SYSTEMATIC REVIEW PROTOCOL

TITLE OF THE REVIEW:

Testosterone Replacement Therapy and the Risk of Venous Thromboembolism: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

AUTHORS

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BRIEF BACKGROUND AND RATIONALE FOR THE REVIEW:

Testosterone replacement therapy (TRT) is prescribed for the management of low testosterone levels and can be administered orally, through injections, or with gels or patches on the skin when hypogonadism interferes with health and quality of life.[1] Guidelines of professional societies such as North America,[2] Europe,[3,4] and an International Society of Urology[5-8] recommend that patients with pathological hypogonadism,[9] defined as recognized pathological disorders of the male reproductive system and/or dysfunctional hypothalamo-pituitary axis, receive testosterone therapy. TRT is also used off-label for sexual dysfunction and/or decreased energy/vitality.[10,11] TRT has been shown to have favorable effects on cardiovascular risk factor levels, improving lipid profiles[12-17]and insulin resistance[12,13] and increasing the time to ST depression during stress testing[18,19]. Non-cardiovascular benefits include improved sexual function[16,17,20-25], and increased bone mineral density[22,24,26-29], free-fat mass,[22,26,30,31] strength,[32,33] and mobility.[34-36] The use of TRT has increased 10-fold in

US[37] over the last two decades. In a study evaluating 41 countries from 2000 to 2011, worldwide testosterone sales increased 12-fold from $150 million to $1.8 billion.[37] The countries mostly driving this growth were Canada, the United Kingdom (UK), and the United States (US).[37,38]

However, concerns have emerged regarding the cardiovascular safety of TRT.[39] Several systematic reviews and meta-analyses, however, reported conflicting results, with some finding an increased risk[40-44] and others no association[45-48] between TRT and risk of cardiovascular diseases. The US Food and Drug Administration[49] and Health Canada[50] now requiring a new general label warning in the product information of all approved TRT products about the risk of venous thromboembolism.[51,52]

While much attention has focused on TRT and the risk of arterial thrombosis, the effect of TRT on the risk of venous thromboembolism (VTE) remains poorly understood. TRT is hypothesized to interact with previously undiagnosed thrombophilia-hypofibrinolysis, leading to deep venous thrombosis (DVT) and pulmonary emboli (PE).[53] Several animal[54,55] and human[56,57] studies complement this hypothesis: the thrombogenetic potential of TRT.[58-69] The incidence of VTE with TRT has been reported as an adverse event in randomized controlled trials (RCT); however, these trials were individually underpowered to examine this safety endpoint, resulting in imprecise estimates. Consequently, the objective of this is to assess the effect of TRT on the risk of VTE via a systematic review and meta-analysis of RCTs.

REVIEW QUESTION (IN PICOT FORMAT):

Overall Objective: To determine if TRT is associated with an increased risk of VTE via a systematic review and meta-analysis of RCTs

Research question: What is the risk of VTE in adult men treated with TRT in comparison to placebo or an active comparator (growth hormones, gonadotropin-releasing hormone antagonist (blocker), or other therapeutics)?

P (Population): Men aged ≥ 18 years
I (Intervention/Exposure): TRT
C (Comparison): Placebo or active comparator
O (Outcome): VTE (including DVT and PE)

CRITERIA FOR CONSIDERING STUDIES FOR THE REVIEW:

Types of studies (designs):

RCTs that compare TRT to either placebo or active comparator that report the risk of VTE by study arm will be included into our study. We will exclude uncontrolled studies, observational studies, previous reviews and meta-analyses, case reports and case series, letters to the editor, editorials, and commentaries. We will also exclude conference abstracts as the results of such studies are often not final, and abstracts contain insufficient information for thorough quality assessment. Finally, we will exclude

trials published in a language other than English or French.

Types of participants:

We will include trials conducted in men aged 18 years or more. We will not further restrict the trials based on age or their participants' indication of use. However, we will stratify the trials based on participants' age and testosterone therapy indication with pathological hypogonadism. We will exclude trials in children (<18 years) because they have different hormone levels.

