Current & Emerging Therapy for Neovascular AMD

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University of Illinois at Chicago
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Neovascular AMD: Current and Emerging Treatments

- Anti-VEGF: Ranibizumab, Bevacizumab, Aflibercept (VEGF Trap)
- Treatment Paradigms
- Combination Therapy with anti-VEGF plus:
  - Anti-Complement
  - Anti-Endothelial cell
  - Anti-Pericyte
  - Radiation Therapy

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Ranibizumab (Lucentis) Trials
Mean Change in Visual Acuity Over Time

ETDRS letters

Month

ANCHOR
MARINA

PIER

+11.3
+8.5
+10.5
+20.0 letter difference*

-0.2
-9.5
-16.3

-20.8 letter difference*
EXCITE Trial: Ranibizumab Quarterly Vs. Monthly Dosing

- Ranibizumab x 3 monthly doses then fixed quarterly compared with monthly ranibizumab (0.3 mg)
- Better than PIER but inferior to monthly dosing
- Mean change at 12 months:
  - + 8.3 letters in ranibizumab 0.3 mg monthly
  - + 4.9 ranibizumab 0.3 mg quarterly
  - + 3.8 ranibizumab 0.5 mg quarterly

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HORIZON: PRN DOSING
Mean Change in Visual Acuity from Initial Baseline

Vertical bars are ± one standard error of the mean. All observed data through 2 years in HORIZON. Month 27 had fewer samples. Ranibizumab Untreated=never received ranibizumab. Benz M. AAO, 2009.
SAILOR: PRN Dosing
Mean Change in Visual Acuity over Time*

*Results are reported using the last observation carried forward (LOCF) to account for missing data and early dropouts.
VEGF Trap (Aflibercept, Eylea)

- Binds VEGFR1 and VEGFR2
- Bind all forms of VEGFA and Placental Growth Factor (PlGF)
- Phase I systemic delivery completed – not pursued


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VIEW 1 & 2
Study Design

Multi-center, active controlled, double masked trial
VIEW 1 N=1217; VIEW 2 N=1240

Patients randomized 1:1:1:1

VEGF Trap-Eye
- 2 mg q4 wks
- 0.5 mg q4 wks
- 2 mg q8 wks

Ranibizumab
- 0.5 mg q4 wks

Primary endpoint:
Maintenance of vision(<15 ETDRS letters lost)

Dosing through Year 1
Capped-PRN through Year 2

Key Secondary endpoint:
Mean change in BCVA

Non-inferiority design
VIEW 1 & 2
Primary Endpoint: Prevention of Moderate Vision Loss

All doses of VEGF Trap-Eye were non-inferior to ranibizumab

*Compared to baseline; LOCF; VIEW 1 pps: Rq4 n=269; 2q4 n=285; 0.5q4 n=270; 2q8 n=265
VIEW 2 pps: Rq4 n=269; 2q4 n=274; 0.5q4 n=268; 2q8 n=270
VIEW 1, VIEW 2 & Integrated
Mean Change in Visual Acuity Compared to Baseline

VIEW 1

VIEW 2

Integrated

\[*P = 0.0054\]
\[\dagger P = NS\]

vs. Rq4
Bevacizumab (Avastin)

- Off-label use for AMD
- Intravitreal injection 1.25 mg in 0.05 ml
- Community: widespread use
- Studies comparing ranibizumab (Lucentis) and bevacizumab (Avastin):
  - CATT (US), IVAN (UK), VIBERA (Germany), LUCAS (Norway), MANTA (Austria), GEFAL (France)
CATT Study

• Non-inferiority Trial
• 1208 patients with neovascular AMD
• Randomized to intravitreal injections of ranibizumab or bevacizumab on either a monthly or PRN schedule with monthly evaluations
• Primary outcome = mean change in visual acuity at 1 year, with a non-inferiority limit of 5 letters


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CATT 1 Year Results

Monthly vs PRN Ranibizumab: Non-inferior
Monthly vs PRN Bevacizumab: Inconclusive


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CATT 1 Year Results

Mean decrease in central OCT thickness was greater in ranibizumab-monthly (196 μm) than other groups (152 to 168 μm, P=0.03 by analysis of variance).


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CATT Safety Results

• Rates of death, MI, and stroke were similar for patients receiving either bevacizumab or ranibizumab (P>0.20)
• Proportion of patients with systemic SAEs (primarily hospitalizations) was higher with bevacizumab than with ranibizumab: 24.1% vs. 19.0%; risk ratio, 1.29 (95% confidence interval, 1.01 to 1.66)
• Excess events broadly distributed in disease categories not identified in previous studies as areas of concern.


