The Association between the Risk of Cardiovascular Disease and Androgen Deprivation Therapy in Patients with Prostate Cancer. A Meta-Analysis and systematic review.

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Abstract

Background : Androgen deprivation therapy (ADT) is widely being applied in men who suffered from prostate cancer, our aim is to evaluate whether ADT is associated with an excess risk of cardiovascular disease (CVD). Method : Literature search in electronic databases was conducted until July 2019 for observational studies and randomized controlled trials (RCT) to select eligible studies. The relationship was evaluated through estimating relative risk ratio (RR) and 95% confidence intervals (CI). Result : A statistically significant association was detected for acute myocardial infarction (AMI) with RR = 1.22; 95% confidence interval CI, 1.05–1.43; P< 0.05 including a total of 142,012 cases and 174,099 controls. Significant relationship between coronary heart disease (CHD) and ADT was also observed, with summary RR=1.19; 95%CI, 1.03-1.38, from 157,165 ADT users and 375,754 non-ADT users. Conclusions : From this study, ADT is associated with increased risk of AMI, CHD, and heart failure (HF); in contrast, this association is not detected in sudden cardiac death (SCD); various modalities of ADT could significantly increase the risk of CHD, AMI, except for oral anti-androgen (AA). Our meta-analysis also suggests that the long-term application of ADT in prostate cancer patients would not result in a significant increase in AMI incidence compared with short-term. Moreover, the combined application of AA and GnRH agonists would lead to a similar risk of AMI compared with orchiectomy or GnRH agonists monotherapy whereas higher risk of CHD was detected when compared GnRH agonists plus AA with orchiectomy.

Background

Prostate cancer (PCa) has become the most common cancer in male and its growing trend in morbidity and mortality has been reported not only in western countries, but also in Asian countries, particularly in the northeast regions [1-3]. Since testosterone has been proved could accelerate the progression of prostate cancer, androgen deprivation therapy (ADT) is regarded as the basic treatment for PCa patients [4, 5]. Unfortunately, its adverse impact on cardiovascular system is still controversial. In a recent study, Mottillo et al. [6] indicated that men with prostate cancer treated by ADT had a 21% higher risk of cardiovascular disease (CVD) than the same-age men. However, when focusing on different ADT modalities, results from former studies demonstrated high heterogeneity in the risk of cardiac disorders.

Recently, Zhao et al. [7] carried out a meta-analysis of prospective studies evaluating the connection between ADT and CVD risk. However, the investigators did not make a direct comparison among each ADT method; in addition, acute myocardial infarction (AMI), heart failure (HF) were not separated from CVD as individual endpoints. Therefore, the present study performed a systematic review by referring to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [8] to address the relationship between ADT for AMI, coronary heart disease (CHD), HF and sudden cardiac death (SCD) respectively.

Methods

Databases including the PUBMED, EMBASE, Web of Science were searched to identify studies published up to April 1, 2018 by two independent investigators (ZL and RH). Disagreements were resolved by discussion with a third author (XL). The search was conducted in English language with the terms: prostate cancer or prostate tumor or prostate carcinoma, androgen and deprivation or androgen suppression or endocrine treatment; and cardiovascular or myocardial infarction or coronary heart disease or congestive heart failure or cardiac death or heart disease. The abstracts of these articles identified by keyword searching were then screened, and went through full texts examination if they fit our criteria (as detailed below). Searches of the included study reference lists were also performed manually to retrieve all relevant data.

2.1 Study selection

Studies were regarded eligible if they (1) designed as observation study or randomized controlled trial (RCT) study; (2) the research object is cardiovascular disease with AMI, CHD, HF or SCD as endpoint; (3) with sufficient data for analysis; (4) ADT type was prespecified and ADT duration was more than 6 months; (5) patients with baseline cardiac comorbidities were separated.

2.2 Quality Assessment and Data extraction

All included observational studies were evaluated for risk of bias by two reviewers (ZL and RH) through Newcastle Ottawa Scale (NOS) [9] with≥7 score representing high-quality while the assessment for RCT studies was based on Cochrane Collaboration's tool for risk of bias [10]. RCTs were evaluated in terms of : Random sequence generation, Allocation concealment (Selection bias); Blinding of participants and personnel (Performance bias); Blinding of outcome assessment (Detection bias); Incomplete outcome data (Attrition bias); Selective reporting (Reporting bias) ; Anything else, ideally prespecified (Other bias). There are three levels: low, unclear, or high risk for the quality of RCT evidence. The quality evaluation was carried out by two independent reviewers (ZL and SS), and a third reviewer was consulted to adjudicate any disagreements (YY). Data were extracted by two researchers (ZL and NA) independently to minimize the bias. The following data were extracted:

1. Basic information about study (total number of participants, number of ADT users, number of control group, follow-up duration, treatment method, definition of CVD)
2. Study elements (first author, median age, country/region, year, design).
3. experimental results (outcomes measure and quantity of AMI, CHD, HF and SCD)

2.3 Statistical Analysis and Subgroups Analyses

The heterogeneity of included studies was evaluated using the Cochrane I^2 statistics and Q test. P < 0.05 was defined as invalid assumption of homogeneity. A frequentist meta-analysis according to random effects model was performed for all outcomes to assess relative risk (RR) and their 95% confidence interval (95%CI). The outcomes were then presented as forest plots. The data analysis was accomplished through STATA version 14.0 and Review Manager (version5.2; the Cochrane Collaboration, Oxford, United Kingdom). Subgroup analyses were carried out based on the various types of ADT (e.g. GnRH agonists, AA, GnRH agonists +AA and Orchiectomy) vs non-ADT and the ADT duration (≤5 year or >5 year)

Results

3.1 Literature Search and Characteristics

Figure 1 represents a flowchart demonstrated the selection process that met our criteria aforementioned, a total of 1541 potential records were initially identified from databases through the search terms listed above. 531 duplicate studies were excluded. 50 were considered closely correlated to the concept of this study and underwent full text review. 14 studies were removed because they did not mention AMI, CHD, HF or SCD separately as outcomes. 2 were excluded due to insufficient data, 7 studies were excluded because ADT duration was shorter than 6 months, 6 did not specifically report the type of ADT. Additionally, we remove 9 retrospective researches from our study, 2 were excluded for using the same databases as studies that were already included. In the end, 8 studies [11-18] consisted of 316,111 patients were included in our meta-analysis of AMI, 7 studies [12-15, 18-20] involving 532,919 patients were identified in the CHD analysis, data from 6 studies [11, 12, 14-16, 19] with 334,093 patients were available in the HF analysis, 5 studies [11, 13, 21-23] containing 182,403 patients were included in the SCD analysis. No additional articles were eligible for meta-analysis through reference searching.

