Moxduo
Status Overview
May 2014

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FDA Advisory Committee Outcome

- Committee members requested guidance during the meeting on evidence standard for a combination opioid product.
  - FDA Review Division did not provide clear, unambiguous guidance.
  - FDA focused on post-hoc nature of Study 022 analyses and asked if the committee saw a clear benefit.
- In the absence of another option, Advisory Committee applied the usual statistical standard of prospective data to evaluate Study 022.
- *Post-hoc* analyses *are not capable* of meeting this statistical standard.
- On this basis, committee voted 14-0 not to approve.

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Lessons Learned

- Expected too much from FDA management.
  - No override of FDA reviewers in Combination Rule interpretation.
- When presented with a novel issue (combination of two drugs from the same class) FDA may default to a higher approval standard.
- Minimise confrontations with FDA.
  - Ongoing protestations regarding FDA rules / process can be unhelpful.
- Too much weight on Study 022 post hoc analyses.
  - Not designed for desaturation as primary endpoint.
  - Did not meet strict statistical criteria.
- Needed prospectively hierarchical statistically significant outcomes, from prospective trials.
- This is the ***best way*** forward for Moxduo.

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What's next?

There are three basic questions:

1. Does Moxduo show a real benefit over its individual components?
   - What's the evidence to support this?

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2. Can we demonstrate the benefit of Moxduo in a clinical trial that regulators will agree with?
   - What are the design requirements (prospective, well-controlled trial(s), with pre-specified endpoints, and statistical metrics)?
   - What will satisfy the novel application of the Combination Rule?
   - What will satisfy the "population intended for" issue?
   - How much will this cost?
   - How long will this take?

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What's next?

There are three basic questions:

3. Will FDA approve Moxduo if the clinical studies are successful?
   - What is the evidence for this?
   - Should QRxPharma use Abuse Deterrent Formulation (ADF) approaches?
   - Will Moxduo have to go before an Advisory Committee again?

1. Does Moxduo show a real benefit over its individual components?

- QRxPharma scientists believe the answer is YES.
- In post-hoc analyses:
  - Incidence (% of Patients) at risk of Opioid Induced Respiratory Depression (OIRD) is lower with the combination product.
  - Not likely due to confounding factors or chance.
  - The lower incidence of deeper oxygen desaturations is particularly evident in patients in high-risk groups.
  - The time-to-first oxygen desaturation is markedly in favor of Moxduo.
  - Slides 25 – 30 in the appendix provide substantial evidence from Study 022 in favor of Moxduo.
- Consistency of these data lead us to believe that we will see the same effect in a pre-specified analysis.

2. Can we demonstrate the benefit of Moxduo in a clinical trial that regulators will agree with?

- The QRxPharma team believes the answer is YES.
- FDA has stated that Moxduo should show a benefit in a specifically defined population.
- QRxPharma proposes to commence a clinical trial(s) in patients at higher risk of Opioid Induced Respiratory Depression (OIRD):
  - Older patients
  - Heavier patients
  - Smokers
- Slides 31 - 47 in the appendix show a more favorable outcome can be predictably obtained.

Other Important Clinical Study Issues:

- FDA appears to have accepted that fewer “deep oxygen desaturations” occur on Moxduo vs. oxycodone and morphine.
- In future studies, it is unclear whether this alone, or in combination with other clinical measures, will be sufficient to show a suitable benefit.
- It is unclear whether FDA will require other measurements (such as blood gasses, etc.) along with oxygen desaturations.
- QRxPharma will meet with FDA in the next month, (approx.) to discuss these issues, and gain additional feedback.
- Further detailed discussions with FDA regarding trial design and overall program will follow in due course.

3. Will FDA approve Moxduo if agreed upon clinical studies are successful?

- QRxPharma believes there is evidence in the record, and in the Advisory Committee discussion:
  - FDA stated they would be “excited” to approve a safer opioid.
  - FDA stated that a reduction in OIRD (respiratory depression) would offer such a benefit. QRxPharma and FDA need to agree on what amount of reduction in OIRD is meaningful.
  - Moxduo would need to demonstrate a benefit in a specific population.
  - Various Advisory Committee members voiced a need, and hope that this drug, or others, could be prospectively shown to have such a benefit.

Advisory Committee Chairman's Summary:

"It is the sense of this committee that the applicant has not provided sufficient evidence to support a claim that Moxduo is safer than morphine and oxycodone. The primary failing was in study design and the inability of the committee to be able to rely with confidence on multiple post-hoc analyses. Future more appropriately designed studies would be helpful in specifically answering the question. The committee does not suggest that Moxduo is either beneficial or not beneficial. The committee simply feels that the evidence is insufficient to make a determination either way."

So, how much will this cost and how long will it take?

- QRxPharma is evaluating possible study protocols that we believe will be acceptable to FDA.
  - Will pursue a SPA review.
  - Will gain FDA agreement on study design.
- One Phase 3 study would be circa US$8MM. It would be best if ***two*** studies were conducted, to assure success at a future Advisory Committee. Two studies would cost circa US$16MM.
- Two studies could potentially result in a label claim, resulting in a differentiated, and thus more valuable label.
- Clinical results anticipated in 15-18 months. Operating costs through to clinical data report would be US$14-17MM.

So, how much will this cost and how long will it take? (continued)

- A renewed clinical effort would result in a new NDA filing, with a PDUFA date ≈ 24-26 months from now.
- Operating costs to file the NDA, go through an Advisory Committee and PDUFA decision is an additional US$8-12MM.
- If Abuse Deterrent Formulations are needed, an additional US$4-6MM will be required. This approach could be seen by FDA as a new NDA filing, at a further cost of US$2MM.
- QRxPharma is evaluating this strategy.

Next Steps for QRxPharma

- Meet with FDA, and agree on next steps:
  - Overall approach to registration of Moxduo.
  - Level of desaturation deemed clinically meaningful.
  - Study Protocol(s), endpoints and statistical analyses.
  - One study, or two?
  - Labelling considerations.
  - Requirement of ADF in the product?
- Assess the cost, timing and probability of success of future programs.
- Discuss these approaches with the investment community.

Frequently Asked Questions

Below are answers to some of the most frequently asked questions regarding the status of Moxduo and interactions with the FDA

- Does the Advisory Committee vote bind FDA in the future?
  - **Answer:** No, FDA uses advisory committee feedback to guide its thinking on a variety of review and approval decisions. The committee vote does not bind the FDA in any way. The vote and the committee's comments are however, carefully considered by FDA.
  - These comments by the committee are less relevant to future NDA submissions, and they do not bind the FDA or future committees on the evaluation of future submissions, either.

Frequently Asked Questions

- Does the 0-14 vote by the committee mean that they don't think Moxduo provides a safety advantage?
  - **Answer:** No, not necessarily. The vote was a representation of the fact that Study 022 was primarily *Post hoc* and that the committee's vote was based on the fact that there weren't "P" (probability) values for the statisticians to evaluate. This is the case with *Post hoc* analyses. Study 022 could not, and did not, meet their expectations in this regard.
  - Various committee members recommended that another study be conducted.

Frequently Asked Questions

- If Study 022 COULD NOT meet a statistical standard, then why did QRxPharma rely on Study 022?
  - **Answer:** During discussions with FDA in our "Formal Dispute Resolution Request" process, we were told, verbally, and in writing that *Post hoc* analyses could be used to show a benefit. After submission, FDA concluded, and told the Advisory Committee, that these analyses in Study 022 were not strong enough to merit approval. FDA and the Advisory Committee then recommended that an additional trial(s) were needed to show this benefit.

Frequently Asked Questions

- Why did QRxPharma appeal in the first place?
  - **Answer:** Following the June, 2012 CRL, QRxPharma entered into a series of discussions with FDA called “Formal Dispute Resolution.” This process is sometimes called an “appeal.” QRxPharma was surprised the Review Division cited an interpretation of the “Combination Rule,” never previously applied by FDA. This was counter to interpretations received verbally and in writing from FDA during the development of Moxduo.

Frequently Asked Questions

- Did QRxPharma have More Than One Appeal?
  - **Answer:** It was our intent from the beginning to appeal and obtain feedback from the Office of New Drugs. FDA's requirement for a "Formal Dispute Resolution" request required an end of review meeting, and submission and review by an intermediary office before making a submission to the Office of New Drugs (OND). The initial steps were mandatory under FDA's guidelines and were part of a continuous appeal process to challenge FDA's revised interpretation of the Combination Rule. There was a single process to obtain review by OND, and it required two phases.

Frequently Asked Questions

- Did FDA conclude that Moxduo did not meet the Combination Rule based on a failure of Study 008 to receive a Special Protocol Assessment agreement?
  - **Answer:** No. QRxPharma followed the Special Protocol Assessment (SPA) process for Study 008, which was designed to meet the requirements of FDA's Combination Rule. QRxPharma received feedback from FDA that Study 008 was sufficient to satisfy the Combination Rule as FDA was interpreting it at that time. Comments were received from FDA regarding the study design, including a change in the primary endpoint.

Frequently Asked Questions

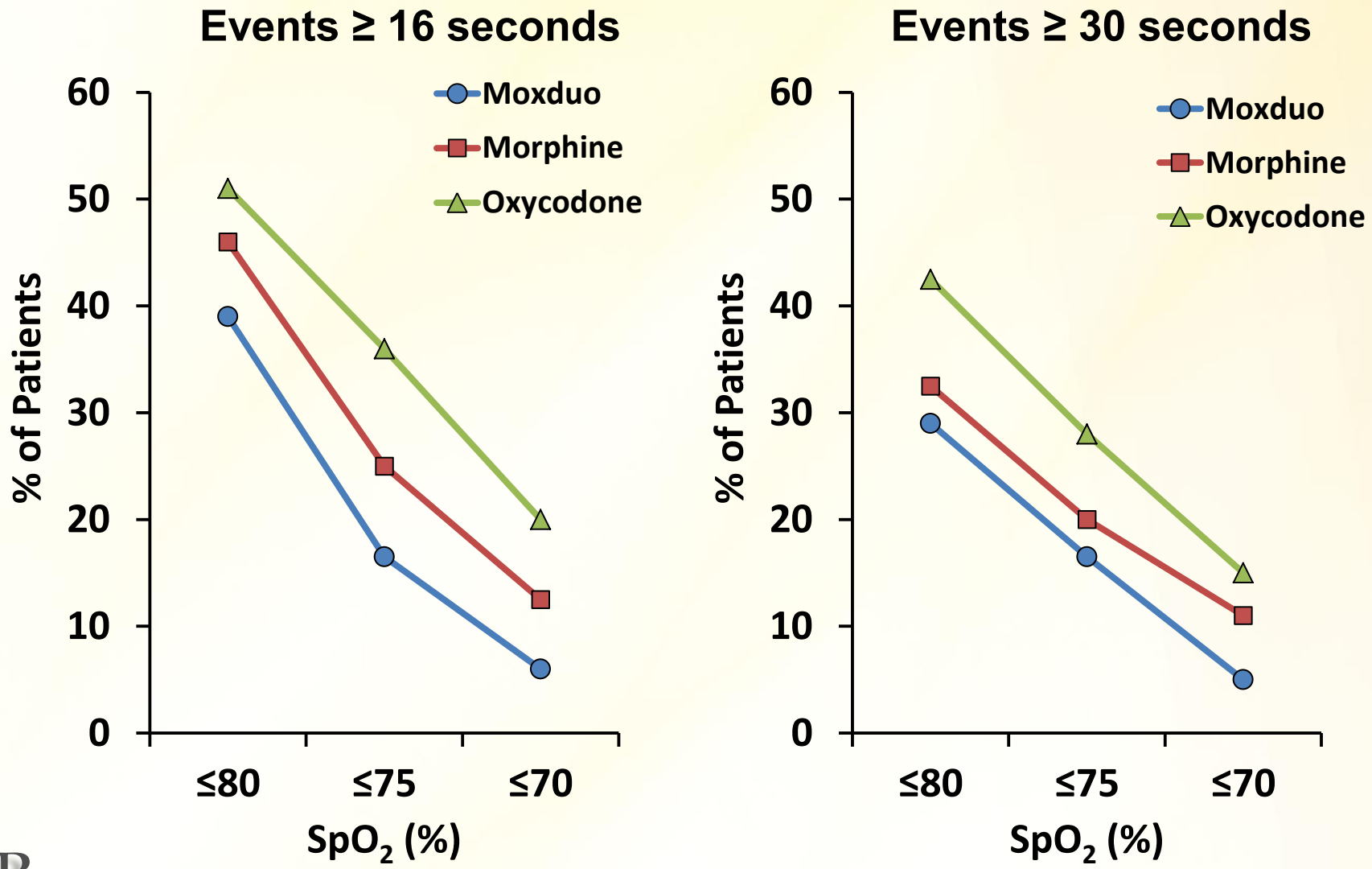
- Did FDA conclude that Moxduo did not meet the Combination Rule based on a failure of Study 008 to receive a Special Protocol Assessment agreement? (continued):
  - **Answer:** That feedback came in a "No Agreement" letter and contained additional comments. QRxPharma incorporated all FDA recommendations in the revised protocol, and re-submitted it for final approval. FDA declined to review the final revised protocol in a third cycle due to resource constraints. QRxPharma then initiated Study 008. Study 008 was successfully completed and met all endpoints specified by FDA, including the primary endpoint.