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CATT 2 Year Results

- Benefit of monthly lost in year 2 when switched to PRN dosing
- Monthly Rx had best results

The CATT Research Group. ARVO 2012.

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Treat and observe

• Initial monthly treatment until resolution of SRF and cysts on OCT

• Re-evaluate monthly x 3 for recurrence: check OCT

• If recurs, then monthly treatment until “dry”
Treat and observe

- If patient shows subjective response but has active CNV on exams:
  - Continue with current Rx
  - Consider adjunctive Rx or shorten dosing interval
- If subfoveal fibrosis develops then stop treatment.
Treat and Extend Regimen

- 3 Initial monthly treatments
- Monthly Rx until stabilized (dry OCT)
- Then return in 6 weeks and Re-Rx regardless of findings
- If stable, then return and Re-Rx in 7-8 weeks
- If renewed disease, shorten interval


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Treat and Extend Regimen

- Reduced treatment burden
- Number of office visits and injections was reduced 25-50% compared with monthly regimen
- No macular hemorrhages noted on retrospective review


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Treat and Extend Regimen vs PRN (Treat and Observe)

- Retrospective study (N=90)
- 52 PRN and 38 T & E arm

<table>
<thead>
<tr>
<th>1 year:</th>
<th>PRN</th>
<th>T &amp; E</th>
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<tbody>
<tr>
<td># Letters Gained</td>
<td>2.3 (± 17.4)</td>
<td>10.8 (± 8.8)</td>
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<tr>
<td>p=0.036</td>
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<tr>
<td># Rx</td>
<td>5.2 (± 1.9)</td>
<td>7.8 (± 1.3)</td>
</tr>
<tr>
<td>p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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Conclusions

- Monthly/ close follow-up is key
- Better VA results are seen with:
  - Close follow-up: exam and OCT
  - Lower threshold for re-Rx
- No proven alternate dosing regimen
- Educate the patient
- Safest = “on label” treatment to achieve results
- Off-label – monthly bevacizumab

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Rationale for Combination Therapy

- Achieve synergy to improve VA outcomes and reduce treatment burden
- Combine anti-angiogenesis drugs with different mechanisms of action: upstream and downstream inhibition
- Combine anti-angiogenic drugs with drugs that have other mechanisms of action
Combination Therapy

- Anti-angiogenic combined with:
  - PDT to occlude vessels
  - Anti-inflammatory agent
    - VEGF overexpression occurs with inflammation
    - Limit fibrosis
  - Radiation
  - Anti-pericytes: Anti-PDGF
  - Immunomodulator: Complement inhibitor
  - Anti-endothelial cell agents
Ranibizumab + PDT: DENALI

- Phase 3b
- N = 318
- 45 sites US, 8 CDN
- *Lucentis™ prn assumes Lucentis™ at baseline, mo 1 and 2 then prn
- Visudyne® at baseline and q3 months PRN
- Monthly follow-up until all reach 12 mo (changed from 24 months)

Purpose:
- Combo not inferior to monthly Lucentis™?
- 3 month Rx free interval after month 2 to month 11

Investigator determines eligibility

Any lesion composition

Randomized 1:1:1

- Ranibizumab*
- Ranibizumab*
- Ranibizumab† Monthly

Verteporfin<sub>SF</sub>  Verteporfin<sub>RF</sub>

Same day Rx for combination arms
DENALI Trial: 12 months

- Non-inferiority trial
- *Did not demonstrate non-inferiority (margin = 7 letters)*
- Mean VA at 12 months:
  - 5.3 letters in std fluence PDT + Ranibizumab
  - 4.4 letters in reduced PDT + Ranibizumab
  - 8.1 letters for Ranibizumab
Ranibizumab + PDT: MONT BLANC Trial

- Phase 2 Non-inferiority trial of 255 pts.
- PDT + Ranibizumab vs. Ranibizumab + Sham
- 3 loading doses Ranibizumab then PRN
- VA results (12 months) were non-inferior (margin = 7 letters)
- No difference after month 2 of Rx-free interval of at least 3 months (85% vs. 72% with at least 4 month Rx-free interval after month 2)

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MONT BLANC Trial: 12 months

- Median time to first re-Rx after month 2 was extended only by 1 month
- Combo group received 4.8 Ranibizumab Rx vs. 5.1 in monotherapy group
- 1.7 PDT vs. 1.9 sham Rx
- No decrease of treatment burden shown
PDT + Dex + Ranibizumab: Triple Therapy RADICAL Trial