The basic characteristics of included studies are provided in table 1. All studies were published from 2011 to 2017. Quality evaluation for observational studies indicated no studies being of low quality in all domains of the Newcastle-Ottawa score. The methodological quality of all RCT studies was shown in Figure 2 and no research was excluded due to low quality.

3.2 Association between ADT and AMI

8 studies included were regarding the relationship between ADT and AMI.

Data from 4 studies with 142,012 ADT users and 174,099 non-ADT users were suitable for AA [12, 15, 16, 18] subgroup-analysis; 3 [12, 15, 18] for GnRH agonists plus AA, 4 [12, 13, 15, 18] for GnRH agonists and 5 [12, 13, 15, 17, 18] for orchiectomy. According to our results illustrated in Figure 3, AMI was statistically significant to ADT application (RR = 1.22; 95% CI, 1.05–1.43; P< 0.05) with AA (RR = 1.34; 95% CI, 1.07–1.69; P< 0.05); orchiectomy (RR = 1.71; 95% CI, 1.03–2.83; P<0.05); GnRH agonists (RR = 1.66; 95% CI, 1.01–2.72; P< 0.05); GnRH agonists plus AA (RR = 2.74; 95% CI, 1.67–4.48; P<0.05); respectively. (Figure 4) It is apparent that no statistically significant difference was detected between GnRH agonists plus AA and other ADT method in causing AMI, except for AA (AA: P<0.05; orchiectomy: P=0.19; GnRH agonists: P=0.16). (Figure 5)

3.3 Association between ADT and CHD

There were a total of 532,919 participants from all the 7 included studies investigating the relationship between ADT and CHD of which 157,165 received ADT and 375,754 were control groups. A significantly increased CHD risk was found in the prostate cancer patients treated with ADT. (RR=1.19; 95%CI: 1.03-1.38); (Figure 6). Subgroup analyses by ADT type showed that each type of ADT correlated to CHD, with orchiectomy (RR = 1.13; 95% CI, 1.08–1.18; P< 0.05); GnRH agonists (RR = 1.98; 95% CI, 1.01–3.92; P< 0.05) GnRH agonists plus AA (RR = 2.77; 95% CI 1.65–4.66; P< 0.05); respectively, except for AA (RR = 1.34; 95% CI, 0.59–3.05; P< 0.05); (Figure 7) Compared with orchiectomy, GnRH agonists plus AA could significantly increase the risk of CHD (P<0.05), while similar risk of CHD was seen when compared GnRH agonists monotherapy with GnRH agonists alone with P value=0.45. (Figure 8)

3.4 Association between ADT and SCD HF

Subgroup analyses of the relationship between ADT and SCD were also investigated with total of 182,403 identified events from 5 studies, among them 79,881 were ADT users and 102,522 were from control groups. We identified that SCD was not significantly associated with ADT usage. Subgroup analysis for different types of ADT was not performed as there was only one study [13] reported exact ADT method. (RR=1.13; 95% CI 0.89–1.45; P< 0.05) . (Figure 9) Figure 10 showed the forest plot of HF for patients with or without ADT treatment. Pooled data for HF were available from 6 studies with a total of 334,093 patients (97,925 with ADT exposure and 236,168 without ADT exposure). Based on our results, ADT was associated with a higher incidence of HF compared to control group. (RR=1.15; 95% CI 1.01–1.33; P< 0.05). Subgroup analysis was also not performed for ADT type because of the small number of trials that reported such outcomes.

3.5 Subgroup by duration of ADT

In order to reduce the impact of inconsistent endpoints on our conclusion, whether the duration of ADT application was associated with a significant effect on the risk of AMI events was also explored in our study. The included studies were separated into different groups based on the duration of ADT application, and we defined 5 year as the cut-off value. 3 studies [11, 13, 16] with 53,115 cases and 53,124 controls were in subgroup with ADT application more than 5 years, and others were in subgroup with ADT application less than 5 years. Pool results of our subgroup meta-analysis revealed patients from >5 group have similar risk of AMI compared with≤5. (RR = 1.35, 95%CI, 1.00–1.82, P=0.05, for≤5 year group) (RR = 1.31, 95%CI: 0.66–2.63,

P=0.44 for>5 year group). (Figure 11) As for the CHD, HF and SCD group, the sum of included studies for each subgroup is quite limited thus the analysis was not conducted.

Discussion

The correlation between ADT and cardiovascular toxicity is a debatable topic in PCa treatment. Multiple researches explored this relationship with different outcomes.

Our results indicated that ADT was associated with a significant increase in risk of AMI, CHD, and HF, but not found to be associated with SCD; the individual administration of each type of ADT was associated with AMI and CHD, except for AA; AA alone was only significantly associated with the increased risk of AMI, but not CHD. In addition, using ADT more than 5 years would not lead to an increased risk of AMI compared with less than 5 years. Three previous researches are diverged with our results due to their small number of endpoints. Furthermore, multiple former studies illustrated that orchiectomy was not associated with CHD events [24, 25]. This may attribute to their enrollment setting, men chose orchiectomy were older, suffered from more advanced stage of PCa and accompanied by more comorbidities, which in turn may affect the risk of CVD endpoints [26]. The distinction in inclusion criteria and duration of ADT may also lead to variation. Furthermore, three studies [5, 27, 28] failed to detect a significant association between ADT and cardiovascular related death, due to the fact that the previous or later ADT users were not ruled out in control group.

ADT is the primary systemic therapy for prostate cancer and nearly half of patients received ADT during their disease course [29]. However, patients initiating ADT suffered from adverse effects including weight gain, insulin resistance, decreased libido, obesity, sarcopenia; as well as cerebrovascular events and metabolic syndrome (MetS) all of which could possibly be induced by deficiency of testosterone [30, 31]. MetS is a major public health challenge due to its effect on the progression of CVD, cardiac mortality and its high prevalence in general population [32]. Clinical features of MetS caused by ADT are different from classically-defined MetS in terms of high-density lipoprotein-C (HDL-C) response and fat accumulation, all of which could elevate triglycerides, blood pressure and glucose levels [33-35]. Such components would also accelerate atherosclerosis [36].