Frequently Asked Questions

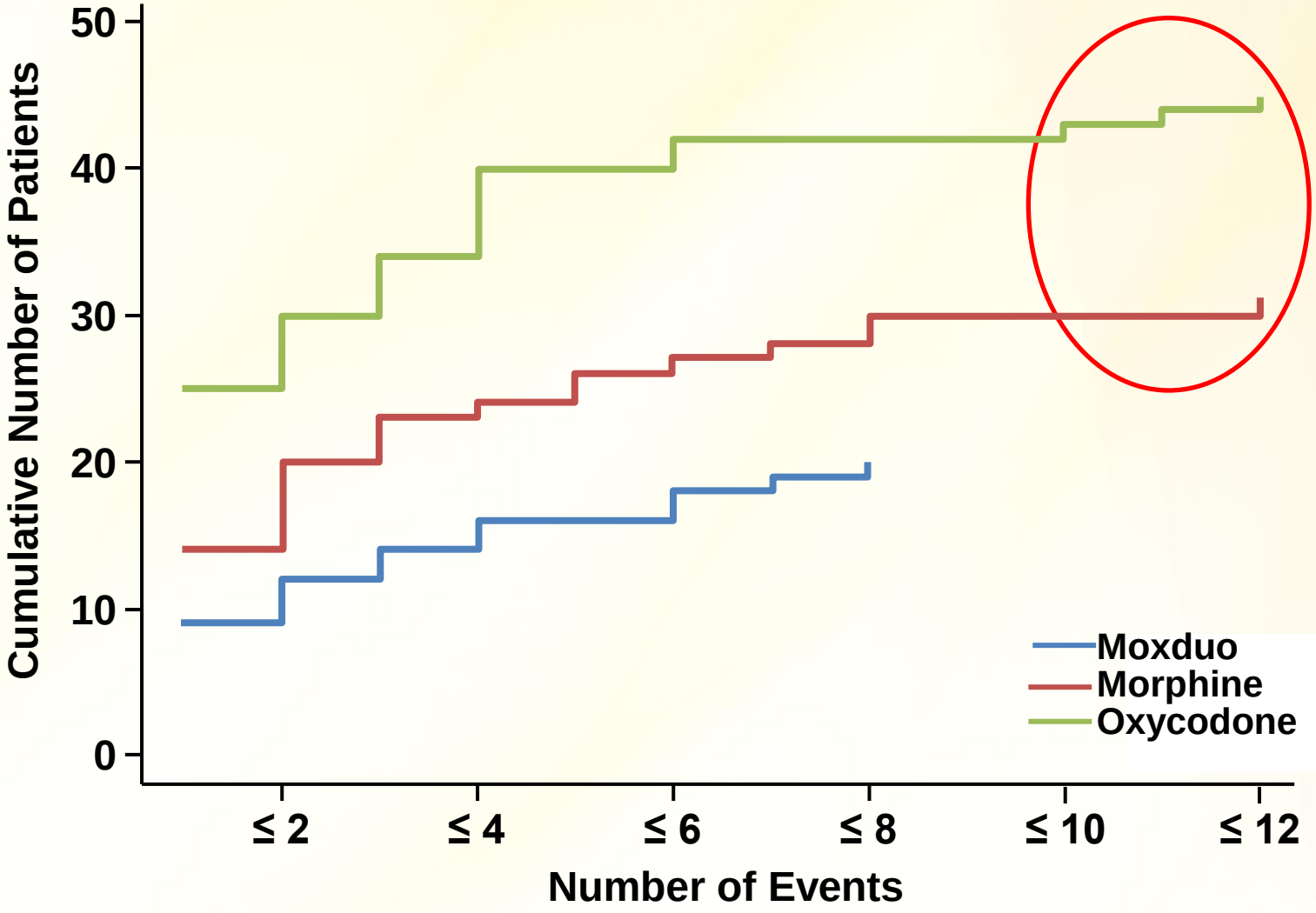
- During the Advisory Committee meeting, there was discussion around the desaturations standard at the 90 percent level. What would constitute as a clinically meaningful desaturation episode?
  - **Answer:** While conducting these clinical trials, clinical thinking began to change around what desaturation levels were clinically relevant, which is why there was discussion around the 90 percent cutoff. Today, 85 or 80 percent is considered the appropriate cut off because 90% is considered a nuisance alarm in most hospitals. This issue is still evolving, but QRx believes the clinical community is moving to lower cutoff levels of oxygen desaturation as more meaningful.

Appendix

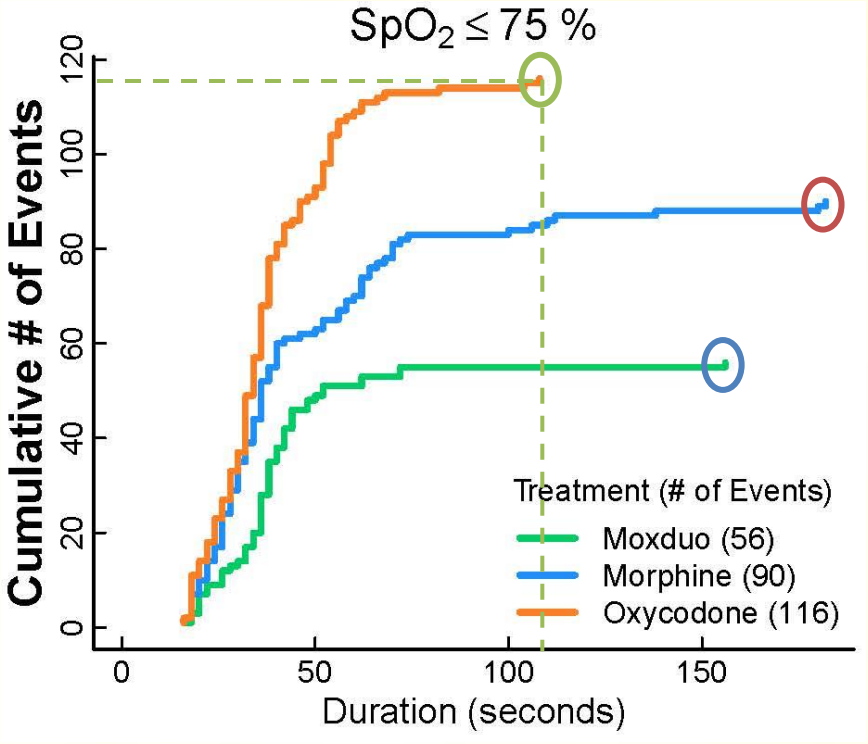
Incidence – Deep Desaturations



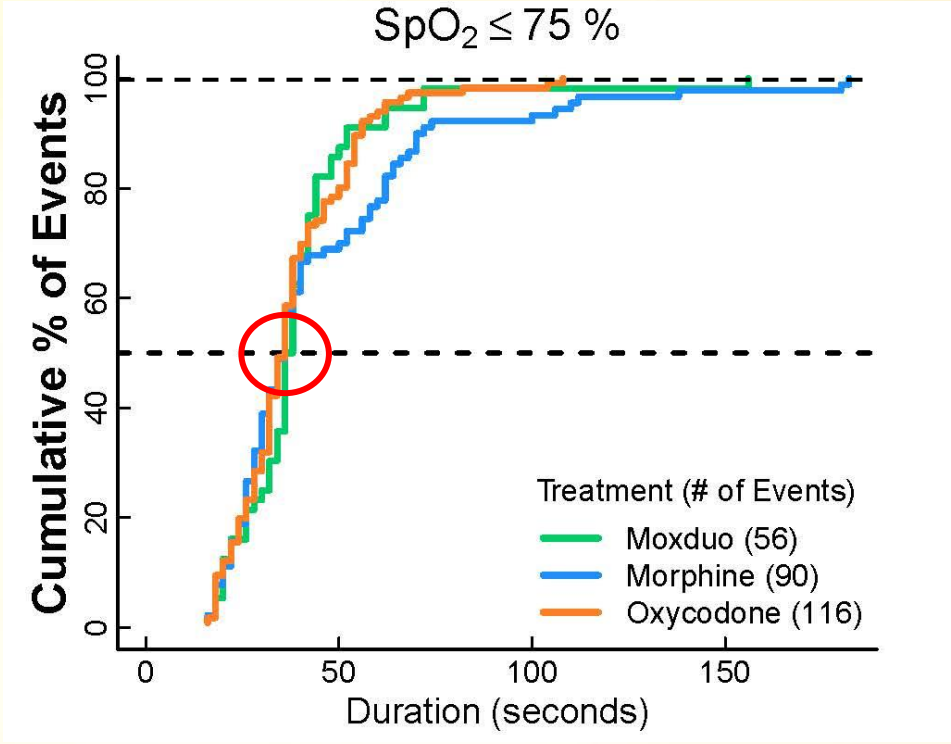
Cumulative Number of Patients vs. Number of Desaturation Events at $SpO_2 \leq 75\%$



