?

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What is the deepest retinal layer in which branches of the retinal vasculature can be found?

The inner nuclear layer (INL) of the retinal vasculature can be found. What is the deepest retinal layer in which branches of the retinal vessels are found?
What are the five layers of Bruch's membrane?

- 1) PR outer segs
- 2) Bipolar cells
- 3) Retinal vessels
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But first:

0) RPE cells

So, the retinal vessels supply the inner retinal layers…
What are the five layers of Bruch’s membrane?

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But first:

0) RPE cells RPE cells

So, the retinal vessels supply the inner retinal layers…Whereas the choroid/choriocapillaris supply the outer retina and RPE
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What does it mean to say ARMD is ‘exudative’?
It means a neovascular membrane, (almost always choroidal in origin) is present.
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What will a pt c/o if a CNVM develops?
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Three types of neovascular membranes occur in ARMD—what are they called?

- CNVM originates from the choriocapillaris and extends into Bruch’s membrane and/or the sub-RPE space
- CNVM originates from the choriocapillaris and extends into the sub-retinal space (i.e., just above the RPE)
- NVM arises from the deep capillary plexus of the retina and grows down toward the RPE

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-- Type 1
-- Type 2
-- Type 3

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--Type 3
-2) Bipolar cells

-1) PR outer segs

0) RPE cells RPE cells

Basement membrane of RPE

1) Inner collagenous layer

2) Inner collagenous layer

3) Elastic layer

4) Outer collagenous layer

5) Basement membrane of choriocapillaris

6) Choriocapillaris

7) Choroid

Type 1 with the CNVM in Bruch's membrane
What are the five layers?
1. Basement membrane of RPE
2. Inner collagenous layer
3. Elastic layer
4. Outer collagenous layer
5. Basement membrane of choriocapillaris

Type 1 with the CNVM in the sub-RPE space

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
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6) Choriocapillaris
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-1) PR outer segs
0) RPE cells RPE cells
Type 1 CNVM with hyperreflective material visible in the PED. Note that the RPE can be seen to ride above the lesion.
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--Type 2: CNVM originates from the choriocapillaris and extends into the sub-retinal space

--Type 3: Blurry vision, metamorphopsia and/or a paracentral scotoma
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

There are two types: **Nonexudative** and **exudative**

By what two other names are each condition commonly known?

- **Nonexudative**: Nonneovascular ARMD; ‘dry’ ARMD
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Three types of neovascular membranes occur in ARMD—what are they called? What are the defining features of each?

- **Type 1**: CNVM originates from the choriocapillaris and extends into Bruch’s membrane and/or the sub-RPE space
- **Type 2**: CNVM originates from the choriocapillaris and extends into the sub-retinal space (i.e., just above the RPE)
- **Type 3**: Blurry vision, metamorphopsia and/or a paracentral scotoma
What are the five layers of Bruch's membrane?

1. Basement membrane of RPE
2. Inner collagenous layer
3. Elastic layer
4. Outer collagenous layer
5. Basement membrane of choriocapillaris

Type 2 with the CNVM in the sub-retinal space
Type 2 CNVM located above the RPE with subretinal fluid (SRF) adjacent to the lesion. Note the RPE can be seen below the lesion.
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Type 3 with the NVM growing down from retinal vessels into the sub-retinal space.
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What does it mean to say ARMD is 'exudative'?

It means a neovascular membrane, (almost always choroidal in origin) is present.

What vessels give rise to the neovascular membrane?

The choriocapillaris (with one exception, to be discussed later).

What will a pt c/o if a CNVM develops?

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Type 3 is the exception to the statement 'CNVM originate in the chorio capillaris' mentioned a few slides ago.
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Ocular histo is high on the DDx for CNVM. What other non-ARMD conditions are important causes of CNVM?
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Coming in hot…
**CNVM DDx:**

- **ARMD**
- **OHS**
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?

*Other than these two, what is the DDx for causes of CNVM?*
CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
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Is there a racial predilection in OHS?

Yes, OHS occurs almost exclusively among whites of Northern European heritage.

Is there a geographic predilection?

Yes, the majority of cases are found in people who reside in the Mississippi/Ohio River valleys of the US.

Does OHS manifest unilaterally, or bilaterally?

Bilaterally (although it can be somewhat asymmetric).

Is OHS associated with vitritis?

Never. If vitritis is present, it's not OHS.

What about AC cell?

Never. If AC cell is present, it's not OHS.
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- **How is the diagnosis of OHS made?**
  - It is a clinical diagnosis based on DFE findings
  - What are you looking for on DFE?
    - The so-called 'classic triad' of OHS:
      - Histo spots
      - Peripapillary atrophy
      - Disciform macular lesion(s)

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- Adult-onset vitelliform dystrophy

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**How is the diagnosis of OHS made?**
It is a clinical diagnosis based on DFE findings.

**What are you looking for on DFE?**
- The so-called 'classic triad' of OHS:
  - Histo spots
  - Peripapillary atrophy
  - Disciform macular lesion(s)

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**Does OHS manifest unilaterally, or bilaterally?**
Bilaterally (although it can be somewhat asymmetric)

**Is OHS associated with vitritis?**
**Never.** If vitritis is present, it’s not OHS.

**What about AC cell?**
**Never.** If AC cell is present, it’s not OHS.
How is the diagnosis of OHS made?
It is a clinical diagnosis based on DFE findings.

What are you looking for on DFE?
The so-called ‘classic triad’ of OHS:
--?
--?
--?

Does OHS manifest unilaterally, or bilaterally?
Bilaterally (although it can be somewhat asymmetric)

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It is a clinical diagnosis based on DFE findings.

What are you looking for on DFE?
The so-called 'classic triad' of OHS:
--Histo spots
--Peripapillary atrophy
--Disciform macular lesion(s)

Does OHS manifest unilaterally, or bilaterally?
Bilaterally (although it can be somewhat asymmetric)

Is OHS associated with vitritis?
Never. If vitritis is present, it's not OHS.

What about AC cell?
Never. If AC cell is present, it's not OHS.
OHS: The classic triad
For more on OHS, see slide-set U21
CNVM DDx:

- ARMD
- OHS
- Angioid streaks

What is the classic DFE appearance of angioid streaks?

- Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane

What proportion of angioid streaks are associated with systemic abnormalities?

- About half

What is the well-known mnemonic for angioid streak's associations? What are these associations?

- PXE
- Ehlers-Danlos syndrome
- Paget's disease of bone
- Sickle-cell disease
- Idiopathic (ie, no association)
What is the classic DFE appearance of angioid streaks?

Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane.
What is the classic DFE appearance of angioid streaks?

**Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane

What proportion of angioid streaks are associated with systemic abnormalities?

About half

What is the well-known mnemonic for angioid streak's associations? What are these associations?

- **P**seudoxanthoma elasticum (PXE)
- **E**hlers-Danlos syndrome
- **P**aget’s disease of bone
- **S**ickle-cell disease
- **I**diopathic (ie, no association)

**CNVM DDx:**

- ARMD
- **OHS**
- **Angioid streaks**
- **Pattern dystrophy**
- Adult-onset vitelliform dystrophy
- **Central serous chorioretinopathy**
- **Traumatic choroidal rupture**
- **Iatrogenic**
- **Idiopathic**
Angioid streaks (arrowheads). Note that only a few of the many present have been marked.
What is the classic DFE appearance of angioid streaks?

**Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?

Adult-onset vitelliform dystrophy
CNVM DDx:

- ARMD
- OHS
- **Angioid streaks**

What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane

What proportion of angioid streaks are associated with systemic abnormalities?
About half

- Adult-onset vitelliform dystrophy
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?
About half.

What is the well-known mnemonic for angioid streak’s associations?
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane

What proportion of angioid streaks are associated with systemic abnormalities?
About half

What is the well-known mnemonic for angioid streak’s associations?
P
E
P
S
I

Adult-onset vitelliform dystrophy
**CNVM DDx:**

- ARMD
- OHS
- **Angioid streaks**

**What is the classic DFE appearance of angioid streaks?**

Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

**What proportion of angioid streaks are associated with systemic abnormalities?**

About half.

**What is the well-known mnemonic for angioid streak’s associations?** What are these associations?

- P
- E
- P
- S
- I

- Adult-onset vitelliform dystrophy
What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).
**CNVM DDx:**

- ARMD

**OHS**

**Angioid streaks**

What is the classic DFE appearance of angioid streaks?

**Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?

About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?

- **P**seudoxanthoma elasticum (PXE)
- **E**hlers-Danlos syndrome
- **P**aget’s disease of bone
- **S**ickle-cell disease
- **I**diopathic (ie, no association)

~ # of cases are associated with one of these.