Types of interventions (or exposures):

RCTs of TRT of any commercially available formulation will be included. Since this study concerns the effects of regular rather than of acute testosterone use, the duration of the intervention shall at least be more than 12 weeks. A previous review of randomized controlled trials indicated that the cardiovascular risk might vary based on the doses and routes of testosterone administration.[41] Consequently, we will collect information on dose and route of administration and assess if the risk of VTE varies by dose and route of administration in the secondary analysis. Comparators can be any androgenic medications such as growth hormones, gonadotropin-releasing hormone antagonist (blocker), or other therapeutics. We will not exclude open-label or head-to-head trials with a testosterone treatment arm; rather, we will run a separate analysis.

Types of outcome measures (primary and secondary):

The primary outcome measure will be the cumulative incidence of VTE among participants randomized to TRT or placebo or active comparator. VTE-related events will be defined as anything reported as such by the authors, that is, events reported as hepatic vein thrombosis, portal thrombosis, splanchnic venous thrombosis, pulmonary embolism, or other venous thrombosis events. The secondary outcomes will be DVT and PE.

SEARCH METHODS

Databases and other sources, time periods, search terms, language restrictions, unpublished data, etc.

Database

The protocol for this systematic review and meta-analysis was written following the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) 2015 checklist.[70,71] (Appendix 1) The results of this study will be reported following the PRISMA guidelines. We will perform a systematic search of Medline, Excerpta Medica dataBASE (EMBASE), Cumulative Index of Nursing and Allied Health (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) with a search strategy tailored to each database. The search will include studies published between 1946 (inception of MEDLINE) up to June 2018. We will restrict our search to randomized controlled trials in Medline (OVID) using the 2005 version of the Centre for Reviews and Dissemination/Cochrane Highly Sensitive Search Strategy filter.[72] In addition, we will search www.clinicaltrials.gov for completed but still unpublished RCTs

of TRT. The search will also be supplemented by a search of the World Health Organization trial registry and by a manual search of bibliographies of identified studies. Moreover, we will use forward and backward citation searching with Scopus. We will also search the European Medical Agency (EMA) and FDA registry for unpublished (pivotal) trials on the safety of testosterone.[73] Finally, we will screen at least the first 10 pages of Google Scholar for additional studies.

Search Terms

We developed the search strategy in collaboration with a medical librarian. Our search strategy's concepts are driven by the two components of the PICO format: testosterone (intervention) and venous thromboembolism (outcome). Ho et.al suggested that the use of a search strategy based on 2 elements of the PICO question can identify a large number of relevant studies compared to a 4 elements search.[74] Since many trials focused their safety assessment on CVD rather than VTE, we will include search terms for CVD to identify any VTE outcome reported as a major adverse event. To restrict the inclusion of randomized controlled trials in humans, we will add a third concept using the MEDLINE Cochrane RCT filter to the search strategy.[72] We will exclude studies published in the languages other than English or French. (Appendix 2)

REVIEW METHODS

Study selection methods:

After running our electronic literature search and removing duplicates, two independent reviewers (HTA and VB) will first screen the titles and abstracts. Any publication deemed potentially relevant by either reviewer will be carried forward to the full-text review. Discrepancies during the full-text review will be resolved by consensus or, when necessary, by a third reviewer (KBF).

Data extraction methods (including methods for resolving disagreements):

Two independent reviewers (HTA and VB) will extract relevant information, and disagreements will be resolved by consensus or by a third reviewer (KBF) if needed. We will contact the authors by email to identify missing information or to clarify key concepts. At least two email attempts will be made for each corresponding author.

Data items that will be collected:

Once included studies have been identified, an electronic data extraction form will be used to collect data from the included studies. Data to be extracted will include: 1) study characteristics: authors' names, journal, year of publication, sample size (total and by groups), intervention definition, duration of follow-up, duration of TRT, route of TRT administration, losses to follow-up, and outcome definition; 2) baseline demographic and clinical characteristics: age, race, ethnicity, education, indication for TRT, dose of TRT, and pre-existing comorbidities; 3) Count data, effect estimates, and the corresponding 95% CI; and 4) study quality: assessed by the Cochrane risk of bias tool.[75,76]

Quality assessment methods [risk of bias in individual studies] and how quality data will be used:

The quality of RCTs will be evaluated using the Cochrane Risk of Bias assessment tool.[75,76] In addition, we will also use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rating the overall quality of evidence.[77,78] In addition to the use of these validated tools, we will assess funding source as a potential source of bias; a trial will be considered partially or completely supported by pharmaceutical companies when declared by the authors and/or when at least one author belongs to any industry company, as previously reported.[79]

Main summary measures (e.g., risk ratio, the difference in means):

The primary summary measure will be cumulative incidence ratio, which we will estimate using count data reported by the included studies. Secondary measures will include risk differences, which we will estimate at fixed follow-up times, and hazard ratios. Trials with zero events will be included using a 0.5 continuity correction; in sensitivity analyses, we will exclude zero-event trials to examine their impact on our results.

Data synthesis and meta-analysis methods (software, random vs. fixed effects, pooling method, etc):

We will conduct Dersimonian and Laird random-effects models to pool data across trials.[80,81] We have pre-specified the use of a random-effects approach because we anticipate some degree of statistical and/or clinical heterogeneity across trials. In sensitivity analyses, we will meta-analyze using a fixed-effects approach with inverse variance. Forest plots will be used to graphically display the results. R version 3.5.0 will be used for the data analysis.[82]

Heterogeneity assessment:

The between-study heterogeneity in testosterone effect will be assessed by the I squared (I^2) statistic and by the estimation of 95% prediction intervals (95% PIs). The I^2 statistic indicates the extent of variability, which describes the proportion of heterogeneity across studies that is not due to chance, thus describing the extent of true inconsistency in results across trials. The 95% PI provides a sense of the heterogeneity in expected benefits of testosterone in future studies since it indicates the true treatment effect of testosterone that can be expected when the intervention is replicated in the new clinical trials.[83]

Additional analyses (e.g., cumulative MA, sensitivity or subgroup analyses, meta-regression):

We will conduct several sensitivity analyses to explore potential sources of heterogeneity. First, we will stratify studies based on the characteristics of participants they included. In particular, we will assess age (less than 65 or more than 65 years), total serum testosterone level at baseline (low if less than 300 ng/dl or 10.4 nmol/l) or defined by the included studies. If testosterone level will not be available, then lower limit of normal for bioavailable or free testosterone levels is considered. If neither total nor free testosterone levels were available, then studies were classified according to participant characteristics. Second, we will stratify based on the intervention: testosterone formulation, route of administration (transdermal, intramuscular, or oral),

and dose (physiologic dose as recommended by The Endocrine Society of US or anything higher (supra-physiologic dose)). Third, we will stratify by study quality based on the result of the risk of bias assessment. Fourth, we will perform a sensitivity analysis for trials with zero events to determine whether continuity corrections used in primary analysis affected the conclusions. Fifth, to assess the long-term, rather than the acute, effects of TRT, we will include only trials with a treatment period of 12 or more weeks. Sixth, we will assess outcome characteristics with the duration of follow-up (less than 6 months vs. more than 6 months). Seventh, we will also examine whether the effect of TRT varied with the funding source. Finally, we will conduct meta-regression analyses to test the effect of different parameters on VTE.

Assessment of publication bias (funnel plot, Egger test, etc):

We will assess the potential of publication bias using the funnel plot and Egger's test. We will also check at www.clinicaltrials.gov, WHO, FDA, and EMA registry website for protocols and findings of studies unpublished in indexed journals.

Dissemination Plan:

The findings of the study will be presented at local and international conferences and submitted to scientific journals.

Funding sources:

The study is unfunded. KBF holds a *Fonds de recherche du Québec – Santé* (FRQS; Quebec Foundation for Health Research) Junior II salary support award, and HTA holds an FRQS postdoctoral training award.