Study 022:
Cumulative Distribution of Events vs. Duration

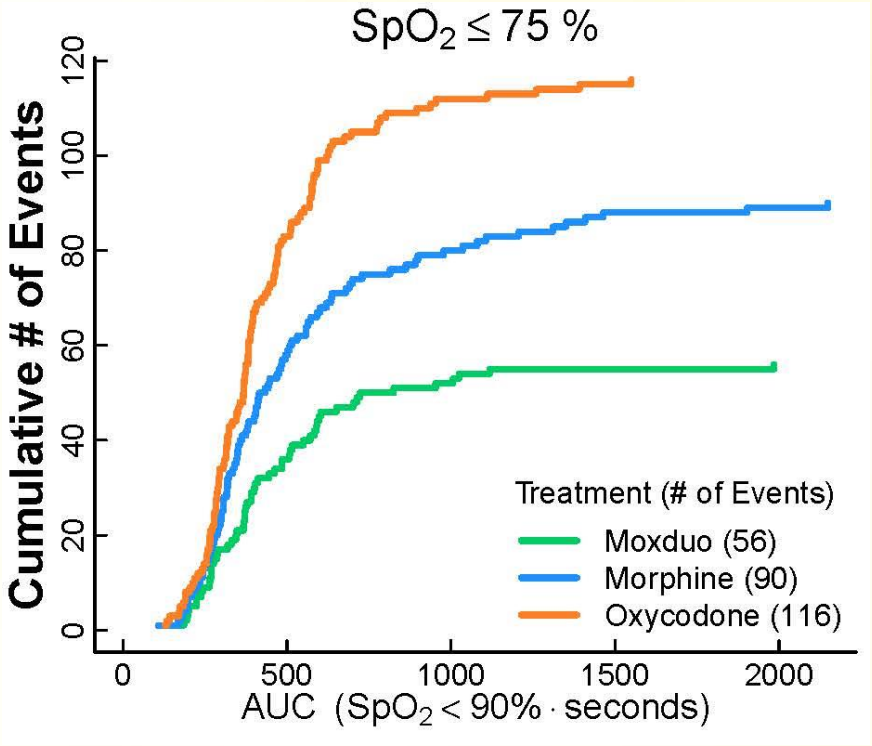


Number of Events

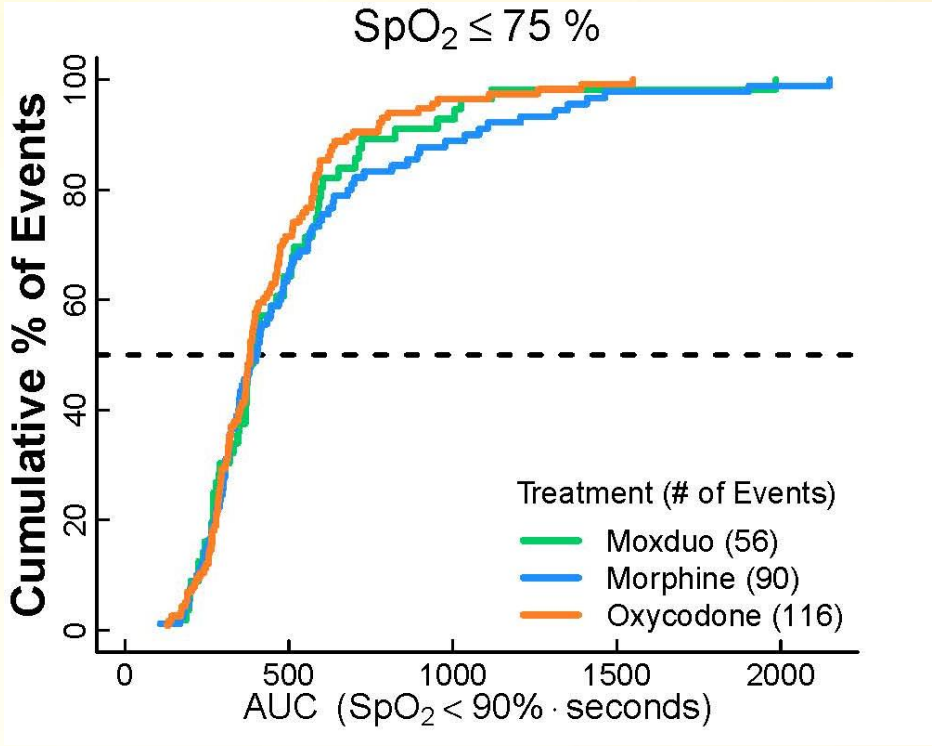


Percent of Events

Study 022:
Cumulative Distribution of Events vs. AUC



Number of Events



Percent of Events

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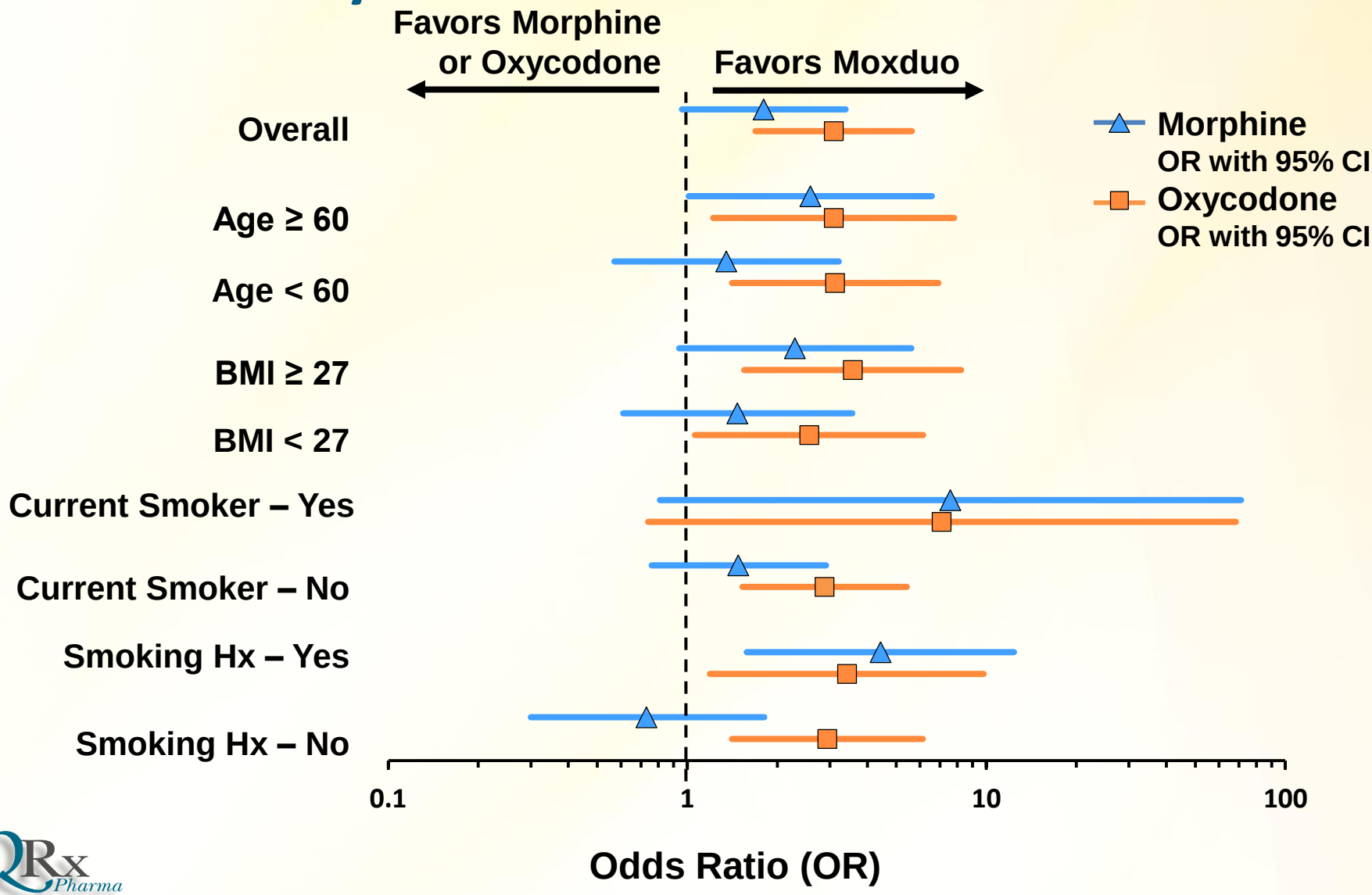
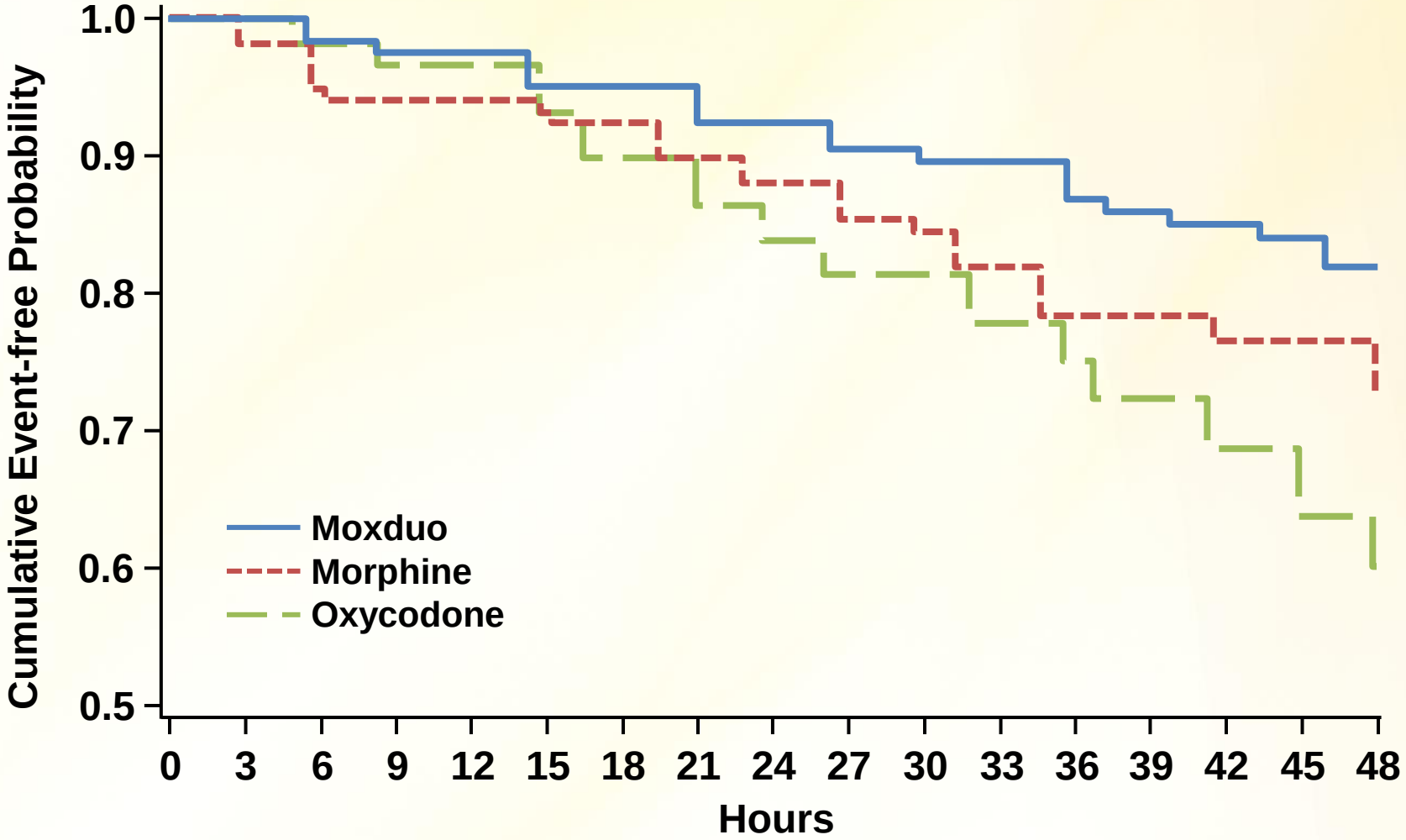
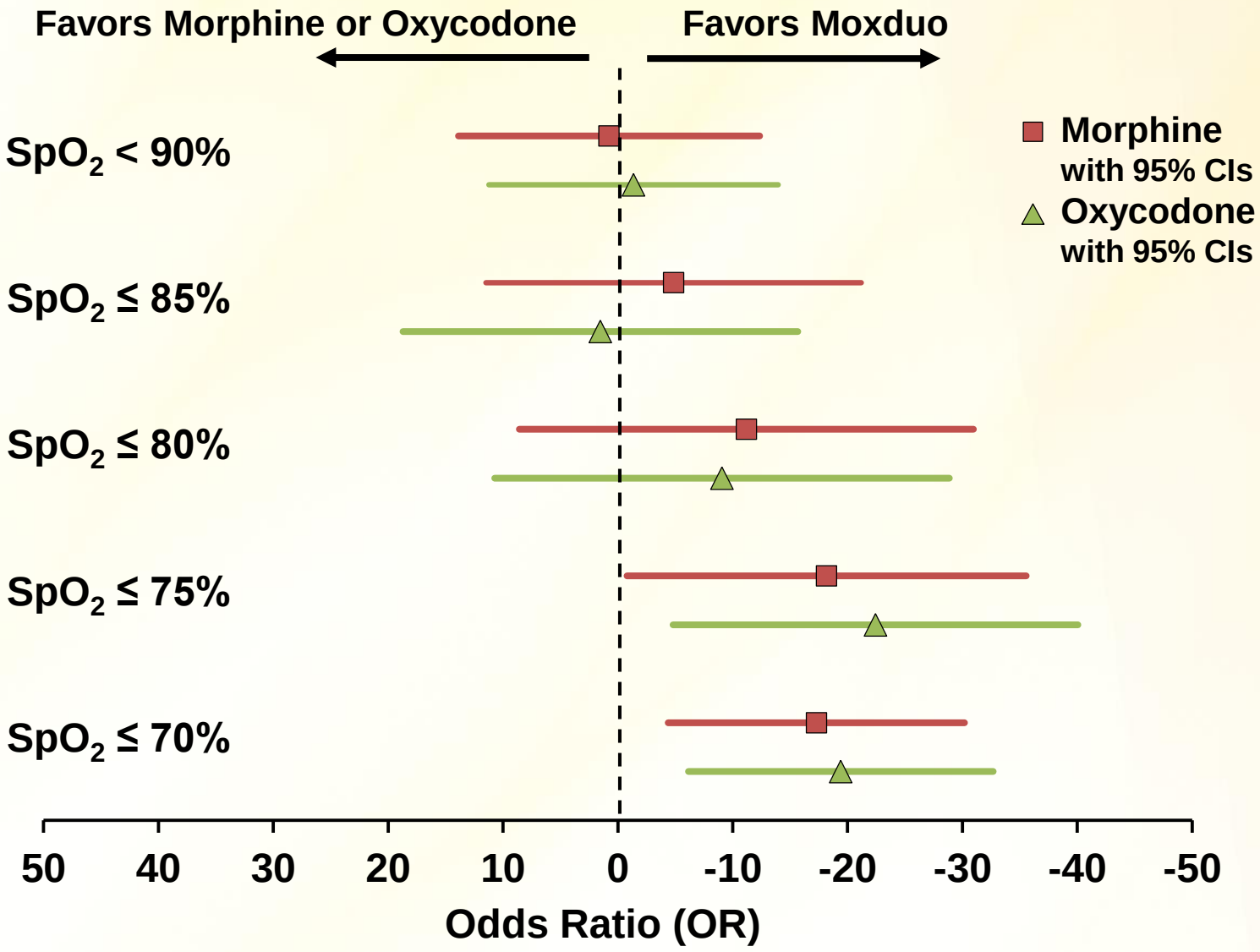
Risk of Deep Desaturations (≤ 75% SpO_2) Stratified by Risk Factors



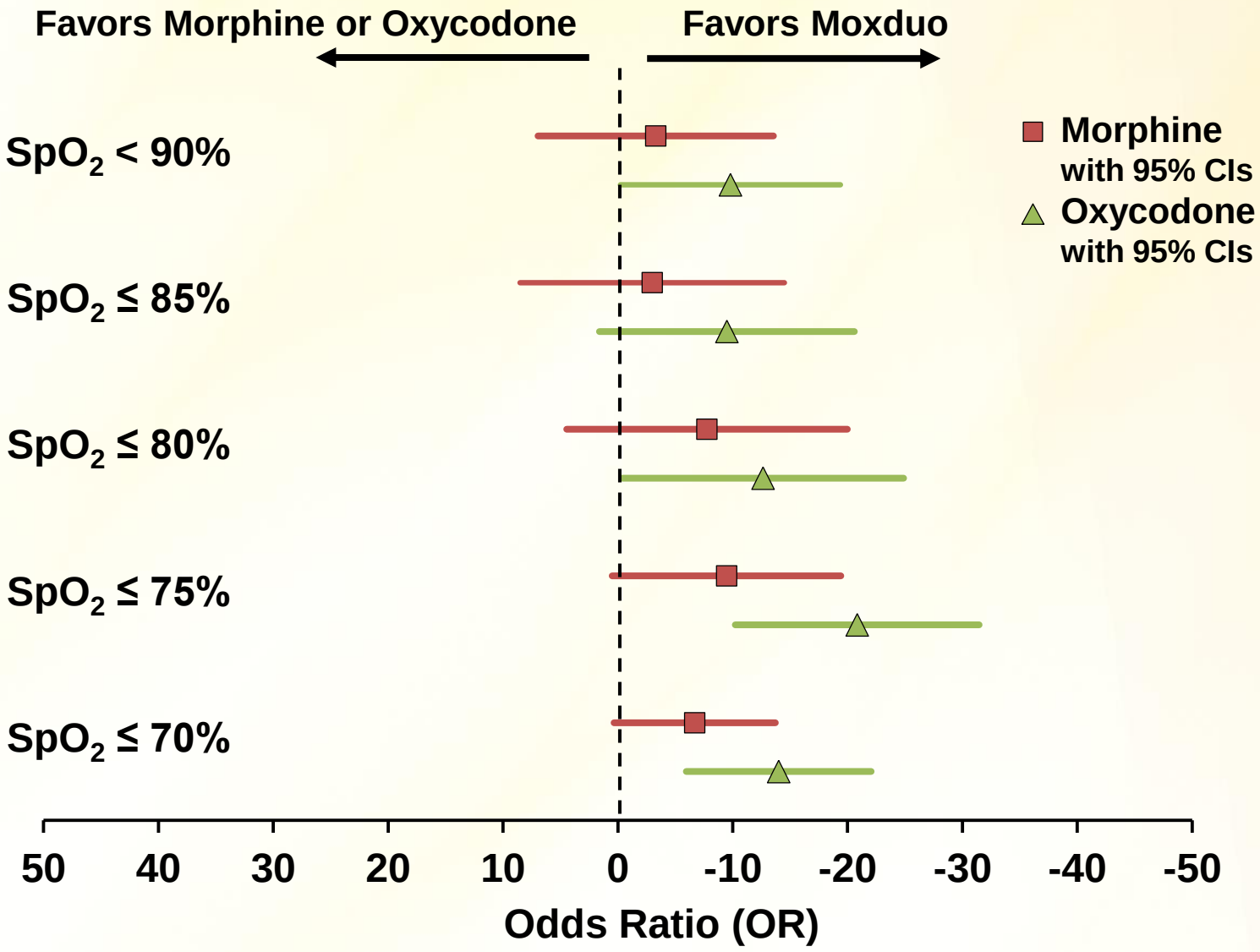
Kaplan Meier Estimate of Time to Initial Desaturation ≤ 75% – Safety Population