Any lesion composition

Randomized 1:1:1:1

Verteporfin VLF 180mW/cm²
Verteporfin RF 300mW/cm²
Verteporfin RF300mW/cm²
Dex 0.5mg
Dex 0.5mg
Ranibizumab 0.5mg
Ranibizumab 0.5mg
Ranibizumab 0.5mg
Ranibizumab 0.5mg
n=40 n=40 n=40 n=40

- Phase 2
- Single-masked
- Lucentis at baseline, M1, M2, then PRN
- Combo therapy at baseline, then intervals of > 2 months PRN
- Visudyne followed within 2 hr by intravitreals and then Dexamethasone
- Dexamethasone = shorter acting, more potent, less chance of elevated IOP, transparent
- **Purpose:** Does combo decrease re-Rx compared to monotherapy with similar VA and safety?
**RADICAL Trial: 12 months**

- 162 pts., Phase 2
- Reduced # retreatments with similar VA

<table>
<thead>
<tr>
<th></th>
<th>Triple therapy, VLF</th>
<th>Triple therapy, RF</th>
<th>Double therapy RF</th>
<th>Ranibizumab Monotherapy</th>
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<tbody>
<tr>
<td><strong>N</strong></td>
<td>39</td>
<td>39</td>
<td>43</td>
<td>41</td>
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<tr>
<td><strong>Mean re-Rx</strong></td>
<td>4.0 (p=0.04)</td>
<td>3.0 (p&lt;0.001)</td>
<td>4.0 (p=0.04)</td>
<td>5.4</td>
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<td><strong>Mean VA improvement</strong></td>
<td>3.6 (p=0.38)</td>
<td>6.8 (p=0.94)</td>
<td>5.0 (p=0.63)</td>
<td>6.5</td>
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<tr>
<td><strong>Difference, CI</strong></td>
<td>-2.9 (-9.5, 3.6)</td>
<td>0.3 (-6.2, 6.7)</td>
<td>-1.6 (-8.0, 4.9)</td>
<td></td>
</tr>
</tbody>
</table>

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RADICAL Trial: 24 months

- Triple therapy with \( \frac{1}{2} \) fluence group had mean of 4.2 re-treatment visits versus 8.9 Ranibizumab monotherapy (\( p<0.001 \)). (Better than 12 months 3 vs. 5.4)

- Mean VAs were not significantly different among the groups although the sample sizes were insufficient to draw definitive conclusions regarding VA outcomes.

- Decreased treatment burden
Combination Studies: Anti-VEGF + Radiation

- Beta particle radiation:
  - 24 Gy EpiRAD device PPVx
  - Sr90 source
  - MERITAGE Study
  - CABERNET and MERLOT

- Oraya I-Ray
  - Stereotactic delivery of low-energy X-rays
  - INTREPID study (I-Ray plus aNti-VEGF TREatment for Patients wIth Wet AMD)

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Anti-VEGF + Beta Particle Radiation:

- 24 Gy EpiRad + Ranibizumab vs. Ranibizumab (2:1)

- **CABERNET Study** = Treatment-naïve AMD pts.
  - N= 450 completed in Nov 2009
  - Did NOT meet primary or secondary endpoints

- **MERLOT Study** = Chronic treatment AMD pts.
  - Target N= 363 in UK

CNV Secondary to AMD Treated with Beta Radiation Epiretinal Therapy

MERLOT (Macular EpiRetinal Brachytherapy versus Lucentis® Only Treatment)

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Anti-VEGF + Beta Particle Radiation: MERITAGE Study Results

• Previously treated patients: N= 53 (minimum of 5 anti-VEGF in prior 12 months or 3 in prior 6 months)
• Mean # anti-VEGF Rx = 3.49 vs. 12.5 prior to entry at 1 yr. and mean of 8.7 Rx by 2 years
• 81% stabilized VA at 1 yr.; 68% at 2 yrs.
  • Mean visual acuity = -4.0 ± 15.1 letters at 1 yr., -6.3 ± 18.9 letters at 2 yrs.
  • One case of nonproliferative radiation retinopathy at 2 yrs.

Dugel PU et al. Ophthalmology 2012

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Combination Studies: INTREPID study

- Oraya I-Ray
  - 16Gy and 24 Gy results positive
  - Reduction in median number of anti-VEGF re-Rx in previously treated patients at one year

- 25% reduction in number of Re-Rx maintained at 2 years

Jackson TL et al. Ophthalmology 2013
Anti-VEGF + Anti-PDGF B

- PDGF-B regulates the recruitment of pericytes
- Pericytes are required for vessel maturation
- E10030 (Ophthotech) = anti-platelet-derived growth factor (anti-PDGF-B) aptamer
- Phase 1 study of combination with ranibizumab showed safety
Anti-VEGF + Anti-PDGF B

• Phase 1
  – Mean gain of 14 letters at 12 weeks
  – 59 % gained 15 or more letters
  – 100 % patients showed vascular regression
  – Mean decrease 86 % of CNV

• Phase 2 trial is recruiting patients with AMD and classic CNV to test hypothesis of synergistic effects.