~ # of cases have no known systemic association.

- Adult-onset vitelliform dystrophy
What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? 
- Pseudoxanthoma elasticum (PXE)
- Ehlers-Danlos syndrome
- Paget’s disease of bone
- Sickle-cell disease
- Idiopathic (ie, no association)

~50% of cases are associated with one of these  
~50% of cases have no known systemic association.
**CNVM DDx:**

- ARMD
- OHS

- **Angioid streaks**

  *What is the classic DFE appearance of angioid streaks?*

  Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane

  *What proportion of angioid streaks are associated with systemic abnormalities?*

  About half

  *What is the well-known mnemonic for angioid streak's associations? What are these associations?*

  - **P**seudoxanthoma elasticum (PXE)?
  - **E**hlers-Danlos syndrome?
  - **P**aget’s disease of bone?
  - **S**ickle-cell disease?
  - Idiopathic (ie, no association)

  **Which condition has the strongest association with angioid streaks?**

- Adult-onset vitelliform dystrophy
**CNVM DDx:**

- ARMD
- OHS

**Angioid streaks**

What is the classic DFE appearance of angioid streaks? **Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? **Pseudoxanthoma elasticum (PXE)**, Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Which condition has the strongest association with angioid streaks? **PXE**, by a mile.

- Adult-onset vitelliform dystrophy
What is the classic DFE appearance of angioid streaks?

Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane.

What proportion of angioid streaks are associated with systemic abnormalities?

About half.

What is the well-known mnemonic for angioid streak's associations? What are these associations?

Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget's disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Which condition has the strongest association with angioid streaks? What are these associations?

PXE, by a mile.
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?
About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Which condition has the strongest association with angioid streaks?
PXE, by a mile.

Other organ-systems affected in PXE?
Skin, Vascular system, GI tract, Eye.
What is the classic DEE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Which condition has the strongest association with angioid streaks? PXE, by a mile.

What is the appearance of affected skin? An area of waxy-yellow, papule-like lesions. The classic informal descriptor for this appearance is ‘chicken skin’.
CNVM DDx:

- ARMD
- OHS

Angioid streaks

What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak's associations? What are these associations? Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget's disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Which condition has the strongest association with angioid streaks? PXE, by a mile.

What is the appearance of affected skin? An area of waxy-yellow, papule-like lesions.

What other organ-systems are affected in PXE? Skin, Vascular, GI tract, Eye.

What is the classic informal descriptor for this appearance? 'Chicken skin'.
**Angioid streaks**

What is the classic DFF appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?
About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Which condition has the strongest association with angioid streaks?
PXE, by a mile.

What is the appearance of affected skin?
An area of waxy-yellow, papule-like lesions.

What is the classic informal descriptor for this appearance?
'Chicken skin'.
- CNVM DDx:
  - ARMD
  - OHS

★ Angioid streaks

What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?
About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
**P**seudoxanthoma elasticum (PXE)
**E**hlers-Danlos syndrome
**P**aget’s disease of bone
**S**ickle-cell disease
**I**diopathic (ie, no association)

Which condition has the strongest association with angioid streaks? PXE, by a mile.

What is the appearance of affected skin?
An area of waxy-yellow, papule-like lesions.

What is the classic informal descriptor for this appearance?
‘Chicken skin’.

Adult-onset vitelliform dystrophy
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak's associations? What are these associations?
- Pseudoxanthoma elasticum (PXE)
- Ehlers-Danlos syndrome
- Paget's disease of bone
- Sickle-cell disease
- Idiopathic (ie, no association)

Which condition has the strongest association with angioid streaks? PXE, by a mile.

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?
- Angioid streaks
- ?
- ?
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?
About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (i.e., no association).

Which condition has the strongest association with angioid streaks?
PXE, by a mile.

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?
--Angioid streaks
--RPE mottling
--Optic disc drusen.

What other organ-systems are affected in PXE?
--Skin
--Vascular system
--GI tract
--Eye
**CNVM DDx:**
- ARMD
- OHS
- **Angioid streaks**

What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
- Pseudoxanthoma elasticum (PXE)
- Ehlers-Danlos syndrome
- Paget’s disease of bone
- Sickle-cell disease
- Idiopathic (ie, no association)

Which condition has the strongest association with angioid streaks? PXE, by a mile.

What other organ-systems are affected in PXE?
- Skin
- Vascular system
- GI tract
- Eye

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?
- RPE mottling
- Optic disc drusen

What mellifluous name is used to describe the RPE mottling? Peau d’orange.

Adult-onset vitelliform dystrophy
CNVM DDx:

- ARMD
- OHS

**Angioid streaks**

What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane.

About half of angioid streaks are associated with systemic abnormalities. About half. What is the well-known mnemonic for angioid streak's associations? What are these associations? Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget's disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two? Angioid streaks, RPE mottling, Optic disc drusen.

What mellifluous name is used to describe the RPE mottling? Peau d’orange.

Which condition has the strongest association with angioid streaks? PXE, by a mile.

Adult-onset vitelliform dystrophy
PXE: *Peau d’orange* fundus
PXE: Peau d’orange fundus

For more on angioid streaks, see slide-set R61
CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - Central serous chorioretinopathy
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - Central serous chorioretinopathy
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

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*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*

26.5 mm
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia? 26.5 mm

What is the classic finding on DFE that puts high myopes at risk for CNVM?
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioiditis
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*

- 26.5 mm

*What is the classic finding on DFE that puts high myopes at risk for CNVM?*

- Lacquer cracks
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

---

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?

26.5 mm

What is the classic finding on DFE that puts high myopes at risk for CNVM?

Lacquer cracks

What are lacquer cracks?
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?
26.5 mm

What is the classic finding on DFE that puts high myopes at risk for CNVM?
Lacquer cracks

What are lacquer cracks?
Breaks in Bruch’s membrane, in color, usually found in the retinal area.
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?
26.5 mm

What is the classic finding on DFE that puts high myopes at risk for CNVM?
Lacquer cracks

What are lacquer cracks?
Breaks in Bruch’s membrane, yellowish in color, usually found in the macula.
Lacquer cracks
**CNVM DDx:**
- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - Central serous chorioretinopathy
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

**Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?**
26.5 mm

**What is the classic finding on DFE that puts high myopes at risk for CNVM?**
Lacquer cracks

**What are lacquer cracks?**
Breaks in Bruch’s membrane, yellowish in color, usually found in the macula. These breaks are the nidus for CNVM ingress in pathologic myopia.
**CNVM DDx:**

- ARMD
- **OHS?**
- **Angioid streaks?**
- **Pathologic myopia?**
- **Idiopathic?**
- **Sorsby macular dystrophy?**
- **Traumatic choroidal rupture?**
- **Iatrogenic?**
- **Central serous chorioretinopathy?**
- **Pattern dystrophy?**
- **Adult-onset vitelliform dystrophy?**

*The ARMD chapter of the Retina book mentions one of these as being particularly likely to be **misdiagnosed** as CNVM, ie, to produce the impression that a CNVM is present when it isn’t—which one?*
CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic

**Central serous chorioretinopathy**

- Pattern dystrophy
- Adult-onset vitelliform dystrophy

The ARMD chapter of the Retina book mentions one of these as being particularly likely to be **misdiagnosed** as CNVM, ie, to produce the impression that a CNVM is present when it isn’t—which one?
In two words, what is the underlying cause of CSC?

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
- Choroidal hyperpermeability

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
- Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

**Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

*To be clear: Is CNVM associated with CSC?*
In two words, what is the underlying cause of CSC?
- Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

*To be clear: Is CNVM associated with CSC?*
- **Yes**—2ndry CNVM can and does occur in CSC, albeit uncommonly.

**Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM and masquerade as it.

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (<i>choriocapillaris hyperpermeability</i> is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM and masquerade as it.

For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?

Central serous chorioretinopathy

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

*To be clear: Is CNVM associated with CSC?*
*Yes*—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM and masquerade as it.

*For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?*
The presence of SRF on OCT

**Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (*choriocapillaris hyperpermeability is correct as well, and may even be preferred*)

*To be clear: Is CNVM associated with CSC?*
**Yes**—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM and masquerade as it.

*For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?*
The presence of SRF on OCT

*What distinguishes SRF seen on OCT in CNVM from that seen in CSC?*
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM and masquerade as it.

For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?
The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly. The takeaway point: CSC can both cause CNVM *and* masquerade as it.

For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?
The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

★ Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
**ARMD**
PED (△) and SRF (↓), along with subretinal hemorrhage (*)

**CSC**
PED and SRF, but no hemorrhage
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

*To be clear: Is CNVM associated with CSC?*
*Yes*—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM *and* masquerade as it.