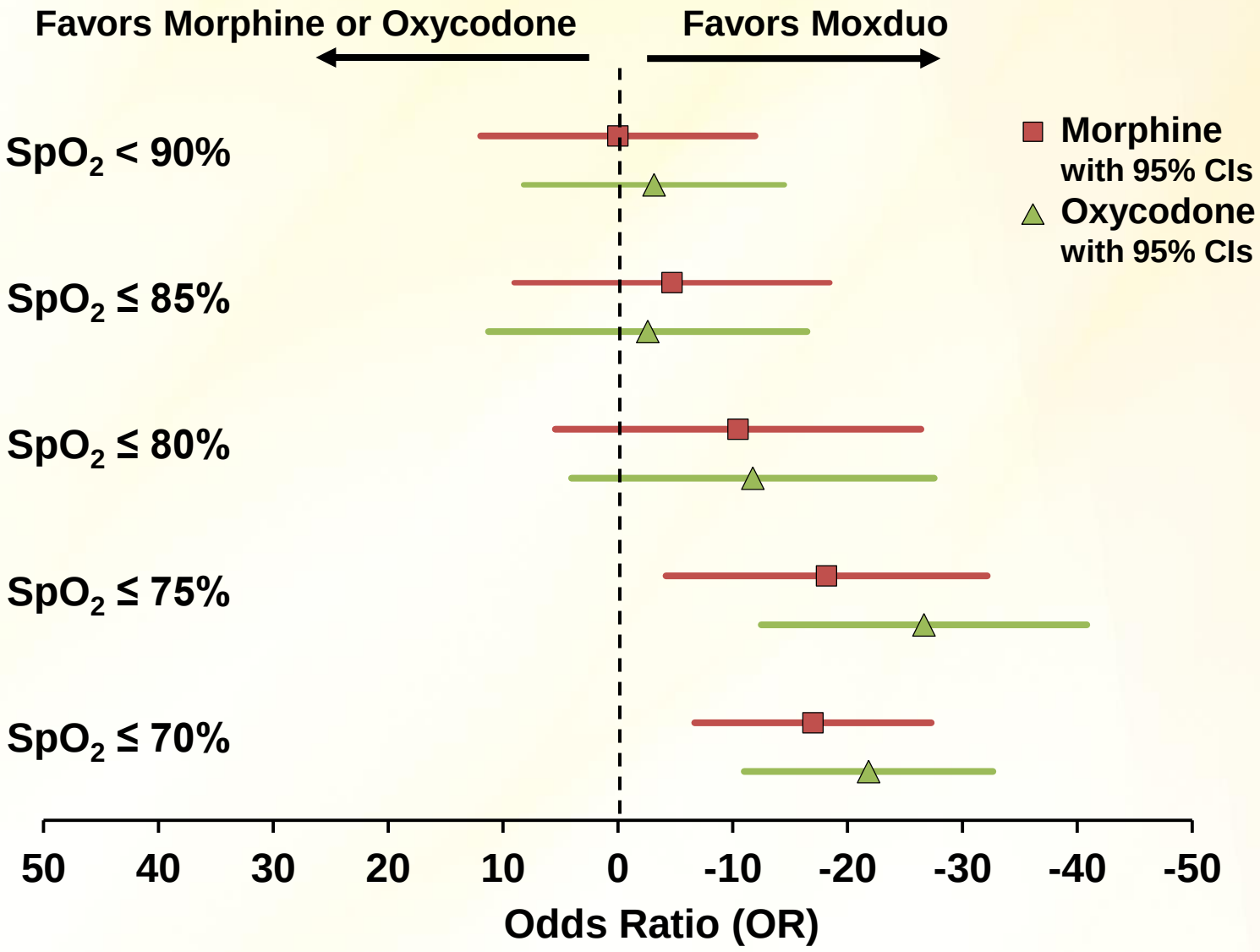
Patients ≥ 60 Years of Age



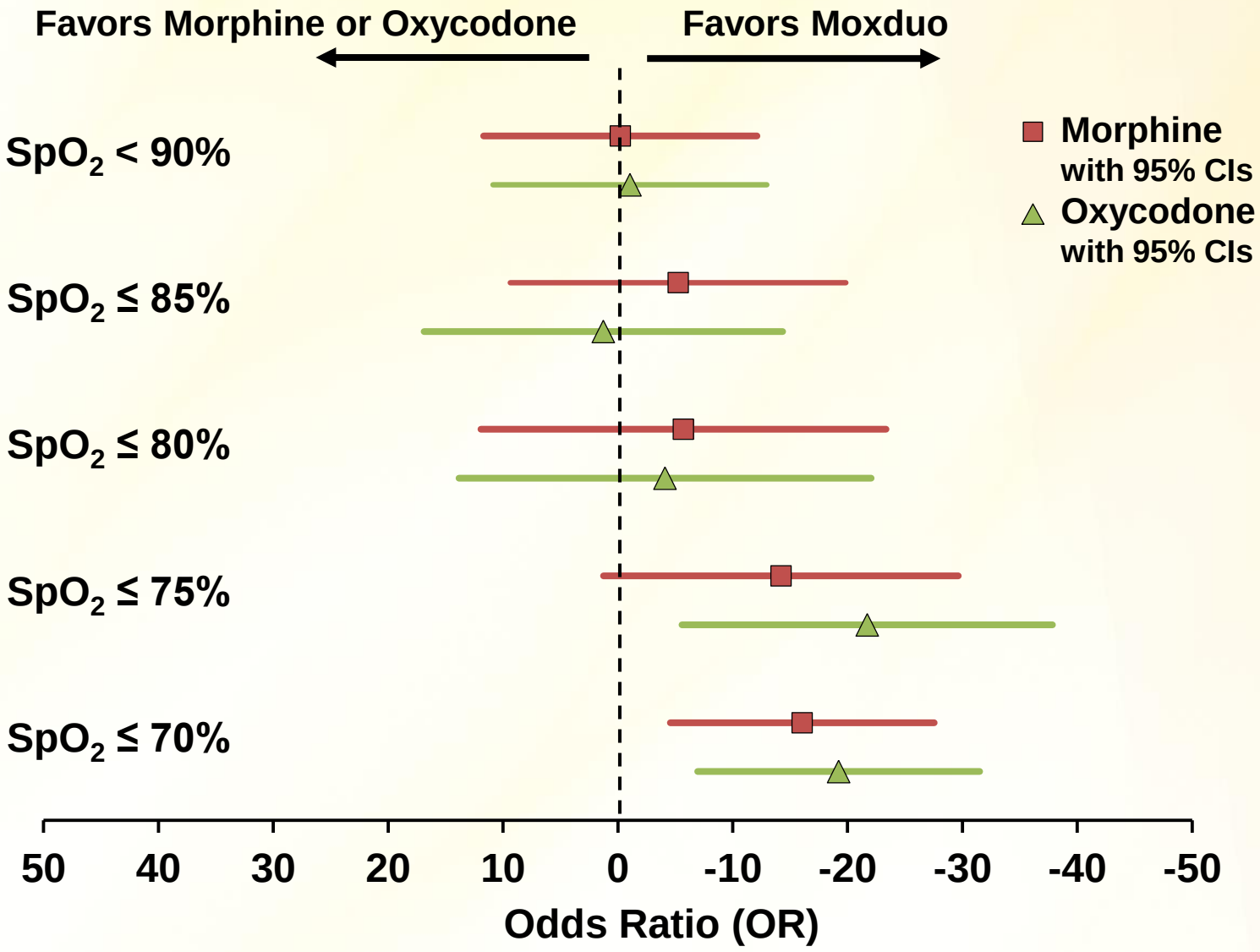
Intention to Treat Population



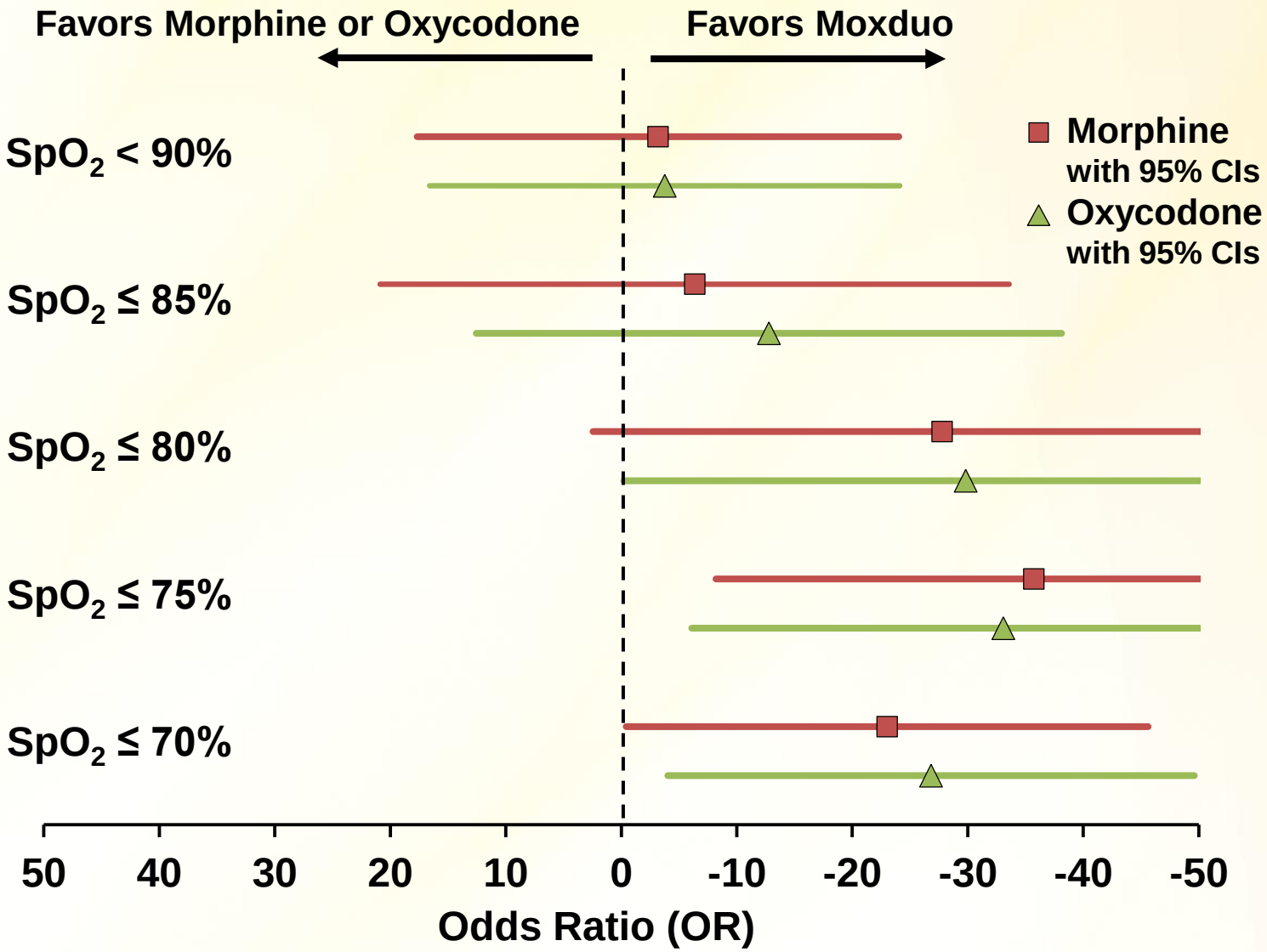
Patients ≥ 50 Years of Age



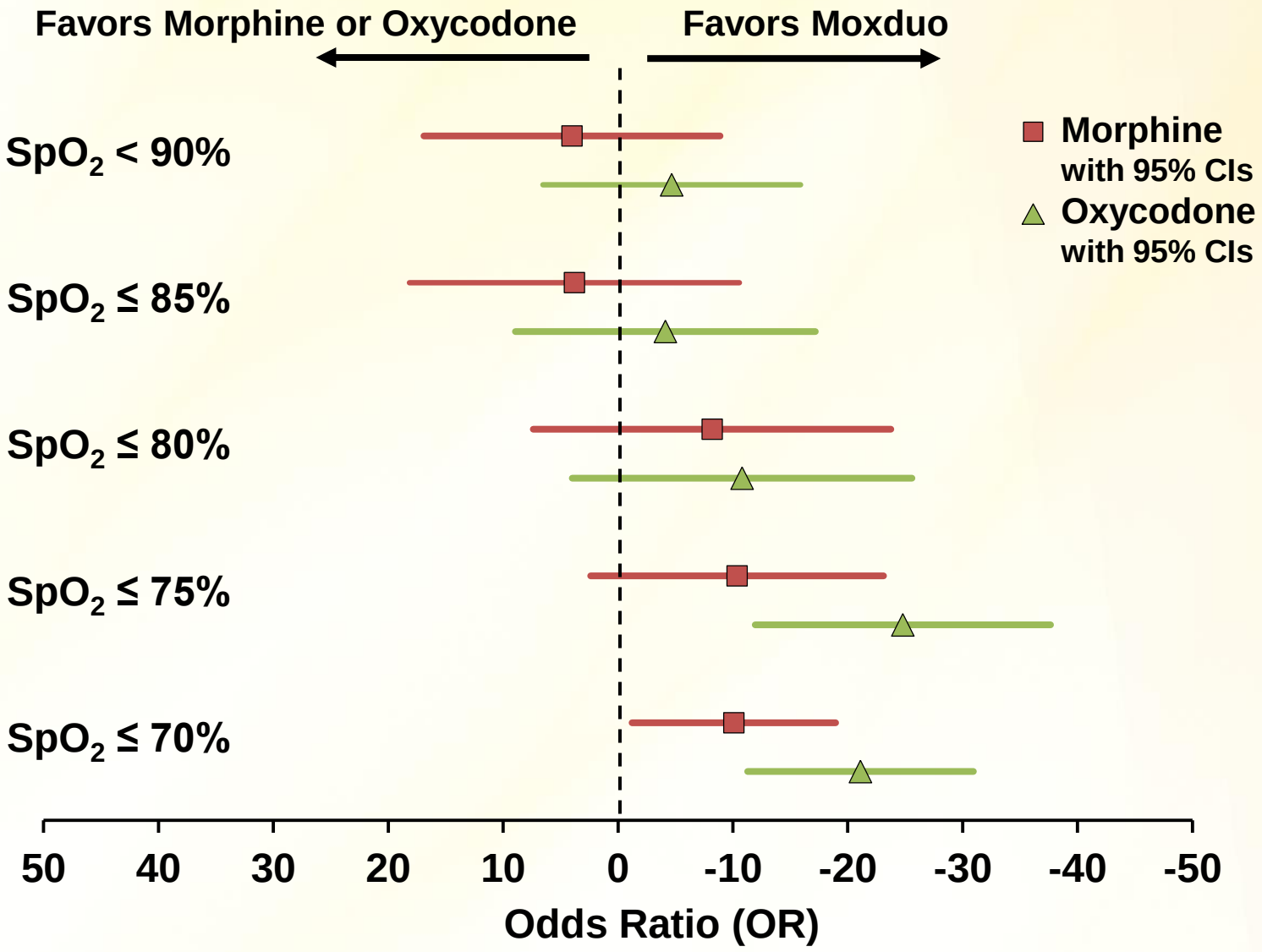
Patients ≥ 55 Years of Age



Patients ≥ 65 Years of Age



BMI ≥ 25


Favors Morphine or Oxycodone
Favors Moxduo
SpO2 < 90%
SpO2 ≤ 85%
SpO2 ≤ 80%
SpO2 ≤ 75%
SpO2 ≤ 70%
Morphine with 95% CIs
Oxycodone with 95% CIs
50
40
30
20
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-20