Boyer DS, Ophthotech Anti-PDGF in AMD Study Group. Combined Inhibition of Platelet Derived (PDGF) and Vascular Endothelial (VEGF) Growth Factors for the Treatment of Neovascular Age-Related Macular Degeneration (NV-AMD). Results of a Phase 1 Study. ARVO paper May 4, 2009
Activated endothelial cell survival requires α5β1 integrin (transmembrane protein) interaction with ECM ligand fibronectin.

Volociximab (Ophthotec) is a human/murine chimeric monoclonal antibody to α5β1.
Anti-VEGF + Anti-integrin

- Ranibizumab + Volociximab (Ophthotec) phase 1 Study

- At 8 weeks:
  - 9.1 letter gain
  - CST OCT decreased from 361 to 246 µ
  - 23 % gained 15 letters or more
Anti-VEGF + Anti-Endothelial Cell Drug Combinations

- Sphingosine-1 phosphate (S1P) inhibition by monoclonal antibodies results in inhibition of retinal NV and CNV in animals + reduced inflammation and fibrosis. (Xie B et al. J Cell Physiol 2009;218:192-198.)

- Nicotinic acetylcholine receptor (nAChR) inhibition suppressed laser induced CNV in animals. (Kiuchi K et al. IOVS 2008;49:1705-1711)
  - ATG003 (CoMentis; topical) in combination with anti-VEGF Phase 1 done
  - Phase 2 in progress
Other Anti-VEGF Combinations

- Ranibizumab + Complement Inhibitors
  - ARC1905 aptamer (Ophthotec)
  - Anti-C5: Phase 1 study
  - POT4- anti-C3 ASaP1 showed evidence of safety
Combination Therapies for Neovascular AMD in 2014

- Combination therapy has not yet shown VA superiority to anti-VEGF monotherapy in phase 3 studies
- Combination therapy (DENALI, RADICAL, MERITAGE) may decrease the number of anti-VEGF injections
- New Combinations hold promise
Current and Novel Therapies for Neovascular AMD in 2014

- Anti-VEGF drugs: Ranibizumab, Aflibercept and Bevacizumab
- Treat & Observe monthly vs. Treat & Extend
- Combination therapy with Anti-VEGF and
  - PDT + Anti-inflammatory agent
  - Radiation
  - Anti-pericytes: Anti-PDGF
  - Anti-endothelial cell agents
Thank you!
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• Grant support: ICON Bioscience, Regeneron
• Advisory Boards: Regeneron, Allergan, QLT
• DMC: Santen, Quark, Alcon

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CATT 1 Year Results

Monthly bevacizumab vs. monthly ranibizumab
Non-inferior:  8 vs.  8.5 letters gained

PRN bevacizumab vs. PRN ranibizumab
Non-inferior:  5.9 vs.  6.8 letters gained


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Monthly vs PRN Ranibizumab: Non-inferior
Monthly vs PRN Bevacizumab: Inconclusive


JI Lim, MD
Mean decrease in central OCT thickness was greater in ranibizumab-monthly (196 μm) than other groups (152 to 168 μm, P=0.03 by analysis of variance)

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- Excess events broadly distributed in disease categories not identified in previous studies as areas of concern.

Anti-VEGF + Anti-Endothelial Cell Drug Combinations

- Integrins ανβ3 and α5β1 are upregulated in angiogenesis and interact with ECM
- α5β1 also upregulated in RPE, macrophage and fibroblast cells
- Volociximab (Ophthotec) is a human/murine chimeric monoclonal antibody to α5β1
Neovascular AMD: Current and Emerging Treatments

- Anti-VEGF: Ranibizumab, Bevacizumab, Aflibercept (VEGF Trap)
- Anti-angiogenic Agents
- Vascular Occlusion: Combretastatin A4-P
- Gene Therapy
- Combination Therapy with anti-VEGF plus:
  - Anti-Complement
  - Anti-Endothelial cell
  - Anti-Pericyte
  - Radiation Therapy
Treat and Extend

• Wills Eye Treat and Extend Study
• 92 eyes, retrospective, mean 1.5 yr follow-up
• New onset neovascular AMD
• 1 year: 96% < 3 lines loss
  32% 3 or more lines gain
  Mean # injections 8.3

Shienbaum, Gupta, Patel et al. ARVO 2009

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Treat and Extend Regimen vs PRN (Treat and Observe)

- Retrospective study (N=166 eyes of 159 pts) of Rx naïve eyes with at least 6 months f/u
- Ranibizumab N=92, bevacizumab N=74
- ETDRS gains 9.7 R vs 10 B at 2 years
- 6-8 injections in year 1


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Monthly vs. Alternative Dosing?