*For the CSC cases in which no CNVM is present: What clinical finding.*
*There is another important OCT finding that distinguishes CSC from ARMD—what is it?*

**Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly. The takeaway point: CSC can both cause CNVM and masquerade as it.

For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?
The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

There is another important OCT finding that distinguishes CSC from ARMD—what is it?
The thickness of the choroid

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
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CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
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- Sorsby macular dystrophy
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Central serous chorioretinopathy
- Pattern dystrophy
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The choroid is seen in cross section. Subfoveal choroidal thickness was measured vertically from the outer border of the RPE to the inner border of the sclera (brackets) in a healthy eye in a 55-year-old man (A) and in 3 representative eyes with CSC: in a 44-year-old man (B), a 57-year-old man (C), and a 63-year-old man (D).
CNVM DDx:

In two words, what is the underlying cause of CSC?

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The thickness of the choroid. It tends to be normal or thinned in ARMD, but thickened in CSC.

Choroidal thickness may not be readily interpretable on spectral-domain OCT (SD-OCT). What OCT modality is preferred for assessing the choroid?

Central serous chorioretinopathy

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
**ARMD**

**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

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**In two words, what is the underlying cause of CSC?**

Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

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**To be clear: Is CNVM associated with CSC?**

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**There is another important OCT finding that distinguishes CSC from ARMD—what is it?**

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**Choroidal thickness may not be readily interpretable on spectral-domain OCT (SD-OCT).**

**What OCT modality is preferred for assessing the choroid?**

Enhanced-depth imaging OCT (EDI-OCT)

---

**Central serous chorioretinopathy**

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
Regarding conditions that can be misdiagnosed as dry ARMD—what feature do they have in common?

Dry ARMD

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
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- Central serous chorioretinopathy
- Pattern dystrophy
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Dry ARMD

CNVM DDx:

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- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Regarding conditions that can be misdiagnosed as dry ARMD—what feature do they have in common? Abnormalities of the RPE
Dry ARMD

CNVM^DDx:

- ARMD
- OHS?
- Angioid streaks?
- Pathologic myopia?
- Idiopathic?
- Sorsby macular dystrophy?
- Traumatic choroidal rupture?
- Iatrogenic?
- Central serous chorioretinopathy?
- Pattern dystrophy?
- Adult-onset vitelliform dystrophy?

The ARMD chapter of the Retina book mentions three of these as being particularly likely to produce a misdiagnosis of dry ARMD— which three?
Dry ARMD

CNVM DDx:

- ARMD
- OHS
- Angioid streaks
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- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic

★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy

The ARMD chapter of the Retina book mentions three of these as being particularly likely to produce a misdiagnosis of dry ARMD—which three?

(Yes, CSC is a prominent member of the DDx for both wet and dry ARMD!)
How does CSC—a choroidal condition that produces serous detachments—acquire the RPE abnormalities that characterize dry ARMD masqueraders?
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CSC: RPE mottling
How does CSC—a choroidal condition that produces serous detachments—acquire the RPE abnormalities that characterize dry ARMD masqueraders? If the SRF is chronic, it can produce RPE mottling.

Because SRF is subject to gravity-induced downward migration, the RPE changes often demonstrate a particular pattern. What are the formal and informal names for this pattern?

★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy
Dry ARMD

How does CSC—a choroidal condition that produces serous detachments—acquire the RPE abnormalities that characterize dry ARMD masqueraders? If the SRF is chronic, it can produce RPE mottling.

Because SRF is subject to gravity-induced downward migration, the RPE changes often demonstrate a particular pattern. What are the formal and informal names for this pattern?

Descending tracts, aka ‘guttering’

Central serous chorioretinopathy

Pattern dystrophy

Adult-onset vitelliform dystrophy
CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.
CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.

For more on CSC, see slide-set R47
Briefly, what is a pattern dystrophy?

Pattern dystrophy

Adult-onset vitelliform dystrophy
Briefly, what is a pattern dystrophy?
An inherited macular dystrophy that has a characteristic appearance (ie, a particular ‘pattern’)
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An inherited macular dystrophy that has a characteristic appearance (ie, a particular ‘pattern’)

What is the inheritance pattern?

Pattern dystrophy
Adult-onset vitelliform dystrophy
Pattern dystrophy
★ Adult-onset vitelliform dystrophy
Dry ARMD

CNVM DDx:

Briefly, what is a pattern dystrophy?
An inherited macular dystrophy that has a characteristic appearance (ie, a particular ‘pattern’)

What is the inheritance pattern?
AD

Are pattern dystrophies associated with severe vision loss?

Pattern dystrophy
Adult-onset vitelliform dystrophy
**Pattern dystrophy**

★ Adult-onset vitelliform dystrophy

*Briefly, what is a pattern dystrophy?*
An inherited macular dystrophy that has a characteristic appearance (ie, a particular ‘pattern’)

*What is the inheritance pattern?*
AD

*Are pattern dystrophies associated with severe vision loss?*
Generally no--vision is only slightly affected
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Do the macular ‘patterns’ appear early in life?

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Briefly, what is a pattern dystrophy?
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Generally no--they usually show up in middle adulthood
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The BCSC Retina book identifies four pattern dystrophies by name--what are they?
--
--
-- The mnemonic is…”

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Adult-onset vitelliform dystrophy
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The BCSC Retina book identifies four pattern dystrophies by name--what are they?
--B
--A
--R
--F

The mnemonic is…BARF?

★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy
Briefly, what is a pattern dystrophy?
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What is the inheritance pattern?
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The BCSC Retina book identifies four pattern dystrophies by name--what are they?
--Butterfly dystrophy
--Adult-onset foveomacular vitelliform dystrophy
--Reticular dystrophy
--Fundus pulverulentus

Pattern dystrophy
Adult-onset vitelliform dystrophy
Butterfly dystrophy

Adult-onset foveomacular vitelliform dystrophy

Reticular dystrophy

Fundus pulverulentus
Briefly, what is a pattern dystrophy?
An inherited macular dystrophy that has a characteristic appearance (ie, a particular ‘pattern’)

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★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy

These terms are awfully similar…Do they refer to the same, or different conditions?
Briefly, what is a pattern dystrophy?
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These terms are awfully similar…Do they refer to the same, or different conditions?
The same (the Retina book uses both)
**Dry ARMD**

- **CNVM DDx:**
  - ARMD
  - OHS
  - Angioid streaks
  - Pathologic myopia
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic

- ★ Central serous chorioretinopathy
- ★ Pattern dystrophy
- ★★ **Adult-onset vitelliform dystrophy**

---

At what age do AOVD lesions appear?

- 30s to 50s
- What do pts c/o initially?
  - Not much—maybe a little blurring or metamorphopsia
- What does DFE reveal?
  - Bilateral vitelliform (which means egg-yolk like) lesions
- How might such a lesion lead to a misdiagnosis of dry ARMD?
  - Its DFE and OCT appearance could be misinterpreted as representative of a drusenoid PED
**Dry ARMD**

**CNVM**

**DDx:**

- ARMD
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**Central serous chorioretinopathy**

**Pattern dystrophy**

**Adult-onset vitelliform dystrophy**

At what age do AOVD lesions appear?

30s to 50s
**Dry ARMD**

**DDx:**
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- Pattern dystrophy

**Adult-onset vitelliform dystrophy**

---

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Adult-onset vitelliform dystrophy
Dry ARMD

CNVM DDx:
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- Central serous chorioretinopathy
- Pattern dystrophy
- **Adult-onset vitelliform dystrophy**

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- Central serous chorioretinopathy
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- **Adult-onset vitelliform dystrophy**

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Not much—maybe a little blurring or metamorphopsia

*What does DFE reveal?*
Bilateral vitelliform (which means **like**) lesions

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*Its DFE and OCT appearance could be misinterpreted as representative of a drusenoid PED two-words*
**Dry ARMD**

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Bilateral vitelliform (which means *egg-yolk like*) lesions
Dry ARMD

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★ Pattern dystrophy
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What does DFE reveal?
Bilateral vitelliform (which means egg-yolk-like) lesions

Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:
-- Color?
Yellow(ish)
-- Shape?
Round
-- Contour?
Domed
Dry ARMD

CNVM \_ DDx:

- ARMD
- OHS
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Central serous chorioretinopathy
Pattern dystrophy

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Central serous chorioretinopathy
Pattern dystrophy

★ Adult-onset vitelliform dystrophy

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What does DFE reveal?
Bilateral vitelliform (which means egg-yolk-like) lesions

Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:
--Color? Yellow(ish)
--Shape? Round

★ egg-yolk like
Typical round, yellow lesion of AOVD
**Dry ARMD**

- **CNVM DDx:**
  - ARMD
  - OHS
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  - Idiopathic
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**Central serous chorioretinopathy**

**Pattern dystrophy**

**Adult-onset vitelliform dystrophy**

---

**At what age do AOVD lesions appear?**

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**What does DFE reveal?**

- Bilateral vitelliform (which means "egg-yolk-like") lesions

**Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:**

- **Color?** Yellow(ish)
- **Shape?** Round
- **Contour?**

---

**egg-yolk like**
Dry ARMD

CNVM DDx:

- ARMD
- OHS
- Angioid streaks
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- Idiopathic
- Sorsby macular dystrophy
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At what age do AOVD lesions appear?
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What does DFE reveal?
Bilateral vitelliform (which means egg-yolk like) lesions

Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:
- Color? Yellow(ish)
- Shape? Round
- Contour? Domed

What does DFE reveal?
Bilateral vitelliform (which means egg-yolk like) lesions
OCT showing dome-like lesion in AOVD
Dry ARMD

At what age do AOVD lesions appear? 30s to 50s

What do pts c/o initially? Not much—maybe a little blurring or metamorphopsia

What does DFE reveal? Bilateral vitelliform (which means egg-yolk like) lesions

How might such a lesion lead to a misdiagnosis of dry ARMD?

**Adult-onset vitelliform dystrophy**
Dry ARMD

CNVM DDx:

- ARM
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic

★ Central serous chorioretinopathy
★ Pattern dystrophy
★★ Adult-onset vitelliform dystrophy

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Bilateral vitelliform (which means egg-yolk like) lesions

How might such a lesion lead to a misdiagnosis of dry ARMD?
Its DFE and OCT appearance could be misinterpreted as representative of a drusenoid PED
Here’s a clinical challenge: AOVD in a patient with extensive drusen. Fundus photo demonstrates drusen, and an ill-defined vitelliform lesion. OCT shows the material over the soft drusen (yellow arrow) that could be misinterpreted as a CNVM related to wet ARMD.
Here’s a clinical challenge: AOVD in a patient with extensive drusen. Fundus photo demonstrates drusen, and an ill-defined vitelliform lesion. OCT shows the material over the soft drusen (yellow arrow) that could be misinterpreted as a CNVM related to wet ARMD.

For more on the pattern dystrophies, see slide-set R11
Dry ARMD

ARMD

OHS

Angioid streaks

Pathologic myopia

Idiopathic

Sorsby macular dystrophy

Traumatic choroidal rupture

Iatrogenic

Central serous chorioretinopathy

Pattern dystrophy

Vitelliform dystrophy

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

CNVM DDx:
- ARMD
- OHS
- Angioid streaks
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- Sorsby macular dystrophy
- Traumatic choroidal rupture
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Central serous chorioretinopathy  ★
Pattern dystrophy  ★
Vitelliform dystrophy  ★
Drug toxicity  ★

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

CNVM DDx:
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★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Vitelliform dystrophy
★ Drug toxicity, especially…

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
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★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Vitelliform dystrophy
★ Drug toxicity, especially... hydroxychloroquine

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

**CNVM DDx:**
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?

**Plaquenil maculopathy is covered in slide-set R25**

- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic

★★ Central serous chorioretinopathy
★★ Pattern dystrophy
★★ Vitelliform dystrophy
★★ Drug toxicity, especially...hydroxychloroquine
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations

Age is the strongest risk factor for ARMD

The clinical hallmark of ARMD is the presence of drusen in the macula

There are two types: Nonexudative and exudative

abnormalities in ARMD are typical
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. Age is the strongest risk factor for ARMD. The clinical hallmark of ARMD is the presence of drusen in the macula. There are two types: Nonexudative and exudative. RPE abnormalities in ARMD are typical.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

There are two types: Nonexudative and exudative.

RPE abnormalities in ARMD are typical.

The two RPE changes most typical of ARMD are:
--Atrophy (we knew this one already because of GA)
--Focal
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

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*The two RPE changes most typical of ARMD are:*
--Atrophy (we knew this one already because of GA)
--Focal hyperpigmentation
ARMD: RPE hyperpigmentation
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

There are two types: Nonexudative and exudative.

RPE abnormalities in ARMD are typical.

Photoreceptors in ARMD are abnormal as well.
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Speaking of being unsure about causality in ARMD…
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--Basal laminar/linear deposits accumulate.

No question—advance when ready.
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So, changes in ARMD include:

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All of them. This is one of the challenges of ARMD—finding a bright line between its pathologic changes and those associated with normal aging. Normal aging changes can be observed in the outer retina, RPE, Bruch’s membrane, and choriocapillaris, and many of these changes are difficult to separate from those seen in ARMD.
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What is the complement system? To answer this, we need to unpack the notion of the immune response...
What are the two fundamental immune responses?
What are the two fundamental immune responses?
Immune response

Innate
aka.. immunity

Adaptive
aka... immunity

*What word is used to capture the essence of each?*
ARMD

Immune response

**Innate**
aka...**natural** immunity

**Adaptive**
aka...**acquired** immunity

*What word is used to capture the essence of each?*
Immune response

**Innate**
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provide immediate protection

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Which provides immediate protection against antigens deemed threatening?
Immune response

**Innate**
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Does not provide immediate protection

*Which provides immediate protection against antigens deemed threatening?*
Immune response

**Innate**
- aka…natural immunity
- Does not provide immediate protection
- Does not require previous contact with the threat

**Adaptive**
- aka…acquired immunity
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*Which must have previous experience with an antigen to gain the capacity to neutralize it?*
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<table>
<thead>
<tr>
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<th>Adaptive</th>
</tr>
</thead>
<tbody>
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<td>--?</td>
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What are the primary effector cells for each?
Immune response

**Innate**

aka... **natural** immunity

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Primary effector cells:
-- PMNs
-- Monocytes/macrophages

**Adaptive**

aka... **acquired** immunity

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Primary effector cells:
-- T cells
-- B cells

*What are the primary effector cells for each?*
The *innate* (or *natural*) immune response relies on ‘preprogrammed’ immune cells to recognize foreign material encountered in tissue or blood, whereas the *adaptive* (or *acquired*) immune response involves ‘education,’ with surveillance cells learning to recognize and remember foreign material.
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**Inflammatory mediators can be a single molecule**

What would be an example of a single-molecule inflammatory mediator?

- Histamine
- Cytokines
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The *complement cascade*
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Complement factor H (CFH)
(This is a good point in the set to take a break)
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Let’s drill down on VEGF for a bit...
What does VEGF stand for?
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What is a growth factor?

-- Epidermal growth factor
-- Fibroblast growth factor(s)
-- Transforming growth factor β(s)
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What does VEGF stand for?
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What is a growth factor?
One of a diverse group of proteins that affect cell function, including cell proliferation and tissue differentiation

ARMD

VEGF-A$_{165}$
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2) ?
3) ?
4) ?
5) ?
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1) Reis-Bücklers
2) Thiel-Behnke
3) Lattice, type 1
4) Lattice, variant types (III, IIIA, I/IIIA, IV)
5) Granular type 1
6) Granular type 2
What does VEGF stand for?
Vascular endothelial growth factor

Broadly speaking, what is VEGF?
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VEGF-A\(^{165}\)
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Does VEGF do anything besides grow new blood vessels? Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor).
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor). This property is important in the development of diabetic macular edema, which explains the effectiveness of anti-VEGF therapies in the treatment of this condition.
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Are there multiple subtypes of VEGFRs?
Yes. VEGF-A binds to two: VEGFR-1 and VEGFR-2.

Is one of these more important in the pathogenesis of ARMD?
Yes, VEGFR-2 seems to be responsible for all of the findings in ARMD.

The function of VEGFR-1 is unclear at this time.
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Very. Elevated VEGF levels are found within the RPE and vitreous of eyes with early ARMD, and within excised choroidal neovascular membranes. The Retina book goes so far as to say the evidence suggests “a causal role for VEGF in the initiation of neovascularization” in ARMD.

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Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations

Age is the strongest risk factor for ARMD

The clinical hallmark of ARMD is the presence of drusen in the macula

There are two types: Nonexudative and exudative

RPE abnormalities in ARMD are typical

Photoreceptors in ARMD are abnormal as well

The pathogenesis of ARMD is not well understood; that said, the complement system is strongly implicated in it

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Next let’s drill down on anti-VEGF therapy…
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment for treatment of ARMD.
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Like many monoclonal antibodies, the parent molecule of ranibizumab was derived from mouse cells. Such murine antibodies would be recognized as foreign by the human immune system and attacked as such. To preclude this, a portion of the mouse antibody is replaced with its human counterpart via recombinant DNA techniques.