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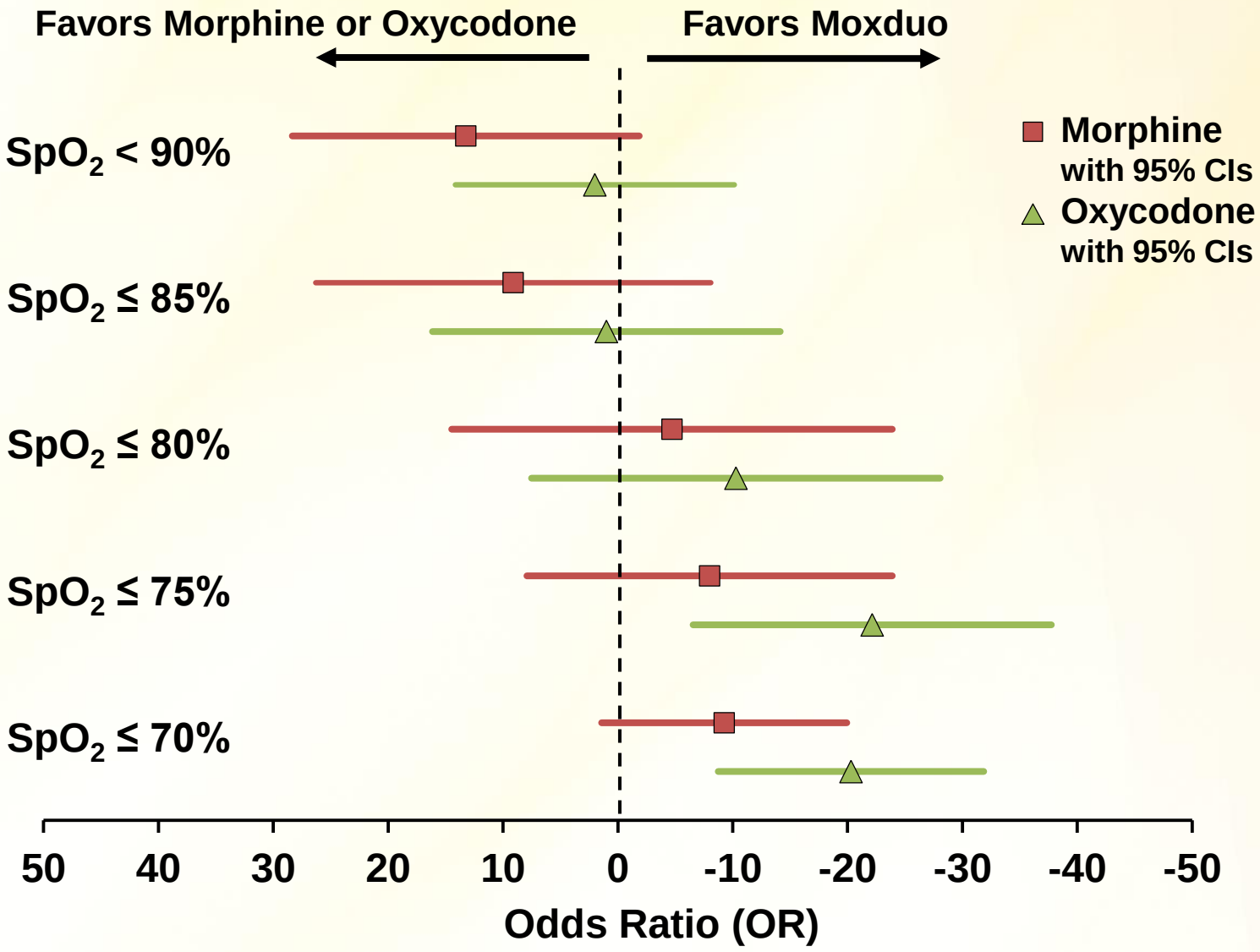
-40
-50
Odds Ratio (OR)

BMI ≥ 27.5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Morphine with 95% CIs
Oxycodone with 95% CIs
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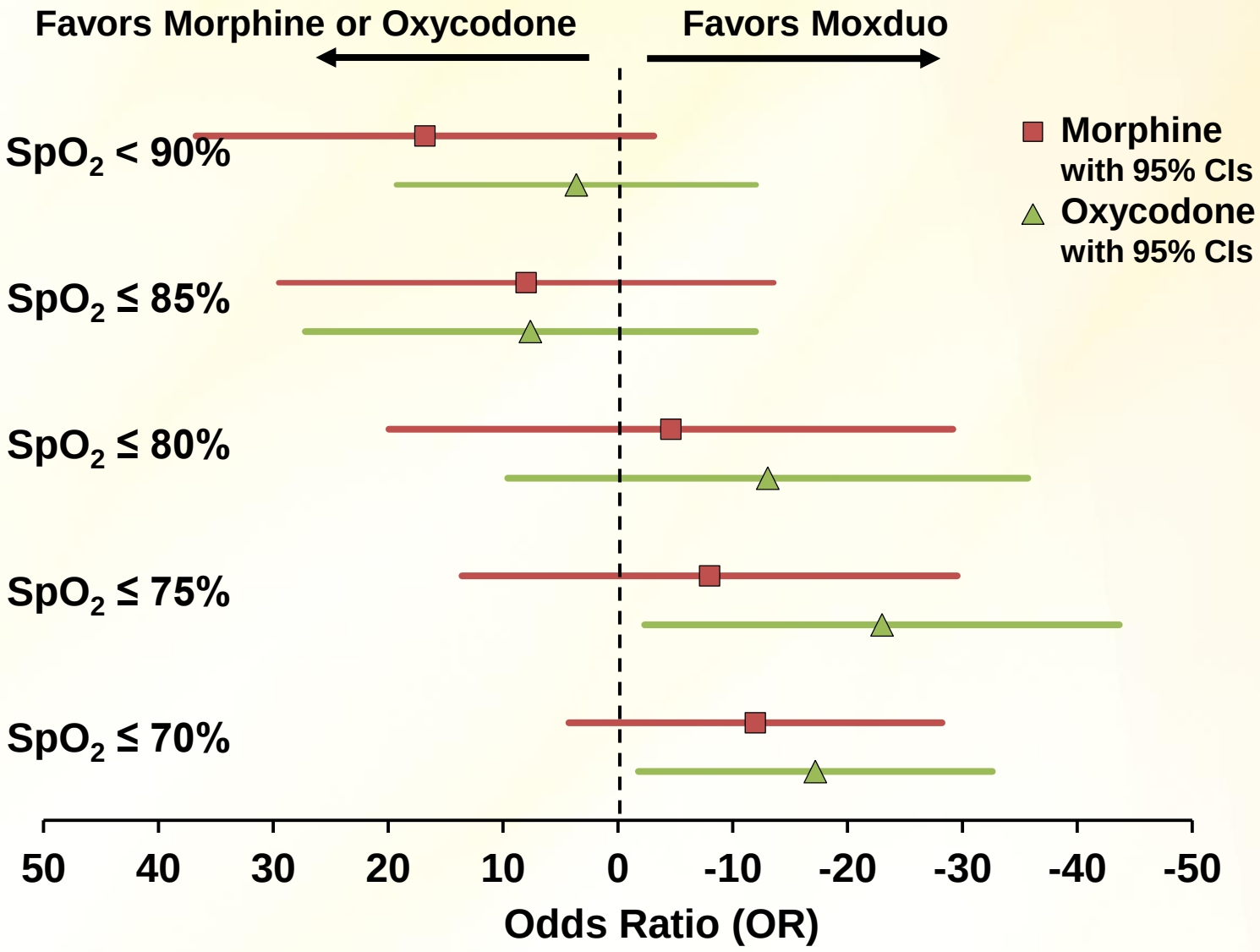
-40
-50
Odds Ratio (OR)

BMI ≥ 30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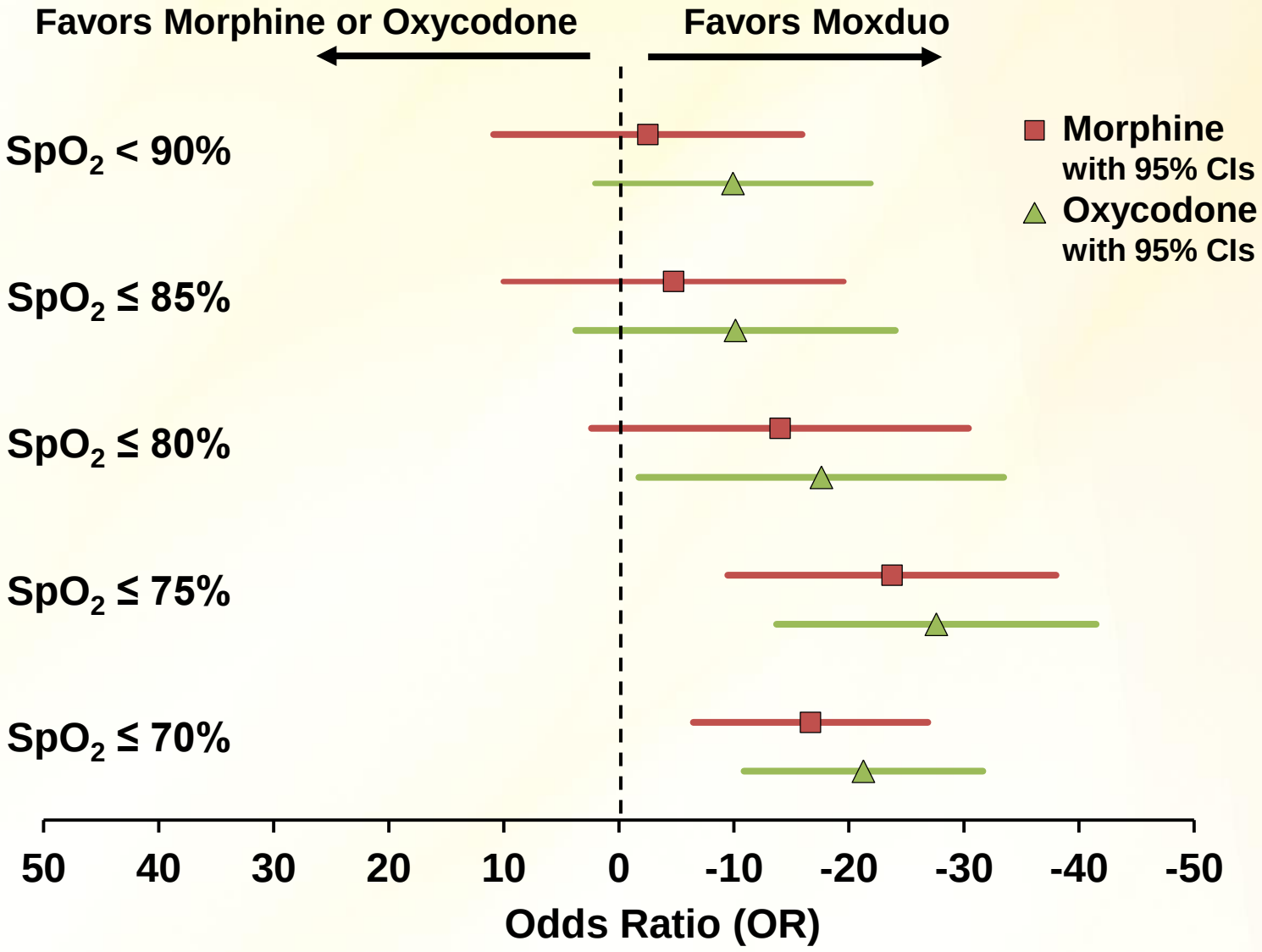
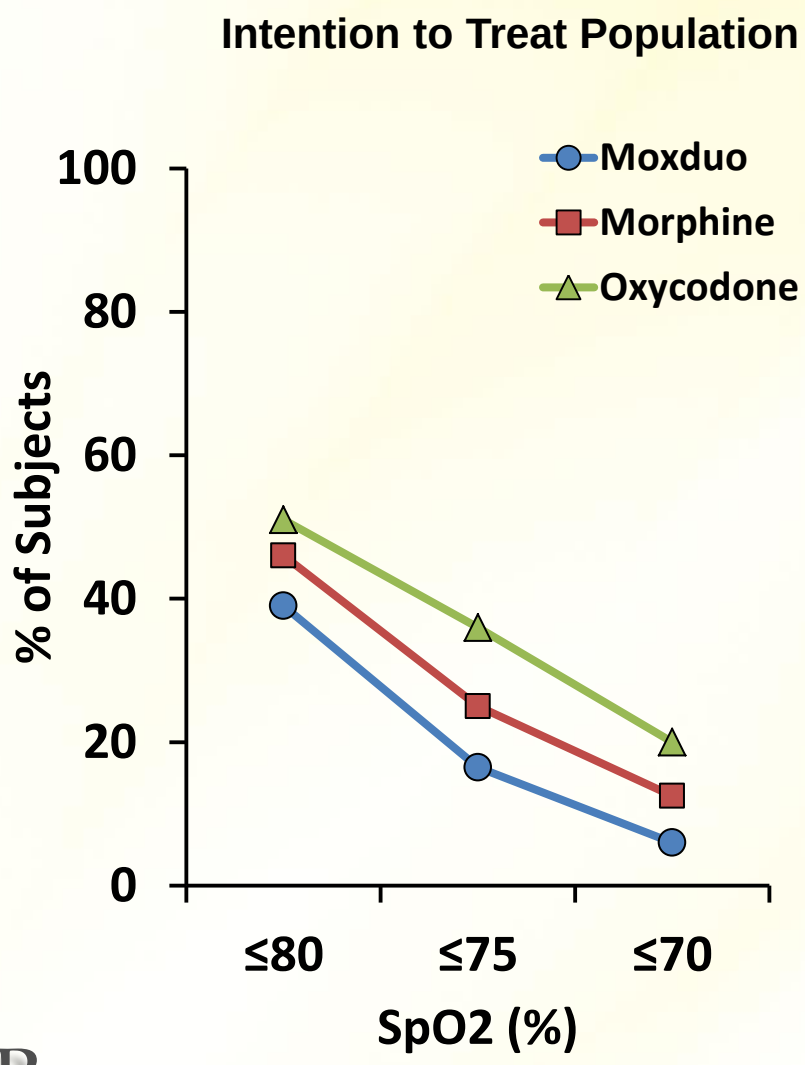
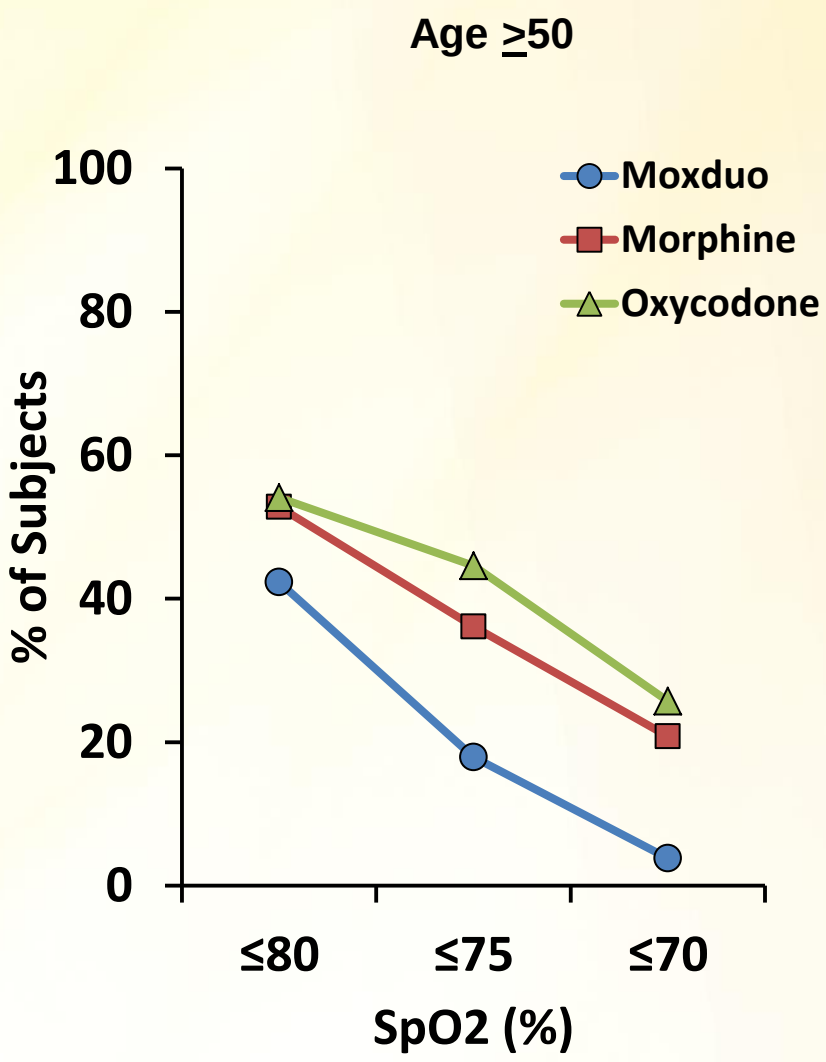
Odds Ratio (OR)