It has been suggested that maximal androgen blockade (MAB), in which surgical (orchiectomy) or medical castration (GnRH agonists) is combined with AA therapy, could improve clinical efficacy [37]. Based on our study, we found although the combined utilization of GnRH agonists and AA could increase the risk of cardiac adverse effects significantly, no significant difference was detected when compared GnRH agonists plus AA with the individual GnRH agonists in the risk of AMI and CHD, but GnRH agonists plus AA was more likely to increase the risk of CHD compared with surgical castration or AA. Therefore, we could draw a conclusion that GnRH agonists, rather than AA, may play a role in increasing risk of cardiac events in MAB therapy. A number of analyses have suggested that CVD was associated with GnRH agonists though its potential mechanism remained unclear. Several risk factors may contribute to the greater risk of CVD during GnRH agonists therapy such as hyperglycemia, dyslipidemia and obesity [38]. Furthermore, it has been proved that human heart tissue expresses the GnRH agonists receptor, and a basic study on rat heart tissue demonstrated that stimulating these receptors with GnRH agonists could cause progression in the contractility of the cardiomyocyte [39]. The promoting effect of GnRH agonists on atherosclerotic through boosting the development of metabolic complications seems to offer another plausible mechanism that could distinguish different forms of ADT in terms of associated CVD risk and hence is worthy of further exploration [29]. Our results revealed the combined application of AA and GnRH agonists had a similar risk of AMI and CHD compared with monotherapy ADT method, therefore, the combined application of AA and GnRH agonists is in prior position in terms of overall survival as the current EAU-ESTRO-SIOG guidelines [40, 41] recommended based on a large Cochrane review which compared different types of ADT and different dosages in subgroup analysis [42],

Multiple earlier studies have proved that GnRH agonists were associated with a higher risk of CVD compared with orchiectomy [43], whereas our study indicated orchiectomy monotherapy could also lead to cardiac events. Orchiectomy can lead to a low level of testosterone though it remains unclear how low testosterone levels causes major cardiovascular events. Callou de Sá et al. [43] indicated that men with CHD had higher oestradiol and free oestrogen index (FEI) levels. As a matter of fact, high level estrogen can increase heart attack risk by accelerating coagulation and platelet aggregation in coronary arteries[44]. A nationwide, population-based study, provided exclusive evidence to show that closed risk of fatal CVD was observed for men treated by GnRH agonists compared with orchiectomy[24]. Further, larger population-based trial is needed to determine whether interventions like orchiectomy that raise estrogen levels might promote the progression of CHD, so that clinical doctors could be conscious of the serious potential risks of orchiectomy and ensure medical safety when deciding the type of ADT for patients.

Our subgroup analysis for the duration of ADT indicated that long-term ADT was not associated with an excess risk of AMI when regarding 5 year as threshold. In an observational study, Efstathiou et al. [22] indicated that long-term ADT administration could not increase the risk of cardiovascular mortality compared with short-term in men with locally advanced PCa. In another study, patients from control group received short-term androgen suppression while patients who received 2-5 years of further treatment were recruited as experiment group, the result demonstrated that no significant difference was observed in overall mortality between short-term group and long-term group [21]. On the other hand, evidence from another more resent study suggested the cardiovascular risk factors such as hyperglycemia, frank diabetes, and MetS are more likely to occur in patients with long-term ADT over 12 months, while with short-term ADT, (3–6 months) users are only affected by temporary insulin resistance [30]. The optimum duration of ADT application should be adapted to comorbidities conditions and risk factors of individual patients.

Based on our results, the administration of ADT was not associated with SCD, but led to an increased risk of HF. Several former analyses have investigated this relationship between SCD and ADT, and came up with very different results. Several studies showed that ADT could significantly improve prostate cancer–specific survival and overall survival [5, 45, 46]. On the other hand, Gandaglia et al. [13] indicated the usage of GnRH agonists

was related to significantly increased risk of SCD in patients with non-metastatic PCa. This distinction could be accounted for the enrollment setting. Clinical trials usually enroll patients younger and healthier with lower risk level of cardiac morbidity and mortality. Further studies with more rational enrollment settings are needed to evaluate the benefits and risks of ADT. Although our results suggested that ADT was not related to an increased risk of cardiovascular mortality, many previous studies have suggested that patients treated by ADT have higher rates of non-cancer death compared with the general population because of diabetes or other adverse effects. Meng et al. [47] demonstrated in a recent meta-analysis that GnRH agonists alone, GnRH agonists plus AA and orchiectomy were significantly related to stroke in patients treated by ADT. This effect is noteworthy because it may reverse the survival benefit of ADT in men affected by PCa. The previous literature also showed conflicting evidence evaluating the link between ADT and HF. Multiple previous studies revealed men treated with ADT was associated with significantly increased of fatal and nonfatal HF in all patients especially for those with pre-existing CVD which met our results [31]; whereas only one propensity-score matching cohort study from Canada demonstrated that incidence of HF was not higher among ADT users with HR= 0.95; 95%CI, 0.90-1.00. Research which explored the impact of ADT on cardiomyocyte contractility at molecular level, and the results of testosterone therapy for HF at clinical level is needed to specify the possible relationship between HF and ADT

This study has limitations. First, although we have strictly followed the PRISMA guidance, tried our best to apply the most extensive keywords and conducted the selection as impartial as possible, we know that some potential studies may still be neglected in our search, which would compromise our results. Second, the quantity of studies included to be eligible was small which means publication bias could not be excluded through funnel plots, besides, they suffered from substantial heterogeneity related to methodological parameters and population characteristics. Third, our analysis pooled together both RCT and observational studies, and subgroup analyses based on study design were not performed in the AMI and CHD subgroup, because all the included studies are designed observationally for AMI and CHD subgroup. Fourth, some included studies do not provide direct data for analysis, so we have to calculate and extract the data we needed by ourselves, this may have an impact on the overall result to some extent.

Conclusions

Our analysis demonstrates an increased risk of CHD, AMI, HF for ADT application; ADT is not connected with SCD occurrence and it requires further exploration; various ADT modalities have different impact on CVD risk in different level, the combined application of AA and GnRH agonists would not significantly increase the risk of AMI compared with individual method; AA is less likely to trigger onset of CHD compared with other methods but would significantly lead to AMI. In addition, this study also reports that that short-term use and long-term use of ADT lead to similar risks of AMI. Therefore, ADT is connected with a significant negative impact on life quality. Cautions and periodic cardiovascular elevation are necessary for patients before the ADT starting. More experimental and epidemiological studies are needed to discriminate the SCD effects on different types of ADT.

Declarations

Ethics approval and consent to participate: Not applicable

Consent to publish: Not applicable

Availability of data: All data is included in the article and additional files.

Competing interests: The authors declare that there are no conflicts of interest.