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Antibodies produced by a set of immune cells that all derived from (i.e., clones of) the same parent cell.

**What does fragment mean in this context?**
Ranibizumab is not a complete antibody; rather, it consists of a portion—or fragment—of an antibody.

Next we will take a deep dive into the key clinical trials that established the safety and effectiveness of ranibizumab in the tx of wet ARMD.

**What does the infix (yes, infix) –zu- indicate?**
That the monoclonal antibody has been humanized.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

**What does recombinant mean?**
That the substance was produced via recombinant DNA; i.e., DNA created by re-combining portions of 2+ different DNA molecules.

**What does humanized mean?**
Like many monoclonal antibodies, the parent molecule of ranibizumab was derived from mouse cells. Such murine antibodies would be recognized as foreign and attacked as such. To preclude this, a portion of the mouse antibody is replaced with its human counterpart via recombinant DNA techniques.

**What does affinity-matured mean?**
Affinity maturation is a process in which antibody-producing cells are repeatedly exposed to the antigen of interest, resulting in antibody crops with progressively greater affinity for the antigen.

**What does the suffix –mab indicate?**
That the drug is a monoclonal antibody.

**What does the infix –zu- indicate?**
That the monoclonal antibody has been humanized.

**What does fragment mean in this context?**
Ranibizumab is not a complete antibody; rather, it consists of a portion—or *fragment*—of an antibody.

Next we will take a deep dive into the key clinical trials that established the safety and effectiveness of ranibizumab in the tx of wet ARMD. Dr Flynn, are we expected (by the authors of the OKAP, WQE and Boards) to know these trials by name? Yes you are. Are we expected to be familiar with their outcomes, as well as the implications of those outcomes? Yes you are.
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?
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ANCHOR: What does ANCHOR stand for?

What does MARINA stand for?
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

What does MARINA stand for?
Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration

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What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

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What was the dosing schedule?

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One injection every month for 24 months

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One injection every month for 24 months
No (other than a sham inj group)

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- One injection every month for 24 months
- No (other than a sham inj group)
- Proportion of patients losing <15 ETDRS letters

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One injection every month for 24 months

What was the dosing schedule?

No (other than a sham inj group)

Was another intervention involved?

Proportion of patients losing <15 ETDRS letters

What was the primary outcome measure?

Proportion of patients gaining >15 ETDRS letters

What was the secondary outcome measure?

Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections

Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters
### MARINA

#### Evaluated ranibizumab for the treatment of minimally classic/occult CNVM

- Either 0.3 and 0.5 mg by intravitreal injection (or sham injections)
- One injection every month for 24 months

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### RESULTS

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### ARMD

- **MARINA**
- **Results**
- **Anchor**

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**RESULTS**
Evaluated ranibizumab for the treatment of minimally classic/occult CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months.

0.3 mg 0.5 mg Sham
Loss <15 letters 95% 95% 62%
Gained >15 letters

Loss <15 letters 94% 96% 64%
Gained >15 letters

Note: Only 1 in 20 tx’d pts lost >15 letters of VA.
Evaluated ranibizumab for the treatment of predominantly classic CNVM
Either 0.3 and 0.5 mg by intravitreal injection (or sham injections)
One injection every month for 24 months
0.3 mg 0.5 mg PDT
Loss <15 letters 94% 96% 64%
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Evaluated ranibizumab for the treatment of minimally classic/occult CNVM
Either 0.3 and 0.5 mg by intravitreal injection (or sham injections)
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0.3 mg 0.5 mg Sham
Loss <15 letters 95% 95% 62%
Gained >15 letters ? ? ?
Evaluated ranibizumab for the treatment of predominantly classic CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months.

- 0.3 mg: 94% loss <15 letters, 36% gained >15 letters
- 0.5 mg: 96% loss <15 letters, 40% gained >15 letters
- Sham: 64% loss <15 letters, 6% gained >15 letters

Evaluated ranibizumab for the treatment of minimally classic/occult CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months.

- 0.3 mg: 95% loss <15 letters, 34% gained >15 letters
- 0.5 mg: 95% loss <15 letters, 34% gained >15 letters
- Sham: 62% loss <15 letters, 5% gained >15 letters

ARMD
Evaluated ranibizumab for the treatment of predominantly classic CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months. 0.3 mg 0.5 mg PDT

Loss <15 letters: 94% 96% 64%
Gained >15 letters: 36% 40% 6%

Evaluated ranibizumab for the treatment of minimally classic/occult CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months. 0.3 mg 0.5 mg Sham

Loss <15 letters: 95% 95% 62%
Gained >15 letters: 25% 34% 5%

Note: --30 to 40% of (0.5) pts gained 15+ letters of VA, compared to only ~5% of sham/PDT pts.
MARINA

Evaluated ranibizumab for the treatment of minimally classic/occult CNVM

Either 0.3 and 0.5 mg by intravitreal injection (or sham injections)

One injection every month for 24 months

Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

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Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

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*Note:* The vast majority of ranibizumab-tx’d pts still hadn’t lost >15 letters at the 24-month mark.
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<td>6%</td>
</tr>
</tbody>
</table>

### RESULTS

<table>
<thead>
<tr>
<th></th>
<th>YEAR ONE</th>
<th>YEAR TWO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MARINA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>95%</td>
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</tr>
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</table>

### ARMD

<table>
<thead>
<tr>
<th></th>
<th>0.3 mg</th>
<th>0.5 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
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</tbody>
</table>
Evaluated ranibizumab for the treatment of minimally classic/occult CNVM or predominantly classic CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months.

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<tr>
<th></th>
<th>MARINA</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>RESULTS</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>0.3 mg</strong></td>
<td>0.3 mg</td>
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<tr>
<td></td>
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</tr>
</tbody>
</table>

**YEAR ONE**

<table>
<thead>
<tr>
<th></th>
<th><strong>YEAR ONE</strong></th>
<th></th>
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</tr>
</thead>
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<tr>
<td><strong>0.3 mg</strong></td>
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<td></td>
<td>4%</td>
<td></td>
<td>6%</td>
</tr>
</tbody>
</table>

**YEAR TWO**

<table>
<thead>
<tr>
<th></th>
<th><strong>YEAR TWO</strong></th>
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</tr>
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<td>4%</td>
<td></td>
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</tr>
</tbody>
</table>
MARINA

Evaluated ranibizumab for the treatment of
minimally classic/occult CNVM

Either 0.3 and 0.5 mg by intravitreal injection
(or sham injections)

One injection every month for 24 months

Proportion of patients losing <15 ETDRS letters

<table>
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<th></th>
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</table>

Proportion of patients gaining >15 ETDRS letters

<table>
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<tr>
<th></th>
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<tr>
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</table>

Note: --And the (0.5) pts maintained their VA gains

RESULTS

YEAR ONE

ANKCHOR

Evaluated ranibizumab for the treatment of
predominantly classic CNVM

Either 0.3 and 0.5 mg by intravitreal injection
(or sham injections)

One injection every month for 24 months

Proportion of patients losing <15 ETDRS letters

<table>
<thead>
<tr>
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YEAR TWO
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

What does MARINA stand for?
Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration

What does ANCHOR stand for?
ANti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration

MARINA and ANCHOR tl;dr:
1) Both were strong Phase III clinical trials
2) Both evaluated monthly injections of ranibizumab for 2 years
3) The studies found that only 1 in 20 (5%) of treated pts lost more than 15 letters of VA at 1 yr, and 1 in 10 (10%) at 2 yrs
4) 30-40% of treated pts gained 15+ letters

Was another intervention involved? Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections

Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters
MARINA

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ANCHOR

What does ANCHOR stand for?
ANti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration

What significant ocular and/or systemic safety issues manifested in the MARINA and/or ANCHOR trials?

One injection every month for 24 months

What was the primary outcome measure?
Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

What was the secondary outcome measure?
Proportion of patients losing <15 ETDRS letters

Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections

Proportion of patients gaining >15 ETDRS letters

What significant ocular and/or systemic safety issues manifested in the MARINA and/or ANCHOR trials?

Nothing too concerning. The rates of ocular complications (endophthalmitis, RD, uveitis, etc.) were comparable between the ranibizumab and sham groups, although there was a trend toward higher rates with ranibizumab. The same was true of possible systemic side effects: There was a trend toward higher rates of HTN, CVA and MI, but these differences were not significant either.
**MARINA**

What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

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MINimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-related Macular Degeneration

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What was the primary outcome measure?