AGE ≥ 65 or BMI ≥ 30 or Current / Previous Smoker

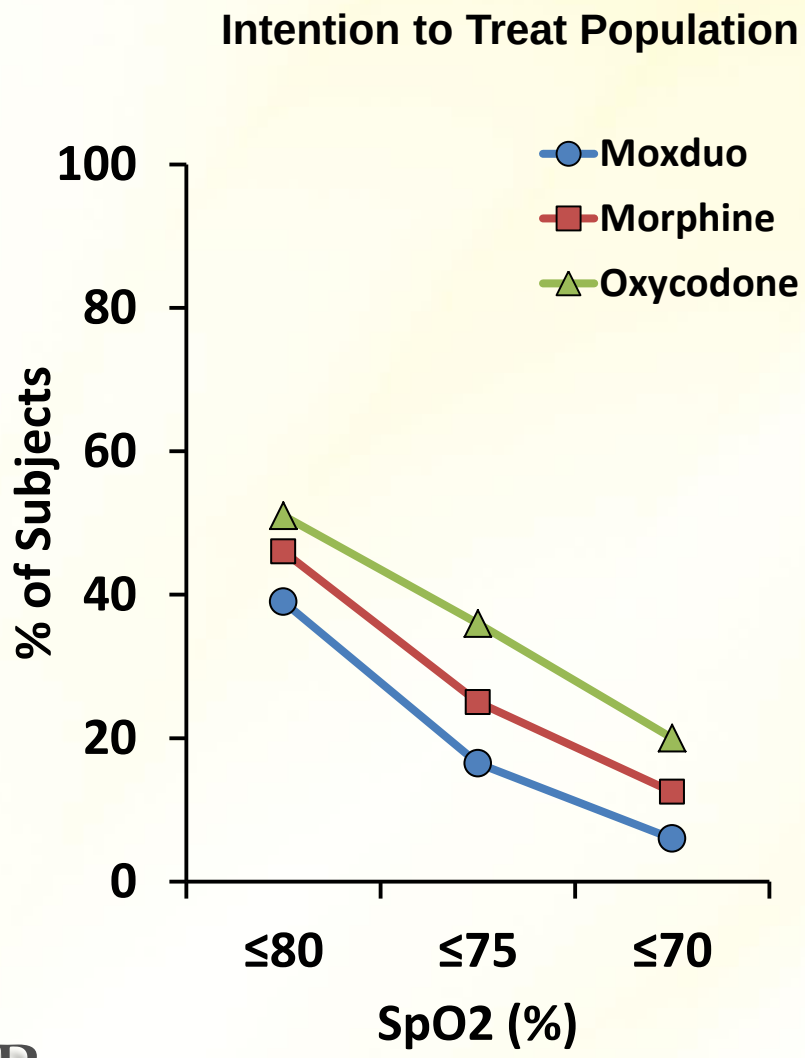


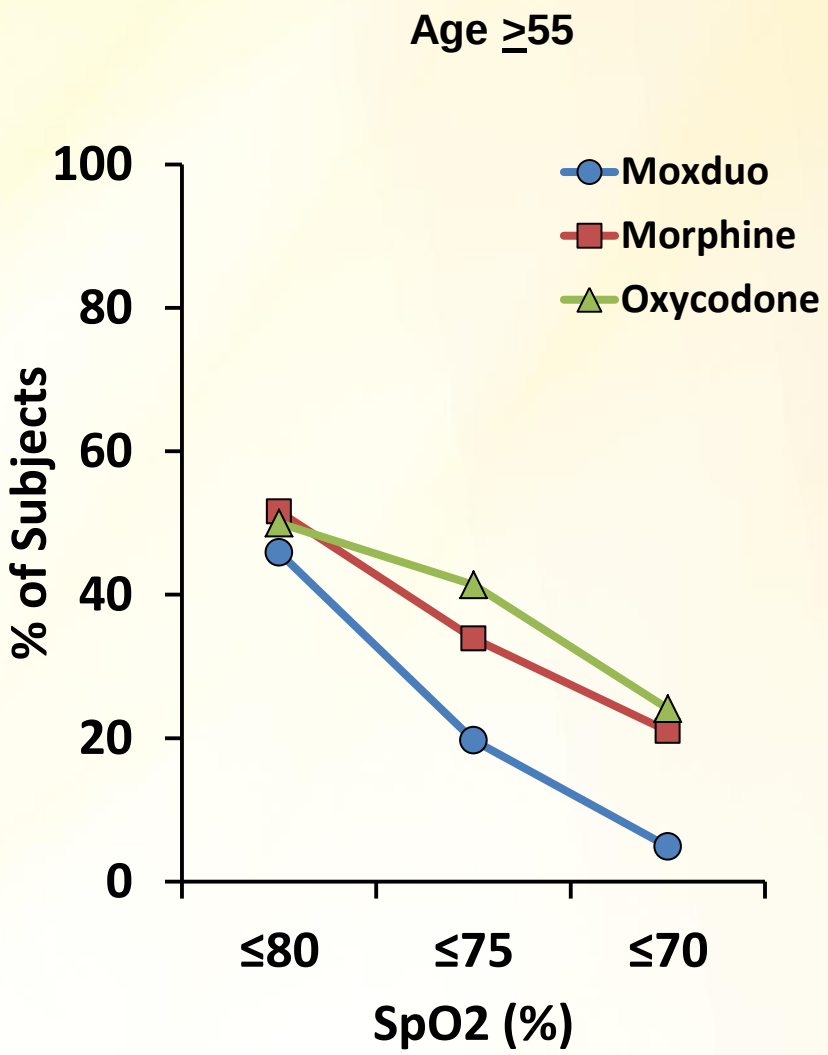
Incidence – Intention to Treat and Age ≥50



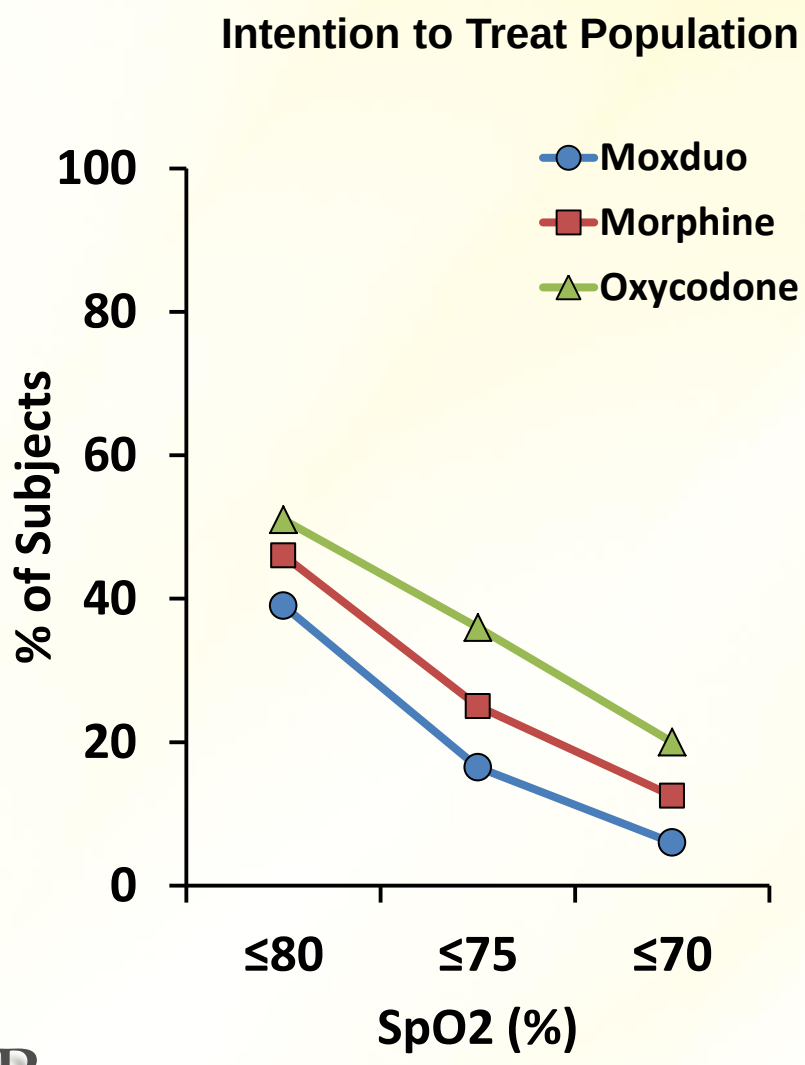


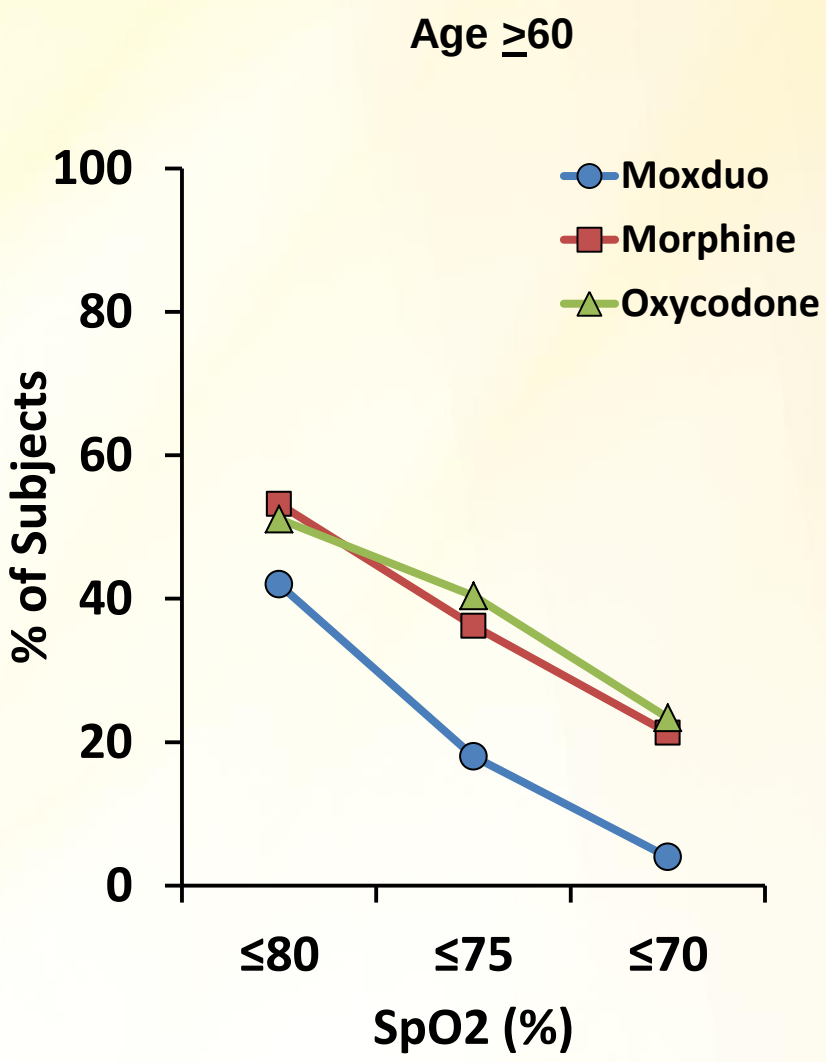
Incidence – Intention to Treat and Age ≥55