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Appendix 1. PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol for a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☐	☒	6
Authors					
Contact	3a	Provide the name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of the corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☐	☒	
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, the state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	6
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	6
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	NA
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	1-2
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	2
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	2-3

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	2-3
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	2-3
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	3
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in the meta-analysis)	☒	☐	3
Data collection process	11c	Describe the planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	4
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with the rationale	☒	☐	3
Risk of bias in individual studies	14	Describe anticipated methods for assessing the risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	4
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	5
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	5
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	5
	15d	If the quantitative synthesis is not appropriate,	☐	☒	

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		describe the type of summary planned			
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	6
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	4

Appendix 2. The preliminary search strategy using a Medline (Ovid) for the literature review

CONCEPT	SEARCH TERMS	RECORDS IDENTIFIED
	TESTOSTERONE	
1	exp TESTOSTERONE CONGENERS/ or Testosterone.mp. or exp TESTOSTERONE/ or exp TESTOSTERONE PROPIONATE/	111986
2	Testosterone blood level.mp.	12
3	Testosterone cipionate.mp.	7
4	Testosterone undecanoate.mp.	549
5	1 testosterone.mp.	197
6	Estradiol plus progesterone plus testosterone.mp.	0
7	exp 17-Hydroxysteroid Dehydrogenases/ or Testosterone 17beta dehydrogenase.mp.	2527
8	Testosterone decanoate.mp.	40
9	Testosterone derivative.mp.	45
10	Testosterone enantate.mp.	38
11	Testosterone ester.mp.	54
12	Testosterone metabolism.mp.	608
13	Testosterone ether.mp.	0
14	Testosterone phenylpropionate.mp.	22
15	Testosterone propionate.mp. or exp Testosterone Propionate/	3296
16	Testosterone release.mp.	199
17	Dihydrotestosterone.mp. or exp DIHYDROTESTOSTERONE/	13416
18	Hydroxytestosterones.mp. or exp HYDROXYTESTOSTERONES/	204
19	Testosterone congeners.mp. or exp Testosterone Congeners/	85008
20	Testosterone.ti,ab,kf.	77073
21	Testosterone Replacement Therap*.ti,ab,kf.	1064
22	(Testosterone adj1 therap*).ti,ab,kf.	1448
23	Testosterone Supplemental Therap*.ti,ab,kf.	4
24	Dihydrotestosterone.ti,ab,kf.	10262
25	(DHT or TS or TT or TTh).ti,ab,kf.	54182
26	Testosterone Replacement Alternatives.ti,ab,kf.	1
27	Testosterone Supplement*.ti,ab,kf.	632
28	(Adrotest or Andro 100 or Androderm or Androfort or Androgel or Androlin or Andronaq 50 or Andronaq or Andropatch or Androsorb or Androst 4 en 17beta ol 3 one or Androstenolone or Androtest or Andrusol or Aquaviron or Aquaviron b12 or Axiron or Beta testosterone or Depot hormon-m or First-testosterone or First-testosterone mc or Fortesta or Fortigel or Free testosterone Geno cristaux or Histerone or Homosteron or Hydroxyandrostenone or Intrinsa or Libigel or Livens or Mertestate or Natesto or Neotestis or Opterone or Oreton f or Orquisteron or Percutacrine androgenique or Percutacrine androgenique forte or Percutacrine androgine or Primotest or Primoteston or Primoteston depot or Primoteston-depot or Striant or Sustanon or Sustenon or Synandrol or Teslen or Testamone or Testandrone or Testaqua or Testerone or Testim or Testo enant or Testoderm ciii or Testoderm tts or Testoderm or Testogel or Testoject 50 or Testoluton or Testoluton forte or Testosterone or Testosterone chloride or Testosterone conjugate or Testro or Testro aq or Testrone or Testryl or Tostrelle or Tostrex or Trans testosterone or Virosterone or Vogelxo or Plasma testosterone or Serum testosterone or serum Testosterone).ti,ab,kf.	77161
29	(Andro cyp or Andronaq la or Ciclosterone or Depandro 100 or Depandro 200 or Depandro or Depo testosterone or Depotest or Depotestosterone or Depo-testosterone or Depovirin or Depoviron or Duratest or Malogen cyp 200 or Pertestis or Testa c or Testodrin prolongatum or Testosterone 17beta cyclopentanepropionate or Testosterone 17beta cypionate or Testosterone beta cyclopentylpropionate or Testosterone cyclopentylpropionate or Testosterone cypionate or Testred cypionate).ti,ab,kf.	169