Proportion of patients losing <15 ETDRS letters

What was the secondary outcome measure?

Proportion of patients gaining >15 ETDRS letters

Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

One injection every month for 24 months

Was another intervention involved?

Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections.

ARMD
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

- **MARINA**
- **ANCHOR**

What does MARINA stand for?

**M**inimally Classic/Occult Trial of the Anti-VEGF Antibody **R**anibizumab **I**n the Treatment of **N**eovascular **A**ge-Related Macular Degeneration

What does ANCHOR stand for?

**A**nti-VEGF Antibody for the Treatment of Predominantly Classic **C**horioidal **N**eovascularization in Age-Related **M**acular Degeneration

One injection every month for 24 months

What was the dosing schedule?

Proportion of patients losing <15 ETDRS letters

What was the primary outcome measure?

Proportion of patients gaining >15 ETDRS letters

What was the secondary outcome measure?

Was another intervention involved?

Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections

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Proportion of patients gaining >15 ETDRS letters

Proportion of patients losing <15 ETDRS letters
MARINA

What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

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ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in Age-Related Macular Degeneration

One injection every month for 24 months

What was the dosing schedule?

One injection every month for 24 months

The MARINA and ANCHOR trials left little doubt re the safety and efficacy of ranibizumab therapy for wet ARMD. But what was in doubt was the treatment schedule, ie, was it really necessary to inject every month?

gaining >15 ETDRS letters

outcome measure?

gaining >15 ETDRS letters
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

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Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration

One injection every month for 24 months

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ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in Age-Related Macular Degeneration

One injection every month for 24 months

The MARINA and ANCHOR trials left little doubt re the safety and efficacy of ranibizumab therapy for wet ARMD. But what was in doubt was the treatment schedule, ie, was it really necessary to inject every month? Clearly, a monthly continuous schedule such as this was not sustainable—the burden imposed (both in cost and labor) would overwhelm the resources of any healthcare system. To address this very important issue, several clinical trials were initiated, including…

- Proportion of patients losing >15 ETDRS letters
- Proportion of patients gaining >15 ETDRS letters
- Proportion of patients gaining >15 ETDRS letters
- Proportion of patients losing <15 ETDRS letters
- Proportion of patients gaining >15 ETDRS letters

outcome measure?
What are 2 key studies addressing the **dosing schedule** of ranibizumab in the treatment of ARMD?
What are 2 key studies addressing the **dosing schedule** of ranibizumab in the treatment of ARMD?

(Other acceptable answers: SAILOR; SUSTAIN; HORIZON; HARBOR)
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

What does PIER stand for?

What does PrONTO stand for?
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

What does PIER stand for?
Phase IIIb, Multicenter, Randomized, Double-Masked, Sham-Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration

What does PrONTO stand for?
Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

**PIER**

What does PIER stand for?
*Phase IIIb, Multicenter, Randomized, Double-Masked, Sham-Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration*

**PrONTO**

What does PrONTO stand for?
*Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab*

What were the dosing schedules?
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

**PIER**

What does PIER stand for?
**Phase IIIb, Multicenter, Randomized, Double-Masked, Sham-Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration**

**PrONTO**

What does PrONTO stand for?
**Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab**

One injection every month for 3 months, then **every 3 months to 12 months**

What were the dosing schedules?

One injection every month for 3 months, then **PRN as indicated** by OCT, VA and DFE findings at monthly exams
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

<table>
<thead>
<tr>
<th>Three Months</th>
<th>0.3 mg</th>
<th>0.5 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

(Note the different outcome variable)

Focus your attention on the 0.5 outcome.

What were the three-month results?
One injection every month for 3 months, then every 3 months to 12 months.

**What were the dosing schedules?**

### Three Months

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↑2.9</td>
<td>↑4.3</td>
<td>↓8.7</td>
</tr>
</tbody>
</table>

What were the **three-month results**?

Consistent with MARINA and ANCHOR, monthly ranibizumab injections led to improved visual acuity.

**ARMD**
One injection every month for 3 months, then every 3 months to 12 months

What were the dosing schedules?

What were the three-month results?
Consistent with MARINA and ANCHOR, monthly ranibizumab injections led to improved visual acuity. Which makes sense, because the first three months of PIER were identical to the first three months of MARINA and ANCHOR (ie, a shot every month).
PIER: Results at 3 months
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

What about the one-year results?

<table>
<thead>
<tr>
<th>One Year</th>
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<th>Sham</th>
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<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↓1.6</td>
<td>?</td>
<td>↓16.3</td>
</tr>
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</table>
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

What about the one-year results?
These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels.
PIER: Results at 12 months
What were the dosing schedules?

<table>
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<th>0.5 mg</th>
<th>Sham</th>
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<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↓1.6</td>
<td>↓0.2</td>
<td>↓16.3</td>
</tr>
</tbody>
</table>

What about the one-year results?
These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels. So while better than no treatment (ie, the sham arm), this was a dramatically worse outcome than what was achieved via monthly injections in MARINA and ANCHOR.

No question—advance when ready
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

What about the one-year results? These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels. So while better than no treatment (ie, the sham arm), this was a dramatically worse outcome than what was achieved via monthly injections in MARINA and ANCHOR. Clearly, a q3 month schedule was not going to be acceptable.

No question—advance when ready.
So if the PIER schedule isn’t effective, what about the PRN PrONTO schedule? Recall these pts received a monthly injection x 3, after which they were examined (not injected!) monthly, receiving an injection only if evidence of worsening was found.
For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials.

<table>
<thead>
<tr>
<th></th>
<th>Year One</th>
<th>MARINA</th>
<th>ANCHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost &lt;15 letters</td>
<td>?</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>?</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td>Mean ↑ in letters</td>
<td>?</td>
<td>7.2</td>
<td>11.3</td>
</tr>
<tr>
<td></td>
<td>Year One</td>
<td>MARINA</td>
<td>ANCHOR</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------</td>
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For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials. Note that the PrONTO protocol (3 monthly injections, then PRN) produced results essentially identical to those of MARINA and ANCHOR (monthly injections)…

ARMD
For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials. Note that the PrONTO protocol (3 monthly injections, then PRN) produced results essentially identical to those of MARINA and ANCHOR (monthly injections)… but with fewer than half the number of injections!

<table>
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<tr>
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<th>Year One</th>
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<tr>
<td>Mean ↑ in letters</td>
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<td>7.2</td>
<td>11.3</td>
</tr>
<tr>
<td>Mean # of injections</td>
<td>5.6</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

ARMD

MARINA/ANCHOR RESULTS

PrONTO RESULTS

PrONTO

MARINA

ANCHOR

Lost <15 letters
95%
95%
96%
Gained >15 letters
35%
34%
40%
Mean ↑ in letters
9.3
7.2
11.3
Mean # of injections
5.6
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ARMD
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Enter the treat-and-extend approach. While specifics vary among clinicians, most do something along these lines: First, the pt is treated monthly until the macula is ‘dry.’ Once dryness has been achieved, the time until the next visit is extended to 6 weeks. At the 6-week visit the pt is both evaluated and injected. If the 6-week evaluation revealed that the macula remained dry, the interval until the next visit is extended to 8 weeks. Again, at the 8-week visit the pt is both evaluated and injected, and if the eval indicates she remained dry, the interval until the next visit is extended by another 2 weeks to 10.
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At present, most clinicians employ some version of treat-and-extend with most of their pts.
For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials. Note that the PrONTO protocol (3 monthly injections, then PRN) produced results essentially identical to those of MARINA and ANCHOR (monthly injections)… but with fewer than half the number of injections!

What doses of ranibizumab were used? What is the dosing schedule? Is another intervention involved? What is the primary outcome measure? What is the secondary outcome measure?

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**PrONTO RESULTS**

**MARINA/ANCHOR RESULTS**

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What doses of ranibizumab were used?
What is the dosing schedule?
Is another intervention involved?
What is the primary outcome measure?
What is the secondary outcome measure?

MARINA ANCHOR
Lost <15 letters 95% 96%
Gained >15 letters 34% 40%
Mean ↑ in letters 7.2 11.3
Mean # of injections 13 13

Year One
Lost <15 letters 95%
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Mean # of injections 5.6

PrONTO RESULTS

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At present, most clinicians employ some version of treat-and-extend with most of their pts.