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Authors' contributions

LZ and HR:Data analysis,project development,Manuscript writing

LX and RH:Data collection,project development,Manuscript editing

WZ and YL: Data analysis,Manuscript editing

YX and LC: Data collection,Project development

YS and YY: Data analysis

JZ and XD: Data collection of revised version

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Tables

Table 1. Characteristics of randomized included studies

First author	year	Types of ADT	Treatment in control group	Definition of CVD	No. of ADT	No. Of Control	Age y(median/average)	Follow up(y)	Study type	NOS
Alibhai	2009	ADT	non-ADT	CHD/SCD	19079	19079	75	6.47	observational	7
Bolla	2010	GnRH agonist	RP WW/AS	SCD	107	203	ADT:71 non-ADT:70	9.1	RCT	
Efstathiou	2009	GnRH agonist	RP WW/AS	SCD	477	468	70	8.1	RCT	
Farrel	2015	AA; GnRH agonist; Orchiectomy; AA GnRH + AA	non-ADT	CHD	41362	187785	ADT:73.7 non-ADT:75.3	4	observational	9
Gandaglia	2014	GnRH agonist; Orchiectomy	non-ADT	CHD/AMI/SCD	59994	82535	median: 73 average:73.6	6.28	observational	9
Haque	2017	ADT	non-ADT	CHD/AMI	2170	5457	NR	3.4	observational	9
Hemelrijck	2010	GnRH agonist; AA GnRH + AA; Orchiectomy	RP WW/AS	CHD/AMI	30642	45958	NR	4.1	observational	8
Iversen	2010	AA	non-ADT	AMI	4052	4061	64.5	9.7	RCT	
Jespersen	2013	GnRH/AA; Orchiectomy	non-ADT	AMI	11264	20307	71	3.3	observational	7
Keating	2009	GnRH agonist AA; GnRH + AA; Orchiectomy	WW/AS	CHD/AMI/SCD	14579	22846	66.9	2.6	observational	9
Merino	2011	GnRH agonist AA; GnRH + AA; Orchiectomy	WW/AS	CHD/AMI	406	594	51	NR	observational	9
Robinson	2010	GnRH agonist; AA; GnRH + AA	non-ADT	CHD	8168	30883	NR	1.9	observational	7
Roach	2008	GnRH agonist AA	RP WW/AS	SCD	224	232	70	13.2	RCT	