30	(Andriolt or Andriol testocaps or Andriol or Andriol-t or Aveed or Nebido or Panteston or Pantestone or Reandron ORRestandol testocaps ORRestandol or Testosterone 17 undecylate or Testosterone undecylate or Undestor testocaps).ti,ab,kf.	66
31	(((Androfemon or Deladumone ob or Deladumone or Ditate-ds or Estradiol valerate plus testosterone enanthate or Primodian depot or Testosterone enanthate) and estradiol valerate) or Steroid 17 beta dehydrogenase or Testosterone 17 beta dehydrogenase or Testosterone dehydrogenases or Estosterone caprate or Undestor).ti,ab,kf.	26
32	(Androject or Retandrol or Akroteston or Anderone or Andronate or Andronex amp or Androsan amp or Androtest p or Androteston or Androxid or Androxil or Andrusol p or Anertar or Bio testiculina or Bio teston or Cosex tp 50 or Enarmon or entestil or Gonadrone or Homandren amp or Hormandren or Hormoteston or Masenate or Napionate or Nasdol or Neo hombreol or Neohombreol or Neo-hombreol or Okasa mascul or Orchiol or Orchiormon or Orchisterone p or Orchisterone or Orchistin or Oreton propionate or Oreton or Oretone or Orquisteron p or Orquisterone p or Pantestin or Penandren or Perandren amp or Perandren propionate or Perandren or Perandrone amp or Perandrone or Primoniat or propiokan or Propionic acid testosterone ester or Recthormone testosterone or ecthormone or Sterandryl amp or Sterandryl retard or Sterandryl or Sterotest or Suprasteron amp or Suprasterone or Synerone or Testaform or Testex or Testodet or Testodrin or Testogen or Testonique or Testormol or Testormon or Testosid or Testosterone propionate or Testosteronepropionate or Testoviron amp or Testoxyl or Testrex or Tostrin or Uniteston or Release, testosterone or Secretion, testosterone or Testosterone secretion or Testosterone buciclate or Testosterone trans 4 butylcyclohexylcarboxylate).ti,ab,kf.	4635
33	**1 - 32/OR**	**162972**
	VENOUS THROMBOEMBOLISM	
34	Venous thrombosis.mp. or exp Venous Thrombosis/	63105
35	Vein thrombosis.mp.	23413
36	Venous thromboembolism.mp. or exp Venous Thromboembolism/	19305
37	Deep vein thrombosis.mp.	14916
38	Leg thrombosis.mp.	48
39	Pulmonary embolism.mp. or exp Pulmonary Embolism/	47984
40	exp Thrombophlebitis/	21603
41	((Acute or leg) adj (Vena or vein or deep vein* or deep-vein* or venous or deep venous) adj (thromb* or emboli*)).ti,ab,kw.	891
42	Phlebothrombo*.ti,ab,kf.	564
43	((budd chiari or budd-chiari or chiari*) adj syndrome).ti,ab,kf.	2827
44	(hepatic adj (vein or venous) adj (thromb* or outflow obstruction)).ti,ab,kf.	579
45	deep thrombophlebitis.ti,ab,kf.	82
46	blood clot*.ti,ab,kf.	8492
47	(Thromb* or Embol*).ti,ab,kf.	474674
48	((gas* or air or fat* or paradox* or pulmonar* or cross*) adj (thrombo* or emboli*)).ti,ab,kf.	45971
49	**34 – 48/OR**	**500928**
	Cardiovascular disease	
50	Cardiovascular diseases/	130782
51	heart diseases.mp. or exp Heart Diseases/	1041930
52	exp arrhythmias, cardiac/ or cardiac tamponade/ or exp Cardiomegaly/ or exp Cardiomyopathies/ or exp Heart Arrest/ or exp Heart Failure/ or exp Heart Valve Diseases/ or Myocardial Stunning/ or exp Ventricular Dysfunction/ or exp Ventricular Outflow Obstruction/	519783
53	vascular diseases.mp. or exp Vascular Diseases/	1546798
54	exp ANEURYSM/ or aneurysm.mp.	134778
55	aortic diseases.mp. or exp Aortic Diseases/	69075
56	arterial occlusive diseases/ or exp arteriosclerosis/ or carotid stenosis/ or leriche syndrome/ or moyamoya disease/	199184
57	cerebrovascular disorders.mp. or exp Cerebrovascular Disorders/	332921

