**Appendix Table E4. Observational Studies of Long-Term Opioid Use and Cardivascular Outcomes**

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| **Author, Year** | **KQ** | **Type of Study, Setting** | **Eligibility Criteria** | **Comparison Groups** | **Population Characteristics** |
| Carman, 2011 | KQ2a, b | Retrospective cohortUnited States | Claim submitted for dispensing of opioids or COX-2 inhibitors for >180 days from July 2002 to December 2005, patients aged >18 years; controls from general populations matched on age, sex, and cohort entry dateExclude: History of MI or revascularization, cancer | 1. Opioids (n=148,657)
2. Rofecoxib (n=44,236)
3. Celecoxib (n=64,072)
4. Valdecoxib (n=20,502)
5. General population not using opioids or COX-2 inhibitors (n=148,657)
	1. 0 to <1350 mg MED per 90 days

2. 1350 to <2700 mg MED per 90 days3. 2700 to <8100 mg MED per 90 days4. 8100 to <18,000 mg MED per90 days5. ≥18,000 mg MED per 90 days | **A vs. B vs. C vs. D vs. E**Age 18-29 years: 4.7% vs. 1.2% vs. 0.8% vs.1.2% vs. 4.7%Age 30-39 years: 16.3% vs. 5.4% vs. 4.1% vs.5.3% vs. 16.3%Age 40-49 years: 33.9% vs. 20.7% vs. 17.6%vs. 20.1% vs. 33.9%Age 50-64 years: 36.7% vs. 56.0% vs. 56.3%vs. 56.5% vs. 36.7%Age >65 years: 8.4% vs. 16.6% vs. 21.2% vs.16.9% vs. 8.4%Female sex: 40.3% vs. 39.5% vs. 39.6% vs.34.9% vs. 40.3%Diabetics: 11.7% vs. 10.2% vs. 12.4% vs.11.1% vs. 4.1%Pain condition: NR Duration of pain: NR severity of pain: NR Opioids prescribed: NR |

**Appendix Table E4. Observational Studies of Long-Term Opioid Use and Cardivascular Outcomes**

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| **Author, Year** | **Method For Assessing Outcomes and Confounders** | **Screened Eligible Enrolled Analyzed****Loss to Followup** | **Adjusted Variables for Statistical Analysis** | **Main Results** | **Funding Source** | **Quality** |
| Carman, 2011 | All relevant claims in database during study period | Screened: NR Eligible, enrolled, analyzed: 426,124 | Incidence rates adjusted for age and sex; incidence rate ratio adjusted for age sex, CV and other other comorbidities, and use of concomitant medications | Adjusted incidence rate of MI, incidence rate ratioA: 5.93 (95% CI 5.58 to 6.30); IRR 2.66 (95% CI 2.30 to3.08)B: 3.54 (95% CI 3.11 to 4.01); IRR 1.94 (95% CI 1.65 to2.29)C: 3.53 (95% CI 3.15 to 3.94); IRR 1.79 (95% CI 1.53 to2.10)D: 3.40 (95% CI 2.76 to 4.14); IRR 1.74 (95% CI 1.41 to2.16)E: 1.58 (95% CI 1.40 to 1.78); IRR 1 (reference)Adjusted incidence rates of MI or revascularization, incidence rate ratioA. 11.91 (95% CI 11.40 to 12.43); IRR 2.38 (95% CI2.15 to 2.63)B. 7.98 (95% CI 7.33 to 8.67); IRR 1.93 (95% CI 1.72 to2.15)C. 7.94 (95% CI 7.36 to 8.54); IRR 1.81 (95% CI 1.62 to2.01)D. 7.53 (95% CI 6.56 to 8.60); IRR 1.75 (95% CI 1.50 to2.01)E. 3.38 (95% CI 3.12 to 3.67); IRR 1 (reference)DosingCompared to a cumulative dose of 0 to 1350 mg MED over 90 days, the IRR for 1350 to <2700 was 1.21 (95%CI 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95%CI 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95%CI 1.54 to 2.33), and for >18,000 mg was 1.73 (95% CI1.32 to 2.26) | GlaxoSmithKline | Fair |

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| **Author, Year** | **KQ** | **Type of Study, Setting** | **Eligibility Criteria** | **Comparison Groups** | **Population Characteristics** |
| Li, 2013 | KQ2a | Case-Control UK General Practice Research Database United Kingdom | Cases (n=11,693): Age 18-80 years, 2 years of medical history data before index (onset of MI symptoms)Controls: (n=44,897): Up to 4 controls matched on age, gender, index date, and practice site using risk-set sampling Excluded: History of cancer, ischemic heart disease, heart failure, stroke, congenital heart disorders, heart transplat, arrhythmias, treated hypertension, diabetes, ETOH/Drug abuse, hepatic or renal disease before index, cardiac surgery in the 90 days prior to index. | 1. Non-use
2. Current (0-30 days from index)
3. Recent (31-365 days out)
4. Past Use (366-730 days out)

Cumulative use (number of prescriptions):1. 1-22. 3-103. 11-504. >50 | Mean age (years): 61.8 vs. 61.6Female sex: : 31.1% vs. 31.3%Current smoker: 38.6% vs. 23.3%Low BMI (<18.5): 1.2% vs. 1.2%Normal BMI: 25.8% vs. 28.9%Overweight: 31.7% vs. 30.2%Obese: 13.8% vs. 11.3%Arthritis: 25% vs. 24.2%Rheumatoid arthritis: 3.2% vs. 1.8%Fibromyalgia: 1.1%Duration or severity of pain: NR Codeine: 16% vs. 15%Dihydrocodeine: 9.6% vs. 8.1%Propoxyphene: 13% vs. 11% |
| Note: The references are located in Appendix C.BMI=body mass index; CI=confidence interval; CV= cardiovascular; IRR=incidence rate ratio; KQ=key question; MI=myocardial infarction; NR=not relevant |

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| **Author, Year** | **Method For Assessing Outcomes and Confounders** | **Screened Eligible Enrolled Analyzed****Loss to Followup** | **Adjusted Variables for Statistical Analysis** | **Main Results** | **Funding Source** | **Quality** |
| Li, 2013 | Used General Practice Research Database, which has been validated on drug exposure and diagnoses (including MI) | Screened: 1,700,000Eligible: Not reported Enrolled: 11,693cases and 44,897 controls Analyzed: 11,693cases and 44,897 controls | Age, gender, smoking, body mass index, number of general practice visits, years of medical history, opioid new versus prevalent use, co- morbidities, concomitant medications, abdominal and pelvic pain and other pain | Risk of MI (adjusted OR)A. 1 (reference)B. 1.28 (95% CI 1.19–1.37)C. 1.17 (95% CI 1.10–1.24)D. 1.06 (95% CI 0.98–1.14)1. 1.10 (95% CI 1.03–1.18)2. 1.09 (95% CI 1.02–1.17)3. 1.38 (95% CI 1.28–1.49)4. 1.25 (95% CI 1.11–1.40) | None disclosed | Good |