Figures

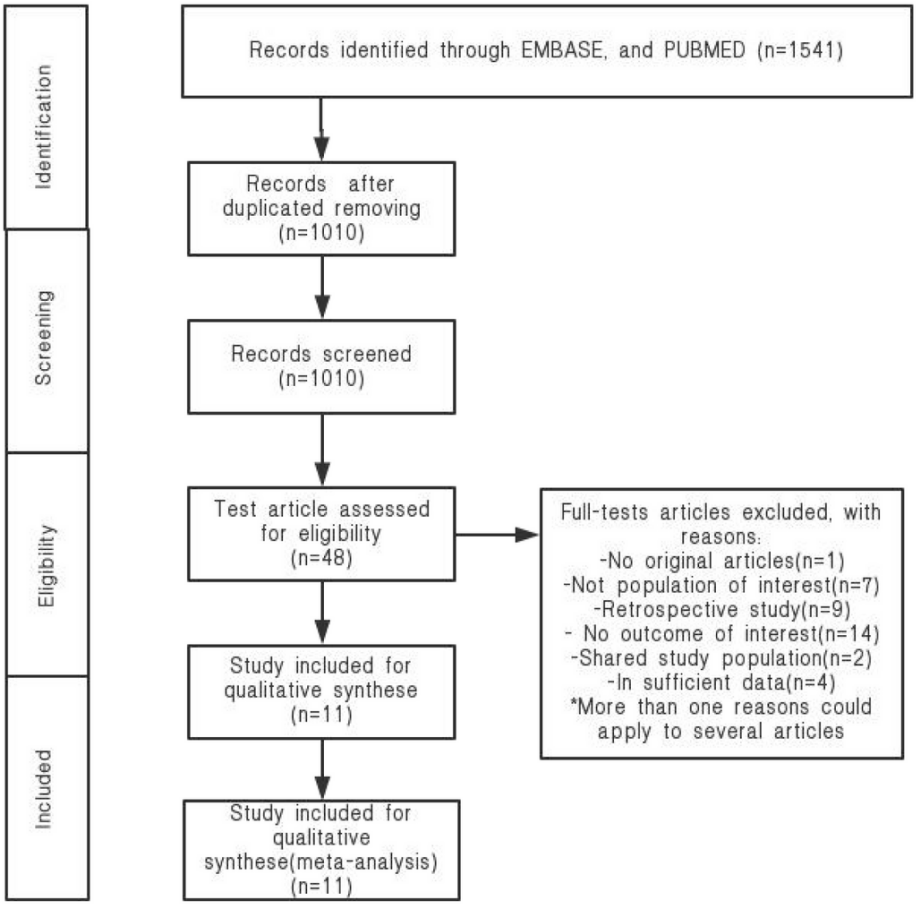

Figure 1

Article selection

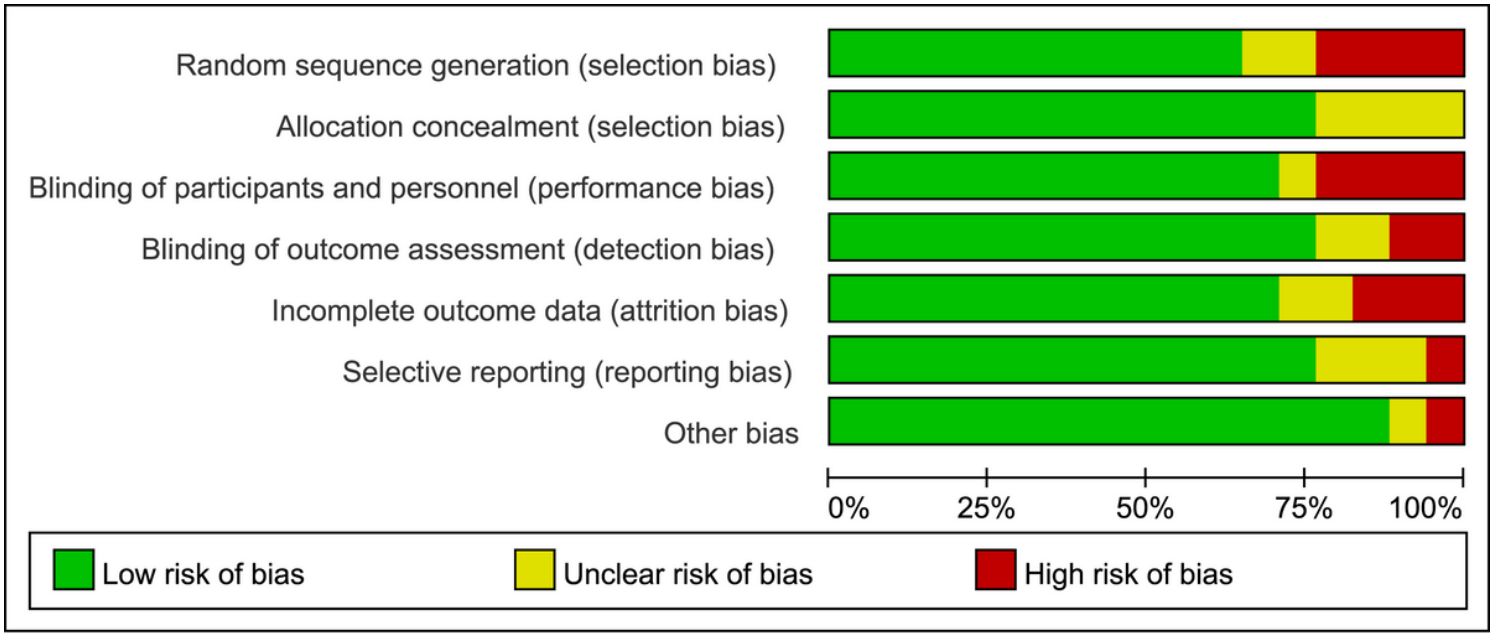

Figure 2

Figure 2

Risk of bias for the included RCT studies

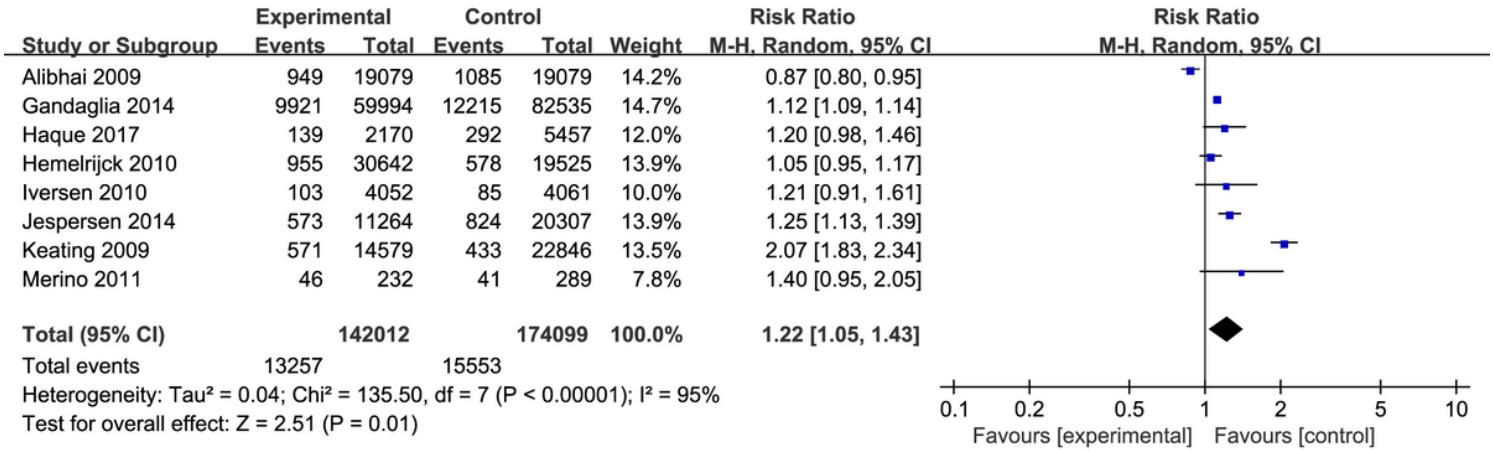

Figure 3

Figure 3