58	myocardial ischemia.mp. or exp Myocardial Ischemia/	408400
59	peripheral vascular diseases.mp. or exp Peripheral Vascular Diseases/	50563
60	CVD.ti,ab,kf.	28861
61	((arter* or cardiac or cardiovascular or cerebral small vessel or cerebral vascul* or cerebrovascul* or coronar* or heart or vascul*) adj3 (death* or disease* or disorder* or dysfunction* or effect? or event? or morbidit* or syndrome*)).ti,ab,kf.	682854
62	(arrhythmi* or cardiac dysrhythmia* or atrial fibrillation or afib or a-fib or atrial flutter* or bradycardi* or ((cardiac or premature) adj complex*) or commotio cordis or heart block* or (adams stokes adj (attack* or syndrome*)) or ((atrioventricular or av) adj2 block*) or ((bundle branch or Fascicular) adj block*) or sick sinus syndrome* or (sinus node adj (disease* or dysfunction* or syndrome*)) or (sinoatrial adj2 block*) or long qt syndrome* or ((andersen or cardiodysrhythmic) adj3 (paralys#s or syndrome*)) or ((romano ward or ward romano) adj syndrome*) or parasystole* or ((pre-excitation or preexcitation) adj (Mahaim Type or syndrome*)) or Lown Ganong Levine Syndrome* or Wolff Parkinson White Syndrome* or tachycardi* or Tachyarrhythmi* or "torsades de pointes" or ventricular fibrillation* or ventricular flutter*).ti,ab,kf.	222841
63	(((cardiac or pericardial) adj tamponade*) or cardiomegal* or cardiomyopath* or myocardial disease* or myocardiopath* or (ventricular adj (hypertroph* or dysplasia*)) or Endomyocardial Fibrosis or Myocardial Reperfusion Injury or Myocarditi* or aneurysm* or ((cardiac or heart) adj arrest*) or ((cardiac or karoshi) adj death*) or ((cardiac or heart) adj failure*) or ((cardio renal or cardiorenal or renocardiac) adj syndrome*) or paroxysmal dyspnea* or (cardiac adj (edema* or oedema*)) or ((cardiac or free wall or heart or ventricular septal) adj ruptur*)).ti,ab,kf.	396137
64	((angina adj (microvascular or pectoris or stable or unstable)) or heart attack* or myocardial infarct* or cardiogenic shock).ti,ab,kf.	203464
65	(((aortic or subaortic or subvalv* or valv*) adj (insufficienc* or stenos#s or prolaps*)) or ((pulmonary or tricuspid) adj atresia*) or pulmonary stenos#s).ti,ab,kf.	39604
66	(myocardial stunning or ventricular dysfunction* or (ventricular adj2 obstruction*)).ti,ab,kf.	18201
67	(arteriosclero* or atherosclero* or ((vascular or multi-infarct) adj dementia*) or (carotid adj3 stenos#s) or leriche syndrome* or moyamoya).ti,ab,kf.	171987
68	(stroke or strokes or apoplex* or ((cerebrovascular or vascular) adj accident*) or (isch?emi* adj3 (brain or cerebral vasc* or cerebrovasc* or cva or attack* or heart or myocardial)) or ((basal ganglia or brain* or cerebell* or cerebral or intracerebral or intracranial or putanimal or subarachnoid) adj3 (haemorrhag* or hemorrhag* or bleed*)) or sneddon syndrome or ((brain or cerebral) adj2 injur*) or ((brain* or cerebral or lacunar) adj2 infarct*) or lateral medullary syndrome* or ((arter* or basilar or vertebrobasilar) adj insufficienc*) or subclavian steal syndrome*).ti,ab,kf.	413497
69	**50 - 68/OR**	**2677464**
RANDOMIZED CONTROLLED TRIALS		
70	randomized controlled trial.pt.	463115
71	clinical trial.pt.	510767
72	randomi?ed.ti,ab.	532737
73	placebo.ti,ab.	194990
74	randomly.ti,ab.	292985
75	trial.ti,ab.	506264
76	groups.ti,ab.	1829978
HUMAN PARTICIPANTS		
77	adolescen*.tw.	238962
78	adult*.tw.	1085224
79	aid worker*.tw.	138
80	amputee*.tw.	4990
81	assistant*.tw.	22251
82	aunt*.tw.	1192
83	brother*.tw.	13062