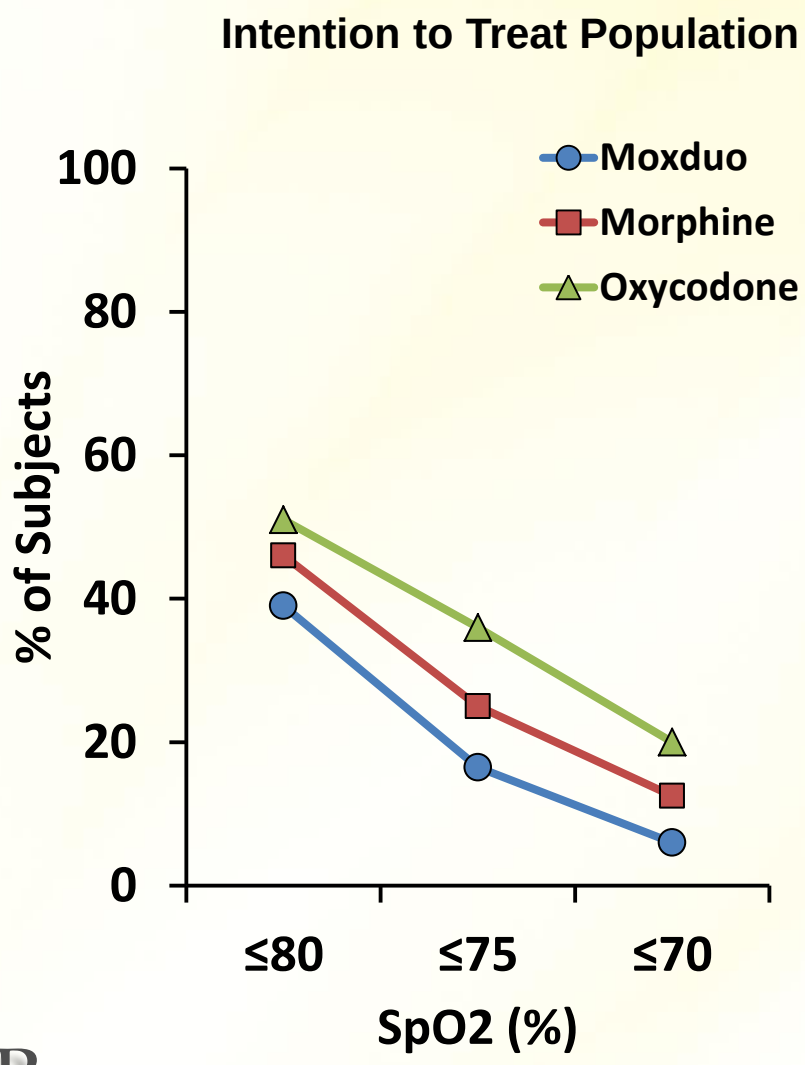


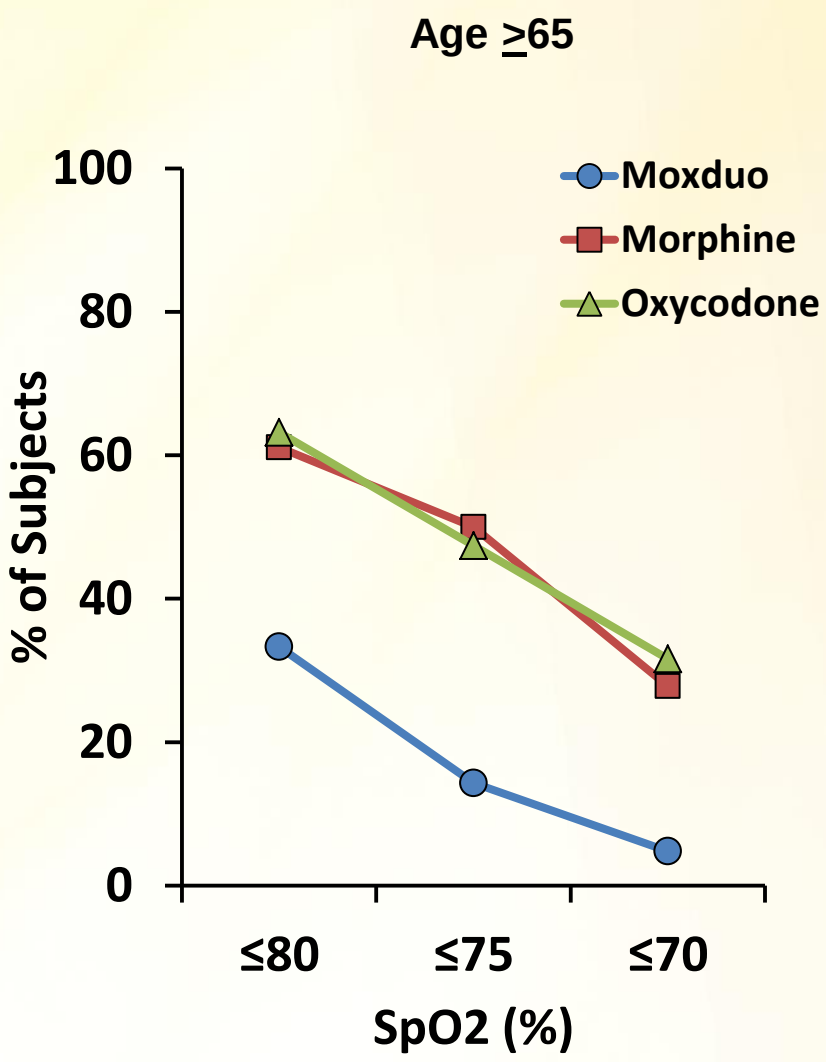
Incidence – Intention to Treat and Age ≥60



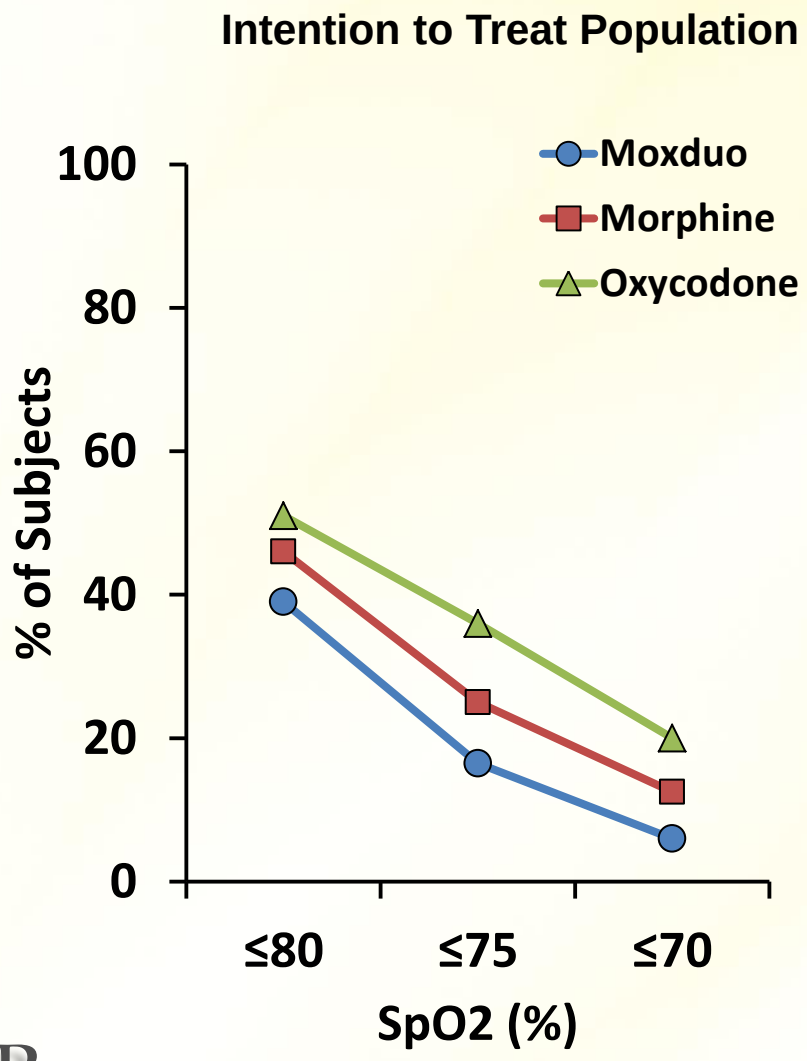


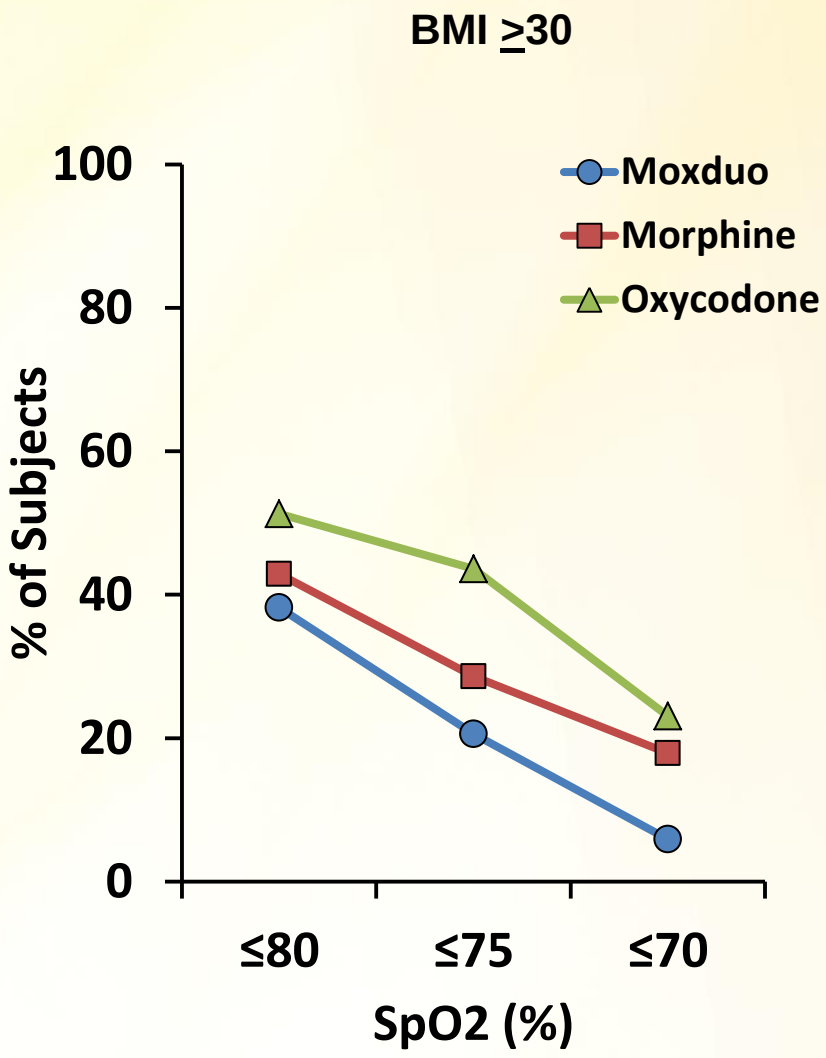
Incidence – Intention to Treat and Age ≥65