Acute myocardial infarction risk associated with ADT

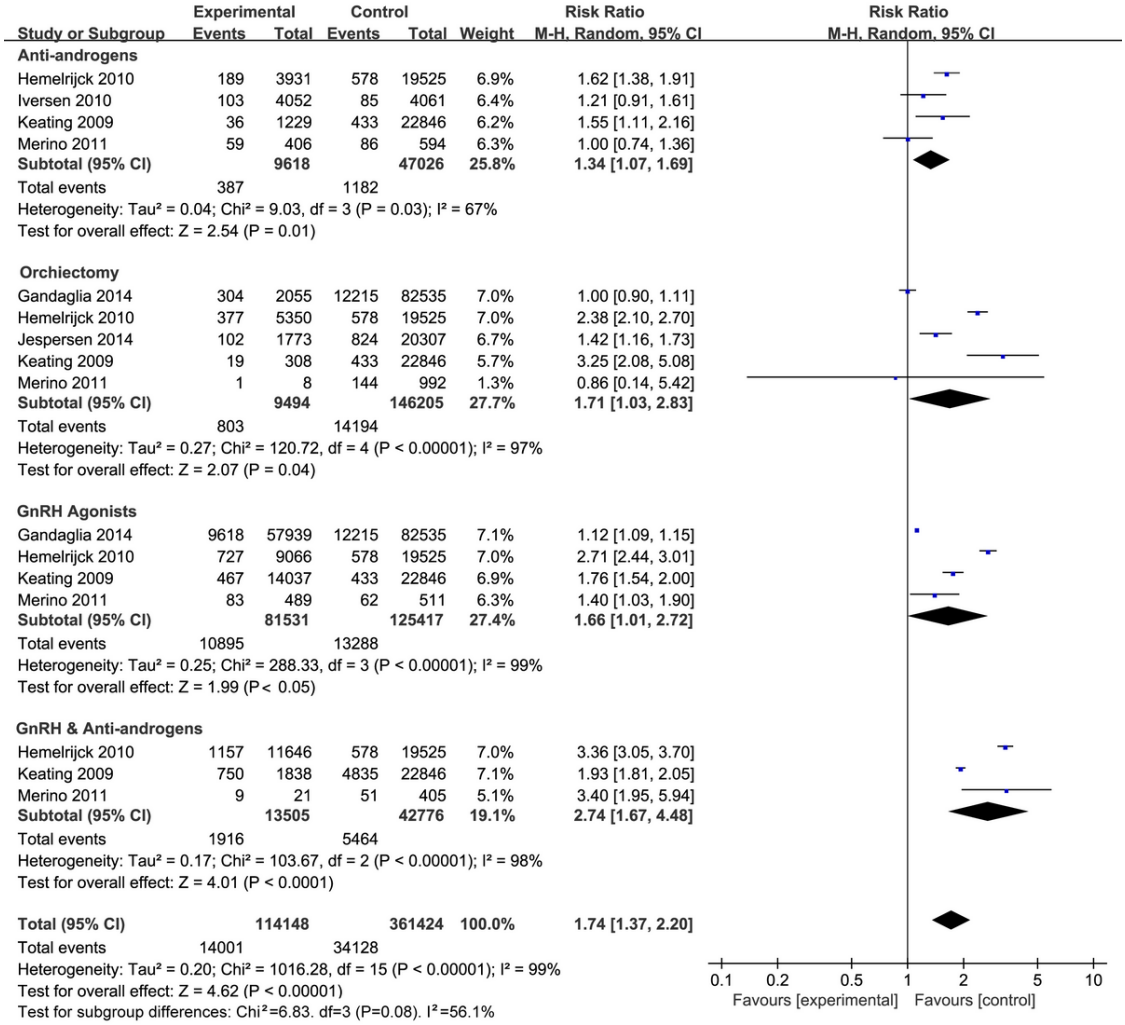

Figure 4

Figure 4

RRs of acute myocardial infarction related to different types of ADT.

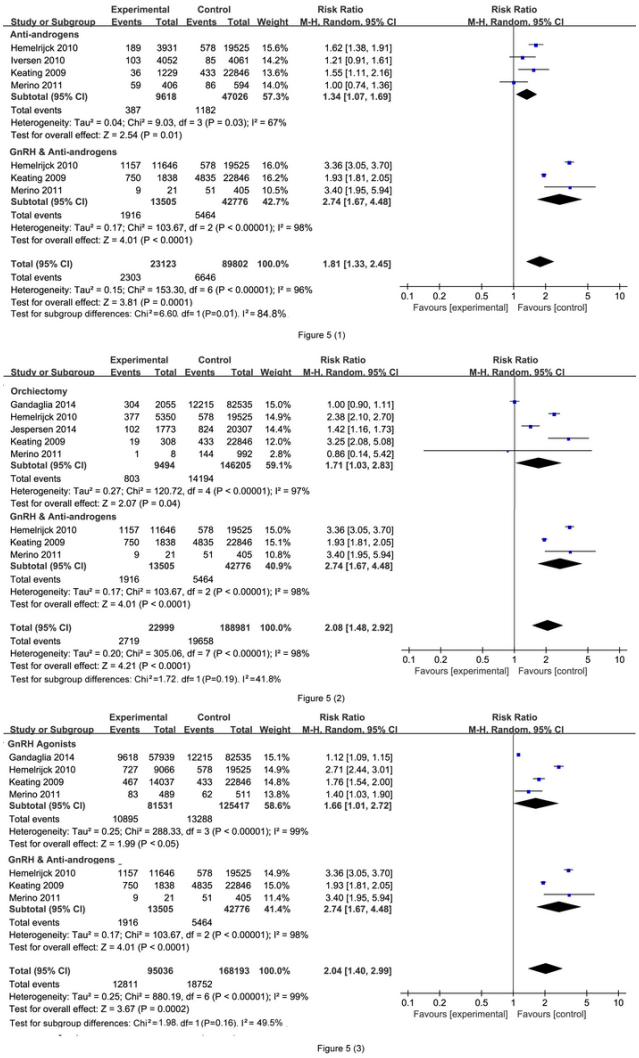

Figure 5 (1)

Figure 5 (2)

Figure 5 (3)