Anti-VEGF injection scheduling tl;dr
Continuous: Pt evaluated and treated monthly
PRN: Pt evaluated monthly, treated if evidence active dz
Treat and extend: After dz resolution achieved, interval between eval/tx visits gradually increased to the max the pt can sustain w/o recurrence (or 12 weeks, whichever comes first)

Next we will turn our attention to another drug that has proven to be hugely important in the management of wet ARMD (and other conditions*)

*But that’s a topic for another slide-set
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

What does recombinant mean? That the substance was produced via recombinant DNA; i.e., DNA created by re-combining portions of 2+ different DNA molecules.

What does humanized mean? Like many monoclonal antibodies, the parent molecule of ranibizumab was derived from mouse cells. Such murine antibodies would be recognized as foreign by the human immune system and attacked as such. To preclude this, a portion of the mouse antibody is replaced with its human counterpart via recombinant DNA techniques.

What does affinity-matured mean? Affinity maturation is a process in which antibody-producing cells are repeatedly exposed to the antigen of interest, resulting in antibody crops with progressively greater affinity for the antigen.

What is a monoclonal antibody? Antibodies produced by a set of immune cells that all derived from (i.e., clones of) the same parent cell.

What is the ‘parent’ antibody from which the ranibizumab fragment is derived? Bevacizumab.

What does fragment mean in this context? Ranibizumab is not a complete antibody; rather, it consists of a portion—or fragment—of an antibody.
**Ranibizumab** is a recombinant, humanized, affinity-matured, monoclonal antibody fragment. 

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Note: Different drug!

Bevacizumab
Bevacizumab is the generic, nonproprietary name. What is the brand name for this drug?

**Bevacizumab** is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
Bevacizumab is the generic, nonproprietary name. What is the brand name for this drug? Avastin

Bevacizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

You know bevacizumab is humanized because of the infix.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

You know Bevacizumab is humanized because of the infix.

You know it is a monoclonal antibody because of the suffix.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

Why did we lose the term affinity matured?

Bevacizumab

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Why did we lose the term affinity matured? Unlike ranibizumab, bevacizumab was not affinity-matured for VEGF-A.

Bevacizumab is a recombinant, humanized, monoclonal antibody fragment.
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Unlike ranibizumab, which consists of an antibody fragment, bevacizumab is a full-length antibody.

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Because it is smaller, ranibizumab clears faster than bevacizumab. What are their systemic half-lives?
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ARMD

Why go to the trouble of engineering an antibody fragment in the first place? Researchers initially believed that the full-length bevacizumab molecule was too large to pass through the ILM and enter the sub-retinal space.
Which drug was created first—ranibizumab, or bevacizumab?

Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
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Bevacizumab

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Bevacizumab

Was bevacizumab developed to treat ARMD?

Bevacizumab

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Was bevacizumab developed to treat ARMD?
No, it was developed and FDA-approved to treat

Bevacizumab

Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
Which drug was created first—ranibizumab, or bevacizumab?
Bevacizumab

Was bevacizumab developed to treat ARMD?
No, it was developed and FDA-approved to treat cancer

Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment
What were the key clinical trials demonstrating the safety and efficacy of bevacizumab in the treatment of ARMD?
To date there have been NO randomized, prospective clinical trials of intravitreal bevacizumab for the treatment of wet ARMD.
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For that matter, there weren’t even any animal trials of intravitreal bevacizumab prior to its use in humans. Clinicians started using it off-label based on what they knew about its ‘next-of-kin’ (ranibizumab).
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?
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What does CATT stand for?
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?

What does CATT stand for? Comparison of Age-related Macular Degeneration Treatments Trial
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?

What doses of each were used?

Ranibizumab:
Bevacizumab:
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What doses of each were used?

Ranibizumab: 0.5 mg
Bevacizumab: 1.25 mg
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What doses of each were used?

What were the two dosing schedules?

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**What doses of each were used?**

- Ranibizumab: 0.5 mg
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**What were the two dosing schedules?**

- Continuous
- PRN

**CATT**
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Was another intervention involved?
- CATT
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Was another intervention involved?

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Was another intervention involved?

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What was the *primary* outcome measure?
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Continuous, and PRN

Was another intervention involved?

No

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Mean change in VA
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- Bevacizumab: 1.25 mg

What were the two dosing schedules?
- Continuous
- PRN

Was another intervention involved?
No

What was the primary outcome measure?
Mean change in VA

What was the secondary outcome measure?
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What were the two dosing schedules?

Continuous, and PRN

Was another intervention involved?

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What was the primary outcome measure?

Mean change in VA

What was the secondary outcome measure?

Number of treatments
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Was another intervention involved?

No

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Mean change in VA

What was the secondary outcome measure?

Number of treatments

What was another oft-discussed secondary outcome measure?

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- Continuous
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Was another intervention involved?
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What was the primary outcome measure?
- Mean change in VA

What was the secondary outcome measure?
- Number of treatments

What was another oft-discussed secondary outcome measure?
- Incidence of adverse events
# CATT RESULTS

*Average Number of Letters Gained at One Year*

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**ARMD**
CATT RESULTS

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*These are statistically equivalent*
## CATT RESULTS

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</tr>
<tr>
<td>PRN Dosing</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

**ARMD**
CATT RESULTS

*Average Number of Letters Gained at One Year*

<table>
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<tr>
<th></th>
<th>Ranibizumab</th>
<th>Bevacizumab</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
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As are these
# CATT RESULTS

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*These are statistically equivalent as well*
## CATT RESULTS

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However, PRN bevacizumab yielded a significantly lower average gain when compared to monthly bevacizumab…
However, PRN bevacizumab yielded a significantly lower average gain when compared to monthly bevacizumab… or when compared to monthly ranibizumab.
**CATT RESULTS**

*Average Number of Letters Gained at One Year (and average number of injections)*

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<tr>
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<th>Bevacizumab</th>
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</thead>
<tbody>
<tr>
<td><strong>Every Month Dosing</strong></td>
<td>8.5(12)</td>
<td>8.0(12)</td>
</tr>
<tr>
<td><strong>PRN Dosing</strong></td>
<td>6.8(?)</td>
<td>5.9(?)</td>
</tr>
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Another important issue concerns the number of injections needed. The fixed-schedule pts received 12 monthly injections over the first year (obviously), but what about in the PRN-dosing conditions?
### CATT RESULTS

**Average Number of Letters Gained at One Year**

*(and average number of injections)*

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Another important issue concerns the number of injections needed. The fixed-schedule pts received 12 monthly injections over the first year (obviously), but what about in the PRN-dosing conditions? On average, the PRN ranibizumab and PRN bevacizumab pts received 7 and 8 injections respectively.
What about adverse events?

CATT RESULTS

*What about adverse events?*
CATT RESULTS

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Certain events were identified a priori to be tracked; these included MI, CVA and death. In terms of these events, no differences obtained between the bevacizumab and the ranibizumab cohorts.
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Is this finding concerning enough to warrant using ranibizumab preferentially?
CATT RESULTS

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Is this finding concerning enough to warrant using ranibizumab preferentially?
Probably not. As of this writing, the opinion seems to be that the increased adverse effects were probably happenstance. This opinion is based on two facts:
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2)
CATT RESULTS

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1) The reported adverse events have not been found in studies involving the *systemic* administration of bevacizumab. If these events were triggered by the minute amounts of bevacizumab that might have entered the systemic circulation after intravitreal injection, the thinking goes, surely they would have occurred during *systemic* bavacizumab trials (in which systemic concentrations were at least 500 times greater).

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Next we drill down on a third drug that has come to play a vital role in the management of wet ARMD
Aflibercept is a recombinant fusion protein
Aflibercept is a *recombinant fusion protein*. 
Aflibercept is a recombinant fusion protein
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**What is a fusion protein?**
A novel protein constructed by joining (fusing) the genetic information coding for two other proteins.
Aflibercept is the generic, nonproprietary name. What is the brand name for this drug?

Aflibercept is a recombinant fusion protein.
Afiblercept is the generic, nonproprietary name. What is the brand name for this drug?
Eylea

Afiblercept is a recombinant fusion protein
What does the suffix –cept indicate?

Aflibercept is a recombinant fusion protein
What does the suffix –cept indicate?
That the drug functions by mimicking a receptor molecule

Aflibercept is a recombinant fusion protein
Afibl**bercept** is a recombinant fusion protein

What does the suffix **–cept** indicate? That the drug functions by mimicking a receptor molecule

What does the infix **–ber**- indicate?
Afli*ber*cept is a recombinant fusion protein

What does the suffix –cept indicate? That the drug functions by mimicking a receptor molecule

What does the infix –ber- indicate? That the mimicked receptor is the VEGF receptor
Afiblercept is a recombinant fusion protein.

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What does the infix –ber- indicate? That the mimicked receptor is the VEGF receptor.