• Loading dose then quarterly dosing
  • PIER- an FDA approved dosing regimen
  • EXCITE- fixed quarterly dosing regimen
• PRN
  • PrONTO
  • HORIZON- extension of MARINA/ANCHOR
  • SAILOR- 3 doses + quarterly PRN
  • SUSTAIN- 3 doses + monthly PRN (VA/OCT)
• Treat and extend
  • Treat until dry, extend intervals until recurrent CNV

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% Patients with APTC Events through 1 Year

### VIEW 1

<table>
<thead>
<tr>
<th></th>
<th>RBZ 0.5q4</th>
<th>VTE 2q4</th>
<th>VTE 0.5q4</th>
<th>VTE 2q8</th>
<th>All VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (safety analysis set)</td>
<td>304</td>
<td>304</td>
<td>304</td>
<td>303</td>
<td>911</td>
</tr>
<tr>
<td>Any APTC event</td>
<td>5 (1.6)</td>
<td>2 (0.7)</td>
<td>7 (2.3)</td>
<td>6 (2.0)</td>
<td>15 (1.6)</td>
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<tr>
<td>Vascular Deaths</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
<td>5 (0.5)</td>
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<tr>
<td>Non Fatal MI</td>
<td>4 (1.3)</td>
<td>1 (0.3)</td>
<td>4 (1.3)</td>
<td>1 (0.3)</td>
<td>6 (0.7)</td>
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<tr>
<td>Non Fatal Stroke(^a)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
<td>4 (0.4)</td>
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### VIEW 2

<table>
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<th>RBZ 0.5q4</th>
<th>VTE 2q4</th>
<th>VTE 0.5q4</th>
<th>VTE 2q8</th>
<th>All VTE</th>
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<tr>
<td>N (safety analysis set)</td>
<td>291</td>
<td>309</td>
<td>297</td>
<td>307</td>
<td>913</td>
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<tr>
<td>Any APTC event</td>
<td>4 (1.4)</td>
<td>4 (1.3)</td>
<td>5 (1.7)</td>
<td>8 (2.6)</td>
<td>17 (1.9)</td>
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<tr>
<td>Vascular Deaths</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>1 (0.3)</td>
<td>4 (0.4)</td>
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<tr>
<td>Non Fatal MI</td>
<td>2 (0.7)</td>
<td>2 (0.6)</td>
<td>2 (0.7)</td>
<td>5 (1.6)</td>
<td>9 (1.0)</td>
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<tr>
<td>Non Fatal Stroke(^b)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td>4 (0.4)</td>
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</table>

\(^a\) All non fatal strokes were ischemic in nature
\(^b\) Includes hemorrhagic and ischemic strokes
# VIEW 1 & 2

## Deaths

### VIEW 1

<table>
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<tr>
<th></th>
<th>RBZ 0.5q4</th>
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<th>VTE 0.5q4</th>
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<td>303</td>
<td>911</td>
</tr>
<tr>
<td><strong>All Deaths</strong>*</td>
<td>5 (1.6%)</td>
<td>2 (0.7%)</td>
<td>2 (0.7%)</td>
<td>8 (2.6%)</td>
<td>12 (1.3%)</td>
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<tr>
<td>Myocardial Infarction</td>
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<td>1</td>
<td>2</td>
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<tr>
<td>Stroke</td>
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<td>Cerebral Hemorrhage</td>
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### VIEW 2

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<th>913</th>
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<tbody>
<tr>
<td><strong>N (safety analysis set)</strong></td>
<td>2 (0.7%)</td>
<td>3 (1.0%)</td>
<td>2 (0.7%)</td>
<td>2 (0.7%)</td>
<td>7 (0.8%)</td>
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<tr>
<td><strong>All Deaths</strong>*</td>
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<tr>
<td>Myocardial Infarction</td>
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<td>Cerebrovascular Accident</td>
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<td>Pyrexia</td>
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<td>Cardiopulmonary Failure</td>
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<tr>
<td>Cancer Related</td>
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<td>1</td>
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