Figure 5

GnRH agonists plus AA compared with other method for acute myocardial infarction

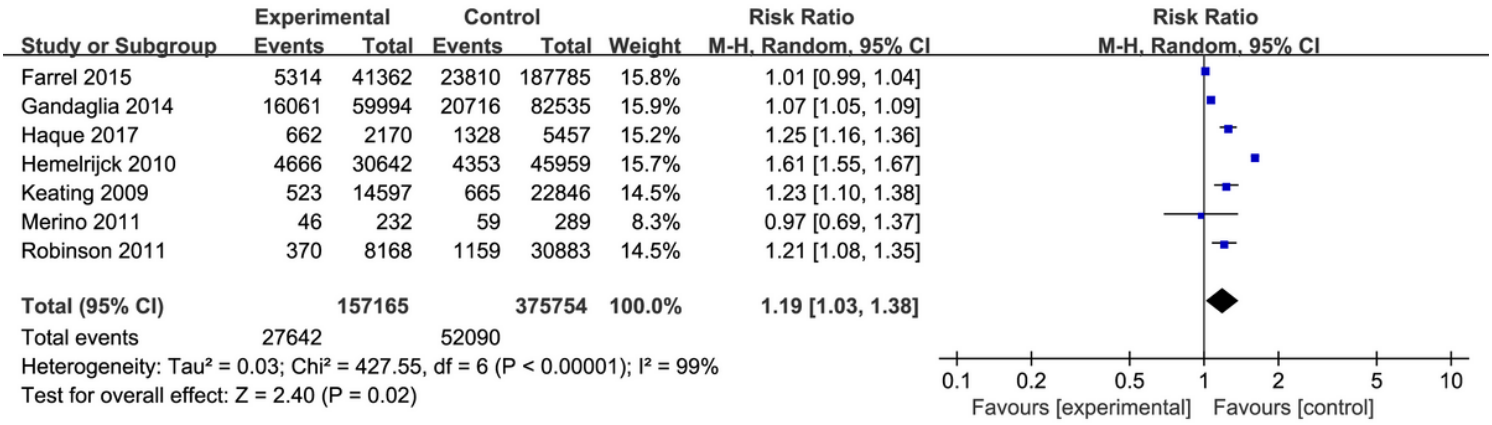

Figure 6

Figure 6

Coronary heart disease risk associated with ADT

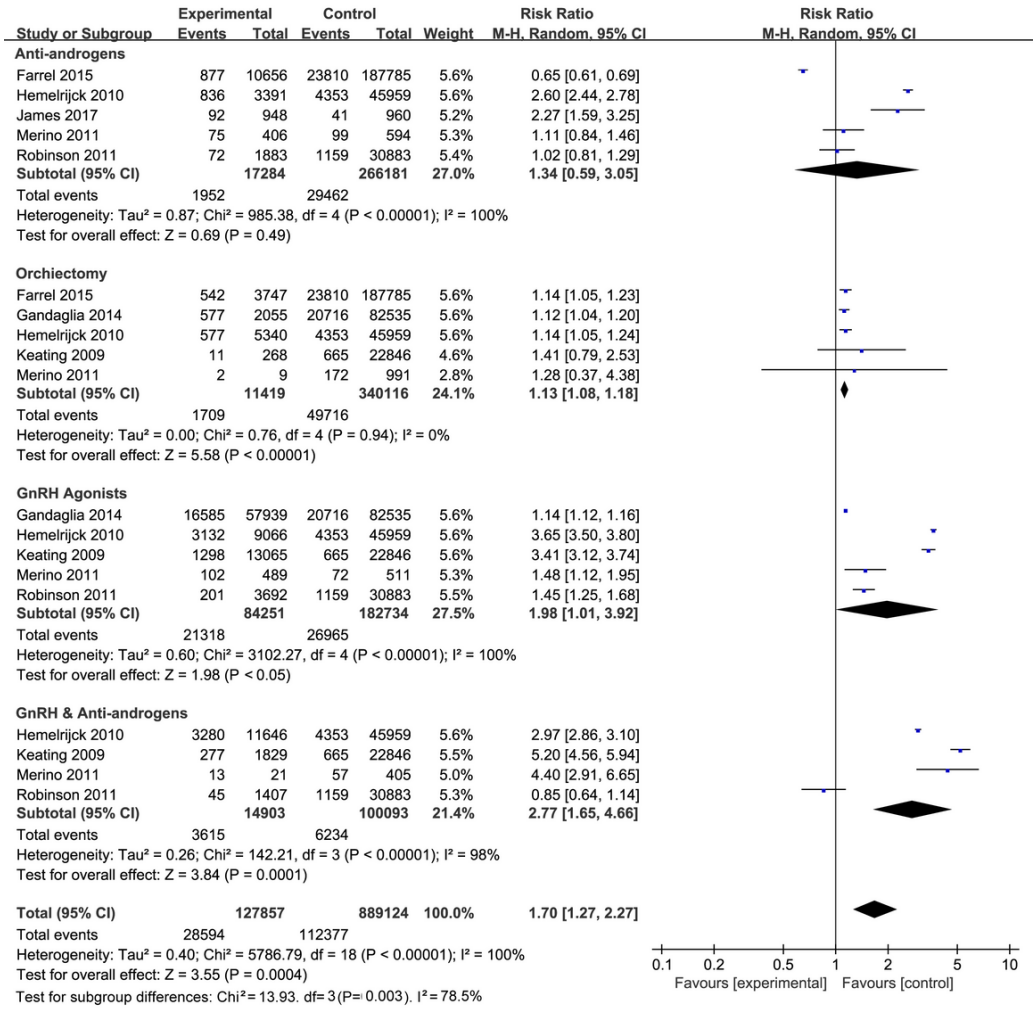

Figure 7

Figure 7

RRs of coronary heart disease related to different types of ADT.

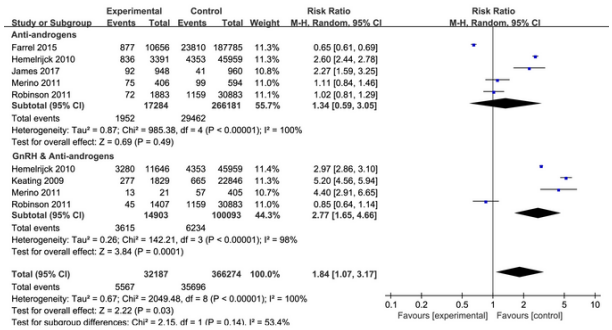

Figure 6 (1)

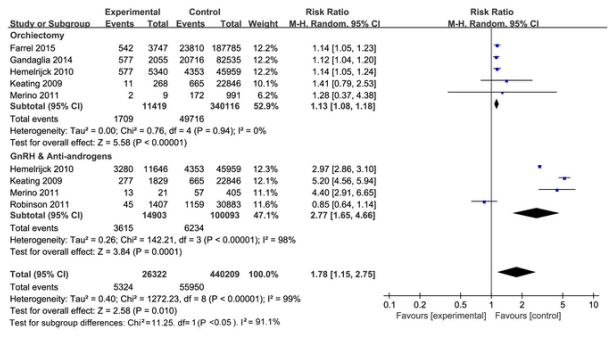

Figure 6 (2)

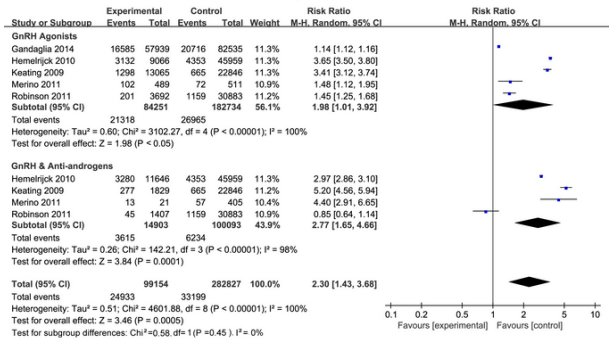

Figure 6 (3)