Spell it out for me—what does it mean to say afiblercept ‘mimics the VEGF receptor’? Put another way: How does afiblercept work?
Aflibercept is a recombinant fusion protein

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Spell it out for me—what does it mean to say aflibercept ‘mimics the VEGF receptor’?
Put another way: How does aflibercept work?
Aflibercept is a decoy receptor that locks up unbound VEGF in the retinal space before it (the VEGF) can find an actual VEGF receptor on a target structure.
Afli\text{bercept} is a recombinant fusion protein

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Aflibercept is a recombinant fusion protein

Which isoforms of VEGF-A does aflibercept bind?
Afiblercept is a *recombinant fusion protein*

*Which isoforms of VEGF-A does afiblercept bind?*
All of them
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*Of bevacizumab, ranibizumab and afiblercept, which binds VEGF-A with the greatest affinity?*
Afiblercept is a recombinant fusion protein.

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In addition to VEGF-A, aflibercept binds another protein implicated in the pathogenesis of CNVM—what is it?
**Aflibercept is a recombinant fusion protein**

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*In addition to VEGF-A, aflibercept binds another protein implicated in the pathogenesis of CNVM—what is it?*
Placental growth factor (PLGF)
Aflibercept is a recombinant fusion protein.

Which isoforms of VEGF-A does aflibercept bind?
All of them

Of bevacizumab, ranibizumab and aflibercept, which binds VEGF-A with the greatest affinity?
Aflibercept

This ability to bind PLGF may account for the fact that aflibercept is effective in some cases of ranibizumab-refractory CNVM—what is it?
Placental growth factor (PLGF)
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?
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Technically, there were two VIEW trials—VIEW1 was conducted in the US and Canada, VIEW2 overseas. However, because the results of the two studies were essentially identical, for simplicity's sake we will treat them as if they were a single study.
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

The VIEW Trap-Eye: Investigation of Efficacy and Safety in Wet ARMD

What does VIEW stand for?
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What was the dosing schedule?
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What doses of aflibercept were used?

Either 0.5 or 2 mg by intravitreal injection

What was the dosing schedule?

There were 3:
- a) 0.5 mg every 4 weeks, or
- b) 2 mg every 4 weeks, or
- c) 2 mg every 8 weeks after three q4 week loading doses
ARMD

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Take note of the *q8 week* condition. Remember, one of the drawbacks of ranibizumab is its q4 week dosing requirement, which places tremendous financial and structural strain on the healthcare system. (Consider: In 2003, prior to the advent of intravitreal anti-VEGF meds, Medicare was billed for ~3000 intravitreal injections. In 2010, it was billed for over a MILLION.) Thus there was considerable interest in whether a q8 week dosing schedule would work.
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

What doses of aflibercept were used?

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Was another intervention involved?

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A control group received ranibizumab 0.5 mg every 4 weeks
The VIEW was a noninferiority trial, meaning the efficacy/safety of a new treatment was being compared to that of a ‘gold standard’ treatment. In other words, the VIEW had to demonstrate that aflibercept was at least as good and at least as safe as ranibizumab in order to gain approval.
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1) the presence of a ranibizumab arm in the study, and
2) that patients in the VIEW have lesions similar to those of the participants in the studies used to prove the safety and efficacy of ranibizumab in the first place (ie, the MARINA and ANCHOR studies).

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ARMD
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Proportion of patients losing <15 ETDRS letters

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What was the secondary outcome measure?

Proportion of patients maintaining (i.e., losing zero ETDRS letters) or gaining ETDRS letters
**VIEW** study:
Year One Results

<table>
<thead>
<tr>
<th>Lost &lt;15 letters</th>
<th>0.5 mg q4 week</th>
<th>2.0 mg q4 week</th>
<th>2.0 mg q8 week</th>
<th>Ranibizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>?%</td>
<td>?%</td>
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<td>?%</td>
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<table>
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<tr>
<th>Mean gain in ETDRS letters read</th>
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<tr>
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<tbody>
<tr>
<td>Lost &lt;15 letters</td>
<td>96%</td>
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| Mean gain in ETDRS letters read | 8.3 | 9.2 | 8.4 | 8.7 |

The key finding is that **q8 weeks** aflibercept worked just as well as **monthly** ranibizumab.
The VIEW was carried into a second year. The basic Year 2 study criteria were:
1) Participants remained in the same treatment condition
2) Participants were evaluated monthly and treated PRN
3) All participants were treated at least every 12 weeks
### VIEW study: Year One Results

<table>
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<tr>
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| Mean gain in ETDRS letters read | 6.6 | 7.6 | 7.6 | 7.9 |

As with the Year One data, the key finding is that q8 weeks aflibercept worked **just as well** as monthly ranibizumab.
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Also of note is the fact that the Year Two results are similar to those of Year One.
**VIEW study:**

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Another much-anticipated outcome concerned the average number of treatments required in the q8 week aflibercept vs ranibizumab conditions.

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(Determined by study protocol)

(Determined by drug efficacy)
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Another much-anticipated outcome concerned the **average number of treatments** required in the q8 week aflibercept vs ranibizumab conditions.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. **Age** is the strongest risk factor for ARMD. The clinical hallmark of ARMD is the presence of **drusen** in the macula. There are two types: **Nonexudative** and **exudative**. RPE abnormalities in ARMD are typical. **Photoreceptors** in ARMD are abnormal as well. The pathogenesis of ARMD is not well understood; that said, the **complement** system is strongly implicated in it. VEGF plays a key role in exudative ARMD; likewise, interdicting VEGF is key in managing it. Nonexudative ARMD is not treatable at present.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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The clinical trial (abb) found that micronutrient supplementation reduces the likelihood of exudative ARMD in at-risk pts.
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ARMD: The AREDS
- AREDS is the
ARMD: The AREDS

- AREDS is the Age-Related Eye Disease Study
**ARMD: The AREDS**

- AREDS is the **Age-Related Eye Disease Study**
- Looked at dietary supplements and ARMD:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene 15 mg
  - Zinc 80 mg
  - Cupric oxide 2 mg

**Findings:**
- Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
- Patients with no/early ARMD: No benefit

**Note:** Don't give AREDS supplements to smokers (β-carotene increases the risk of lung Ca in these patients)

**antioxidants**

**minerals**
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**Antioxidants**: Vitamin C, Vitamin E, β-carotene

**Minerals**: Zinc, Cupric oxide
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  - Dose?
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*Next, let’s drill down on the AREDS2*
ARMD: The AREDS2

- Follow-up to the AREDS

- **Vitamin C** 500 mg
- **Vitamin E** 400 IU
- **β-carotene** 15 mg
- **Zinc** 80 mg
- **Cupric oxide** 2 mg
**ARMD: The AREDS2**

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene
  - **Vitamin C** 500 mg
  - **Vitamin E** 400 IU
  - **β-carotene** \(?\) & \(?\)
  - **Zinc** 80 mg
  - **Cupric oxide** 2 mg
**ARMD: The AREDS2**

- Follow-up to the AREDS
- Subbed **xanthophylls** for β-carotene
  - **Vitamin C** 500 mg
  - **Vitamin E** 400 IU
  - **β-carotene** [Lutein & Zeaxanthin] *(These are the two xanthophylls employed)*
  - **Zinc** 80 mg
  - **Cupric oxide** 2 mg
ARMD: The AREDS 2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added

- **Vitamin C** 500 mg
- **Vitamin E** 400 IU
- **β-carotene** Lutein & Zeaxanthin
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ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene: Lutein & Zeaxanthin
  - Zinc 80 mg
  - Cupric oxide 2 mg
  - Omega-3 fatty acids
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
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- Study findings:
  - Reaffirmed vs Disputed results of the AREDS
ARMD: The AREDS2

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● **ARMD: The AREDS**
  2
  
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  ● **Study findings:**
    
    ● **Reaffirmed** results of the AREDS
    
    ● Xanthophylls effective vs ineffective substitute for β-carotene
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  - β-carotene
  - Lutein & Zeaxanthin
  - Zinc 80 mg
  - Cupric oxide 2 mg
  - Omega-3 fatty acids

**Study findings:**

- Reaffirmed results of the AREDS
- Xanthophylls suitable substitute for β-carotene
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Why is this important?
**ARMD: The AREDS2**

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C 500 mg
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- Study findings:
  - Reaffirmed results of the AREDS
  - Xanthophylls suitable substitute for β-carotene

*Why is this important?* Because it means β-carotene can be dropped, obviating this concern

- Note: Don’t give AREDS supplements to smokers
  - β-carotene increases the risk of lung Ca in these patients
**ARMD: The AREDS2**

- Follow-up to the AREDS
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