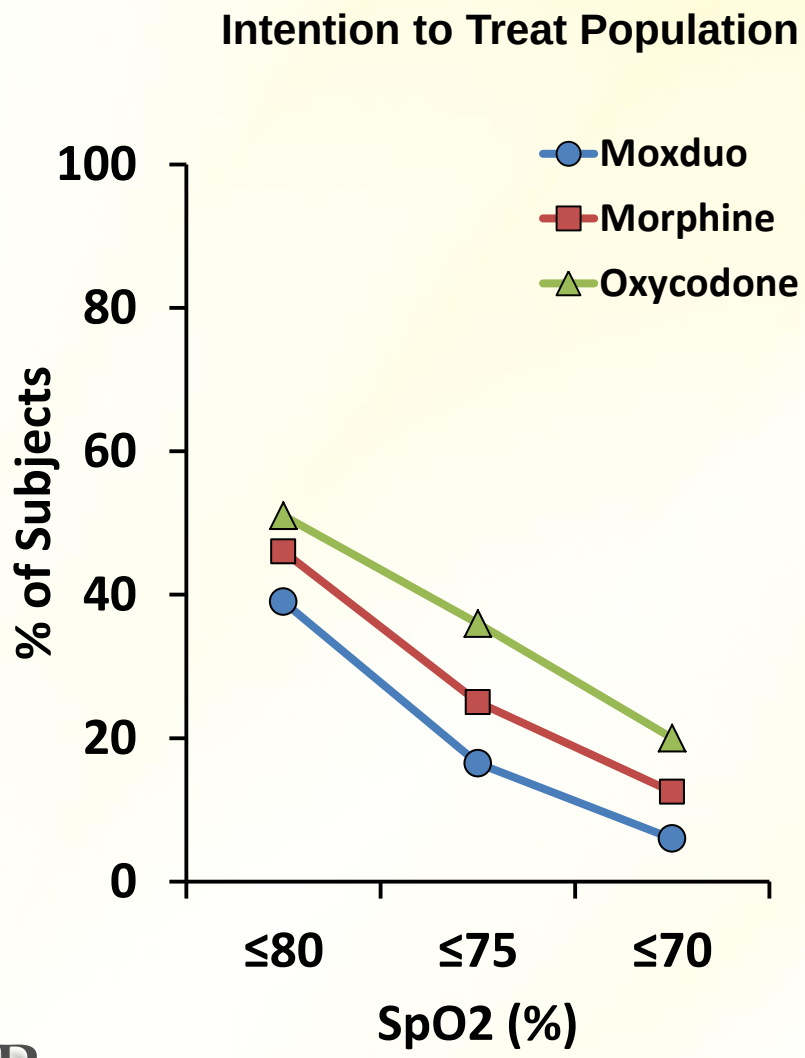


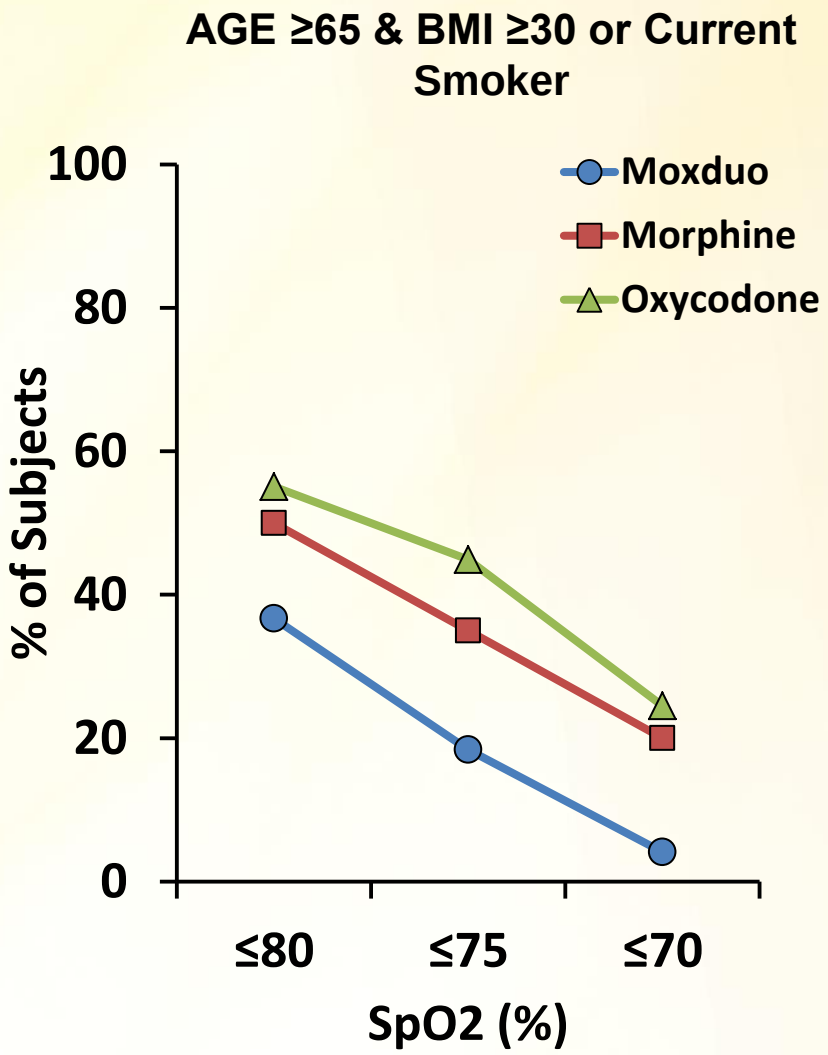
Incidence – Intention to Treat and BMI ≥30





AGE ≥ 65 or BMI ≥ 30 or Current Smoker





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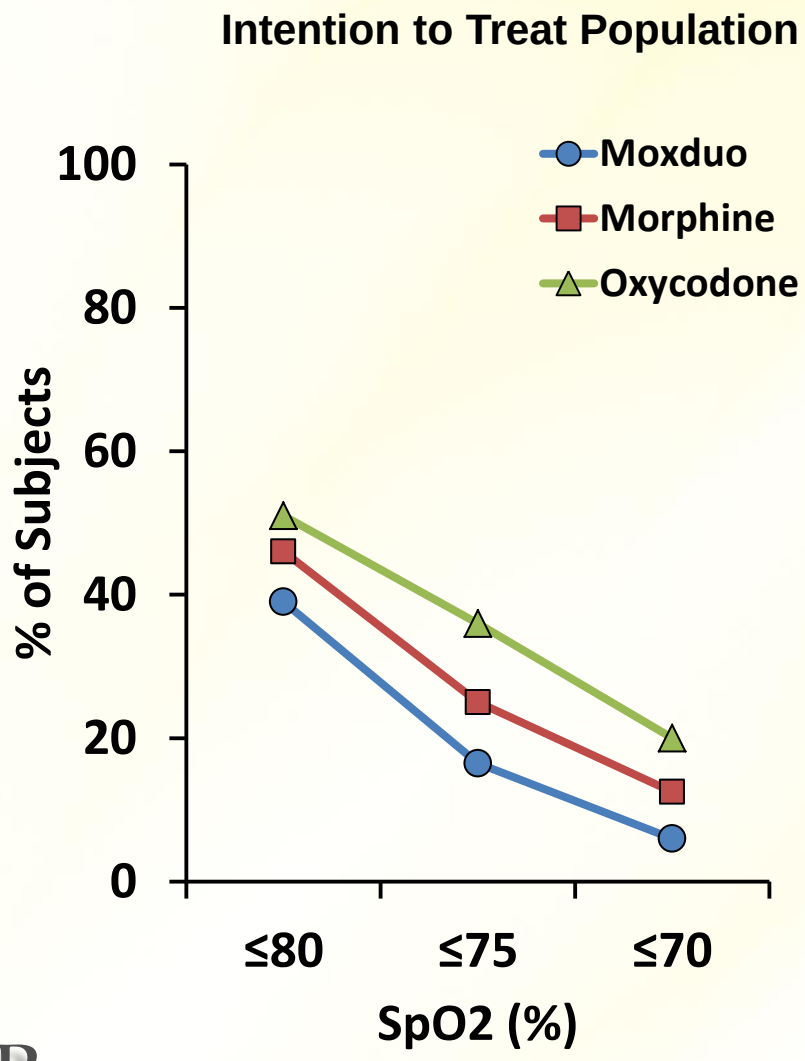
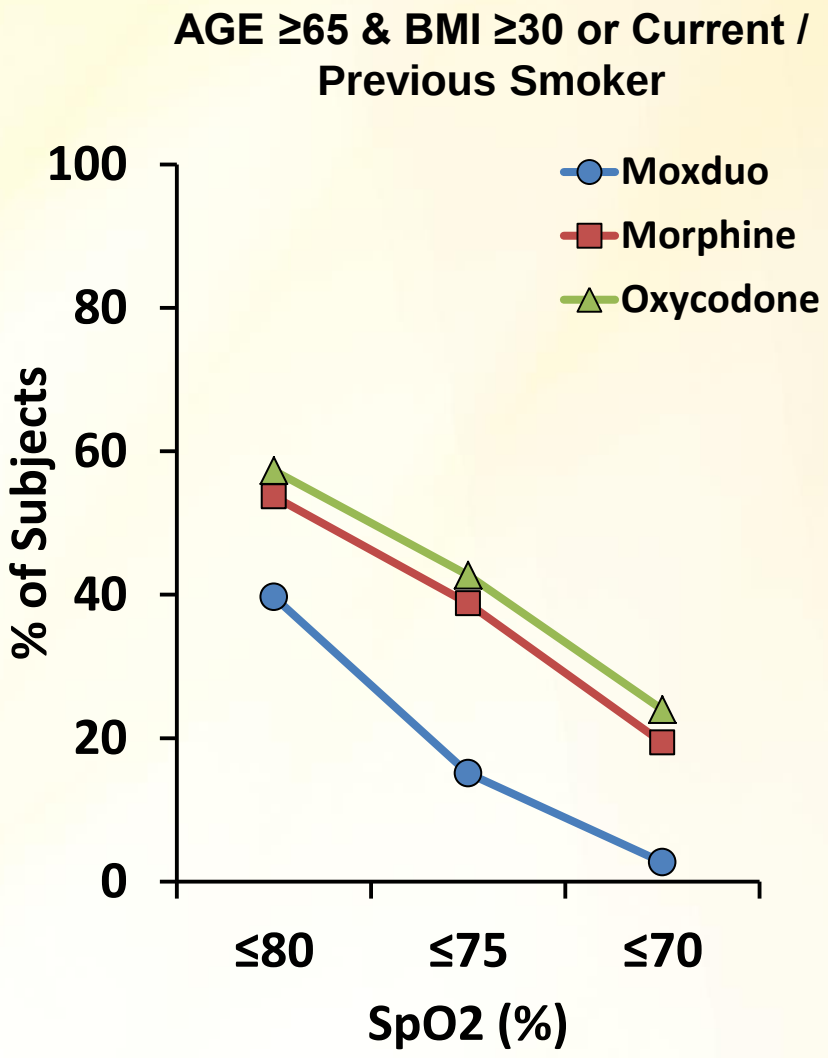
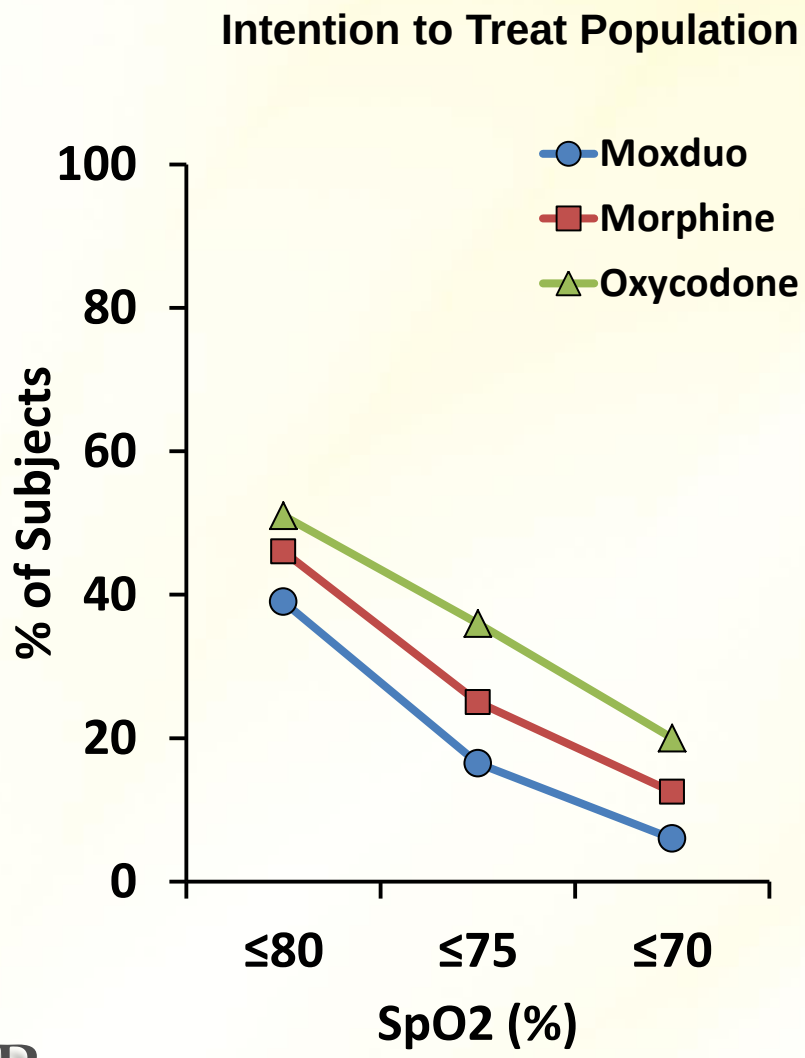
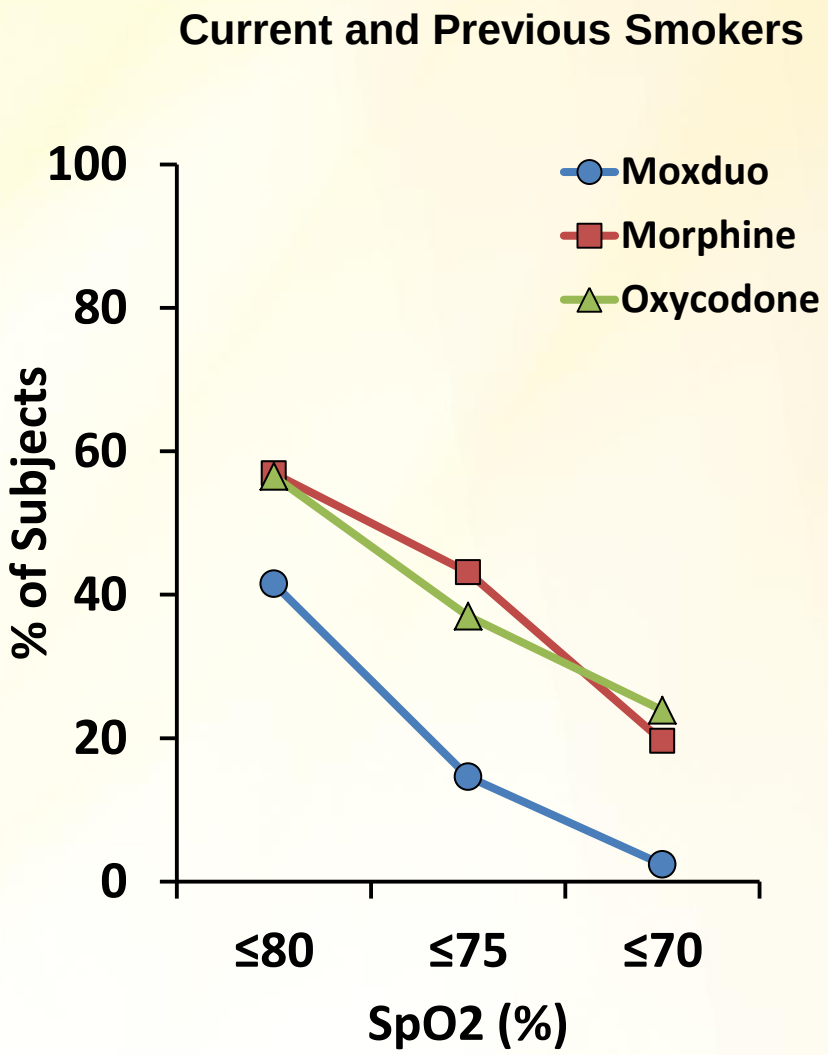




Current and Previous Smokers





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