84	care giver*.tw.	2401
85	caregiver*.tw.	50835
86	carer*.tw.	12338
87	exp child/	1773877
88	child*.tw.	1241853
89	clinician*.tw.	187358
90	community member*.tw.	5765
91	community network*.tw.	488
92	companion*.tw.	12963
93	coroner*.tw.	2376
94	cousin*.tw.	3967
95	daughter*.tw.	23701
96	dentist*.tw.	64857
97	displaced.tw.	32273
98	doctor*.tw.	113410
99	donor*.tw.	275199
100	exp family/	288412
101	families.tw.	214129
102	family.tw.	701178
103	father*.tw.	37328
104	female*.tw.	824467
105	fire fighter*.tw.	352
106	firefighter*.tw.	1784
107	focus group*.tw.	36911
108	exp focus groups/	24725
109	Foreign professional personnel/	1973
110	friend.tw.	12813
111	friends.tw.	23515
112	grand father*.tw.	26
113	grand mother*.tw.	39
114	grand parent*.tw.	77
115	grandfather*.tw.	1310
116	grandmother*.tw.	2446
117	grandparent*.tw.	2781
118	guardian*.tw.	6469
119	Homeless Persons/	6824
120	homeless*.tw.	8983
121	human*.tw.	2461793
122	(humanitarian adj2 worker*).tw.	86
123	Humans/	17124672
124	husband*.tw.	15538
125	individual*.tw.	1352323
126	infant*.tw.	367169
127	inpatient*.tw.	90357
128	inspector*.tw.	2272
129	interview*.tw.	307039
130	investigator*.tw.	76583
131	male*.tw.	1011181
132	medical examiner*.tw.	3258
133	missionar*.tw.	826
134	mother*.tw.	194798

135	nephew*.tw.	1094
136	next of kin.tw.	1266
137	niece*.tw.	376
138	nurse*.tw.	247568
139	offspring*.tw.	64300
140	orphan*.tw.	14865
141	outpatient*.tw.	146372
142	paramedic*.tw.	6992
143	parent*.tw.	369561
144	participant*.tw.	617988
145	partner*.tw.	148656
146	exp Patients/	57162
147	patient*.tw.	5912871
148	people*.tw.	382403
149	person*.tw.	597764
150	exp Persons/	9000565
151	pharmacist*.tw.	27259
152	physician*.tw.	347912
153	planner*.tw.	6212
154	refugee*.tw.	8510
155	exp Refugees/	8643
156	relief team*.tw.	49
157	relief work/	3735
158	research subject*.tw.	2448
159	respond?nt*.tw.	97850
160	exp self-help group/	9711
161	self help group*.tw.	1557
162	sibling*.tw.	45965
163	sister*.tw.	35451
164	exp social support/	64031
165	social support*.tw.	32650
166	specialist*.tw.	83343
167	spouse*.tw.	15586
168	staff*.tw.	146176
169	exp Survivors/	25235
170	step father*.tw.	31
171	step mother*.tw.	10
172	step parent*.tw.	79
173	stepfather*.tw.	226
174	stepmother*.tw.	81
175	stepparent*.tw.	140
176	sufferer*.tw.	6920
177	support group*.tw.	6357
178	survivor*.tw.	87397
179	team*.tw.	136628
180	therapist*.tw.	33694
181	uncle*.tw.	265031
182	victim*.tw.	47206
183	Voluntary Workers/	8952
184	volunteer*.tw.	177158
185	wife.tw.	5145

186	wives.tw.	4958
187	woman*.tw.	202986
188	women*.tw.	872226
189	worker*.tw.	160025
190	young adult*.tw.	80866
191	**77 – 190/OR**	20256077
192	**70 – 76/OR**	2851557
193	**33 and 49**	2217
194	**33 and 69**	11480
195	**193 or 194**	12688
196	**192 and 195**	3478
197	**191 and 196**	3317