Figure 8

GnRH agonists plus AA compared with other method for coronary heart disease

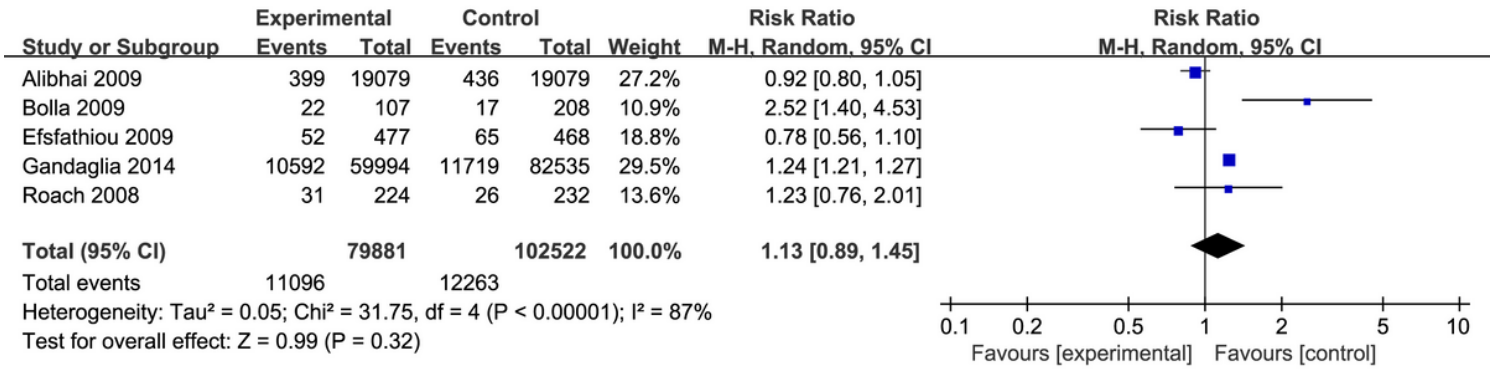

Figure 9

Figure 9

Sudden cardiac death risk associated with ADT

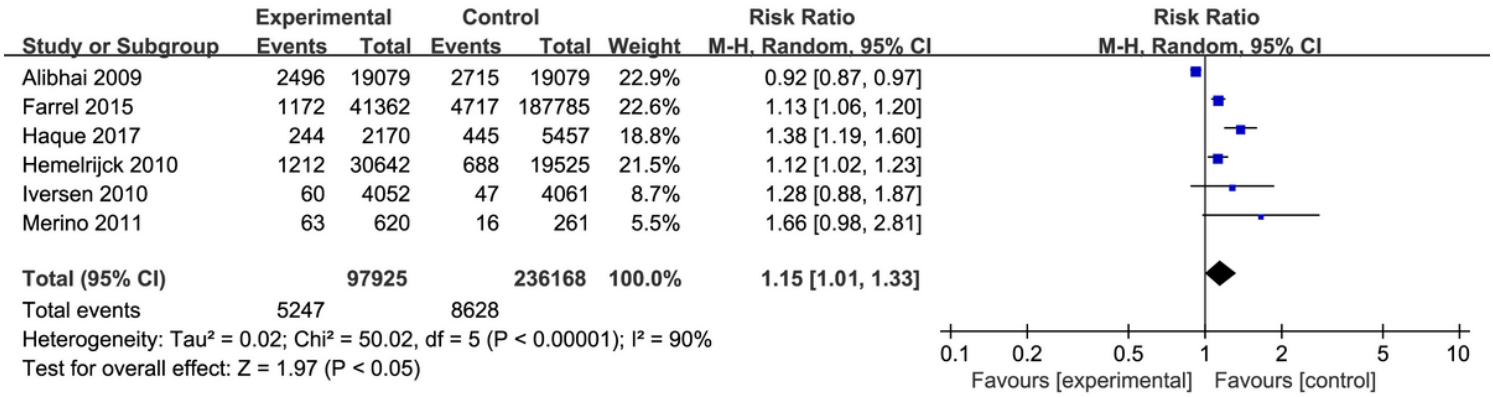

Figure 10

Figure 10

Heart failure risk associated with ADT

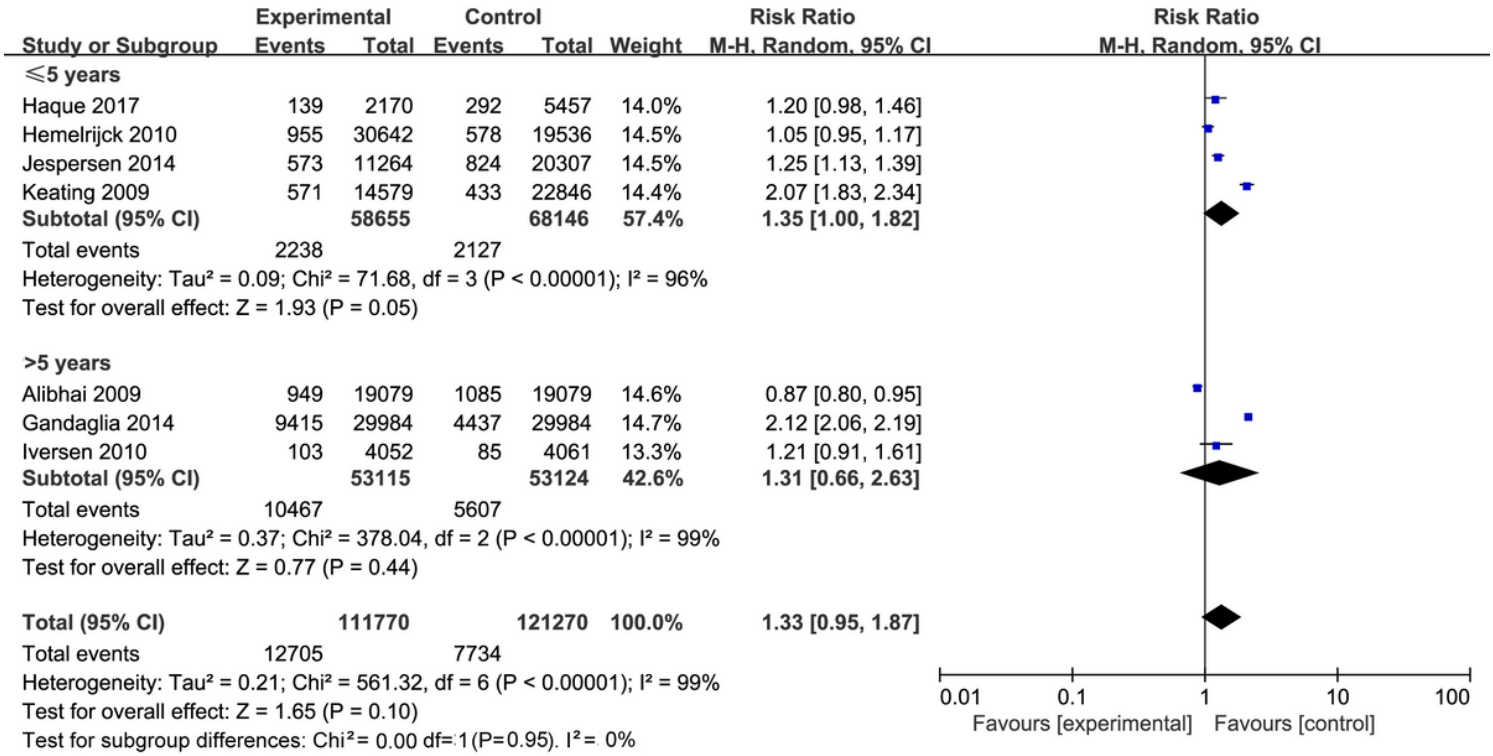

Figure 11

Figure 11

RRs of acute myocardial infarction related to different duration of ADT application.